ISSN: 2444-0507

CIRUGÍA Y CIRUJANOS

ÓRGANO DE DIFUSIÓN CIENTÍFICA DE LA ACADEMIA MEXICANA DE CIRUGÍA

FUNDADA EN 1933

Content

Original articles

PERMANYER MÉXICO
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Volume 91, No. 4, July-August 2023

Journal Citation ReportsTM from Clarivate, 2022, Medline/PubMed, EBSCO Essentials™

7571AX224

ORIGINAL ARTICLE

The relationship between results of coronary angiography, Mediterranean-type lifestyle, type D personality, and healthy life expectancy

Relación entre los resultados de la angiografía coronaria intervencionista, el estilo de vida mediterráneo, los rasgos de personalidad tipo D y la expectativa de vida libre de enfermedad

Füsun Afşar[1], Ahmet Güler[2], and Habip Yılmaz[3]*

[1]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital; [2]Department of Cardiology, Istanbul Başakşehir Çam and Sakura City Hospital, University of Health Sciences; [3]Department of Management, Istanbul 1st Region Public Hospitals Presidency. Istanbul, Turkey

Abstract

Aim: *The aim of this study was to determine the relationship between coronary angiography results and Mediterranean-type lifestyle and type D personality.* **Methods:** *Mediterranean-type lifestyle index and type D personality scale were administered to 230 participants.* **Results:** *In univariate analysis according to coronary angiography results, a statistically significant effect was determined between the decision for treatment with percutaneous coronary intervention (PCI) and diabetes mellitus, and total and subscale points of Mediterranean lifestyle index, and between the decision for treatment with bypass and body mass index, Mediterranean diet, physical activity, and total points. In multivariate analysis, there was determined to be an effect between the PCI and systolic pressure, and between bypass and body mass index and subscale of physical activity. When disease-free life expectancy was examined, there was seen to be a negative effect of smoking and low Mediterranean diet points for participants with PCI, and of smoking, presence of hypertension, family history, and high type D personal characteristics score for those with bypass decision.* **Conclusion:** *The evidence-based recommendations for a Mediterranean-type lifestyle stated in cardiovascular disease (CVD) preventative guidelines may have a positive effect on the prevention of CVD, disability-free life, and mortality.*

Keywords: *Coronary angiography. Mediterranean. Lifestyle behaviors. Personality characteristics. Healthy expectancy.*

Resumen

Objetivo: *Este estudio se llevó a cabo para determinar la relación entre los resultados la angiografía coronaria y el estilo vida mediterráneo y los rasgos personalidad tipo D.* **Método:** *El índice de estilo de vida de tipo mediterráneo y la escala de personalidad de tipo D se administraron a 230 participantes* **Resultados:** *Según el resultado angiografía coronaria, subdimensiones intervención coronaria percutánea y diabetes y estilo de vida mediterráneo y puntajes totales en análisis univariante, circunvalación, cuanto a índice masa corporal, dieta estilo mediterráneo, actividad física y puntuación total; en análisis multivariado, se encontró que la intervención coronaria percutánea se asoció con la presión arterial sistólica, circunvalación con el índice masa corporal y subdimensión actividad física. Mirando la esperanza vida libre enfermedades, el tabaquismo y la baja puntuación la dieta tipo mediterránea del participante para el que se tomó la intervención coronaria percutánea, el índice masa corporal bajo, tabaquismo, hipertensión, los antecedentes familiares y los rasgos de personalidad tipo D altos del participante con la circunvalación afectan negativamente la esperanza de vida libre enfermedades.* **Conclusión:** *Como se indica en las pautas de prevención enfermedades cardiovasculares, el estilo vida mediterráneo puede tener efectos positivos en la prevención enfermedades cardiovasculares, discapacidad y mortalidad.*

***Palabras clave*:** *Angiografía coronaria. Mediterráneo. Estilo de vida. Características de personalidad. Expectativa de vida.*

***Correspondence:**
Füsun Afşar
E-mail: fusunafsar@maltepe.edu.tr

Date of reception: 31-08-2022
Date of acceptance: 17-04-2023
DOI: 10.24875/CIRUE.M23000619

Cir Cir (Eng). 2023;91(4):423-429
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

According to the 2018 global disease burden report, cardiovascular disease (CVD) was the cause of an estimated 17.8 million deaths worldwide in 2017, and this number constituted 31% of all deaths[1]. The development and prognosis of CVD have been strongly associated with nutritional habits and lifestyle. In the globally accepted cardiac health guidelines, a reduction in saturated fats and trans-fatty acids is recommended as an important protective factor, and it has been emphasized that there is a strong relationship between a healthy diet and lifestyle, and a reduction in the incidence of CVD.

Studies in recent years have shown a significant reduction in CVD risk in individuals with a Mediterranean-type diet. The potential effect mechanisms of a Mediterranean-type lifestyle include protection against oxidative stress, inflammation and thrombocyte aggregation, modification of hormones and growth factors, inhibition of nutrient perception pathways with specific amino acid restriction, the intestinal microbiota-mediated production of metabolites that affect metabolic health, and the high beneficial effects on these biomarkers at the start of atherosclerosis[2]. An increase in adherence to a healthy lifestyle determined by combinations of adherence to a Mediterranean diet, physical activity, smoking, and alcohol consumption has been found to be associated with a decrease of > 50% in mortality for all these reasons[3]. A healthy lifestyle has been associated with a 66% risk reduction for CVD, a 60% decrease in stroke, and a 69% decrease in heart failure[4].

In protective cardiac health guidelines, Mediterranean lifestyle cardiovascular risk factors have also been associated with lower mortality. The personal characteristics and lifestyle of an individual are important determinants of health status. A series of studies have found that type D personality is an independent predictor of cardiac events following percutaneous coronary intervention (PCI). To determine the personality traits of a group of heart patients, the type D personality scale was developed by Denollet, and its validity and reliability were performed in many countries[5,6]. While a Mediterranean lifestyle is a model of healthy living contributing to health status, there are ongoing studies that type D personal characteristics may be a risk factor in the formation of coronary diseases[7]. Intravascular imaging is the most valuable method to determine the treatment process in detecting lesions and fragility markers in patients presenting with CVD. The aim of this study was to determine the relationship between coronary angiography results and a Mediterranean-type lifestyle and type D personality characteristics.

Methods

The study was conducted with face-to-face interviews of all the patients who underwent coronary angiography in an A1-level Specialism Training and Research Hospital. It was calculated to be necessary to include 207 patients F-test family used 0.90 power, 0.05 error, 0.25 effect size. Demographic data were recorded and the Mediterranean-type lifestyle index and type D personality scale were applied to all the participants[8]. Mediterranean-type lifestyle index (MEDLIFE) is a 28-item derived index consisting of questions about food consumption (fifteen items), traditional Mediterranean dietary habits (seven items) and physical activity, and rest and social interaction habits (six items). Participants who report that they do not consume the Mediterranean lifestyle index are given 0 points, and participants who do consume 1–points.

Type D personality scale comprises seven items each for the negative affectivity and social inhibition subscales. Examples of the items are “I often feel unhappy” (NA) and “I feel inhibited in social interactions” (SI). The items are rated on a 5-point Likert scale from 0 (*false*) to 4 (*true*)[5,8].

In the statistical analyses, G*Power 3.1.9.4, RStudio version 2022.02.1, and IBM SPSS vn. 22.0 software were used. When evaluating the data was used with frequency tables, Shapiro-Wilk test (for normality), differences were with the Kruskal-Wallis H test, Mann-Whitney U-test (with Bonferroni correction), univariate/multivariate logistic regression analysis for risk factors, and effect of age with Cox regression analysis.

A descriptive statistical analysis and univariate/multivariate logistic regression model for risk factors were performed.

Ethical approval

The study was carried out with the permission of the Health Sciences Hospital Clinical Research Ethics Committee (decision no: KAEK/2022.07.231). Written informed consent was obtained from all the study participants.

Results

The patients were examined in three different categories according to the coronary angiography results.

Table 1. Distribution of the demographic data of the patients according the coronary angiography results

Angio result	Medical treatment		PCI		Bypass		p*
	Mean ± SD	Kurtosis; skewness	Mean ± SD	Kurtosis; skewness	Mean ± SD	Kurtosis; skewness	
Age (years)	57.79 ± 9.59	1.26; –0.35	58.96 ± 11.45	6.95; –1.66	64.61 ± 6.95	–1.12; –0.04	0.0001†
Weight (kg)	80.07 ± 13.7	–0.29; 0.18	83.54 ± 12.44	0.02; 0.17	77.03 ± 12.64	–0.95; –0.25	0.028†
Height (cm)	165.98 ± 9.22	0.55; 0.13	167.83 ± 8.78	–0.46; –0.06	167.21 ± 8.49	0.3; 0.23	0.469
BMI	29.15 ± 5.19	2.24; 1.18	29.74 ± 4.58	1.17; 0.84	27.52 ± 3.84	–0.77; –0.55	0.069
SBP	138.02 ± 16.5	0.69; 0.57	142.14 ± 13.23	–0.09; 0.37	145.41 ± 15.94	–1.4; 0.18	0.025†
DBP	80.94 ± 10.14	–0.15; –0.51	81.01 ± 8.21	–0.25; –0.34	82.56 ± 14.01	–0.96; 0.18	0.764

*Kruskal-Wallis H test.
†p < 0.05 statistically significant.
BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Distribution of the type D personality characteristics and Mediterranean-type lifestyle index according to the coronary angiography results

Angio result	Medical treatment		PCI		Bypass		p*
	Mean ± SD	Kurtosis; skewness	Mean ± SD	Kurtosis; skewness	Mean ± SD	Kurtosis; skewness	
Consumption of food	11.21 ± 2.82	–0.67; –0.43	9.8 ± 3.29	1.73; –1.13	9.24 ± 2.5	1.18; –0.47	0.000[1,2‡]
Diet ability	6.33 ± 1.56	0.55; –1.02	5.3 ± 2.06	–0.65; –0.5	5.93 ± 1.83	0.58; –1.14	0.003[1‡]
Physical activity	5.67 ± 1.73	–0.74; –0.34	4.73 ± 2.01	–0.77; –0.25	4.12 ± 2.11	–0.9; –0.44	0.0001[1,2‡]
Total	23.21 ± 5.05	–0.73; –0.23	19.83 ± 5.84	0.58; –0.94	19.29 ± 3.96	0.88; –0.38	0.0001[1,2‡]
D type personality	21.15 ± 8.19	0.78; 0.72	21.63 ± 9.34	–0.31;0.43	21.08 ± 6.94	0.9; 0.57	0.979

*Kruskal–Wallis H test.
†p < 0.05 statistically significant.
‡Mann-Whitney U-test.
1: Medical treatment versus PCI.
2: Medical treatment versus bypass.
BMI: body mass index; SBP: systolic blood pressure.

The treatment decisions were made of medical treatment for 84 (36%) patients, PCI for 71 (31%), and a bypass procedure for 75 (33%).

The mean age of the patients was determined to be 60.37 ± 9.99 years (46-79), body mass index (BMI) was 28.80 ± 4.67 (19.53-46.06), and systolic blood pressure was 141.70 ± 15.62 (100-188). In all three groups, BMI was in the range of 25-30 (overweight) and systolic blood pressure was > 135 mmHg. A statistically significant difference was determined between the medical treatment and the bypass group in respect of systolic blood pressure ($p < 0.0001$), and age ($p = 0.012$) (Table 1).

The bypass group patients were determined to have statistically significantly lower subscale and total points in the MEDLIFE compared to the other groups ($p < 0.05$). Consumption of food was statistically significantly higher at 11.21 ± 2.82 in the medical treatment group, compared to 9.80 ± 3.29 in the PCI group and 9.24 ± 2.50 in the bypass group ($p = 0.006$, $p < 0.0001$) (Table 2).

For the patients consuming Mediterranean-type food, the decision was made for medical treatment as a result of the coronary angiography. The diet ability was recorded as 6.33 ± 1.56 for the medical treatment group, 5.93 ± 1.83 for the bypass group, and 5.3 ± 2.06 for the PCI group, and there was determined to be a statistically significant difference between the medical treatment and PCI groups ($p = 0.001$). The physical activity subscale points were statistically significantly higher at 11.21 ± 2.82 in the medical treatment group than in the PCI (9.80 ± 3.29) and bypass (9.24 ± 2.50) groups ($p = 0.006$ and $p < 0.0001$, respectively). The total points of the MEDLIFE were determined to be statistically significantly higher in the medical treatment group (23.21 ± 5.05) than in the PCI group (21.63 ± 9.34) and the bypass group (21.08 ± 6.94) ($p < 0.0001$).

Table 3. The effect of Mediterranean-type lifestyle and type D personality characteristics on the patients in the medical treatment and PCI groups

Angio medical and PCI	Univariate*				Multivariate†			
	p	Exp (B)	95% C.I. for EXP (B)		p	Exp (B)	95% C.I. for EXP (B)	
			Lower	Upper			Lower	Upper
Age	0.487	(+) 1.011	0.980	1.043	0.544	(+) 0.988	0.950	1.027
BMI	0.454	(+) 1.025	0.961	1.094	0.456	(+) 1.028	0.956	1.106
Systolic BP	0.095	(+) 1.018	0.997	1.041	0.027‡	(+) 1.034	1.004	1.064
Smoking	0.332	(+) 0.834	0.578	1.204	0.978	(+) 1.006	0.649	1.559
Family history	0.129	(+) 0.734	0.493	1.094	0.606	(+) 0.885	0.557	1.407
DM	0.030‡	(+) 0.697	0.504	0.965	0.061	(+) 0.692	0.471	1.017
HT	0.548	(+) 1.103	0.802	1.516	0.084	(+) 1.445	0.951	2.195
Consumption of food	0.006‡	(–) 0.857	0.766	0.957	0.618	(–) 0.961	0.823	1.123
Diet ability	0.001‡	(–) 0.73	0.605	0.879	0.060	(–) 0.796	0.627	1.010
Physical activity	0.003‡	(–) 0.765	0.641	0.913	0.064	(–) 0.802	0.634	1.013
Total	0.0001‡	(–) 0.89	0.834	0.949	-	-	-	-
D type personality	0.732	(+) 1.006	0.970	1.044	0.149	(+) 1.033	0.988	1.080

*Univariate logistic regression analysis.
†Univariate logistic regression analysis p < 0.05.
‡Statistically significant.
BMI: body mass index; SBP: systolic blood pressure; DM: diabetes mellitus.

The effects of demographic characteristics, MEDLIFE, and type D personality characteristics were investigated in the patients who applied with PCI compared to the patients who received medical treatment, according to the coronary angiography results. As a result of the analysis, it was seen that age, BMI, systolic blood pressure, smoking, family history, diabetes mellitus (DM), and hypertension (HT) increased the decision for PCI, and the statistical significance was determined to be associated with a diagnosis of DM in univariate analysis, and with systolic blood pressure in multivariate analysis ($p < 0.05$). As both the total and subscale points of the MEDLIFE decreased, so there was an increase in the decision for PCI, and this was determined to show statistical significance in univariate analysis ($p < 0.05$) (Table 3).

The effects of demographic characteristics, MEDLIFE, and type D personality characteristics were investigated in the patients applied with bypass compared to the patients who received medical treatment, according to the coronary angiography results. As a result of the analysis, it was seen that age, systolic blood pressure, smoking, family history, the presence of DM, and HT increased the decision for bypass, and the statistical significance was determined to be associated with age, systolic blood pressure, smoking, family history, and a diagnosis of DM in univariate analysis and with age, smoking, and family history in multivariate analysis ($p < 0.05$). As the BMI and both the total and subscale points of the MEDLIFE decreased, so there was an increase in the decision for bypass, and BMI, Mediterranean-type diet, physical activity, and total points were determined to show statistical significance in univariate analysis, and BMI and the physical activity subscale in multivariate analysis ($p < 0.05$) (Table 4).

Smoking and low Mediterranean-type diet points of the patients in the PCI group had a negative effect on disease-free life expectancy ($p < 0.05$) (Fig. 1A). Low BMI, smoking, the presence of HT, family history, and high type D personality characteristics points of the patients in the bypass group had a negative effect on disease-free life expectancy ($p < 0.05$) (Fig. 1B).

Discussion

The content of the previous randomized controlled studies, systematic examinations, meta-analyses, and observational studies in respect of the primary prevention of CVDs has focused on subjects such as

Table 4. The effect of Mediterranean-type lifestyle and type D personality characteristics on the patients in the medical treatment and bypass groups

Angio medical versus bypass	Univariate*				Multivariate†			
	p	Exp (B)	95% C.I. for Exp (B)		p	Exp (B)	95% C.I. for Exp (B)	
			Lower	Upper			Lower	Upper
Age	0.0001‡	(+) 1.105	1.058	1.155	0.0001‡	(+) 1.139	1.065	1.219
BMI	0.031‡	(–) 0.923	0.858	0.993	0.0001‡	(–) 0.769	0.670	0.884
Systolic BP	0.006‡	(+) 1.028	1.008	1.049	0.068	(+) 1.032	0.998	1.068
Smoking	0.019‡	(+) 0.658	0.464	0.933	0.007‡	(+) 0.496	0.298	0.827
Family history	0.0001‡	(+) 0.47	0.324	0.682	0.028‡	(+) 0.556	0.330	0.938
DM	0.004‡	(+) 0.627	0.454	0.865	0.120	(+) 0.678	0.415	1.107
HT	0.073	(+) 0.738	0.529	1.029	0.277	(+) 0.747	0.442	1.263
Consumption of food	0.0001‡	(–) 0.759	0.667	0.864	0.354	(–) 0.922	0.776	1.095
Diet ability	0.140	(–) 0.869	0.720	1.047	0.901	(–) 1.018	0.767	1.352
Physical activity	0.0001‡	(–) 0.661	0.550	0.794	0.042‡	(–) 0.748	0.565	0.990
Total	0.0001‡	(–) 0.828	0.764	0.897	-	-	-	-
D type personality	0.950	(–) 0.999	0.958	1.041	0.151	(+) 1.043	0.985	1.104

*Univariate logistic regression analysis.
†Univariate logistic regression analysis $p < 0.05$.
‡Statistically significant.
BMI: body mass index; SBP: systolic blood pressure; DM: diabetes mellitus.

risk evaluation, diet, exercise/physical activity, obesity and weight loss, type 2 DM, blood cholesterol, HT, stopping smoking, and the use of aspirin. At the core of all these issues, it is stated that atherosclerotic cardiovascular diseases can be prevented only if clinicians can provide individuals with healthy lifestyle behaviors with evidence-based recommendations[9].

The results of the present study showed that the group for whom medical treatment was decided had higher subscale and total MEDLIFE points. In a study of 5966 patients showing the relationship between a Mediterranean diet and cardiovascular events, it was shown that adherence to a Mediterranean diet reduced the risk of CVD independently of risk factors[10]. In a pioneering primary prevention study in Spain, which included patients at high cardiovascular risk, a Mediterranean diet was seen to reduce CVD by 30% compared to a low-fat diet[9]. There are also studies showing the relationship of CVD with physical activity in the Mediterranean lifestyle in addition to the Mediterranean diet as evidence-based lifestyle recommendations stated in the CVD prevention guidelines[11]. In studies in Spain, the combined effect of good adherence to a Mediterranean diet with increased physical activity showed positive effects on mortality[12-14]. In a meta-analysis of 45 studies which evaluated four randomized controlled studies and 32 independent observation groups, a Mediterranean diet was seen to be associated with positive cardiovascular health outcomes[15].

In the present study of 230 participants, the BMI value was in the range of 25-30 (overweight) and systolic blood pressure was > 135 mmHg. Despite the strong relationship between obesity and the development of CVD in the previous studies, the results obtained from large meta-analyses have shown that patients with CVD and BMI above the normal range generally have a better prognosis[16]. In a prospective study that initially included 717 patients, there was no correlation between BMI and major advanced cardiovascular events in 201 patients in a 3.9-year follow-up period, but the percentage of body fat mass showed an effect[17]. In the present study, the BMI of the bypass group patients was determined to be lower than the values of the other two groups. Life expectancy is especially affected in patients with bypass. Consistent with findings in the literature, the systolic blood pressure was also found to be higher in the bypass group of the present study. In the literature related to systolic blood pressure as one of the risk factors for coronary

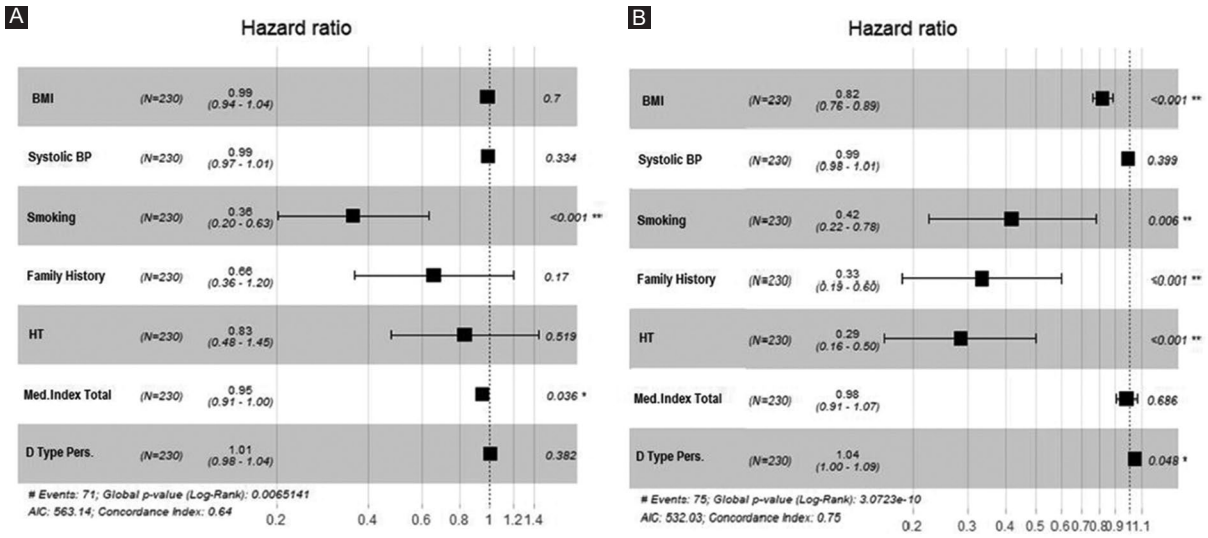

Figure 1. A: *disease-free life expectancy in the percutaneous coronary intervention group patients.* **B:** *bypass group patients.*

artery disease, a study with 1457 participants reported that for every 10 mmHg increase in systolic blood pressure, there was a 53% higher risk of atherosclerotic CVD[18]. The analysis at the temporary patient level of seven randomized clinical studies which included 3912 patients from 2004 to 2016, there was seen to be a significant step-by-step relationship of increasing quartiles of systolic blood pressure with survival curves, and cumulative major adverse cardiovascular events[19]. The previous studies have shown a relationship between the Mediterranean lifestyle and BMI and systolic blood pressure. When the effects of BMI and diet quality on mortality have been examined independently, it has been determined that individuals with a normal BMI but low Mediterranean diet points have high mortality compared to those with high Mediterranean diet points and obese or normal BMI values, and obese individuals showed a lower increase in cardiovascular mortality[20].

There are several studies in the literature showing a relationship between diabetes and CVD risk, and when there are major adverse cardiovascular events, the negative effects have been stated of several factors related to diabetes such as instant blood glucose, fasting blood glucose, and glycosylated hemoglobin A1c[21,22]. Studies in recent years in particular have been directed at determining the effect and prognosis in major adverse CVDs. It is thought that in the evaluation of major adverse cardiovascular events, the TyG index, independently of known cardiovascular risk factors, will predict future major adverse cardiovascular events in patients with diabetes and acute coronary syndrome and could be a beneficial marker for risk classification and prognosis in patients with the acute coronary syndrome[23-25]. In the present study, a diagnosis of diabetes and MEDLIFE were seen to have a statistically significant effect, especially on the patients who applied with PCI[26].

In addition to the known risk factors in patients who underwent bypass in the present study, type D personality characteristics showed a negative effect on disease-free life expectancy. Although there are few studies in the literature with large samples, it has been emphasized that type D personality characteristics are an important part of the psychosocial risk factors that affect coronary artery disease prognosis. In a meta-analysis of 12 studies including 5341 participants, there was seen to be a significant increase in the mortality risk of coronary artery disease patients with type D personality characteristics[27].

Conclusion

The results of this study demonstrated a relationship between Mediterranean-type lifestyle, type D personality characteristics, the known risk factors of CVD, and the treatment decision made according to the result of coronary angiography. As an evidence-based lifestyle recommendation stated in the CVDs prevention guidelines, a Mediterranean-type lifestyle may have positive effects on the prevention of CVD, a disability-free life, and mortality. To be able to reach a conclusion about

the relationship with type D personality characteristics, there is a need for further studies with larger samples.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Prevalence, causes, and clinical course of patients with surgical reintervention due to complications during cesarean section

Prevalencia, causas y curso clínico de pacientes con reintervención quirúrgica debido a complicaciones durante la cesárea

Juan G. Vázquez-Rodríguez[1], Juan Serrano-Rodríguez[2], Silvia A. Arredondo-Andrade[1], Fabián G. Chable-Chan[3], Juan A. García-Bello[4], and Carlos M. Nájera-Coutiño[1]*

[1]Intensive Care Unit, Unidad Médica de Alta Especialidad, Hospital de Gineco Obstetricia No. 3; [2]Department of Maternal Fetal Medicine, Unidad Médica de Alta Especialidad, Hospital de Gineco Obstetricia No. 3; [3]Department of Emergency, Hospital General "Dr. Gaudencio González Garza"; [4]Health Research Division, Unidad Médica de Alta Especialidad, Hospital de Gineco Obstetricia No. 3. Centro Médico Nacional "La Raza", Instituto Mexicano del Seguro Social. Mexico City, Mexico

Abstract

Objective: *The objective of the study is to identify the prevalence, causes, and clinical evolution of patients with surgical reintervention due to complications during cesarean section.* **Materials and methods:** *The file of the Toco-Surgical Unit of the Gynecological Obstetrics Hospital No. 3 of the National Medical Center "La Raza" Mexican Institute of Social Security was reviewed to know the total number of patients undergoing cesarean section from January to December 2019 and cases with reintervention due to complications during cesarean section were selected. Their general data, the cause of reintervention, stay in the intensive care unit (ICU), hospital stay, and mortality were studied. The data were analyzed with descriptive statistics using the statistical program SPSS version 20.* **Results:** *It was found that 3371 patients underwent cesarean section, of which 1.60% (54 cases) underwent reoperation for the following reasons: Unpacking 27.79%, obstetric hemorrhage 20.37%, bleeding due to uterine atony 20.37%, hysterotomy commissure hematoma 18.52%, uterine infiltration 3.70%, vascular injury 3.70%, bladder injury 3.70%, and colonic injury 1.85%. The ICU stay was 3.79 ± 2.03 days, hospital stay was 13.67 ± 11.16 days, and mortality was 1.85%.* **Conclusion:** *The prevalence of reintervention was reduced, bleeding was the main cause, and the clinical evolution was satisfactory with low mortality.*

Keywords: *Cesarean section. Cesarean section complications. Abdominal reoperation. Obstetric intensive care.*

Resumen

Objetivo: *Identificar la prevalencia, causas y evolución clínica de las pacientes con reintervención quirúrgica por complicaciones durante la cesárea.* **Material y métodos:** *Se revisó el archivo de la Unidad de Toco-Quirúrgica del Hospital Ginecobstetricia No. 3 del Centro Médico Nacional "La Raza" Instituto Mexicano del Seguro Social para conocer el total de pacientes sometidas a cesárea desde enero hasta diciembre de 2019 y se seleccionaron los casos con reintervención por complicaciones durante la cesárea. Se estudiaron sus datos generales, la causa de reintervención, estancia en la Unidad de Cuidados Intensivos (UCI), estancia en hospital y la mortalidad. Los datos se analizaron con estadística descriptiva utilizando el programa estadístico SPSS versión 20.* **Resultados:** *Se encontró que 3371 pacientes fueron sometidas a cesárea de las cuales 1.60% (54 casos) se reintervinieron por las siguientes causas: desempaquetamiento 27.79%, hemorragia obstétrica 20.37%, sangrado*

***Correspondence:**
Juan G. Vázquez-Rodríguez
E-mail: juangustavovazquez@hotmail.com

Date of reception: 11-05-2022
Date of acceptance: 26-07-2022
DOI: 10.24875/CIRUE.M22000620

Cir Cir (Eng). 2023;91(4):430-434
Contents available at PubMed
www.cirugiaycirujanos.com

por atonía uterina 20.37%, hematoma de la comisura de histerotomía 18.52%, infiltración uterina 3.70%, lesión vascular 3.70%, lesión vesical 3.70% y lesión colónica 1.85%. La estancia en UCI fue 3.79 ± 2.03 días, estancia en hospital 13.67 ± 11.16 días y mortalidad 1.85%. **Conclusión:** *La prevalencia de reintervención fue reducida, el sangrado fue la principal causa y la evolución clínica resultó satisfactoria con baja mortalidad.*

Palabras clave**:** *Cesárea. Complicaciones de la cesárea. Reintervención abdominal. Cuidados intensivos obstétricos.*

Introduction

Surgical resolution of pregnancy through cesarean section is one of the most important advances in contemporary perinatal medicine. Cesarean section has had an extraordinary impact in reducing maternal and perinatal mortality[1]. It is the most frequently performed surgery in the world and is increasing every year. Reports have documented its increase in both developed nations and developing countries[2,3]. Frequencies exceed the 10-15% recommended by the World Health Organization for performing said surgery[4]. The experts have explained that the preference of the method for the convenience of the doctor, surgery at the request of the patient, and pathologies secondary to a first surgery are situations that have been added to the maternal, placental, and fetal indications that are ordinarily taken into account to perform a cesarean section[5].

With this scenario, it is possible that the number and nature of complications during cesarean section also have some change compared to previous reports, particularly when the cesarean section is repeated one or more times[6]. Possible complications during caesarean section have been known for decades, including bleeding in the layer of the surgical bed, bleeding from the hysterotomy commissures, uterine infiltration, hematomas, accidental damage to arterial or venous vascular structures, injuries to the ureters, urinary bladder, and intestines[7]. Liver rupture during manual revision of the gland and splenic tear are rare or infrequent complications, but they can occur. In any case, all of them can force a subsequent intervention.

Surgical reintervention is a relatively frequent entity that is usually derived from a first surgical procedure that could have been unsatisfactory that detected a problem that was not resolved due to the hemodynamic or ventilatory conditions of the patient, due to post-surgical complications derived from intrinsic factors and/or extrinsic and even due to deficiencies in the surgical technique itself. A new operation constitutes an extra trauma with greater possibilities of imbalance of the patient's homeostatic mechanisms, increased complications and higher mortality[8-10]. In addition, the number of reinterventions is part of the parameters used to evaluate the quality and efficiency of hospital services[11]. The objective of this research is to identify the prevalence, causes, and clinical course of patients with surgical reintervention due to complications during cesarean section.

Materials and methods

This is an observational, longitudinal, retrospective, retrolective, and descriptive study in a series of cases. The admission record to the Toco-surgery Unit of the Gynecology-Obstetrics Hospital No. 3 of the National Medical Center "La Raza" of the Mexican Institute of Social Security Mexico City was reviewed to know the total number of patients undergoing cesarean section in the period from January to December 2019. Patients who were reoperated due to complications during cesarean section were selected. Routinely, after their reintervention, all the patients were admitted to the intensive care unit (ICU) for surveillance and were later transferred to a general ward. The files were consulted to document general data, the cause of reinterventions, their clinical course, ICU stay, hospital stay, and mortality. Before conducting the study, authorization was obtained from the local Health Research and Health Research Ethics Committees (Registration R-2019-3504-11). Data were analyzed with descriptive statistical measures (mean, median, standard deviation, and range) using the statistical program SPSS version 20.

Results

It was found that during the year 2019, the cesarean section was performed on 3371 patients, of which 1.60% (54 cases) underwent a surgical reintervention, which were the subjects of the present study. Their mean age was 32.12 years and parity 3 with a pregnancy of 35 ± 3.5 weeks. The following comorbidities were found: Overweight 64.81% (35 cases), previous pregnancy with placenta previa 44.4% (24 cases), history of severe pre-eclampsia 20.37% (11 cases), type 1 diabetes mellitus 14.81% (8 cases), primary hypothyroidism 7.4% (4 cases), exogenous grade I

obesity 7.4% (4 cases), previous pregnancy with HELLP syndrome 5.5% (3 cases), uterine myomatosis 3.7% (2 cases), congenital scoliosis 1.85% (1 case), exogenous obesity Grade II 1.85% (1 case), chronic systemic arterial hypertension 1.85% (1 case), and primary antiphospholipid antibody syndrome 1.85% (1 case). It was found that 51.85% of the patients had a previous cesarean section (28 cases) and 18.52% had two previous cesarean sections (10 cases). For 29.63% of the patients, the cesarean section was their first surgery (16 cases).

The indications for cesarean section in the 54 patients studied had the following distribution: Placental alterations 53.70% (29 cases), unreliable fetal status 27.78% (15 cases), and maternal indications 18.52% (10 cases). In no case was the cesarean section performed by the doctor's preference or at the request of the patient. Complications during cesarean section that required reintervention were related to bleeding 94.45% (51 cases) followed by urinary bladder injuries 3.70% (2 cases) and large intestine injury 1.85% (1 case). Figure 1 in turn, the distribution of complications related to bleeding was as follows; Surgical bed bleeding 27.79% (15 cases), obstetric hemorrhage 20.37% (11 cases), persistent bleeding due to uterine atony 20.37% (11 cases), hemorrhage from a hysterotomy commissure 18.52% (10 cases), uterine infiltration 3.70% (2 cases), and bleeding due to accidental injury of a uterine artery 3.70% (2 cases). In all cases, the complications were corrected by performing only one reintervention table 1.

The mean stay in the ICU was 3.79 ± 2.03 days and in the hospital was 13.67 ± 11.16 days. There were no patients transferred to other hospitals. Mortality was 1.85% (1 case), and it was a patient with an urgent cesarean section indicated for severe pre-eclampsia with HELLP syndrome and a bleeding ruptured hepatic hematoma that was managed during surgery with the Pringle maneuver, packing, and closure of the abdominal cavity. This patient had to undergo immediate surgical reintervention due to persistent bleeding that was uncontrollable and progressed to Class IV hypovolemic hemorrhagic shock, cardiorespiratory arrest, and death in the operating room.

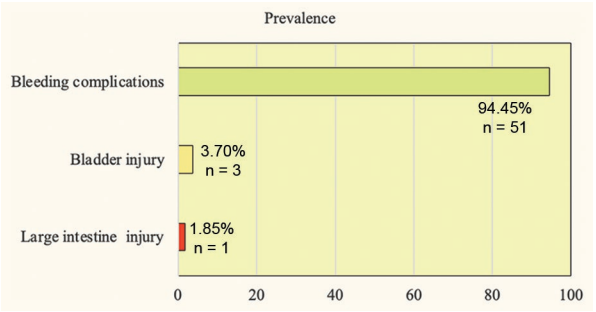

Figure 1. *Complications during cesarean section that required reintervention in 54 patients (100%).*

Discussion

3371 women who underwent cesarean section in 2019 were studied. It was found that the prevalence of patients with reintervention due to complications during surgery was 1.60% (54 cases), a very low figure compared to data from series from other countries such as Holland 1997[7], Brazil 2004[12], Sudan 2014[13], and India 2016[14]. As can be seen in table 2, the number of cases studied in this investigation is greater than the number of patients in any of the other series. It also highlights that the highest frequency of complications during cesarean section corresponds to the report by Umbeli et al.[13] in patients from Sudan 49.80% and that the lowest frequency was that of our study. The data from this series showed that the main complications that led to reintervention were hemorrhagic, followed by bladder injury and colonic injury with very low percentages. Thus, the causes were not different from the type of intraoperative complications identified in previous reports[7,12-14].

The stay in the ICU of the 54 patients studied was similar to the average of other patients in the same highly specialized center, but the hospital stay was longer[15]. These data could have been a consequence of the longer post-surgical recovery time in a general ward, but not in the ICU, which imply a rapid recovery from his critical condition. Mortality in our series was very low (1.85%), and it was a patient with severe pre-eclampsia and HELLP syndrome with massive bleeding due to a ruptured hepatic hematoma, a situation of extreme severity, and poor prognosis in any scenario. In general, the data support the opinion that the clinical course of the patients studied was successful.

Finally, the following comments are pertinent. The data presented here correspond to patients from a highly specialized medical unit that concentrates the most complicated cases of high-risk pregnancy in Mexico City and the central zone of the country and does not necessarily have a general representativeness. The hospital that hosts this research belongs to an institution affiliated with the Mexican health sector (Mexican Institute of Social Security), so in no case was the cesarean

Table 1. Complications during cesarean section, prevalence, and reintervention in 54 patients

Complications during cesarean section	Prevalence	Number of cases	Reintervention technique
Bleeding complications	94.45	51	
Of the surgical bed	27.79	15	Unpacking
Obstetric hemorrhage	20.37	11	Local hemostasis
Uterine atony	20.37	11	Hysterectomy
Commissure hemorrhage	18.52	10	Local suture
Uterine infiltration	3.70	2	Hysterectomy
Vascular injury	3.70	2	Uterine artery ligation
Bladder injury	3.70	2	Primary closure
Large intestine injury	1.85	1	Primary closure
Total	100	54	

Table 2. Historical comparison of the prevalence of complications during cesarean section

Author, country and year	Cases	Complications	
		Prevalence	Type
Van Ham et al.[7] Holland (1997)	2,647	14.8%	Uterine laceration 10.1% Hemorrhage > 1,000 cc 4% Others 0.7%
Nomura et al.[12] Brazil (2004)	998	13.8%	Extend of hysterorrhaphy 7% Obstetric hemorrhage 6% Uterine atony 0.7% Bladder injury 0.1%
Umbeli et al.[13] Sudan (2014)	470	49.8%	Obstetric hemorrhage 23.1% Extended of hysterorrhaphy 22.7% Intestine injury 2.8% Bladder injury 0.6% Ureteral injury 0.2%
Jain et al.[14] India (2016)	1,349	2.5%	Obstetric hemorrhage 1.3% Extended of hysterorrhaphy 0.9% Uterine infiltration 0.3%
Vázquez et al.[15] México (2019) Current study	3,371	1.60% n 54*	Bleeding from the surgical bed 0.44%, n 15 Obstetric hemorrhage 0.33%, n 11 Uterine atony 0.33%, n 11 Commissure hemorrhage 0.29%, n 10 Uterine infiltration 0.060%, n 2 Accidental arterial injury 0.060%, n 2 Bladder injury 0.060%, n 2 Large intestine injury 0.030%, n 1

*The data are shown as the percentage and number of cases (n) for each type of complication since they are very small fractions.

section performed due to the doctor's preference for the method or at the request of the patient. In addition, the casuistry corresponds to the year 2019, which represents the last regular year before the COVID-19 pandemic, a disease that changed the routine of humanity, so the frequency of cesarean sections may possibly be different due to the effect of viral illness such as a maternal factor, due to deterioration of the fetal state, due to the preference of the medical staff, or due to the express request of the patient. Thus, the reports on the

frequency of the cesarean section and its intraoperative complications in times of the COVID-19 pandemic and after it will be relevant because they can show different results.

Conclusion

The prevalence of reintervention due to complications during cesarean section was 1.60%, the main cause was hemorrhage, and the clinical course was satisfactory with very low mortality.

Funding

The authors declare that no funding was received from any public or private institutions

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Agreement between incisional and excisional biopsies for hormone receptors and her2 in breast cancer

Concordancia de biopsia incisional y escisional en receptores hormonales y her2 en cáncer de mama

Fernando Candanedo-Gonzalez[1], Juan C. Cordova-Ramón[2], Jessica Smeke-Smeke[3], Wilfredo Valenzuela-Gonzalez[4], and Armando Gamboa-Dominguez[5]*

[1]Departmento de Patología. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México; [2]Departmento de Patología. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México; [3]Facultad de Medicina, Universidad Anahuac, Ciudad de México; [4]Facultad de Medicina, Universidad Autónoma de Sinaloa, Culiacán, Sinaloa; [5]Departamento de Patología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México. Mexico

Abstract

Introduction: *Breast cancer is the leading cause of cancer mortality in Mexican women.* **Objective:** *The objective of the study was to identify concordances among core needle biopsy (CNB) and excisional biopsies (EB) regarding diagnosis, hormonal receptors (HR), and human epidermal growth factor receptor 2 (Her2).* **Materials and methods:** *Core number, demographic data, histological type, and treatment were documented for each sample. Reported HR and Her2 score from both samples were compiled.* **Results:** *70 women with both CNB/EB were included. Median age was 58 (36-87) years; initial diagnosis in CNB were invasive ductal 56 (80%), lobular 10 (14%), and mixed 4 (6%) carcinomas. Diagnostic agreement among CNB and EB was of 97%, k = 0.65. A concordance of 92% (k = 0.75), 75% (k = 0.26), and 67% (k = 0.46) was observed for estrogen receptors, progesterone receptors, and Her2 determinations, and positive predictive values in CNB were 0.96, 0.89, and 0.44, respectively.* **Conclusion:** *HR and Her2 concordances using manual-immunohistochemistry (IHC) were found within the range of values obtained using automatized-IHC. When compared to tumor heterogeneity, technical/reading errors contribute more to discordances.*

Keywords: *Concordance. Core needle biopsy. Breast cancer. Hormonal receptors. Her2.*

Resumen

Introduction: *El cáncer de mama es la principal causa de mortalidad por cáncer en mujeres mexicanas.* **Objetivo:** *Identificar la concordancia entre la biopsia con aguja de corte (BAC) y la biopsia escisional (BE) con respecto al diagnóstico, receptores hormonales (RH) y Her2.* **Material y Métodos:** *Se registró el número de fragmentos cilíndricos, datos demográficos, tipo histológico y tratamiento. Se recopilaron resultados de RH y Her2.* **Resultados:** *Se incluyeron 70 mujeres con mediana de edad de 58 años. El diagnóstico inicial en BAC fue carcinoma ductal invasivo 56 (80%), lobular 10 (14%) y mixtos 4 (6%). El acuerdo de diagnóstico entre BAC y BE fue del 97%, k = 0.65. Se observó una concordancia de 92% (k = 0.75), 75% (k = 0.26) y 67% (k = 0.46) para las determinaciones de receptor de estrógenos (RE), receptor de progesterona (RP) y Her2, y los valores predictivos positivos en BAC fueron 0.96, 0.89 y 0.44, respectivamente.* **Conclusión:** *Los RH y la concordancia de Her2 mediante inmunohistoquímica (IHC) manual se encuentran dentro del rango de valores obtenidos mediante el uso de IHC automatizada. Los errores técnicos/de lectura contribuyeron más a discordancia que la heterogeneidad tumoral.*

Palabras clave: *Concordancia. Biopsia con aguja gruesa. Cáncer de mama. Receptores hormonales. Her2.*

***Correspondence:**
Fernando Candanedo-Gonzalez
E-mail: fa_candanedo@yahoo.com.mx

Date of reception: 28-03-2022
Date of acceptance: 24-08-2022
DOI: 10.24875/CIRUE.M22000621

Cir Cir (Eng). 2023;91(4):435-440
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Breast cancer is the leading cause of cancer mortality in Mexican women since 2006, accounting for 14% of cancer-related deaths[1], and yet, scarce information is available on tumor sampling and subcellular determinations[2]. Estrogen receptors (ER) and progesterone receptors (PR) along with c-erbB2 human epidermal growth factor receptor 2 (Her2) and Ki-67 expression are currently used to classify invasive epithelial breast tumors into four clinically relevant categories[3]. Immunohistochemistry (IHC) is the current method to accomplish such measurements, quantifying its nuclear or membrane signals[2,3]. Concern about IHC results compelled its automatization and nowadays to "next generation IHC"[4]. However, for economic reasons in developing countries most laboratories are still doing them manually. How much confidence should be given to measurements in these settings?

The trend for less radical surgeries as a treatment for breast cancer brings the opportunity to use core needle biopsies (CNB) and excisional biopsies (EB) in the same patient and, it offers the chance to bring about concordance studies regarding IHC analyses. Few studies addressing concordance of ER, PR, and Her2 have been published[5-17]. Such studies have shown a good proficiency of CNB for morphologic diagnosis and subcellular studies. Most of the published series are based on automatized protocols of IHC excluding patients submitted to neoadjuvant therapy and showed a concordance rate for ER, PR, and Her2 in core needle biopsies and excisional resections of 62-98%, 69-89%, and 60-98%, respectively[5-17].

Our aim was to calculate concordances among core needle biopsies and EB regarding histological type, ER, PR, and Her2 in consecutive patients, including those receiving neoadjuvant treatments without a complete pathologic response.

Materials and methods

Study population

A search of medical records at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran was performed and patients with suspicious breast lesions submitted to CNB with subsequent EB, being lump excision, radical mastectomy, or cuadrantectomy due to *in situ* or invasive breast carcinoma were retrieved since January 2008 through December 2012. Medical charts of each patient were reviewed, and clinical information on gender, presentation, and age at diagnosis was recorded. The pathology reports from the diagnostic CNB and EB were reviewed. The data recorded from the CNB were core number, histological type of lesion, and IHC results. Data recorded from the excision were type of excision, tumor type according to the WHO classification, size, and ER, PR, and Her2 results. In both samples, the reported ER, PR, and Her2 score was compiled. The study followed the guidelines of the Declaration of Helsinki and was approved by the institutional review board. Patient identity and its pathological specimens remained anonymous in the context of this study. Cases were grouped as tumors as *in situ* carcinoma (either ductal or lobular), invasive carcinoma (either ductal or lobular), mixed, or other types of invasive carcinoma.

IHC analyses

In our institution, IHC is done manually and is interpreted according to the college of the American pathologists guidelines. Briefly, deparaffinized 1.5 μm tissue sections on charged slides were submitted to antigen retrieval for 20´ in an electric pressure cooker and mounted in cover plates in a plastic rack (Thermo Scientific, Cashire UK). Protein and endogen peroxidase was blocked for 5´ and the primary antibody incubated for 45´. After washing with Tris-buffered saline (TBS), two drops of mouse/rabbit immunodetector biotin link was applied for 10´ and rinsed with TBS. Finally, two drops of mouse/rabbit immunodetector HRP were used and slides developed with DAB under microscopic (Olympus CH2) observation. Extension of the stain was evaluated in neoplastic cells and classified as 0% or negative, 1-25%, 26-50%, 51-75%, and > 75% as positive and, nuclear staining intensity in a scale from 0 to 3+. Her2 score was obtained according to the American society of clinical oncology guidelines, considering 0/1+ as negative, 3+ as positive, and 2+ equivocal. ER detection was performed with 6F11, RBT11, or 1D5 clones, for PR either 16, RBT22, or PgR636 clones were used. All Her2 assessments were made using HercepTest™, Dako (Glostrup, Denmark), and the manufacturer protocol. Equivocal Her2 results were considered in the analysis only if gene amplification was confirmed or discarded by either chromogenic (CISH) or fluorescent (FISH) *in situ* hybridization.

Disagreement among CNB and EB was considered when a change from noninvasive to invasive carcinoma or vice versa was observed in hematoxylin and eosin sampling or when a change from positive/negative in incisional biopsy turned on negative/positive in excisional resection for hormonal receptors (HR) and Her2 determinations.

Statistical analyses

Descriptive statistics were employed to summarize the characteristics of the study population. Discordant reports led us to review all samples from that patient to ascertain pre analytical, analytical, or post-analytical reasons. Concordance analysis by means of a kappa coefficient test was performed using SPSS 15.0 for Windows. Sensibility, specificity, and predictive values were calculated considering excisional resections as the gold standard. Significance test was two sided.

Results

Clinicopathologic characteristics of the study population

We recorded 424 surgical specimens from 321 patients, and 70 women with both CNB and surgical excision turn out to be the body of this study. When a patient had more than two breast biopsies, the one obtained closer to CNB sampling was preferred, if complete pathologic response was observed in the final excision, the case was discarded. Median age was 58 (36-87) years. Initial diagnosis of the patients in CNB was invasive ductal 56 (80%), lobular 10 (14%), and mixed 4 (6%) carcinomas; four were *in situ* lesions. Half of the patients had stage I/II disease, and neoadjuvant chemotherapy was received by 38 (54%).

The concordance rate of primary diagnosis of *in situ* or invasive cancer between the core biopsy and the excision specimens was 97%. Nine discordances in morphologic diagnosis were explained by mixed phenotypes of the invasive carcinoma in four EB (two ductal in CNB become lobular in EB; two lobular in CNB become ductal in EB), and because only two *in situ* lesions were observed in CNB, whereas infiltrative carcinoma admixed with the *in situ* lesion was identified in EB or because in 2 CNB of invasive ductal carcinoma, only *in situ* carcinoma was observed in EB. The one left was a poorly sampled CNB (one tissue fragment) with crushing artifact diagnosed as ductal invasive, which turned out to be invasive lobular carcinoma in the final excision.

IHC findings

Six pairs of samples were excluded from the IHC analysis because the surgical pathology report of CNB (2) and EB (4) did not include ER, PR, or Her2 determinations. In addition, four Her2 misleading samples lacking CISH/FISH amplification procedures were excluded. Thus, concordance analysis was based on 64 patients for HR and in 60 pairs of samples for Her2. A concordance of 92% (kappa 0.75), 75% (kappa 0.26), and 67% (kappa 0.47) was observed for ER, PR, and its two determinations between CNB and EB, and the positive predictive values were 0.96, 0.89, and 0.44, respectively.

ER discordances between CNB and EB in six patients were due to tumor heterogeneity with weak nuclear staining (2 cases), associated with neoadjuvant treatment (1 case), as well as with technical variations in IHC, leading to slides without adequate external controls (2 cases) and misinterpretation of the slide by the original observer (1 case). Discordances with PR were identified in 18 patients and its source attributed to technical and reading mistakes (7 each), neoadjuvant chemotherapy (4 cases), and signal heterogeneity (3 cases); some pairs having more than one factor. Her2 variations were observed in seven patients among CNB and EB. Variations were associated with tumor heterogeneity (3 cases), technical (3 cases), and reading errors (3 cases). Any discordance in diagnosis and HR/Her2 interpretation was more frequent if the number of tissue fragments by CNB sampling was less than three 29/31 (93%) versus 8/39 (21%), ($p < 0.0001$).

Discordances in HR and Her2 determinations were observed in 27 patients; the consequences of these variations were clinically irrelevant in 26 because hormonal treatment was granted using ER or PR results in CNB and Her2 treatment based on a positive result in either core biopsy or excision specimen. Serious implications were observed in one patient (Fig. 1).

Discussion

A concordance series of CNB and excisional resections of malignant breast tumors, -without excluding those submitted to the current neoadjuvant

Table 1. Concordance of core needle and excisional biopsy interpretation of immunohistochemistry performed on infiltrative lesions

Author	Countryn	n	IHC method	ER%	PR%	HER2%
Mann GB, et al., 2005[6]	Australia	100	A	86	83	80
Cahill RA, et al., 2006[7]	Ireland	95	U	70	72	64
Burge Ch, et al., 2006[8]	USA	87	A	95	89	96
Usami S, et al. 2007[9]	Japan	111	A	95	88	88
Wood B, et al., 2007[10]	Australia	100	U	96	90	87
Sutela A, et al., 2008[11]	Finland	41	A	83	88	93
Arnedos M, et al., 2009[12]	UK	336	U	98	85	98
Park SY, et al. ,2009[13]	Korea	104	U	99	97	86
Richer C, et al., 2009[14]	Germany	164	U	75	75	54
Tamaki K, et al., 2010[15]	Japan	353	A	93	78	89
Lorgis V, et al., 2011[16]	France	175	A	84	78	98
Ricci MD, et al., 2012[17]	Brazil	69	U	95	87	78
Present study	Mexico	64	M	92	75	67

IHC: immunohistochemistry; A: automatic; M: manual; U: unknown.

therapies, accurately reveal the day-to-day surgical pathology practice. None of the published articles[5-16] (Table 1) is based on manual IHC and frequently do not mention the type of clones used. The present series include consecutive cases, even those receiving neoadjuvant therapies without complete pathologic response and, performing the IHC procedures manually. This is a common practice in countries with limited resources.

Factors more frequently associated with discordances among both measurements were sampling and IHC omissions (pre-analytical) and interpretation of the slides (analytical). In contrast with previous studies[5-17], tumor heterogeneity and neoadjuvant treatments were less related to discrepancies. Some information is available on the impact of tumor sampling in diagnosis and IHC interpretation in CNB. Patients with less than four tissue cores have higher probabilities of inadequate diagnosis/subcellular measurements, than those with more than four[9,13,15,18]. This finding move us to qualify the sampling we receive as adequate (≥ 4 cores) or inadequate (< 4 cores) in our surgical pathology report, to prospectively share possible disagreements in excisional specimens. As we did not find relevant clinical disagreements with HR in both measurements, only a warning was made to our technical staff to select and use in every run adequate positive/

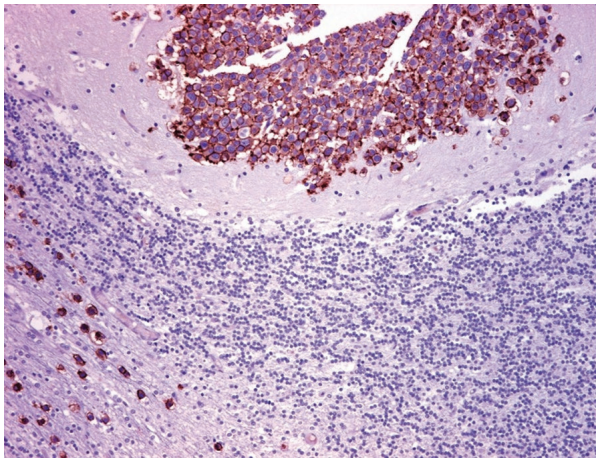

Figure 1. *A discordant her2 evaluation with cerebellar metastases. Epithelial cells had strong membrane signal and a CNB of the primary lesion read negative. The breast cancer was evaluated before the introduction of the "Seguro Popular."*

negative controls; a frequent omission observed in this review. Since hormonal blocking agents are prescribed using data from ER and PR, none of our tested patients with discordances was excluded of receiving this therapy.

A different picture was observed regarding Her2 with 33% of discordant evaluations in CNB and EB. A reading mistake excluded of specific blocking

agent therapy to a patient in whom we observed the natural history of a Her2 type invasive ductal carcinoma. Reading mistakes, technical omissions, and heterogeneity in IHC expression contribute to Her2 discordances. Although within previous series concordance rates (Table 1)[5-16], the observed Her2 discordances were too high for current pathology practice. As a consequence, all 1+, 2+, and 3+ Her2 IHC results will be submitted to chromogenic amplification assessments in this facility for the next 12 months, and a blind double check of the slides was advised for all breast samples. Mexico lacks of a national proficiency assessment programs of IHC and pathologist should contrast the IHC results with the morphology of the infiltrative lesion, i.e., consider features suggestive of Her2 discordances the presence of a positive result in a Grade 1 tumor. Recommendations sustained and shared in some previous reports[14,19,20].

IHC automatization brings more interlaboratory consistency but without statistically significant differences in the estimation of nuclear HR percentage/intensity signal when compared with manual procedures[21]. Besides, the percentage of HR-positive cells assessment is more reliable than intensity signal interpretation, suggesting that combining percentage of positive cells and signal intensity as a score, lack of a practical advantage[22]. Budget availability is considered the main reason for IHC automation, our current cost of a manual slide is less than US 20 dollars, and it will rise more than the double with the marketed closed IHC platforms. We wager here for a model of morphological tests in sound with our pockets, in contrast with other scenarios[23].

In conclusion, acceptable concordances were observed for diagnosis and HR, but worrisome results were identified for Her2 determination using handmade IHC protocols. The main sources of disagreements were analytical and poor sampling of suspicious breast lesions with fewer than three core needle biopsies.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical responsibilities

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Anti-adhesive effect of naturally obtained dicalcium phosphate dihydrate nanoparticles in the rat uterine wound model

Efecto antiadhesivo de nanopartículas de dihidrato de fosfato dicálcico obtenidas naturalmente en el modelo de herida uterina de rata

Begum Kurt[1], Kerim E. Oksuz[2], Zeynep D. Sahin-Inan[3], and Ceylan Hepokur[4]*

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Sivas Cumhuriyet University; [2]Department of Metallurgical and Materials Engineering, Sivas Cumhuriyet University; [3]Department of Histology and Embryology, Faculty of Medicine, Sivas Cumhuriyet University; [4]Department of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University. Sivas, Turkey

Abstract

Objective: *In this study, we aimed to compare the anti-adhesive effects of contractubex and dicalcium phosphate dihydrate (DCPD) particles in rats treated with the uterine horn adhesion model.* **Materials and methods:** *Newly adult, 60 Wistar albino rats were used as experimental animals. The modified rat uterine horn adhesion model was used to induce intra-abdominal adhesion. Tumor necrosis factor (TNF)-α, interleukin (IL)-1, vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β1 were studied for biochemical and immunohistochemical examination.* **Results:** *TNF-α decreased in each group, while it decreased more in G2 and G3 than in G1. IL-1β decreased in each group, while it decreased the most in G3. TGF-β1 and VEGF localization was less in the G2 compared to G1, the least TGF-β1 and VEGF immunolocalization was detected in the G3 and G4. For both antibodies, the least localization among all groups belonged to G3. From day 7 to day 21, the highest TGF-β1 immunolocalization was observed in G1, lesser localization in G2 and lowest in G3.* **Conclusion:** *DCPD nanoparticles show promise as a clinical antiadhesive agent and should be further evaluated in experimental animal models and human trials.*

Keywords: *Dicalcium phosphate dihydrate. Gynecologic surgery. Nanoparticles. Wistar rats.*

Resumen

Objetivo: *En este estudio, nuestro objetivo fue comparar los efectos antiadhesivos de las partículas de contractubex (CTX) y fosfato dicálcico dihidratado (DCPD) en ratas tratadas con el modelo de adhesión del cuerno uterino.* **Materiales y métodos:** *Como animales de experimentación se utilizaron 60 ratas Wistar albinas, recién adultas. Se usó el modelo de adhesión del cuerno uterino de rata modificado para inducir la adhesión intraabdominal. Se estudiaron TNF-α, IL-1, VEGF y TGF-β1 para examen bioquímico e inmunohistoquímico.* **Resultados:** *el TNF-α disminuyó en cada grupo, mientras que disminuyó más en G2 y G3 que en G1. IL-1β disminuyó en cada grupo, mientras que disminuyó más en G3. La localización de TGF-β1 y VEGF fue menor en G2 en comparación con G1, la menor inmunolocalización de TGF-β1 y VEGF se detectó en G3 y G4. Para ambos anticuerpos, la localización mínima entre todos los grupos pertenecía a G3. Desde el día 7 hasta el día 21, la mayor inmunolocalización de TGF-β1 se observó en G1, menor localización en G2 y menor en G3.* **Conclusión:** *las nanopartículas de DCPD se muestran prometedoras como agentes antiadhesivos clínicos y deben evaluarse más en modelos animales experimentales y ensayos en humanos.*

***Palabras clave*:** *Fosfato dicálcico dihidratado. Cirugía ginecológica. Nanopartículas. Ratas Wistar.*

***Correspondence:**
Begum Kurt
E-mail: begumkurt@cumhuriyet.edu.tr

Date of reception: 24-02-2023
Date of acceptance: 15-04-2023
DOI: 10.24875/CIRUE.M23000622

Cir Cir (Eng). 2023;91(4):441-451
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Adhesions are the results of the inflammatory response to tissue trauma, infection, bleeding, or foreign matter in the peritoneal space[1-3]. There are many studies on the development of barrier materials, hormones and their agonists/antagonists, hyaluronic acid, fibrinolytic agents, nonsteroidal anti-inflammatory drugs, and antioxidants to prevent postoperative adhesion formation[4,5]. The vast majority of them could not enter surgical practice, and a significant part could not gain applicability in our surgical technique because of the high cost[3,4,6].

CTX gel (Merz Pharma GmbH and Co., Frankfurt, Germany) is applicated to reduce inflammation and fibroblast proliferation that occurs in the early stages of wound healing[7,8]. Studies have shown that CTX application causes a decrease in the immunoreactivity of transforming growth factor-β (TGF-β), laminin, and fibronectin. It has been shown in previous studies that there is no adhesion, toxic effect or granuloma when applied intra-abdominal[9]. Due to its known antioxidant, anti-inflammatory, and fibroblast-inhibiting effects, it reduces histopathological damage scores when applied to extracutaneous tissues[10].

DCPD nanopowders calcium phosphate, orthophosphates (PO43-), metaphosphates or pyrophosphates (P2O74-), and especially hydrogen or hydroxide ions together with calcium ions are mineral groups. In animal and clinical experiments, it has been observed that the in-vivo solubility of biocompatible tissue-healing biomaterials with DCPD as the main phase after crystallization and curing or containing DCPD particles is high. It is completely dissolved in 3-4 months at the latest, and very positive effects on the new tissue formation process in the applied areas have been reported[11,12]. It has been proven by characterization studies that naturally obtained DCPD nanoparticles have the potential to be used as an adhesion inhibitor[13,14].

This study aimed to compare the anti-adhesion effects of contractubex (CTX) and dicalcium phosphate dihydrate (DCPD) particles in rats treated with the uterine horn adhesion model, with histological and immunohistochemical tests and biochemical measurements.

Material and methods

Synthesis of nanocrystalline dicalcium phosphate dihydrate from eggshells

The collected white chicken eggshells were washed with distilled water to remove impurity and then boiled in distilled water for 60 min to remove the membrane. Cleaned eggshell materials were dried in the oven at 60°C for 24 h. Afterward, they were manually crushed with agate mortar and pestle and calcined at 900°C for two hours with a heating-cooling rate of 5°C/min. The decomposition of eggshell powder ($CaCO_3$) to CaO occurs according to the equation (1).

$$CaCO_3 \xrightarrow{900°C} CaO + CaO_2 \quad (1)$$

To obtain the purified form of calcium hydroxide Ca(OH)2, CaO were ball milled in the stoichiometric amount of distilled water for 6 h.

Precipitation process

To obtain DCPD crystals was done by direct synthesis in solution. All chemicals were of analytical grade, purchased from Merck, and used as received in the experimental study. A solution (200 mL) containing $Ca(OH)_2$ (0.5 M) and H_3PO_4 (0.3 M) were prepared with the appropriate dilutions. The 0.5 M $Ca(OH)_2$ suspension was vigorously stirred at 70°C for one hour, and the H_3PO_4 (0.3 M) solution was added dropwise and stirred for about 30 min. The pH of the solution was adjusted to 10 by adding 30% NH_3 solution. After the complete edition of the H_3PO_4 solution, an additional vigorous stirring was carried out for one hour at 90°C to activate the chemical reaction. The obtained slurry was left at room temperature overnight for the aging process. During aging at room temperature, the DCPD was precipitated. The excess NH_3 solution obtained over the white precipitate powder was removed, and the precipitate powder was washed several times with distilled water to remove the NH^{4+} ions. The residue was dried at 60°C for 48 h. The chemical reaction between $Ca(OH)_2$ and H_3PO_4 is equation (2)

$$Ca(OH)_2 + H_3PO_4 \rightarrow CaHPO_4.2H_2O \quad (2)$$

Cell culture

In this study, L929 (mouse fibroblast cell line) cells were purchased from American Type Culture Collection. The medium used in our research was DMEM containing 10% fetal bovine serum, 1% L-glutamine, and 1% penicillin-streptomycin. L929 cells were cultured in DMEM in an incubator with 5% CO_2 at 37 ° C.

Cell culture, tissue and organ cultures are used in in-vitro cytotoxicity tests, the most used systems are cell cultures[15]. The use of L929 or Balb/3T3 mouse fibroblast cell line is recommended for the evaluation of cytotoxicity[16,17]. These cells are cell types that can be found easily, reproduce

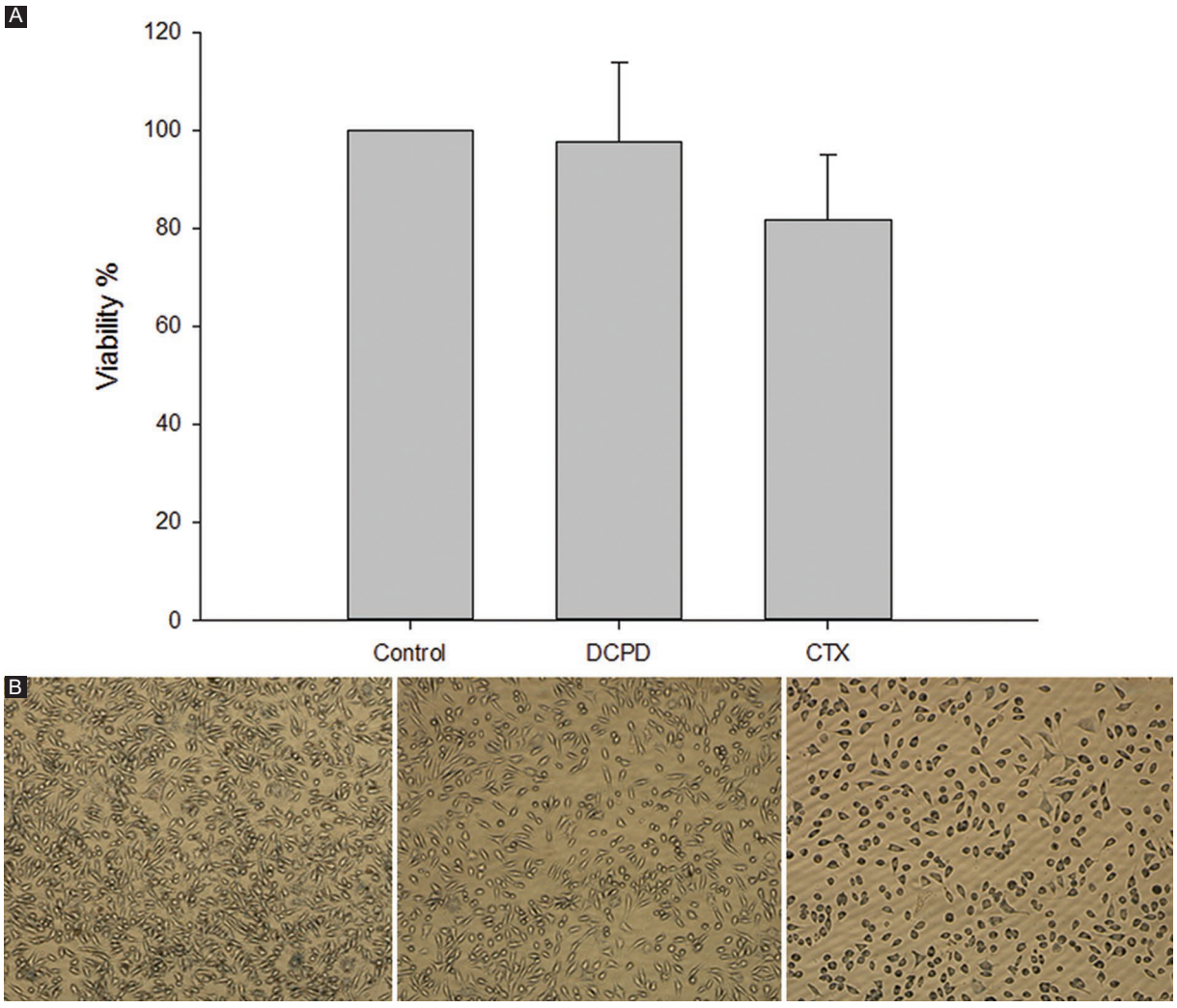

Figure 1. A: *% viability values of DCPD.* **B:** *cell viability of DCPD and CTX in L929 cells.*
DCPD: dicalcium phosphate dihydrate; CTX: contractubex.

rapidly and have a homogeneous morphology. With their growth characteristics, they ensure that the experiment can be repeated in cytotoxicity evaluations[18].

The cytotoxicity of DCPD and CTX were compared in the study. In the study performed at different concentrations, it was observed that both substances were not cytotoxic, and DCPD had a more negligible effect on cell viability when counting cells (Fig. 1A and B).

Test animals

In the study, 60 Wistar albino rats, newly adult, 16 weeks old, unmated, female, 200-220 g, were used as experimental animals[3,19,20]. All experimental procedures applied in this study were examined by Sivas Cumhuriyet University Experimental Animal Research Ethics Committee and approved on 25 December 2020 with the number 469. Minimal numbers of animals were used and every efforts were made to minimize their suffering. Wistar albino rats were chosen because of their robustness and low cost compared to large animals[9]. After the rats were purchased, they were kept for one week to acclimate to the laboratory conditions. Rats were kept as two individuals in a cage with standard animal housing conditions in the laboratory, 12 h of light-darkness, 21°C temperature, 50-60% humidity, and standard pellet rat chow and water[3,5,21,22].

Animal model

Experimental groups

G1: Control group, G2: DCPD powder 0.25 g. administration group, G3: DCPD powder 0,5 g. application

group, G4: CTX 1 g application group[23]. A total of 60 rats were randomly divided into four groups. Each group was divided into 7th, 14th, and 21st day groups among themselves. There were 5 rats in subgroups.

The modified rat uterine horn adhesion model to induce intra-abdominal adhesion was chosen because it is a standardized qualitative and quantitative model, mimics reproductive surgery and provides reproducible results and consistent adhesion formation[3,24-26].

All rats have fasted for 12 h before surgery. Anesthesia was administered through intraperitoneal injection of 10 mg/kg xylazine (Rompun; Bayer, Turkey) and 50 mg/kg ketamine (Ketalar; Parke Davis, Turkey, Istanbul), and spontaneous breathing was achieved. All surgical procedures were performed by the same surgeon. The rats were fixed in the supine position; the midline lower abdomen of each rat was shaved and disinfected with iodine solution. The abdomen was entered with a midline vertical incision of approximately 3 cm in length. Five standard lesions were created with 10 W unipolar cautery on the antimesenteric face of the right uterine horns of the rats. The two layers of abdominal wall were closed with 4/0 prolene sutures after the surgery. Second laparotomy was performed in the 7th, 14th and 21st day groups. Intracardiac blood was taken from the animals according to the groups, and the animals were euthanized by the neck dislocation method.

Adhesion scoring

Adhesions formed after laparotomy was evaluated macroscopically by two independent researchers unaware of the applications. The mean score of both researchers was used for that rat. Grading of adhesions was evaluated in terms of adhesion prevalence and severity, with scores from 0 to 4[27]. Adhesion prevalence and severity scores for each rat were added to give the respective rat's total adhesion score.

Biochemical examination

After the animals were sacrificed, 5cc of blood was taken into a tube with EDTA by intracardiac route[28,29]. The collected blood was centrifuged at 3000 rpm for 15 minutes and then separated into the serum. Tumor necrosis factor (TNF)-α (Cat No: E0764Ra) and interleukin (IL)-1 (Cat No: E010Ra) from cytokines and vascular endothelial growth factor (VEGF, Cat No: E065Ra) from the growth factor were studied in serum samples taken following the guide of the kit for the enzyme-linked immunosorbent assay (ELISA) method.

Histopathological studies

Uterine horns were removed from sacrificed rats and fixed in 10% neutral buffered formalin for 48 hours for histological examination. Tissues washed in tap water were embedded in paraffin blocks after tissue follow-up processes according to standard protocol. 3-5 μm sections were taken from paraffin blocks, and routine hematoxylin-eosin (H&E) staining was performed to evaluate the layers of the organ and the healing rates in the wound.

For immunohistochemical evaluation, tissue blocks were re-sectioned, deparaffinized, passed through a decreasing series of ethyl alcohol (100-90-96-80-70%), and washed in buffered phosphate solution (PBS) for 5 min. At the end of the period, the sections were boiled in buffered citrate at pH 6 for 20 min in the microwave for antigen retrieval. Sections cooled at room temperature were washed in PBS for 5 min and kept in a 3% hydrogen peroxide (H2O2) solution prepared with distilled water for 10 min to suppress endogenous peroxidase activity. At the end of the time, the sections were washed with PBS for 3 × 5 min and then kept at room temperature for 20 min by dripping ultra V block (Thermo Scientific, USA) to prevent non-specific binding. With the help of blotting paper, the block solution was removed without washing, and the primary antibodies VEGF (monoclonal antibody, JH121, ThermoFisher, USA) and TGF-β1 (ThermoFisher, USA) were kept in a humid and dark environment for 1.5 h at 36°C.

After the primary antibody application, the sections were washed with PBS for 3 × 5 min, and the first Biotinylated Goat Anti Polyvalent was dripped, washed with PBS, then Streptavidin peroxidase (Thermo Scientific, USA) was dropped and kept in a humid and dark environment at 36°C for 20 min. At the end of the time, the sections were washed with PBS, and chromogen (Thermo Scientific, USA) was dripped onto 3,3'Diaminobenzidine (DAB) and waited for 5 min. Colored sections were washed with PBS, treated with Mayer's hematoxylin for 1 min, ground dyed, rewashed, covered with a particular concealer, examined under a microscope, and photographed (Olympus BX51, Japan)[30].

Statistical analyzes

The mean (standard deviation/standard error) or median (25-75% interquartile range) of the data were

calculated. In the analysis of the data, correlational tests such as ANOVA or Kruskal–Wallis (followed by post hoc tests such as Tukey or Mann–Whitney when significant) and correlation tests were used. A $p < 0.05$ was considered statistically significant. The sample size for each group was calculated with the online program "StatsToDo: Sample Size for Measurement Differences Between Unpaired Groups" module. (http://www.statstodo.com/SSizUnpairedDiff_Pgm.php) power was taken as 80% (1-b = 0.80) and 5% significance level (a < 0.05) with the desired statistical data.

Results

Adhesion scoring

Adhesion was observed most in G1. The results of G3 and G4 were similar but less than G2 (Table 1). It was observed that the amount of adhesion decreased as the DCPD dose increased, and the amount of adhesion was the least compared to the CTX group when high doses were used. It was determined that adhesion decreased within days in both CTX and DCPD groups (Table 2).

Table 1. Adhesion scoring

Total adhesion score	7th day	14th day	21st day
G1	7, 8, 8, 7, 8	6, 7, 7, 6, 7	6, 7, 7, 5, 6
G2	6, 6, 5, 5, 5	5, 5, 4, 3, 3	5, 4, 4, 3, 3
G3	3, 3, 3, 3, 2	3, 2, 3, 3, 2	2, 2, 2, 2, 2
G4	5, 5, 4, 4, 3	5, 5, 4, 3, 3	4, 4, 3, 3, 3

Table 2. Adhesion score statistics

Groups	Adhesion			p
	7th day	14th day	21st day	
G1	8 ± 1	7 ± 1	6 ± 1	*0.010*[a]
G2	5 ± 1	4 ± 2	4 ± 1	*0.009*[b]
G3	3 ± 0	3 ± 1	2 ± 0	*0.039*[c]
G4	4 ± 1	4 ± 2	3 ± 1	*0.039*[d]
p	*0.001*[e]	*0.002*[f]	*0.001*[g]	

In italics: statistically significant.
[a] $p_{7\ day\text{-}14\ day} = 0.025$; $p_{7\ day\text{-}21\ day} = 0.038$.
[b] $p_{7\ day\text{-}14\ day} = 0.038$; $p_{7\ day\text{-}21\ day} = 0.038$.
[c] $p_{7\ day\text{-}21\ day} = 0.046$.
[d] $p_{7\ day\text{-}21\ day} = 0.046$.
[e] $p_{G1\text{-}G2} = 0.007$; $p_{G1\text{-}G3} = 0.006$; $p_{G1\text{-}G4} = 0.008$; $p_{G2\text{-}G3} = 0.006$; $p_{G2\text{-}G4} = 0.033$; $p_{G3\text{-}G4} = 0.018$.
[f] $p_{G1\text{-}G2} = 0.008$; $p_{G1\text{-}G3} = 0.007$; $p_{G1\text{-}G4} = 0.008$; $p_{G2\text{-}G3} = 0.033$; $p_{G3\text{-}G4} = 0.033$.
[g] $p_{G1\text{-}G2} = 0.011$; $p_{G1\text{-}G3} = 0.005$; $p_{G1\text{-}G4} = 0.008$; $p_{G2\text{-}G3} = 0.005$; $p_{G3\text{-}G4} = 0.005$.

Biochemical examination

TNF-alpha, IL-1β, and VEGF levels in intracardiac blood taken from animals were measured by the ELISA method.

TNF-α was found in G1 at 121.8889 ng/mL ± 13.7400 on day 7, 77.4444 ng/mL ± 15.7300 on day 14, and 60.7778 ng/mL ± 15.9300 on day 21. In G3, it was found 93.0000 ng/mL ± 10.4626 on day 7, 68.0741 ng/mL ± 20.0890 on day 14, and 53.3704 ng/mL ± 11.4156 on day 21. While the amount of TNF-α decreased as the number of days increased within the groups, the amount of TNF-α decreased more in G2 and G3 compared to G1 (Fig. 2A).

IL-1β was found in G1 to be 22.5397 ng/mL ± 0.8900 at day 7, 20.1587 ng/mL ± 0.8600 at day 14, and 14.9206 ng/mL ± 0.5590 at day 21, while G3 It was found to be 15.7143 ng/mL ± 0.7800 on day 7, 11.9841 ng/mL ± 0.6500 on day 14, and 11.9048 ng/mL ± 0.7400 on day 21. While the amount of IL-1β decreased as the number of days increased within the groups, the amount of IL-1β decreased even more in G3 compared to the control group (Fig. 2B).

VEGF was found to be 454.000 ng/mL ± 10.6483 on day 7, 334.6667 ng/mL ± 15.7380 on day 14, and 270.0000 ng/mL ± 12.8469 on day 21 in G1. In G3, it was found to be 298.6667 ng/mL ± 32.0740 on the 7th day, 242.0000 ng/mL ± 19.6186 on the 14th day, and 107.3333 ng/mL ± 31.6287 on the 21st day. The amount of VEGF decreased with days in G2 and G3 more than the other groups (Fig. 2C).

Histopathological evaluation

For general light microscope evaluation, H&E staining and post-incision healing sites were evaluated for the integrity of the uterine layers and inflammatory cell density. G2 and G3 recovered faster than G4. The integrity of the tissue layer was quickly preserved, with less inflammatory cell density in G3 than G4 in the healing areas. In G4, inflammatory cells were less than in the control group but more than in the experimental groups (Fig. 3).

Immunohistochemical localization evaluation was made by including the perimetrium layer, the adjacent border of the uterus with the peritoneum. Accordingly, TGF-β1 and VEGF localization gradually increased in

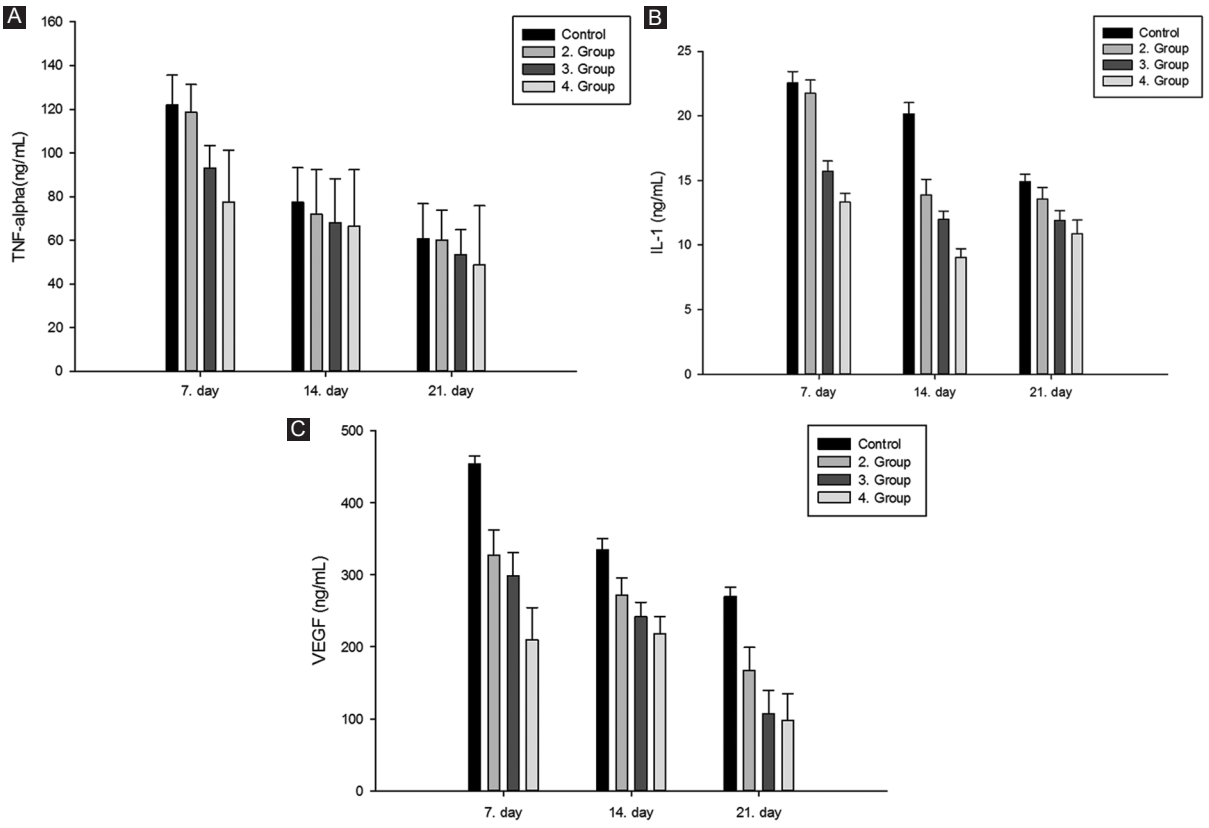

Figure 2. A: *amounts of TNF-α on days 7, 14 and 21 between groups.* **B:** *amounts of IL-1β between the groups on days 7, 14 and 21.* **C:** *VEGF amounts on days 7, 14 and 21 between groups.*
TNF-α: tumor necrosis factor alpha; IL-1β: interleukin-1β; VEGF: vascular endothelial growth factor.

G1 on the 7th, 14th, and 21st days, and it was evaluated as having the highest localization degree when compared to all groups (Tables 3 and 4).

Although TGF-β1 and VEGF localization were less in the G2 group compared to G1, the least TGF-β1 and VEGF immunolocalization were detected in the G3 and G4 groups. For both antibodies, the least localization among all groups belonged to G3. The highest TGF-β1 immunolocalization was observed from day 7 to day 21 in G1, with less localization in G2 and lowest localization in G3 (Fig. 4).

When TGF-β1 immune localization score statistics were compared, on the 14th day, the TGF-β1 level was found to be higher between G1 and G3. When G1 and G4 were compared, it was observed that the TGF-β1 level in G1 was higher. TGF-β1 level was higher in G2 than in G3 (Table 3). As DCPD dose increased in G2 and G3, TGF level decreased and the highest decrease was observed in G4 (Table 5).

The highest VEGF immune localization was observed in G1 from day 7 to day 21, with lesser localization in G2 and the lowest localization in G3 (Fig. 5).

As the number of days increased, while the most VEGF immune localization score statistics were in G1 and G2, it was found at least in G3 (Table 6).

Discussion

Intra-abdominal adhesions resulting from a surgical procedure can cause complications even decades later. Patient symptoms include chronic abdominal pain, infertility, and intestinal obstruction and often cannot be attributed to their cause. Chronic lower abdominal pain severely impairs the quality of life of those affected and is an indication for 30-50% of all laparoscopies and 5% of hysterectomies[31]. With a better understanding of the morbidity and mortality associated with pelvic adhesions, the development of models to help prevent adhesions remains an important research topic. In this context, researches are carried out in which the anti-adhesive properties of various agents applied as nanoparticles are also tested[1,2,5]. Anti-adhesion prophylactic agents should provide an anti-adhesive action that is highly biocompatible and absorbable, protecting

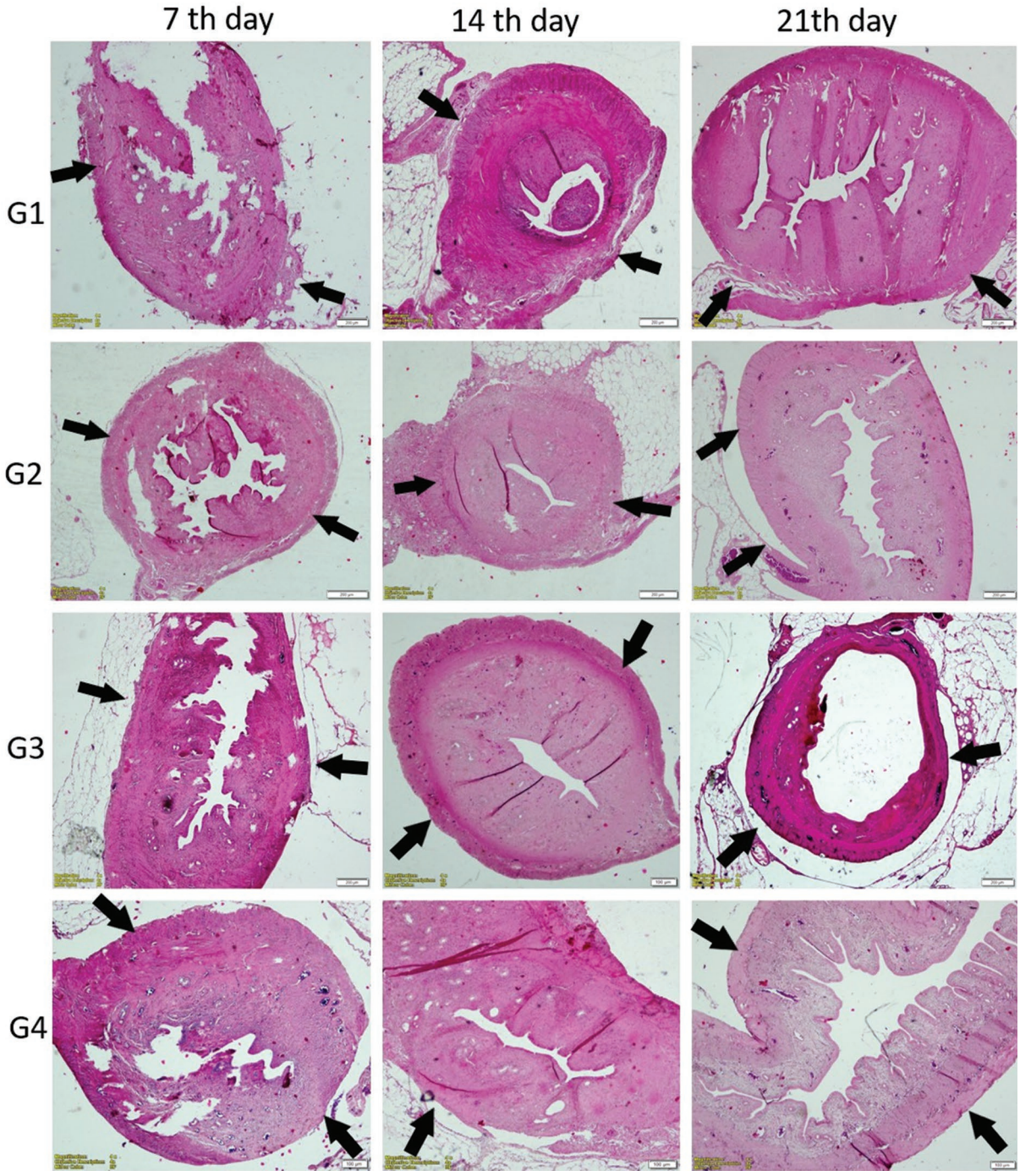

Figure 3. *In the G1, G2, G3, G4 groups, the general histological image of the adhesion areas of the uterus with the perimetrium layer on days 7, 14 and 21, and the incision area in the perimetrium layer are marked with a black arrow (H&E staining, ×10 magnification). Due to the rapid recovery, especially in G3, the uterine tissue layers were observed more regularly.*

against new and recurrent adhesions, tissue separation, and protection of peritoneal surfaces. Low cost is also of great importance. In our study, we compared the anti-adhesion effect of DCPD nanoparticles with CTX with proven effectiveness.

Postoperative adhesion formation involves three basic processes: 1. inhibition of fibrinolytic and extracellular matrix degradation systems, 2. induction of cytokines production and an inflammatory response involving TGF-β, and 3. induction of tissue hypoxia

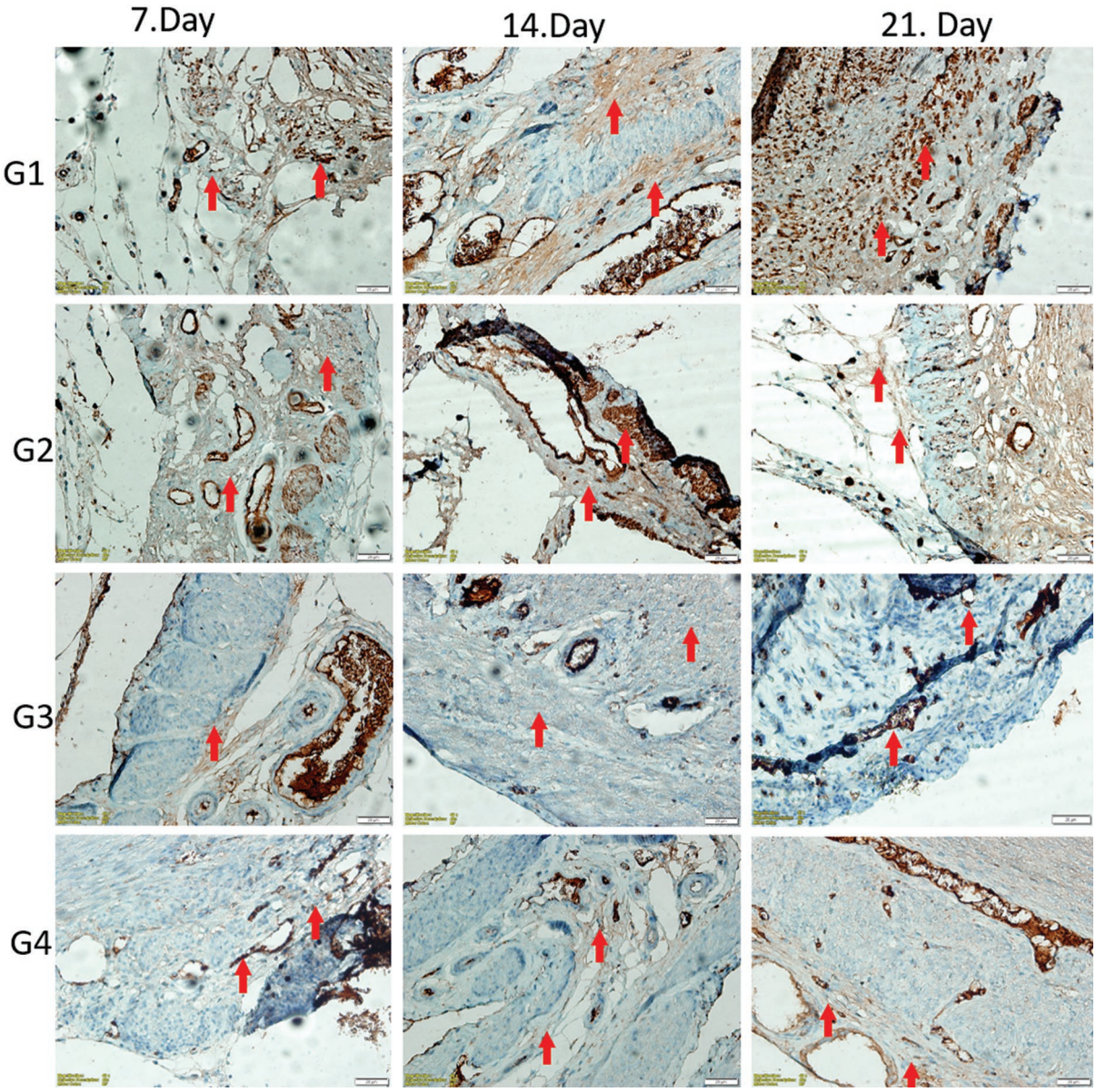

Figure 4. *In G1, G2, G3, G4 groups, brown areas showing TGF-β1 immune localization on the 7th, 14th and 21st days of the uterine perimetrium layer and adhesion areas are observed with a red arrow (TGF-β1 antibody, ×40 magnification). It was determined that the highest TGF-β1 immunolocalization was in G1 from day 7 to day 21, lesser localization in G2 and the least localization in G3.*
TGF-β1: transforming growth factor-beta 1.

leading to increased expression of VEGF[1,32]. Changes in cytokine levels TGF-β and VEGF are critical molecules in pathological tissue fibrosis. TGF β1 has a well-defined role in cell differentiation, angiogenesis, and fibroblast activation. It has been suggested to be the major profibrotic mediator of the process[33]. As the number of days increased, the lowest localization among all groups was seen in G3 for both antibodies. This finding was similar to the adhesion level detected in all groups. The amount of adhesion developed the most in G1 and G2, and the least in the group G3 and G4. In addition, in the histopathological evaluation of our study G2 and G3 recovered faster than G4. The integrity of the tissue layer was rapidly preserved, and less inflammatory cell density was determined in G3 than G2 in the healing areas. In G4, inflammatory cells were found to be less than in the G1, but more than in G2 and G3.

In the biochemical evaluation, it was determined that the highest decrease in VEGF level was observed

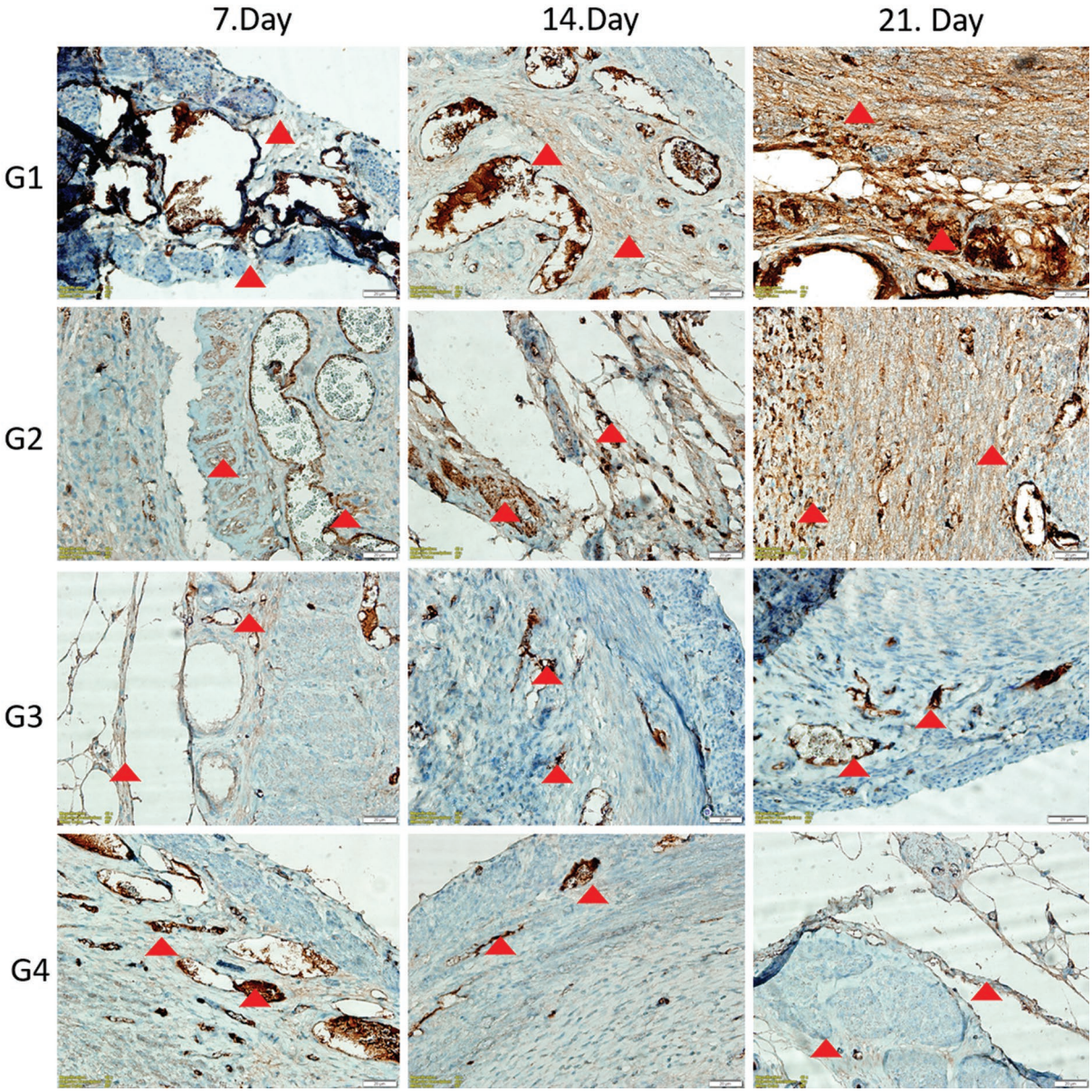

Figure 5. *In G1, G2, G3, G4 groups, brown areas showing VEGF immune localization on the 7th, 14th and 21st days of the uterine perimetrium and adhesion areas are observed with a red triangle (VEGF antibody, ×40 magnification). It was determined that the highest VEGF immunolocalization was in G1 from day 7 to day 21, lesser localization in G2 and the least localization in G3.*
VEGF: vascular endothelial growth factor.

Table 3. TGF-β1 immune localization scoring

TGF-β1	7th day	14th day	21st day
G1	1, 1, 1, 1, 2	2, 2, 1, 1, 1	2, 3, 2, 2, 1
G2	1, 2, 1, 1, 2	2, 3, 3, 2, 3	3, 3, 3, 4, 4
G3	2, 2, 2, 2, 1	2, 4, 4, 4, 3	4, 4, 4, 3, 4
G4	1, 1, 3, 2, 2,	2, 3, 3, 3, 3, 1	2, 3, 3, 3, 3

TGF-β1: Transforming growth factor-β 1.

in G4, followed by G3 and G2, respectively. In G3 IL-1 levels showed a significant decrease after the 14th day. TNF-α can promote interleukin production from mesenchymal cells. High TNF-α levels in peritoneal fluid and serum correlate with adhesion severity[34]. In our study, it was observed that TNF-α levels decreased as the number of days increased. The decrease in TNF-α levels was greater in G3 than in G1 and G2.

Table 4. VEGF immune localization scoring

VEGF	7th day	14th day	21st day
G1	1, 1, 1, 1, 2	3, 2, 1, 1, 1	2, 2, 1, 1, 1
G2	1, 2, 1, 1, 2	2, 3, 3, 2, 3	2, 3, 2, 2, 2
G3	2, 2, 2, 2, 1	4, 4, 4, 4, 3	2, 3, 3, 3, 4
G4	1, 1, 3, 2, 2,	2, 2, 2, 2, 3	2, 2, 1, 3, 3

VEGF: Vascular endothelial growth factor.

Table 5. TGF immune localization score statistics

Groups	TGF			p
	7th day	14th day	21st day	
G1	3 ± 0	4 ± 1	5 ± 0	*0.010*[a]
G2	3 ± 1	3 ± 0	4 ± 1	0.097
G3	2 ± 1	2 ± 1	1 ± 0	0.368
G4	2 ± 0	2 ± 0	2 ± 1	0.584
p	0.081	*0.005*[b]	*0.001*[c]	

In italics: statistically significant.
[a]$p_{7\ day\text{-}21\ day} = 0.041$; $p_{14\ day\text{-}21\ day} = 0.034$.
[b]$p_{G1\text{-}G3} = 0.007$; $p_{G1\text{-}G4} = 0, 013$; $p_{G2\text{-}G3} = 0.016$.
[c]$p_{G1\text{-}G2} = 0.016$; $p_{G1\text{-}G3} = 0.005$; $p_{G1\text{-}G4} = 0.006$; $p_{G2\text{-}G3} = 0.006$; $p_{G2\text{-}G4} = 0.007$.
TGF: transforming growth factor.

Table 6. VEGF immune localization score statistics

Groups	VEGF			p
	7th day	14th day	21st day	
G1	3 ± 1	3 ± 1	4 ± 1	*0.014*[a]
G2	2 ± 1	3 ± 2	4 ± 1	*0.024*[b]
G3	2 ± 0	2 ± 0	1 ± 1	0.174
G4	2 ± 0	2 ± 0	2 ± 0	0.926
p	0.365	*0.014*[c]	*0.001*[d]	

In italics: statistically significant.
[a]$p_{7\ day\text{-}14\ day} = 0.046$; $p_{7\ day\text{-}21\ day} = 0.041$.
[b]$p_{7\ day\text{-}21\ day} = 0.041$.
[c]$p_{G1\text{-}G3} = 0.006$; $p_{G1\text{-}G4} = 0.016$; $p_{G2\text{-}G3} = 0.045$.
[d]$p_{G1\text{-}G3} = 0.007$; $p_{G1\text{-}G4} = 0.006$; $p_{G2\text{-}G3} = 0.008$; $p_{G2\text{-}G4} = 0.007$.
VEGF: vascular endothelial growth factor.

Conclusion

These experimental results show that DCPD nanoparticles show promise as a clinical antiadhesive agent and should be further evaluated in experimental animal models and human trials. DCPD nanoparticles are easy to administer and cost advantageous, and could be helpful in surgical practice if their efficacy is confirmed in clinical trials. It appears valuable and safe for clinical practice and prevents adhesion formation after abdominal surgery.

Funding

This study was supported by Sivas Cumhuriyet University Scientific Research Projects (CUBAP) with project number 2021 T-910.

Conflicts of interest

Authors declare no conflicts of interest for this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Are YouTube videos on smell dysfunction a good source of information for patients seeking a cure for their illness?

¿Son los videos de YouTube sobre la disfunción del olfato una buena fuente de información para los pacientes que buscan una cura para su enfermedad?

Sumeyra Doluoglu and Elif K. Celik*

Department of Otorhinolaryngology Head and Neck Surgery, Dıskapi Yildirim Beyazit Training and Research Hospital, University of Health Sciences Turkey, Ankara, Turkey

Abstract

Objective: *To conduct unbiased research into the quality and reliability of videos published on YouTube on the subject of smell dysfunction and treatment through two Ear, Nose, and Throat (ENT) specialists using three different tools.* **Methods:** *The videos were separated into two groups (reliable: Group 1; non-reliable: Group 2) according to whether or not the content was scientifically reliable, proven, accurate, and useful, as determined by two ENT specialist physicians. The DISCERN reliability tool, Global quality scale (GQS), and JAMA scoring system were used as video scoring tools in the evaluations.* **Results:** *Group 1 included 173 videos, and Group 2, 16 videos. The GQS (First ENT specialist) points were 3 (2-5) and GQS (Second ENT specialist) points were 3 (2-5) in Group 1, and 2 (2-3) and 2 (1-3) in Group 2, respectively (p = 0.0001). The points in the DISCERN and JAMA scoring systems were found to be higher in Group 1 than in Group 2 (p = 0.0001).* **Conclusion:** *Although the majority of videos on YouTube related to smell dysfunction are reliable, the number of unreliable videos is not inconsiderable. When videos related to medical information are accepted onto YouTube, weighting should be given to videos which include scientifically proven evidence uploaded by specialist professionals and institutions.*

Keywords: *Reliability. Smell dysfunction. Smell dysfunction treatment. Videos. Youtube.*

Resumen

Objetivo: *realizar una investigación imparcial sobre la calidad y la confiabilidad de los videos publicados en YouTube sobre el tema de la disfunción y el tratamiento del olfato, a través de dos especialistas en oído, nariz y garganta que utilizan tres herramientas diferentes.* **Métodos:** *Los videos se separaron en dos grupos (confiables: Grupo 1; no confiables: Grupo 2) según si el contenido era o no científicamente confiable, probado, preciso y útil, según lo determinado por dos médicos especialistas en Otorrinolaringología. La herramienta de confiabilidad DISCERN, la escala de calidad global (GQS) y el sistema de puntuación JAMA se utilizaron como herramientas de puntuación de video en las evaluaciones.* **Resultados:** *el Grupo 1 incluyó 173 videos y el Grupo 2, 16 videos. Los puntos GQS (Primer especialista en ORL) fueron 3 (2-5) y los puntos GQS (Segundo especialista en ORL) fueron 3 (2-5) en el Grupo 1, y 2 (2-3) y 2 (1-3) en el Grupo 2, respectivamente (p= 0.0001). Se encontró que los puntos en los sistemas de puntuación DISCERN y JAMA eran más altos en el Grupo 1 que en el Grupo 2 (p= 0.0001).* **Conclusión:** *aunque la mayoría de los videos en YouTube relacionados con la disfunción del olfato son confiables, la cantidad de videos poco confiables no es despreciable. Cuando se aceptan videos relacionados con información médica en YouTube, se debe dar peso a los videos que incluyen evidencia científicamente probada y subidos por instituciones y profesionales especialistas.*

***Palabras clave*:** *Confiabilidad. Disfunción del olfato. Tratamiento de la disfunción del olfato. Vídeos. YouTube.*

***Correspondence:**
Sumeyra Doluoglu
E-mail: sumeyradoluoglu@gmail.com

Date of reception:18-06-2022
Date of acceptance: 26-07-2022
DOI: 10.24875/CIRUE.M22000623

Cir Cir (Eng). 2023;91(4):452-457
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Smell dysfunction is defined as decreased or impaired ability to smell when smelling (orthonasal smell) or eating (retronasal smell), and generally mild and even asymptomatic cases have been reported. The quality of life of patients is affected as those with smell dysfunction may experience problems in cooking, personal hygiene, social relationships, and have emotional problems such as depression. Smell plays an important role in the perception of dangers in daily life such as the presence of gas and chemicals[1].

The most common means of acquiring information is through the Internet. Patients tend to use it as a cheaper and more easily accessible source to find a response to health concerns and suspicions before seeing a doctor and sometimes, even before receiving a definitive diagnosis. Unfortunately, these sources are not always unbiased or of high quality[2,3].

YouTube is a free-of-charge, video publication Internet site, where approximately 65,000 videos are uploaded each day, with more than 100 million viewers per day and more than 1 billion per month[4-6]. The videos uploaded to YouTube are not controlled in respect of either content or quality. Therefore, it is important to emphasise that health-related inappropriate and prejudiced information on YouTube can affect patients making irrational decisions[7]. In studies that have evaluated informative videos related to Ear, Nose, and Throat (ENT) which have been uploaded to YouTube, both the content and quality of the videos have been found to be insufficient[8,9]. To the best of our knowledge, there is no study in literature that has evaluated the reliability of the dozens of uploaded videos related to smell dysfunction. Therefore, the aim of this study was to conduct unbiased research into the quality and reliability of videos published on YouTube on the subject of smell dysfunction and treatment, through two ENT specialists using three different tools.

Materials and methods

On 20 August 2021, YouTube was searched using the terms “smell dysfunction” and “smell dysfunction treatment.” At this level, the first 500 videos were listed. These video links were recorded because the order can change every day with new videos being uploaded. All the videos were evaluated by 2 ENT specialists, independently and blinded to the evaluations of each other. Videos were excluded from the analysis if the content was irrelevant, if there was no sound or only music, if they were not in English, or if they were shorter than one minute.

A record was made for each video of the upload date, the upload source, the total number of likes, dislikes, comments, and views, and the daily number of views and comments. The video power index was calculated using the formula “(likes/likes+dislikes) × 100”. The upload source was classified as physicians/universities/professional organizations (source 1), health-related websites (source 2), individual users/patients (source 3), non-physician healthcare personnel (source 4), and television program (source 5). The videos were separated into two groups by the two ENT specialist physicians taking previous studies as reference for whether or not the video content was scientifically reliable, proven, correct, and useful[10,11].

Group 1 included videos with content accepted as reliable information with scientifically correct content about smell dysfunction and treatment (definition, symptoms, epidemiology, diagnosis, and treatment). Group 2 included videos defined as unreliable information with scientifically unproven and non-medical content. In any case of disagreement between the specialist raters, consensus was reached, and the video was assigned to the appropriate group.

The DISCERN reliability tool, Global quality scale (GQS), and JAMA scoring system were used as video scoring tools in the evaluations. The original DISCERN is a scale of 15 items used for the evaluation of health information quality. In this study, a 5-point modified DISCERN tool was used to score video reliability, as in previous studies[10,12].

The GQS is used to evaluate the general quality of videos. In the 5 items of the GQS, a score of 1-2 points indicates low quality, 3 points intermediate quality, and 4-5 points high quality[13]. JAMA is a well-known quality tool that is used to evaluate information obtained from health-related internet sites. It includes four criteria of authorship, attribution, disclosure, and currency. Each criterion is scored with 1 point to give a maximum total of 4 points, indicating high quality[14].

Statistical analysis

The data analyses were performed using PASW 18 software (SPSS/IBM, Chicago, IL, USA). Visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov test) methods were used to determine the conformity of the variables to normal distribution. The results were reported as mean ± standard

deviation, or when distributions were skewed, as median (minimum–maximum) values. Categorical variables were stated as number (n) and percentage (%). The significance of the differences between the groups in terms of median values was investigated with the Mann–Whitney U-test. Kruskal–Wallis variance analysis was used for intergroup comparisons of continuous variables (*Post hoc*: Bonferroni). The Student's t-test was used for the intergroup analysis of continuous variables. Nominal variables were assessed with the Pearson's Chi-square or Fisher's Exact test. Inter-rater agreement was determined using Cohen's kappa score. Interobserver reliability for the three tools was quantified by calculating the intraclass correlation coefficient. A value of $p < 0.05$ was considered statistically significant.

Results

From the first 500 videos added to the playlist, 189 videos that met the study criteria were included for evaluation in the study (Fig. 1). Group 1 (reliable information) included 173 videos, and Group 2 (unreliable information), 16 videos. The inter-rater agreement in the formation of the groups was excellent (Kappa coefficient = 0.93, p = 0.0001). The number of likes and dislikes were 64 (0-67.000), and 2 (0-9.300), respectively, in Group 1, and 79 (0-52.000) and 14 (0-2.200) in Group 2 (p = 0.907, p = 0.08, respectively). The video power index was calculated as 96.9 (0-100) in Group 1, and 89.1 (0-100) in Group 2 (p = 0.005) (Table 1).

When the groups were evaluated with GQS scoring, the scores of the videos containing reliable information were found to be higher by both raters. The GQS (First ENT specialist) points were 3 (2-5) in Group 1 and 2 (2-3) in Group 2 (p = 0.0001). The GQS (Second ENT specialist) points were determined to be 3 (2-5) in Group 1, and 2 (1-3) in Group 2 (p = 0.0001). The points given by both raters in the DISCERN and JAMA scoring systems were found to be higher in Group 1 than in Group 2 (p = 0.0001 in all comparisons). The differences were determined to be statistically significant (Table 1). The intraclass correlation coefficients for the GQS, DISCERN, and JAMA scoring systems were determined as 0.96, 0.98, and 1.0, respectively (p = 0.0001 in all comparisons).

The number of videos uploaded by physicians/universities/professional organizations was determined to be 80 (42.4%) in Group 1, and 1 (0.5%) in Group 2 (p = 0.001) (Table 1). The videos in Group 1 had richer content in terms of etiology, general information, symptoms, and treatment. The comparisons of the GQS, DISCERN, and JAMA scores according to the source of the videos are shown in table 2.

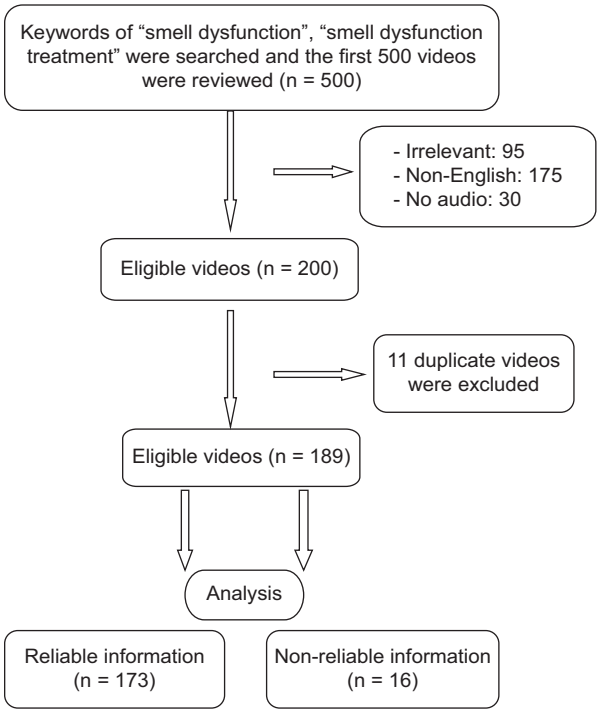

Figure 1. *Flowchart of the selection of appropriate Youtube videos.*

Discussion

YouTube is a video-sharing platform established in California, USA, in 2005. After Google Search, YouTube is the second most visited website worldwide[4]. 95% of Internet users use YouTube as it is easily accessed, is free of charge, and videos can be accessed in different languages[5]. Although the information is easy to access, there is a real difficulty of obtaining the correct material. The fundamental concern related to expanding resources such as YouTube is "which source can we trust and is the information sufficient?".

The current research revealed a total 500 videos when the search terms of "smell dysfunction" and "smell dysfunction treatment" were used. When the analyses were narrowed down, it was discovered that 71 (37.5%) of the 189 videos that met the study criteria had been uploaded by individual users or patients or non-physician healthcare personnel or television programs. This finding means that only the remaining 118 (62.5%) relevant videos were uploaded by physicians/universities/professional organizations or a health-related website.

Table 1. Comparison of the video characteristics between the groups

Video scoring tools and video charecteristics	Reliable information (n = 173)	Nonreliable information (n = 16)	p-value
DISCERN score[&]	3 (2-5)	2 (1-3)	0.0001*‡
GQS score[&]	3 (2-5)	2 (2-3)	0.0001*‡
JAMA score[&]	2 (1-4)	1 (1-2)	0.0001*‡
DISCERN score[Ω]	3 (2-5)	2 (2-3)	0.0001*‡
GQS score[Ω]	3 (2-5)	2 (1-3)	0.0001*‡
JAMA score[Ω]	2 (1-4)	1 (1-2)	0.0001*‡
Views	5.532 (9- 4.417.908)	18.083 (180-5.710.551)	0.234*
Views per day	11.9 (0.03-46.504)	9.3 (0.33-2059.34)	0.789*
Comments	13 (0-16.593)	18 (0-3.705)	0.521*
Comments per day	0.0208 (0-174.66)	0.0143(0-5.86)	0.996*
Duration of video (min)	5.27 (1.03-62.2)	3.33 (1.4-14.44)	0.037*‡
Duration of Youtube (day)	387 (74-4.036)	1404 (128-2.860)	0.011*‡
Likes	64 (0-67.000)	79 (0-52.000)	0.907*
Dislikes	2 (0-9.300)	14 (0-2.200)	0.08*
Video power index	96.9 (0-100)	89.1 (0-100)	0.005*‡
Source of upload, n, %			
Source 1[Π]	80 (42.4%)	1 (0.5%)	0.001†‡
Source 2[Π]	34(18%)	3 (1.6%)	
Source 3[Π]	17 (9%)	7 (3.7%)	
Source 4[Π]	6 (3.2%)	1 (0.5%)	
Source 5[Π]	36 (19%)	4 (2.1%)	

*Mann-Whitney U test.
†Chi-square test.
‡Statistically significant.
[Π]physicians/universities/professional organizations (source 1), health related website (source 2), individual users/patients (source 3), non physician health personel (source 4) ve TV program show (source 5).
[&]Rater 1.
[Ω]Rater 2.

Table 2. Comparison of DISCERN, GQS, and JAMA scores according to source of video

Video scoring tools	Physicians/universities/ professional organizations	Health related website	Individual users/patients	Non physician health personel	TV program show	p-value
DISCERN score[&]	4 (2-5)	3 (1-5)	3 (2-4)	3 (2-4)	3 (1-5)	0.0001*
GQS score[&]	4 (2-5)	4 (2-5)	3 (2-4)	4 (2-4)	4 (2-4)	0.0001*
JAMA score[&]	3 (2-4)	3 (1-4)	2 (1-3)	3 (1-3)	2 (1-4)	0.0001*
DISCERN score[Ω]	4 (2-5)	3 (1-5)	3 (2-4)	3 (2-4)	3 (1-5)	0.0001*
GQS score[Ω]	4 (2-5)	4 (2-5)	3 (2-4)	3 (2-4)	4 (2-4)	0.0001*
JAMA score[Ω]	3 (2-4)	3 (1-4)	2 (1-3)	3 (1-3)	2 (1-4)	0.0001*

*Kruskal Wallis test.
[&]Rater 1.
[Ω]Rater 2.

The source of the current study videos containing unreliable information was determined to be more individual users or patients or non-physician healthcare personnel or television programs. This heterogeneous and uncontrolled information pollution on YouTube has been examined before by Keelan et al.[15] and Roshan et al.[16] in studies on vaccination and tonsillectomy, respectively. A similar heterogeneity and lack of control in the information available online was shown by Hassona et al.[17] in a study of oral cavity cancer, and by Enver et al. in a study of larynx cancer[18].

Smell dysfunction is defined as impaired perception of odors. This has a negative impact on quality of life with effects on personal hygiene and social relationships, and the person may not be able to notice dangerous conditions such as gas or chemicals. If treatment of the disease is delayed, or time is lost with incorrect or invalid treatment, the individual may experience life-threatening situations as they cannot smell. The results of the current study showed that 71 of 189 videos related to smell dysfunction had been uploaded to YouTube by people unqualified in this subject. Of these, 12 (17%) were found to be unreliable, demonstrating that approximately 1 in every 5 patients obtains unreliable information.

The rates of videos found to be reliable and non-reliable in the current study were similar to the rates in most studies in literature[7-11]. However, there are also studies which have reported higher or similar rates of unreliable videos to reliable videos[15-18]. Those studies have also reported that, unfortunately, the number of total views of these videos is higher than those of videos containing reliable information. Videos that have been most watched and most liked must not be thought to be the most correct scientifically. As the YouTube search engine orders videos according to the number of views, likes, and dislikes, videos containing unreliable information are among the recommended videos. In the ordering of videos related to health, YouTube should be sensitive on the point of prioritizing videos prepared by professional health-care specialists and physicians specialized in the field.

In the current study, the points of the GQS, DISCERN, and JAMA tools completed by two ENT specialists were determined to be statistically significantly higher in Group 1. This objectively showed the quality and reliability of the videos containing reliable information. In a previous study that used these three tools to measure the health information quality of videos, statistically higher scores were seen to have been objectively obtained by the reliable videos compared to the unreliable videos[19].

In the current study, the number of daily views and likes were found to be similar in the Group 1 and Group 2 videos. However, there are also studies showing that videos containing reliable information have been determined with statistically significantly lower levels of daily views and likes[19]. This demonstrates that viewers on the social platform cannot differentiate which videos are more correct and have content of a high scientific level.

This study had some limitations. First was that a playlist was formed at the same time by the two raters of the first 500 videos. Only the videos available at that time were included for evaluation, but YouTube is a dynamic platform with new videos constantly emerging. Second, as different languages could not be understood, only videos in the international common language of English could be included. A further limitation may be that only the first 500 videos on the subject were evaluated, and these may not have been representative of all the videos. However, this study can be considered of value as the first study to have evaluated the reliability of smell dysfunction videos on YouTube using the three evaluation tools together which have been used in previous studies of the quality and reliability of videos.

Conclusion

The results of the evaluations in this study showed that although the majority of videos on YouTube related to smell dysfunction are reliable, the number of unreliable videos is not inconsiderable. Unreliable videos can cause negative outcomes for patients. Therefore, when videos related to smell dysfunction or including other medical information are accepted onto YouTube, weighting should be given to videos which include scientifically proven evidence uploaded by specialist professionals and institutions.

Funding

There is no financial support in the study.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Determination of homeodomain interacting protein kinase 2 polymorphisms rs2058265, rs6464214, and rs7456421 in patients with kidney stone

Determinación de los polimorfismos rs2058265, rs6464214 y rs7456421 de la proteína cinasa 2 que interactúan con el homeodominio en pacientes con cálculos renales

Cavit Ceylan[1], Omer Gokhan-Doluoglu[2], Sedat Taştemur[1], Ibrahim Keleş[3], Gulay Ceylan[4], Ahmet Cevdet-Ceylan[4], Emre Uzun[1], and Eda Tokat[2]*

[1]Department of Urology, University of Medical Sciences, Ministry of Health, Ankara City Hospital, Ankara; [2]Department of Urology Clinic of Ankara Training and Research Hospital, FEBU, University of Medical Sciences, Ankara; [3]Department of Urology, Afyon Kocatepe University, Faculty of Medicine, Afyon; [4]Department of Genetics, Yildirim Beyazit University, Faculty of Medicine, Ankara. Turkey

Abstract

Objective: *This study aimed to investigate whether homeodomain interacting protein kinase 2 (HIPK2) polymorphism is associated with renal stone formation in a Turkish population.* **Materials and methods:** *A total of 129 patients with calcium nephrolithiasis and 67 sex- and age-matched healthy controls were enrolled in the study. Blood samples were collected into EDTA tubes. The DNA of patients was extracted using a QIAsymphony® automated DNA isolation system. The Chi-square test was applied in the comparisons between the patient and control groups in respect of the differences in the genotype and allele frequencies.* **Results:** *No statistically significant difference was found between the groups in terms of single nucleotide polymorphism (SNP) incidence in single allele and double alleles in the rs2058265 and rs6464214 regions (p = 0.13 and 0.37, respectively). The SNP incidence in double alleles in nephrolithiasis patients at rs7456421 was statistically significantly lower than in the control group (p = 0.001).* **Conclusion:** *Distributions of the genotype and allele of the three polymorphisms (rs2058265, rs6464214, and rs745642 in HIPK2) were not associated with an increased risk of kidney stone in this Turkish population.*

Keywords: *Allele. HIPK2 gene. Kidney. Nephrolithiasis. Polymorphism. Stone.*

Resumen

Objetivo: *Investigar si el polimorfismo de la proteína cinasa 2 que interactúa con el homeodominio (HIPK2) está asociado con la formación de cálculos renales en una población turca.* **Método:** *Se inscribieron en el estudio 129 pacientes con nefrolitiasis cálcica y 67 sujetos control sanos, emparejados por sexo y edad. Las muestras de sangre se recogieron en tubos con EDTA. El ADN de los pacientes se extrajo mediante un sistema de aislamiento de ADN automatizado QIAsymphony®. Se aplicó la prueba χ^2 en las comparaciones entre los grupos de pacientes y control con respecto a las diferencias de las frecuencias genotípicas y alélicas.* **Resultados:** *No se encontraron diferencias estadísticamente significativas entre los grupos en términos de incidencia de polimorfismo de nucleótido simple (PNS) en alelo simple y alelo doble en las regiones rs2058265 y rs6464214 (p = 0.13 y 0.37, respectivamente). La incidencia de PNS en alelos dobles en pacientes con nefrolitiasis en*

Correspondence:
Omer Gokhan-Doluoglu
E-mail: drdoluoglu@yahoo.com.tr

Date of reception: 16-09-2022
Date of acceptance: 09-12-2022
DOI: 10.24875/CIRUE.M22000624

Cir Cir (Eng). 2023;91(4):458-462
Contents available at PubMed
www.cirugiaycirujanos.com

rs7456421 fue menor que en el grupo control, con una diferencia estadísticamente significativa (p = 0.001). **Conclusiones:** *Las distribuciones de genotipo y alelo de los tres polimorfismos (rs2058265, rs6464214 y rs745642 en HIPK2) no se asociaron con un mayor riesgo de cálculos renales en esta población turca.*

Palabras clave: *Alelo. Gen HIPK2. Riñón. Nefrolitiasis. Polimorfismo. Cálculo.*

Introduction

Kidney stone incidence depends on geographical, climatic, ethnic, dietary and genetic factors, and so accordingly, the prevalence rates for urinary stones vary from 1% to 20%[1,2]. Many studies have shown there to be a strong family history in patients with kidney stones, especially in those with recurrence. In a comprehensive genetic study in Iceland of 5954 patients with kidney stones significantly more kidney stones were determined to be seen in family members compared to the general population[3,4]. Genetic polymorphism also causes nephrolithiasis. The most known polymorphic genes are the calcium-sensing receptor (CASR), vitamin D receptor (VDR), matrix Gla protein, and plasminogen activator, urokinase[5,6]. Furthermore, the concordance rate of stone disease in monozygotic twins is substantially higher than in dizygotic ones (32.4% vs. 17.3%) demonstrating that genetic factors play a vital role in the formation of nephrolithiasis[7].

Homeodomain interacting protein kinase 2 (HIPK2) has been shown to be a new androgen receptor regulator. HIPK2 and androgen have been shown to mediate kidney tubular epithelial cell injury and apoptosis[8,9]. In a recent study, Lin et al. found that the HIPK2 gene polymorphism also increased kidney stone risk in Chinese males[10]. Some studies have stated that renal tubular epithelial cell (RTEC) damage is closely associated with early basic lesions of kidney stones[11,12]. The shedding and death of these cells as a result of damage expose the basal membrane. Stone formation is facilitated by crystals adhering to these parts. Information related to HIPK2 polymorphism and renal stone formation is new-found and inconclusive. To the best of our knowledge, there is only one study in literature which has investigated the effect of HIPK2 polymorphism on nephrolithiasis[10]. This study aimed to investigate whether HIPK2 polymorphism is associated with renal stone formation in a Turkish population.

Materials and methods

Approval for the study was granted by the Hospital Local Ethics Committee (E1-20-334). The clinical trials registration ID of this study is NCT04804436. Informed consent was obtained from all the patients. Between August 2018 and October 2019, patients with idiopathic calcium nephrolithiasis were recruited to the study, and patients with other stone compositions were excluded. The age and gender of patients were recorded. The study included a total of 129 patients with calcium nephrolithiasis and 67 age- and gender-matched healthy controls. Blood and urine tests were performed on all patients. Nephrolithiasis was diagnosed on the basis of non-contrast enhanced computed tomography (CT). Stone specimens were obtained after shock-wave lithotripsy and analyzed with X-ray diffraction. Patients with a history of chronic urinary tract infection, renal failure, gastrointestinal diseases, increased levels of vitamin D, sarcoidosis, primary hyperoxaluria, polycystic kidney disease, gout, renal tubular acidosis, primary or secondary hyperparathyroidism, and a history of cancer or anatomic abnormalities were not included in the study.

Blood samples were collected into EDTA tubes. The DNA of patients was extracted with a QIAsymphony® automated DNA isolation system (Qiagen Inc. Mississauga, ON, Canada). The real-time PCR amplification was performed using Human rs2058265, rs6464214, and rs7456421 TaqMan® SNP Genotyping Assays (Thermo Fisher, Waltham, MA, USA) in a final volume of 20 μL reaction mixture, including 10 ng of genomic DNA, 5 μL of TaqMan® Universal PCR Master Mix, and 0.5 μL of 40× TaqMan® assay. Thermal cycling conditions were as follows: initial denaturation at 94°C for 3 min, then 40 cycles of 94°C for 15 secs, and 60°C for 1 min. The Rotor-Gene Q Series Software Version Q 2.3.1 (Rotor-Gene Q Series, Qiagen) was used for allelic discrimination.

Data analysis was performed using SPSS for Windows, version 20 software (SPSS Inc., Chicago, IL, USA). Continuous variables showing normal distribution were reported as mean ± standard deviation values, and when not normally distributed, as median (minimum-maximum) values. Categorical variables were stated as number (n) and percentage (%). The Chi-square test was utilized to compare the differences in the genotype and allele frequencies between

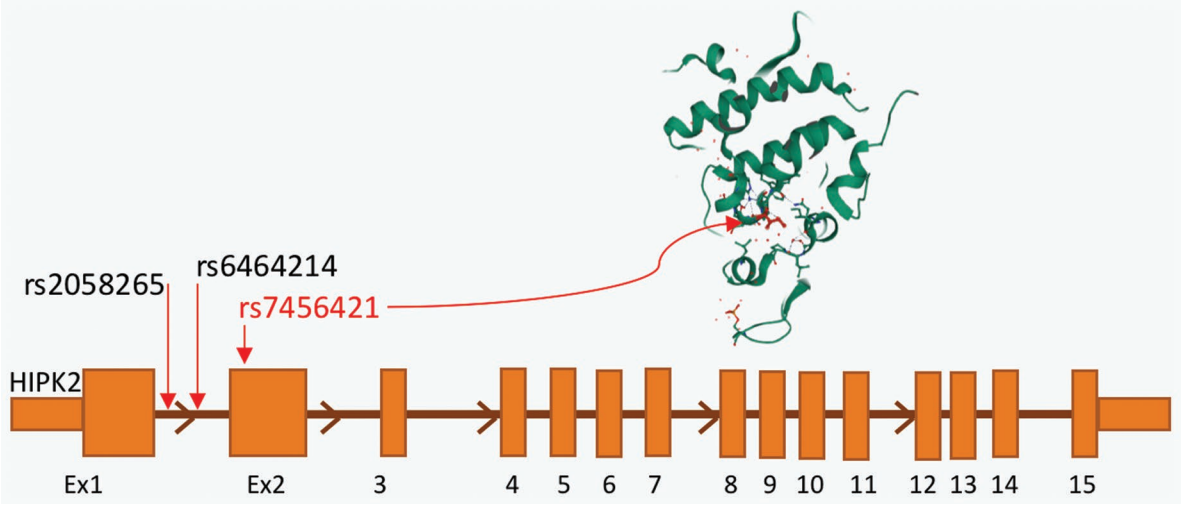

Figure 1. *The position of SNPs reported in this publication on the HIPK2 gene is shown at the bottom of the figure. The "kinase domain" of the HIPK2 protein (from uniProt) affected by the rs7456421 change is shown (in the circle) at the top of the figure. The HIPK gene consists of 15 exons and the SNPs included in the study are located in the first parts of the gene. rs 2058265 and rs6464214 are located at intron 1 of HIPK2, rs7456421 is located at exon 2 of HIPK2 and affects the "kinase domain" of the HIPK2 protein.*

the patient and control groups. All statistical tests were two-tailed. A value of $p < 0.05$ was considered statistically significant.

Results

The evaluation was made of a total of 196 subjects, 129 with calcium nephrolithiasis, aged 52 ± 12 years, and 67 age-matched control subjects with no familial history of urinary stone diseases, abnormal urine analysis findings, and no findings of kidney stones on non-contrast-enhanced CT examinations.

The incidence of single nucleotide polymorphism (SNP) in single allele and double alleles in the rs2058265 region was found to be 25% and 3.1%, respectively, in the nephrolithiasis patient group, and 29.9% and 9% in the control group ($p = 0.13$). The rates of SNP in the rs6464214 region in single allele and double alleles were found to be 20.3% and 8.6%, respectively, in the nephrolithiasis patient group, and 26.9% and 11.9% in the control group ($p = 0.37$). No statistically significant difference was determined between the groups in respect of these two results. The SNP incidence in double alleles in nephrolithiasis patients at rs7456421 was statistically significantly lower than in the control group (25.6% and 52.2% respectively, $p = 0.001$). SNP incidence at rs7456421 in single allele was statistically significantly higher in nephrolithiasis patients than in the control group (66.7% and 44.8% respectively $p = 0.013$) (Fig. 1).

The genotype and allele frequencies of the rs2058265, rs6464214, and rs7456421 HIPK2 polymorphisms in patients with kidney stones and the control subjects are listed in table 1. The distributions of the genotype and allele of the three polymorphisms (rs2058265, rs6464214, and rs745642 in HIPK2) were not associated with an increased risk of kidney stones in a Turkish population. With the exception of SNP incidence at rs7456421 in a single allele, the three polymorphisms in HIPK2 were higher in the control group in this Turkish population.

Discussion

Calcium oxalate stones are the most common type of renal stones and occur in approximately 75%-80% of cases[13]. Genetic analysis can identify susceptible individuals who may develop calcium stones and helps in understanding the stone formation mechanism and predicting the response to drugs and nutrients. Studies of families and twins have proven the importance of genetic predisposition in calcium stones. It has been shown that stone prevalence is higher among relatives of patients with nephrolithiasis when compared to relatives of healthy controls. Family studies have also demonstrated that the genetic transition pattern of the stone is not mendelian and is compatible with the complex polygenic substrate[14,15].

Findings of genetic studies demonstrated that Claudin 14, CASR, Osteopontin, and VDR genes may be

Table 1. Comparisons of the allele frequencies of the polymorphisms in patients with nephrolithiasis and healthy controls

Polymorphism	Patients with nephrolithiasis (n, %)	Control group (n, %)	p-value
rs2058265			
Single allele	32 (25%)	20 (30%)	0.13
Double alleles	4 (3.1%)	6 (9%)	
rs6464214			
Single allele	26 (20.3%)	18 (27%)	0.37
Double alleles	11 (8.6%)	8 (12%)	
rs7456421			
Single allele	86 (66.7%)	30 (44.8%)	0.001*
Double alleles	33 (25.6%)	35 (52.2%)	
	129 (100%)	67 (100%)	

*Statistically significant.

implicated in human calcium nephrolithiasis. The pathogenetic significance of these genes has not been fully established, although the expression of these genes has been seen to be altered in patients with stones[16-18].

Increasing evidence has shown that RTEC damage is closely related to early lesions responsible for the formation of renal stones[11,12]. These damaged epithelial cells undergo some pathophysiological changes and the adaptive response of these cells plays an important role in kidney stone formation[19]. An increase in HIPK2 expression in response to DNA damage and oxidative stress stimulates apoptosis through phosphorylation and triggers p53 activation. It has been suggested that these events have a potential role in the apoptosis of RTECs[20-22]. Lin et al. investigated the relationship between HIPK2 polymorphism in the rs2058265, rs6464214, and rs7456421 regions and kidney stones in a Chinese population, and reported that no difference could be found between nephrolithiasis patients and the control group in terms of these three gene polymorphisms. When only males were evaluated, a significantly increased risk of kidney stones was detected with polymorphism present in these three regions (rs2058265: OR = 2.48, rs6464214: OR = 2.46, rs7456421 OR = 2.84). The authors attributed this situation to the fact that HIPK2 and androgens are involved in RTEC damage and apoptosis. Damaged RTECs play an important role in stone formation by forming the nucleus of kidney stones. HIPK2 may therefore upregulate androgen receptors in male patients. Oxalate synthesis increases in the liver and stone formation is facilitated by increasing androgen receptors[8-11,23]. In the current study, the role of HIPK2 polymorphism in rs2058265, rs6464214, and rs7456421 regions in nephrolithiasis formation was evaluated in a Turkish population. Interestingly, the study results showed that HIPK2 SNP in these three regions was significantly higher in both alleles of control group subjects than in stone patients. The results were similar when only male patients were evaluated. Only the HIPK2 SNP in the rs7456421 region in a single allele was found to be higher in patients with kidney stones than in the control group. HIPK2 polymorphism, which stimulates RTEC damage and therefore kidney fibrosis, is expected to play an important role in the formation of renal stones when the mechanisms described above are considered logically. However, in this study population, no explanation could be found for why HIPK2 polymorphism was detected at higher rates in both alleles of the control group subjects. This demonstrates that a single gene is not responsible for the stone formation mechanism and that environmental factors play an important role together with many genetic changes. The relationship between HIPK2 polymorphism and stone formation and the underlying pathophysiological mechanisms are more complex than expected. Apart from these two studies, there is no other that has evaluated the association between HIPK2 polymorphism and stone formation.

There were some limitations to this study, primarily that the relatively low number of patients could have caused Type II statistical error. Although secondary diseases which could cause stone formation were excluded, confounding factors cannot be completely excluded as several environmental factors are responsible for stone formation. Moreover, that there was no investigation of other genetic disorders which could cause similar stone formation could also be considered a limitation.

Conclusions

Our study showed that the distributions of the genotype and allele of the three polymorphisms (rs2058265, rs6464214, and rs745642 in HIPK2) were not found to be associated with an increased risk of kidney stone in a Turkish population. Further studies with large patient series are needed to clarify the association of HIPK2 polymorphisms with nephrolithiasis.

Funding

The authors declare that they have not received funding for this study.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Intravenous antibiotic therapy after laparoscopic appendectomy in acute complicated appendicitis: the patient clinical response is the key

Terapia antibiótica intravenosa posterior a apendicectomía por laparoscopia en apendicitis aguda complicada: la respuesta clínica del paciente es la clave

Andres Mendoza-Zuchini[1], Laura C. Arce-Polania[2], and Carlos J. Pérez-Rivera[1]*

[1]Department of General Surgery, Universidad El Bosque; [2]Department of General Surgery, Universidad Militar Nueva Granada. Bogotá, Colombia

Abstract

Introduction: *The guidelines about acute complicated appendicitis (ACA) recommend 3–5 days of postoperative intravenous antibiotics (IVA). Nevertheless, the time selected by the surgeon can vary according to patient clinical response, ACA type, and professional experience. Once an adequate clinical response is obtained, the change from IVA to oral antibiotic (OA) could be realized without the waiting time established with satisfactory results.* **Objective:** *Determine if a short course of IVA and/or switch to oral route is safe based on the patient clinical response.* **Materials and methods:** *Observational prospective cohort study from a general surgery reference center database since July 2019.* **Results and conclusion:** *48 patients with ACA intraoperative findings were included. Regarding postoperative antibiotic management, only preoperative IVA: 7 (14.58%), IVA 1-3 days: 1 (20.83%), IVA 1-3 days and change to OA: 21 (43.75%), IVA > 3 days: 6 (12.5%), and only OA: 3 (27.08%). The bivariate analysis did not show statistically significant differences in reconsultation (p = 0.81), rehospitalization (p = 0.44), and surgical site infection (p = 0.56) between the antibiotic scheme based on the postoperative clinical response and the traditional one regarding intra-abdominal collection rate, the hospital stays, and hospitalization costs.*

Keywords: *Acute complicated appendicitis. Intravenous antibiotic. Oral antibiotic management. Patient clinical response.*

Resumen

Introduction: *Las guías sobre apendicitis aguda complicada (ACA) recomiendan 3-5 días de antibióticos intravenosos (IVA) postoperatorios. No obstante, el tiempo seleccionado por el cirujano puede variar según la respuesta clínica del paciente, tipo de ACA y experiencia profesional. Una vez obtenida una adecuada respuesta clínica, el cambio de IVA a antibiótico oral (OA) podría realizarse sin esperar el tiempo establecido con resultados satisfactorios.* **Objetivo:** *Determinar si un ciclo corto de IVA y/o el cambio a OA según la respuesta clínica del paciente es seguro.* **Materiales y métodos:** *Estudio observacional de cohorte prospectivo a partir de la base de datos de un centro de referencia en cirugía general desde julio del 2019.* **Resultados y Conclusión:** *Se incluyeron 48 pacientes con hallazgos intraoperatorios de ACA. En cuanto al manejo antibiótico postoperatorio, solo IVA preoperatorio: 7 (14.58%), IVA 1-3 días: 1 (20.83%), IVA 1-3 días y cambio OA: 21 (43.75%), IVA > 3 días: 6 (12.5%) y solo OA: 3 (27.08%). El análisis bivariado no mostró diferencias estadísticamente significativas en la reconsulta (p = 0.81), la rehospitalización (p = 0.44) y la infección del sitio operatorio (p = 0.56) entre el esquema de antibióticos basado en la respuesta clínica postoperatoria y el tradicional con respecto a tasa de colección intrabdominal, estancia hospitalaria y costos de hospitalización.*

Palabras clave: *Apendicitis aguda complicada. Antibiótico intravenoso. Manejo antibiotico oral. Respuesta clínica del paciente.*

***Correspondence:**
Andres Mendoza-Zuchini
E-mail: andreszuchini@hotmail.com

Date of reception: 30-06-2021
Date of acceptance: 15-10-2022
DOI: 10.24875/CIRUE.M22000625

Cir Cir (Eng). 2023;91(4):463-469
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Acute appendicitis (AA) is the most common cause of acute abdomen in the world, with an incidence of 5.7-50/100,000 inhabitants per year, with a peak incidence between 10 and 30 years[1,2]. Acute complicated appendicitis (ACA) (perforation, phlegmon, abscess, or peritonitis) and uncomplicated are two entities that require treatments due to the notable difference in complications associated with each other[3,4].

Usually, after surgical management in ACA, additional antibiotic management is provided to prevent or avoid residual infectious complications. In accordance with the guidelines of the Surgical Infection Society and the Infectious Diseases Society of America, an additional 4-7 days of antibiotic are recommended after surgical management in ACA[5]. The latest WSES Jerusalem guidelines for the diagnosis and treatment of AA 2020 update recommend against prolonging antibiotics longer than 3-5 days postoperatively in case of complicated appendicitis with adequate source-control (QoE: High; Strength of recommendation: Strong; 1A) and an early switch (after 48 h) to oral administration of postoperative antibiotics in children with complicated appendicitis, with an overall length of therapy shorter than 7 days (QoE: Moderate; Strength of recommendation: Strong; 1B)[1]. In addition, currently considered the gold standard in the management of AA, laparoscopic appendectomy has already shown to be a protective factor in patients with AA, and it provides clinically beneficial advantages over open method, including shorter hospital stay, decreased need for postoperative analgesia, early food tolerance, earlier return to work, and lower rate of wound infection[5,6]. A recent study questioning whether ambulatory appendectomy should be the standard treatment for AA suggests that this could be considered a standard procedure for both complicated and uncomplicated AA[6].

In most cases of ACA, the treatment length of intravenous antibiotics (IVA) is determined by the surgeon based on the patient's clinical response. Given that not all types of ACA are the same, the study was conducted to identify which patients could be susceptible to switch from IVA to oral antibiotic (OA) after laparoscopic appendectomy in ACA. The hypothesis in mind is considers that once the patient has an adequate clinical response after the procedure, even on an outpatient basis, there is no need to wait 3-5 days of IV antibiotic in safe form while still providing satisfactory outcomes, low complication rates and establish in whom of these are at higher risk of residual infectious complications. This study is carried out to determine if a short course of IVA and/or switch to oral route is feasible and safe based on the patient clinical response and if it increases the risk of intra-abdominal collection and decreases the length of hospital stay or not.

Methods

Study design

A prospective cohort observational study was carried out in a reference center in general surgery since July 2019. A descriptive and bivariate analysis was performed 1 year after the intervention as partial results of a 5-year study. All patients underwent laparoscopic appendectomy with an intraoperative finding of complicated AA. Preoperative antibiotic management was administered in all patients and posteriorly had either a change to OA and outpatient management or continued intravenous scheme based on the intraoperative findings and clinical response of the patient (control of the systemic inflammatory response, oral intake, bowel transit, and pain control).

This project was submitted to the Institutional Review Board, and upon evaluation was granted exemption, as this was a prospective retrospective chart review. The protocol was implemented in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Regarding the inclusion criteria, all patients were older than or equal to 18 years old at the time of the surgery and had undergone laparoscopic appendectomy with intraoperative diagnosis of complicated AA, also, all patients, or their next of kin, provided informed consent before the study inclusion. On the other hand, concerning patients excluded were those who received antibiotic management during the first postoperative month for any other reason than AA or its complications. Other excluded patients included intraoperative suspicion of appendicular neoplasm, chronic or acute malnutrition, and finally, medical failure with antibiotics for AA before surgery.

Intervention

Patients who underwent laparoscopic appendectomy with finding of ACA received preoperative IVA in all cases, a switch to oral OA and outpatient management or prolongation of IVA based on intraoperative findings and clinical response of the patient.

The same antibiotic was used in all patients according to the institutional guidelines for the management of AA, including pregnant patients in whom a safe use of these antibiotics has been proven. The initial antibiotic treatment was 95% of the time a beta-lactam plus a beta-lactamase inhibitor (ampicillin-sulbactam). In the remaining 5% of cases due to penicillin allergy, the antibiotic of choice was clindamycin with aminoglycoside (Amikacin or Gentamicin), and in pregnant patients, this was replaced by metronidazole as the institutional guidelines recommend.

Antibiotics regimens used

1. Only IVA prior to surgery
2. IVA before surgery and switch to oral route
3. Only IVA for 1-3 days
4. IVA for 1-3 days and switch to oral route
5. IVA > 3 days.

Statistical analysis

Clinical findings or characteristics based on the surgical approach were assessed using a Student's t-test and Mann–Whitney U-test or Fisher's test to compare the means between groups for normally distributed and non-normally distributed data, respectively. The χ^2-test was used to compare proportions/frequencies between groups. Primary endpoints were evaluated independently as binary outcomes. Statistical significance was considered $p \leq 0.05$. This study complied with the STROBE guidelines.

Results

A total of 48 patients met the inclusion criteria, 29 patients were women (60%), whereas four of them pregnant, and 19 patients were male (39%). The average age was 34, 4 years old. AA was diagnosed through clinical suspicion (60%), abdominal ultrasound (8%), or computerized tomography scan (27%). The distribution of intraoperative findings is described in table 1.

Table 1. Description of intraoperative findings

Intraoperative findings	n = 48 (%)
Gangrenous appendix	9 (18.75)
Appendicolith free in abdominal cavity	6 (12.5)
Perforated appendix	21 (43.75)
Localized abscess	12 (25)
Pelvic peritonitis	20 (42.6)
Generalized peritonitis	12 (25)
Phlegmon	23 (47.9)

Table 2. Complications presented with an antibiotic regimen based on the patient's clinical response

Complication	n (%)
SSI grade I	3 (6,25)
SSI grade III	2 (4,16)
Ileus	1 (2)

Peritoneal lavage was not performed in any of the patients, only suction and cleaning. The appendix stump closure technique was polymeric clip 51.4% (or endoloop 37.5%), and also there were used ligasure (56.25%), hook (43.75%), or endobag (39.58%). In the postoperative period, two of the 35 patients presented postoperative ileus and five surgical site infections (SSI), three being superficial and the remaining two organ space (Table 2).

The distribution of antibiotic management and the evaluated postoperative results (complications and length of hospital stay) are described in Tables 3 and 4, respectively.

The descriptive analysis is detailed in Table 5. In the bivariate analysis, no statistically significant difference was found in *reconsultation* (p = 0.81), *rehospitalization* (p = 0.44), and *infection of the surgical site* (p = 0.56) between the traditional scheme or the one based on the clinical response of the patient (Table 6).

Discussion

AA is one of the most common general surgical emergencies worldwide, representing a mortality risk about 8.6% and 6.7%, for men and women, respectively[7,8]. One-third of patients with AA who assist to

Table 3. Distribution of postoperative antibiotic management

Postoperative antibiotic management	n (%)
Only preoperative AB and outpatient management	7 (14.58)
Preoperative IVA and OA	3 (27.08)
IVA 1-3 days only	11 (22.91)
IVA 1-3 days + OA	21 (43.75)
IVA for more than 3 days only	6 (12.5)

Table 4. Length of hospital stay in patients on an antibiotic regimen based on clinical response

Length of hospital stay	n (%)
Ambulatory	11 (22.9)
1 day	12 (25)
2 days	7 (14.5)
3 days	13 (27)
4 days	1 (2)
5 days	2 (4.16)
More than 5 days	2 (4.16)

the emergency service have a complicated appendicitis, which translates into increased risk of postoperative problems, compared to patients with uncomplicated appendicitis[7,8].

Bhangu et al. sustained that the AA may be classified as uncomplicated or complicated. The first one mentioned is about a simple and non-perforated appendicitis, which can be suppurative/phlegmonous, and is less often accompanied by localized or diffuse pus than gangrene; the other one, is a more complex appendicitis, can be gangrenous with friable appendix with purple, green, or black color changes associated with the transmural inflammation and necrosis. This can also perforate, which is not always visible on microscope and finally, abscess may have a pelvic or abdominal location found during examination, in a preoperative imaging or as an operative finding. In the latest WSES Jerusalem guidelines, described that Mällinen et al. argued their hypothesis that the presence of an appendicolith is an independent predictive factor for both perforation and the failure of non-operative management of uncomplicated AA.

The administration of an appropriate antimicrobial therapy, as a precept in gastrointestinal surgery to prevent SSI[8,9]. As is already known, in uncomplicated appendicitis, antimicrobial therapy following surgery is not indicated and can produce adverse events[8,9]. Nevertheless, the time of IVA therapy after laparoscopic appendectomy in complicated appendicitis has not been described. According to the current evidence-based guideline of Jerusalem 2020, the antibiotic regimen is defined by the surgeon and the patient's clinical response, showing that the antibiotic administration, which is about 3-5 days, depends on the source control grade, the appendix aspect, and the degree of peritonitis.

Based on our results, 75% of the patients were managed with an in-hospital stay < 3 days, representing a significant decrease translated to the reduction of hospitalization costs. Compliance rates are similar as expected to the current literature for complicated AA. Saar et al. carried out a controlled trial, with only 24-h antibiotic therapy in a controlled source of a complicated appendicitis, proving safety associated with short length of hospital stay and lower costs[8-11]. de Wijkerslooth et al., carried out a study among 181 patients with gangrenous appendicitis, postoperative antibiotic during less or equal than 24 h in 57 patients (31.5%) and more than 24 h in 124 patients, although there were different factors such as older patients, higher median CRP levels at presentation, and local or diffuse peritonitis during surgery, they showed more infectious complications although not statistically significant, but did correlate with a longer length of stay[12,13].

Additionally, it was observed that of the two patients who developed postoperative abscess, both had in common an appendicolith free in the abdominal cavity as an intraoperative finding. One patient received IVA for 3 days and then OA, whereas the other patient received IVA more than 5 days given a generalized peritonitis, which could explain whether or not this finding constitutes a risk factor for SSI grade III.

Finally, there were no statistically significant differences in *reconsultation* ($p = 0.81$), *rehospitalization* ($p = 0.44$), and SSI ($p = 0.56$) between the traditional scheme or the one based on the patient clinical response. The main limitation in the study design is data without a larger sample needed to confirm the hypothesis; however, it has shown promising results. The previous limitation could be minimized by performing a randomized clinical trial to evaluate safety

Table 5. Descriptive analysis

Variable name	n (%)	Median	Interquartile range
Gender	Female 29 (60) Male 19 (39)	-	-
Year	-	31	16.5
Body mass index	-	27.2	5.05
Clinical diagnosis	No 19 (39) Yes 20 (60)	-	-
Ultrasound diagnosis	No 44 (91) Yes 4 (8)	-	-
Tomography computerized diagnosis	No 35 (72) Yes 13 (27)	-	-
Pregnant	No 44 (91) Yes 4 (8)	-	-
Evolution timeline (hours)	-	3.0	2.0
Leukocytes	-	1548	5854
Gangrenous appendix	No 39 (81.25) Yes 9 (18.75)	-	-
Appendicolith into the abdominal cavity	No 42 (87.5) Si 6 (12.5)	-	-
Perforated appendix	No 27 (56.25) Yes 21 (43.75)	-	-
Perforation	No 46 (95.83) Yes 2 (4.16)	-	-
Localiced abscess	No 36 (75) Yes 12 (25)	-	-
Pelvic peritonitis	No 28 (58.33) Yes 20 (41.66)	-	-
Generalized peritonitis	No 36 (75) Yes 12 (25)	-	-
Appendiceal phlegmon	No 25 (52.08) Yes 23 (47.91)	-	-
Ligasure	No 21 (43.75) Yes 27 (56.25)	-	-
Hook	No 27 (56.25) Yes 21 (43.75)	-	-
Endobag	No 29 (60.41) Yes 19 (39.58)	-	-
Drain	No 40 (83.33) Yes 8 (16.66)	-	-
Hemolock	No 22 (45.83) Yes 26 (54.16)	-	-
Endoloop	No 30 (62.5) Yes 18 (37.5)	-	-
Peritoneal lavage	No 48 (100) Yes 0	-	-

(Continue)

Table 5. Descriptive analysis *(continued)*

Variable name	n = (%)	Median	Interquartile range
Postoperative ileus	No 46 (95.83) Yes 2 (4.16)	-	-
SSI	No 43 (89.58) Superficial 3 (6.25) Organ-space 2 (4.16)	-	-
Length of hospital stay	-	1.0	3.0
Duration of postoperative hospital stay (days)	0: only preoperative antibiotic 7 (14.58) 1: intravenous antibiotic 1-3 days 1 (20.83) 2: intravenous antibiotic 1-3 days and switch to oral antibiotic administration 21 (43.75) 3: intravenous antibiotic more than 3 days 6 (12.5) 4: only oral antibiotic 3 (27.08)	-	-
Outpatient antibiotic treatment	No 8 (16.66) Yes 40 (83.33)	-	-
Reintervention	No 48 (100) Yes 0	-	-
Reconsultation	No 44 (91.66) Yes 4 (8.33)	-	-
Rehospitalization	No 46 (95.83) Yes 2 (4.16)	-	-

SSI: surgical site infection.

Table 6. Bivariate analysis

Outcomes	0	1	2	3	4	p-value
Reintervention	0	0	0	0	0	0
Reconsultation	0	0	2	1	1	0.81
Rehospitalization	0	0	1	1	0	0.44
Infection of the surgical site	0	0	2	3	0	0.05

0: only preoperative antibiotic; 1: intravenous antibiotic 1-3 days; 2: intravenous antibiotic 1-3 days and switch to oral antibiotic administration; 3: intravenous antibiotic more than 3 days; 4: only oral antibiotic.

and effectiveness of the different treatment regimens.

Conclusion

The use of an antibiotic regimen based on the postoperative clinical response of the patient turned out to be effective and safe after laparoscopic appendectomy for complicated AA. There were no statistically significant differences between the traditional scheme and the scheme based on the postoperative clinical response of the patient in the intra-abdominal collection rate. The antibiotic scheme based on the postoperative clinical response of the patient could decrease the time of hospital stay and consequently the reduction of hospitalization costs based on the above.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Prognostic analysis and outcome of hilar cholangiocarcinoma after radical resection: a retrospective study

Análisis pronóstico y resultado del colangiocarcinoma hiliar tras la resección radical: un estudio retrospectivo

*Ziyang Xu[1], Zunqiang Zhou[1], Jiao Guan[1], Dawei Liu[2], Xiaodong Li[2], and Zhengyun Zhang[1]**

[1]Department of Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai; [2]Department of Surgery, Heilongjiang Provincial Hospital Affiliated to Harbin Institute of Technology, Harbin. China

Abstract

Objectives: *The predictive factors affecting the survival of hilar cholangiocarcinoma (HC) are ambiguous. This study aimed to identify the predictors and recurrence patterns of HC.* **Methods:** *A retrospective analysis of the clinicopathological findings of 126 patients with HC from 2009 to 2019 was performed.* **Results:** *The proportion of Bismuth I and II HC in the recurrence group was higher than that in the non-recurrence group ($p < 0.01$). The recurrence group had poorer tumor differentiation, a more advanced N stage, and a higher incidence of perineural invasion compared with the non-recurrence group. N stage and tumor differentiation were independently associated with disease-free and overall survival of patients ($p < 0.01$). Bile duct resection (BDR) combined with hepatectomy was more favorable to disease-free and overall survivals than BDR alone in Bismuth I and II HC, although p values were marginal ($p = 0.072$ and $p = 0.045$). A higher proportion of patients in the non-recurrence group underwent BDR combined with hepatectomy than that in the recurrence group ($p < 0.01$).* **Conclusions:** *N stage and tumor differentiation are the two independent predictors of patient survival. BDR combined with hepatectomy is recommended for patients with Bismuth I and II hilar cholangiocarcinoma.*

Keywords: *Hilar cholangiocarcinoma. Bismuth classification. Survival. Bile duct resection. Hepatectomy.*

Resumen

Objetivos: *Los predictores que afectan a la supervivencia del colangiocarcinoma hiliar son ambiguos. Este estudio tiene como objetivo identificar los factores predictivos y los patrones de recurrencia del colangiocarcinoma hiliar.* **Métodos:** *Se aplicó un análisis retrospectivo con126 pacientes con colangiocarcinoma hiliar desde 2009 hasta 2019.* **Resultados:** *La proporción de colangiocarcinoma hiliar Bismuth I y II en el grupo de recurrencia fue mayor que en el grupo de no recurrencia ($p < 0.01$). El tumor del grupo de recidiva tenía un estadio N más avanzado que el del grupo de no recidiva. El estadio N se asocia de forma independiente con la supervivencia libre de enfermedad y global del paciente ($p < 0.01$). La resección de la vía biliar combinada con la hepatectomía benefició más a la supervivencia libre de enfermedad y global que la resección de la vía biliar sola en el colangiocarcinoma hiliar ($p = 0.072$ y $p = 0.045$). Una mayor proporción de pacientes se sometió a resección de la vía biliar combinada con hepatectomía en el grupo de no recidiva que en el de recidiva ($p < 0.01$).* **Conclusiones:** *El estadio N fue el predictor independiente. Se recomienda la resección de la vía biliar combinada con hepatectomía para los pacientes con colangiocarcinoma hiliar Bismuth I y II.*

***Palabras clave*:** *Colangiocarcinoma hiliar. Clasificación de Bismuth. Supervivencia. Resección de la vía biliar. Hepatectomía.*

***Correspondence:**
Zhengyun Zhang
E-mail: zhengyunzhshjtu@126.com

Date of reception: 21-11-2022
Date of acceptance: 06-01-2023
DOI: 10.24875/CIRUE.M23000626

Cir Cir (Eng). 2023;91(4):470-477
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Surgical resection is the only strategy to improve survival rates for hilar cholangiocarcinoma (HC), even though, the 5-year survival rate of HC is unsatisfactory, ranging from approximately 14% to 45%[1,2]. Despite the advances in surgical techniques and perioperative supportive care, the treatment of HC remains challenging. Due to its longitudinally extended infiltrative nature and proximity to vital vascular structures, surgical resection of HC is limited and has unfavorable oncological outcomes[3,4]. Extended major hepatectomy with concomitant vascular and biliary resection and reconstruction is associated with high perioperative morbidity and mortality rates, and thus, the evolution of surgical management for HC is ongoing. Predictors reported in some previous studies include resection margins, tumor differentiation, and lymph node metastasis[5,6]. These studies identified a wide range of prognostic factors due to the variation of the follow-up period, including palliative or numerous surgical approaches and R1 resection. Therefore, at present, the predictive factors affecting the survival of HC are ambiguous. The aim of this study is to investigate the predictors and recurrence patterns of HC in a large cohort of patients who underwent R0 resection and had long-term follow-ups.

Methods

Patients

The data of 126 consecutive patients with HC from January 2009 to December 2019 at two hospitals were retrospectively reviewed. Computed tomography (CT) and magnetic resonance imaging (MR) were used to assess tumor infiltration. PET-CT was used to detect suspected distant metastases. Endoscopic ultrasound was also suggested to evaluate biliary and vascular involvement. If patients had obstructive jaundice, endoscopic nose biliary drainage through endoscopic retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage was routinely performed. This study was approved by the hospital's ethics committee, under the approval number 2008-117-(1), and was conducted according to the principles outlined in the Declaration of Helsinki. Each patient provided a written informed consent.

Surgical procedures

During this procedure, bile duct resection (BDR) was routinely performed with both the proximal and distal bile duct margins examined by frozen examination. Resection margins of the distal bile duct and proximal hepatic duct were sent for frozen-section examination during operation. R1 resection was obtained when the resection margin (distal bile duct or proximal hepatic duct or both) was not free from cancer cells under microscope observation. Re-resection of the bile duct or hepatectomy was performed if the bile duct margin was positive on frozen section analysis. All 126 patients underwent R0 resection approved by the frozen section analysis. Lymphadenectomy was also performed by skeletonizing the hepatoduodenal ligament as well as harvesting the lymph nodes along the common hepatic artery and retro-pancreatic region. Other lymph nodes are removed only if they are found to be enlarged or positive on pre-surgical imaging. Overall, however, whether and how a BDR or hepatectomy was performed depended largely on the decision of the surgeon. Complications were ranked in accordance with Clavien–Dindo classifications[7]. T and N staging was performed following the American Joint Committee on Cancer 8th edition. Chemotherapy (gemcitabine+cisplatin) was administered to patients with lymph node metastasis if they did not refuse, and those with R1 resection received 5-FU-based concurrent chemoradiotherapy.

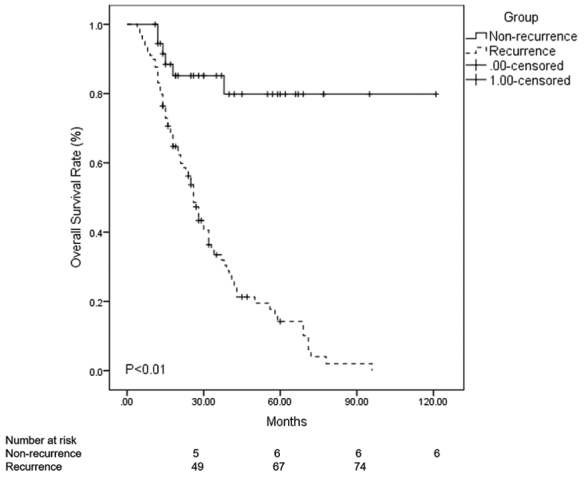

Figure 1. *Comparison of overall survival between non-recurrence and recurrence groups (p < 0.01).*

Follow-up

Patients were followed up at a 3-month frequency during this decade, including a physical examination and a laboratory test. CT or MR was arranged every 3 months for the 1st year and then every 6 months for

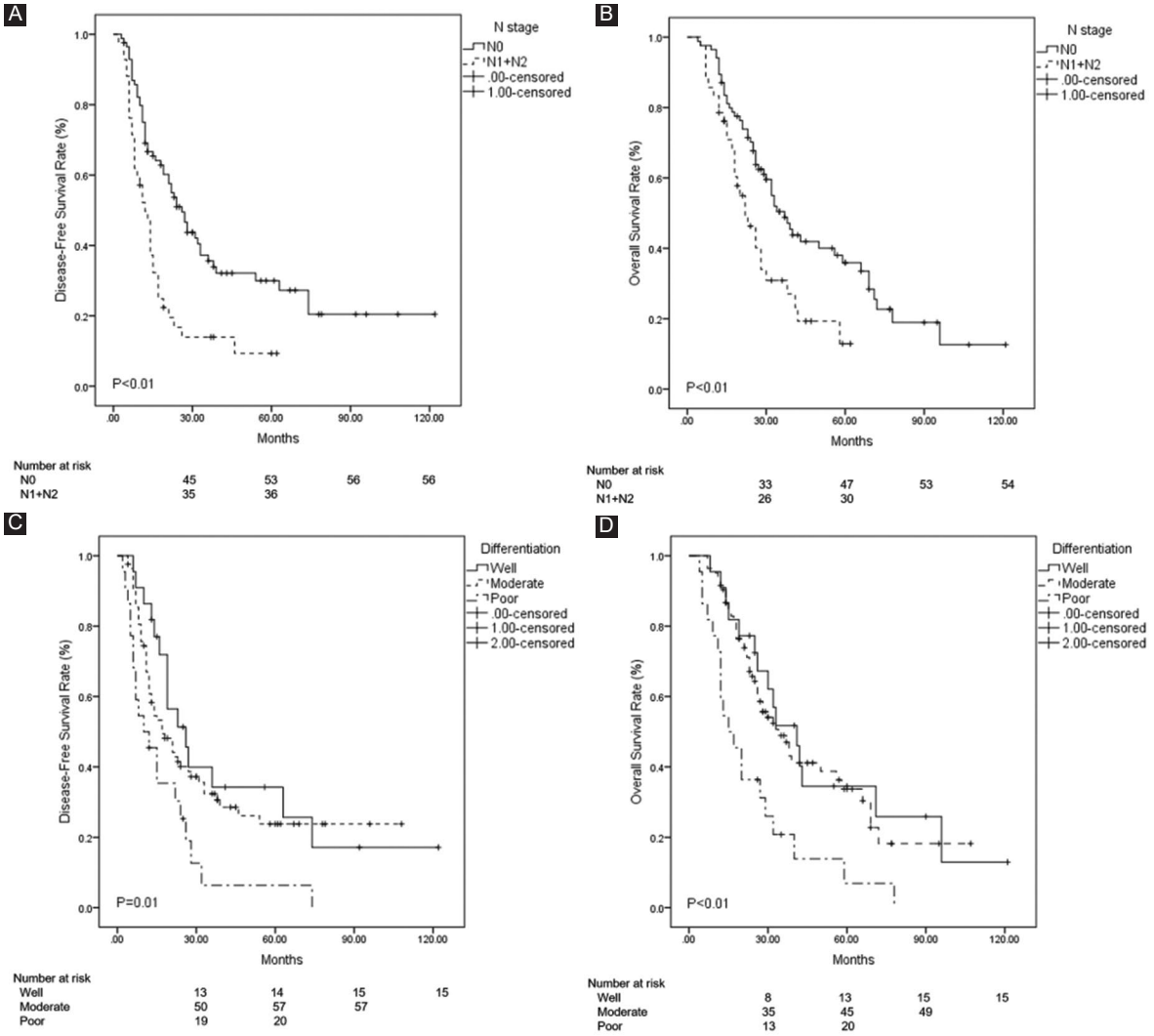

Figure 2. *Comparison of survivals in non-recurrence and recurrence groups.* **A** *and* **B:** *the disease-free and overall survivals shortened dramatically with the advancement of N stage (p < 0.01).* **C** *and* **D:** *patients with poor tumor differentiation had the worst disease-free and overall survivals than those with moderate and well differentiation (p = 0.01 and p < 0.01).*

the 2nd year. CT of the thorax, bone scan, and MR of the brain were performed if clinical examination led to a suspicion of metastasis or PET-CT was performed if other metastases were suspected. The primary endpoint of the study was recurrence. The secondary endpoints were disease-free survival and overall survival. Recurrence was defined as suspicious or confirmed lesions on imaging or histological examination.

Statistical analysis

Continuous variables were expressed as median and range or mean ± standard deviation, whereas categorical variables were expressed as number and percentage. Chi-squared test was used for nominal data. Univariate analysis with χ^2 test or Fisher's exact test was used for categorical variables. When the data did not follow normal distributions, the nonparametric Mann-Whitney U-test was applied. Kaplan-Meier survival was compared using log-rank test. Univariate and multivariate analyses were analyzed through Cox proportional hazard regression. Significance was considered at $p < 0.05$. SPSS 22 (SPSS, Chicago, IL) was used for statistics.

Results

Baseline and clinicopathological features of HC patients

Thirty-seven patients were included in the non-recurrence group while 89 patients were found to have a

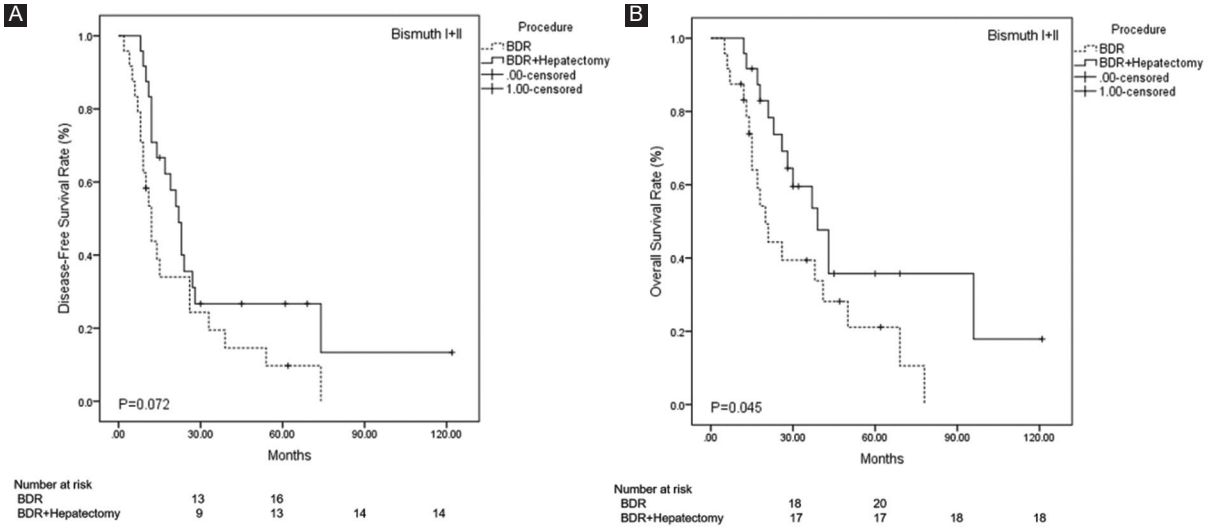

Figure 3. A *and* **B***: survival analysis stratified by surgical strategy in Bismuth I and II hilar cholangiocarcinoma patients. Bile duct resection combined with hepatectomy benefited the disease-free and overall survivals more than BDR alone in Bismuth I and II hilar cholangiocarcinoma (p = 0.072 and p = 0.045).*

recurrence during follow-up. None of the patients in these two groups underwent additional portal vein or hepatic artery resection. No differences were detected between the two groups in terms of age, gender, laboratory tests, proportion of preoperative biliary drainage, proportion of transfusions, incidence of serious surgical complications, and length of hospital stay. Noticeably, the proportion of Bismuth I and II HC was significantly higher in the recurrence group than that in the non-recurrence group (43.8% vs. 24.3%, $p < 0.01$). In addition, the recurrence group had poorer tumor differentiation, a more advanced N stage, and a higher incidence of perineural invasion compared to the non-recurrence group. No differences were observed in other clinicopathological features between the two groups (Table 1).

Survival analysis in non-recurrence and recurrence groups

Overall survival was significantly worse in the recurrence group than in the non-recurrence group ($p < 0.01$) (Fig. 1). In both univariate and multivariate analyses, N stage and tumor differentiation were independently associated with disease-free and overall survival of patients (Tables 2 and 3). Disease-free and overall survivals decreased dramatically with the advancement of N stage ($p < 0.01$) (Fig. 2A and B). Patients with poorly differentiated tumors had the worst disease-free and overall survivals than those of moderate and well differentiation ($p = 0.01$ and $p < 0.01$) (Fig. 2C and D).

Patterns of postoperative recurrence

In the recurrence group, local lymph node recurrence was identified to occur more frequently than local anastomosis recurrence, vascular recurrence, isolated locoregional recurrence, distant recurrence, and other recurrences. For distant recurrences, lung metastasis occurred more frequently, followed by liver, abdomen wall, brain, and bone metastasis (Table 4).

Survival analysis stratified by surgical strategy in Bismuth I and II HC patients.

We found that the proportion of Bismuth I and II HC in recurrence group was larger than that of the non-recurrence group. Hence, we further determined the factors that contributed to this difference. It was found that the surgical strategy contributed to this difference. BDR combined with hepatectomy was more beneficial than BDR alone for the disease-free and overall survival in Bismuth I and II HC, although the p value was marginal ($p = 0.072$ and $p = 0.045$) (Fig. 3A and B). Moreover, in the non-recurrence group, a larger proportion of patients underwent BDR combined with hepatectomy than that in recurrence group ($p < 0.01$) (Table 5).

Discussion

HC is a relatively rare cancer with an extremely poor prognosis. Radical hepatectomy is the only

Table 1. Baseline features of patients with hilar cholangiocarcinoma

Variables	Non-recurrence (n = 37)	Recurrence (n = 89)	p value
Age (mean ± SD)	62.1 ± 6.4	61.5 ± 7.8	NS
Sex (male) (n, %)	27 (73.0)	67 (75.3)	NS
BMI (kg/m2) (mean ± SD)	21.1 ± 3.1	23.2 ± 2.4	NS
Hb (g/dL, mean ± SD)	15.3 ± 2.3	14.7 ± 2.8	NS
Albumin (g/dL, mean ± SD)	3.8 ± 0.5	3.9 ± 0.5	NS
Bilirubin (mg/dL, mean ± SD)	1.9 (0.3-3.2)	2.1 (0.4-4.4)	NS
CEA (median, range)	3.2 (0.3-43.4)	4.0 (0.6-39.2)	NS
CA199 (median, range)	121.6 (2.2-2220.0)	132.1 (4.5-2490.0)	NS
Biliary drainage (n, %)	7 (18.9)	15 (16.9)	NS
Transfusion (n, %)	6 (16.2)	14 (15.7)	NS
Complication (≥ IIIa) (n, %)	2 (5.4)	6 (6.7)	NS
Hospital stay (days, mean ± SD)	24.2 ± 12.5	22.5 ± 10.6	NS
Tumor size (cm, mean ± SD)	3.5 ± 1.9	3.8 ± 1.1	NS
Bismuth type (n, %)			
I + II	9 (24.3)	39 (43.8)	
III + IV	28 (75.7)	50 (56.2)	< 0.01
T stage (n, %)			
1	1 (2.7)	3 (3.4)	
2	26 (70.3)	64 (71.9)	
3	8 (21.6)	18 (20.2)	
4	2 (5.4)	4 (4.5)	NS
N stage (n, %)			
0	31 (83.8)	54 (60.7)	
1	5 (13.5)	29 (32.6)	
2	1 (2.7)	6 (6.7)	< 0.01
Differentiation (n, %)			
Well	8 (21.6)	10 (11.2)	
Moderate	25 (67.6)	51 (57.3)	< 0.01
Poor	4 (10.8)	28 (31.5)	
Lymphovascular invasion (n, %)	8 (21.6)	18 (20.2)	NS
Perineural invasion (n, %)	23 (62.2)	67 (75.3)	< 0.05
Adjuvant therapy (n, %)	7 (18.9)	20 (22.5)	NS

NS: not significant; Hb: hemoglobin; CEA: carcinoembryonic antigen; CA199: cancer antigen 199.

curative treatment strategy for HC. Surgeons have made tremendous efforts to perform an aggressive surgical approach in spite of technique difficulties[8,9]. Despite the efforts to improve the prognosis of HC, the 5-year survival rate remains low[10]. In the past few years, several prognostic factors such as tumor differentiation, lymph node status, and resection margin have been identified. However, the predictive factors for HC are still ambiguous presently. We designed this study to investigate the predictors and recurrence patterns of HC using of a large cohort. We divided the study cohort into a non-recurrent and a recurrence group to compare the recurrence patterns and predictors of HC. As a result, we did find similar results to those previously reported[5,6]. First, the recurrence group had poorer tumor differentiation, a higher incidence of perineural invasion, and a more advanced N stage compared to the non-recurrence group. Second, in both univariate and multivariate models, N stage and tumor differentiation were

Table 2. Univariate and multivariate analysis of the risk factors associated with patients' disease-free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Biliary drainage	0.32	0.11-2.09	NS			
Transfusion	1.21	0.24-4.42	NS			
Complication (≥ IIIa)	1.33	0.36-5.31	NS			
Tumor size (≥ 3cm)	0.68	0.33-2.55	NS			
Bismuth type	0.86	0.25-1.31	NS			
T stage	2.33	0.76-3.44	NS			
N stage	3.23	2.12-4.37	< 0.01	3.27	1.87-4.50	< 0.01
Differentiation	2.72	1.49-3.58	< 0.01	1.87	1.21-2.80	< 0.01
Lymphovascular invasion	0.49	0.10-2.56	NS			
Perineural invasion	3.13	0.29-4.86	NS			
Adjuvant therapy	0.36	0.12-5.22	NS			

NS: not significant ; HR: hazard ratio; CI: confidence interval.

Table 3. Univariate and multivariate analysis of the risk factors associated with patients' overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Biliary drainage	0.29	0.03-3.12	NS			
Transfusion	2.5	0.25-3.36	NS			
Complication (≥ IIIa)	2.03	1.03-4.44	< 0.05			
Tumor size (≥ 3cm)	0.91	0.46-1.91	NS			
Bismuth type	3.11	0.27-5.85	NS			
T stage	2.20	0.60-3.97	NS			
N stage	2.05	1.12-3.28	< 0.01	3.11	1.60-4.24	< 0.01
Differentiation	2.91	1.78-5.38	< 0.01	2.22	1.10-4.76	< 0.01
Lymphovascular invasion	2.02	0.72-3.85	NS			
Perineural invasion	1.40	0.26-2.84	NS			
Adjuvant therapy	2.22	0.22-3.34	NS			

NS: not significant; HR: hazard ratio; CI: confidence interval.

independently associated with disease-free and overall survival, which decreased sharply as N stage advanced. Third, patients with poorly differentiated tumors had the worst disease-free and overall survival than those with moderate and well differentiation. Fourth, noticeably, we found that the proportion of Bismuth I and II HC in the recurrence group was higher than that in the non-recurrence group with a great significance, which has not been reported in previous investigations.

We further tried to identify possible answers that could explain this new finding. Previously, there was no survival advantage for HC patients undergoing aggressive surgical approaches due to high mortality[11]. However, with the advances in surgical techniques and preoperative management, this condition has changed a lot.

Table 4. Patterns of postoperative recurrence

	Recurrence (n = 89) (n, %)
Locoregional metastasis (n, %)	
Local lymph node	40 (44.9)
Local anastomosis site	13 (14.6)
Hepatic and portal vessels	4 (4.5)
Isolated locoregional recurrence (n, %)	30 (33.7)
Distant metastasis (n, %)	
liver	5 (5.6)
Abdomen wall	5 (5.6)
brain	3 (3.4)
lung	7 (7.9)
bone	1 (1.1)
Others (n, %)	3 (3.4)

Table 5. Surgical procedure of Bismuth I and II hilar cholangiocarcinoma

Surgical procedure	Non-recurrence (n = 9) (n, %)	Recurrence (n = 39) (n, %)	p value
BDR	3 (33.3)	21 (53.8)	
BDR + hepatectomy	6 (66.7)	18 (46.2)	< 0.01

BDR: bile duct resection.

Mortality rates have become acceptable and survival benefits have been achieved[9,12,13]. BDR combined with hepatectomy is now a standard procedure for Bismuth III and IV HC, but the benefit of hepatectomy in Bismuth I and II HC remains controversial. A few investigations have suggested that BDR alone was sufficient for Bismuth I and II HC. Otani et al. found that the R0 resection rate and overall survival were similar between local resection for Bismuth I and II HC and combined hepatectomy for Bismuth III and IV HC[14]. Chen et al. also demonstrated no diversity in long-term survival and recurrence between the two groups[15]. However, the sample size was relatively small, and thus, selection bias might exist in these studies. In the present study, we found that BDR combined with hepatectomy was beneficial to the disease-free and overall survival in patients with Bismuth I and II HC though the p value was marginal. Nakanishi et al. recommend left hepatectomy for Bismuth type I and II HC without extra ductal tumor invasion in the right side of the hepatic portal region[16]. However, Zhang et al. found that similar rates of R0 resection were achieved among patients who had BDR versus BDR+ hepatectomy for Bismuth I and II HC. The addition of hepatectomy with or without caudate lobectomy did not result in any survival or recurrence benefits than BDR alone, as long as R0 margin was achieved[17]. The main limitation of these retrospective studies is the small sample size. We suggest that the need for hepatectomy for Bismuth I and II is condition dependent. Once R0 margin can be achieved and evaluated by the surgeon, hepatectomy is an alternative option. However, future large multicenter studies are still needed to define the optimal surgical strategies for patients with Bismuth type I and II HC. Recent studies pointed out that a positive radial margin is the common cause of R1 resection and has a negative impact on survival[18]. Similarly, we found a larger proportion of patients who underwent BDR combined with hepatectomy in non-recurrence group than that in recurrence group in the present study of R0 resection patients. Therefore, we believe that more aggressive surgical strategies, such as combined hepatectomy, are critical to achieve R0 resection and improve the survival of Bismuth I and II HC. In addition, local lymph node recurrence was identified to occur more frequently than other recurrences, so we suggest an extensive regional lymph node dissection contributing to curative resection. In summary, it comes into view that the contents mentioned above may support the possibility that a larger proportion of Bismuth I and II HC occupies the recurrence group.

As for the issue of vascular resection, if resection and reconstruction are possible, combined vascular resection can be performed with an acceptable mortality rate and can offer long-term survival to some patients with advanced HC previously considered inoperable[19,20]. Combined procedures should be encouraged as an option to cure intractable disease as suggested by a meta-analysis[21]. Nowadays, surgical treatment of HC has steadily evolved, with decreasing mortality and increasing survival rates. Previous reports have emphasized lymph node metastasis, histopathologic status, resection margin, and adjuvant chemotherapy as important prognostic factors for HC[22-25]. Moreover, recent studies have recommended adjuvant chemotherapy conducted as a bridge modality to improve radical resection rates in locally advanced HC[26,27]. However, in the present study, we did not find the survival benefit of adjuvant chemotherapy in both univariate and multivariate analyses. Therefore, we advocate that the impact of surgical technique and approach remains important in such malignant tumors.

Conclusions

This study had some limitations because of its retrospective design. Although there were limitations,

the new findings of the present study are remarkable and may have some impact on the current guidelines and contribute to the clinical practice in the following aspects. First, N stage and tumor differentiation are the two independent predictors of survival in patients with HC. Second, local lymph node recurrence is the predominant pattern of recurrence in HC. Therefore, we recommend extensive regional lymph node dissection to facilitate curative resection. Third, at present, however, we recommend BDR combined with hepatectomy for patients with Bismuth I and II HC.

Funding

This study was supported by grants from the National Natural Science Foundation of China (81974379).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Predictivity of aspartate aminotransferase to alanine aminotransferase (De Ritis) ratio for detecting bowel necrosis in incarcerated inguinal hernia patients

Predicción de la proporción de aspartato aminotransferasa a alanina aminotransferasa (De Ritis) para detectar necrosis intestinal en pacientes con hernia inguinal incarcerada

*Umit Turan[1] and Ahmet Baris-Dirim[2]**

[1]Department of General Surgery, Adana City Research and Training Hospital, Adana; [2]Department of General Surgery, Balıklıgol Government Hospital, Sanlıurfa. Turkey

Abstract

Purpose: *Early diagnosis of necrotic bowel segment resulting from incarcerated inguinal hernia (IIH) is crucial for reducing morbidity and mortality. The aim of this study was to investigate the efficacy of the De Ritis ratio (DRR), also known as the ratio of aspartate aminotransferase to alanine aminotransferase, as a biomarker for intestinal necrosis.* **Methods:** *This retrospective study included 132 patients who underwent emergency surgery for IIH. Patients were divided into two groups: those who underwent bowel resection for necrosis (Group 1) and those who did not (Group 2). Patients' demographic and clinical data were recorded. Using laboratory test results, DRR, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and lymphocyte-to-CRP ratio (LCR) were calculated.* **Results:** *The morbidity and mortality rates and the length of stay for Group 1 were statistically significantly different ($p < 0.0001$). The DRR, NLR, PLR, LMR, and LCR values of the same group were also significantly different ($p < 0.05$).* **Conclusion:** *DRR can be used as a biomarker for early diagnosis of bowel necrosis in patients with IIH.*

Keywords: *De Ritis ratio. Bowel necrosis. Incarcerated. Inguinal. Hernia.*

Resumen

Antecedentes: *El diagnóstico temprano del segmento intestinal necrótico resultante de una hernia inguinal incarcerada es crucial para reducir la morbilidad y la mortalidad.* **Objetivo:** *Investigar la eficacia del índice de De Ritis (IDR), también conocido como cociente de aspartato aminotransferasa a alanina aminotransferasa, como biomarcador de necrosis intestinal.* **Método:** *Estudio retrospectivo que incluyó a 132 pacientes que fueron intervenidos de urgencia por hernia inguinal incarcerada. Los pacientes se dividieron en dos grupos: los que se sometieron a resección intestinal por necrosis (grupo 1) y los que no (grupo 2). Se registraron los datos demográficos y clínicos de los pacientes. Usando los resultados de las pruebas de laboratorio, se calcularon el IDR, el índice neutrófilos-linfocitos (INL), el índice plaquetas-linfocitos (IPL), el índice linfocitos-monocitos (ILM) y el índice linfocitos-proteína C reactiva (ILPCR).* **Resultados:** *Las tasas de morbilidad, mortalidad y duración de la estancia para el grupo 1 fueron estadísticamente significativas ($p < 0.0001$). Los valores de IDR, INL, IPL, ILM, ILPCR del mismo grupo también fueron significativamente diferentes ($p < 0.05$).* **Conclusiones:** *El IDR puede utilizarse como biomarcador para el diagnóstico precoz de necrosis intestinal en pacientes con hernia inguinal incarcerada.*

Palabras clave: *Índice de De Ritis. Necrosis intestinal. Incarcerado. Inguinal. Hernia.*

***Correspondence:**
Ahmet Baris-Dirim
E-mail: drbarisdirim@yahoo.com

Date of reception: 17-05-2022
Date of acceptance: 10-10-2022
DOI: 10.24875/CIRUE.M22000627

Cir Cir (Eng). 2023;91(4):478-484
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Inguinal hernia repair is one of the most frequently performed surgical operations in general surgery practice. Inguinal hernias usually require emergency surgery if any serious complications develop. The most common complications include incarceration, strangulation, and obstruction[1]. Of patients with inguinal hernia, 10-15% require surgery for incarceration and about 15% require resection for intestinal necrosis due to strangulation[1-3]. Bowel necrosis is the most significant factor that predicts morbidity and mortality in incarcerated hernias[4]. The reported risk factors for intestinal necrosis are female gender, advanced age (> 65 years), intestinal obstruction, and femoral hernia[5]. Previous studies have reported a morbidity rate ranging from 6% to 43%, and a mortality rate ranging from 1% to 7% in patients operated for incarcerated inguinal hernia (IIH)[1,5-7]. In cases of IIH requiring emergency surgery, the time from incarceration to operation is the major prognostic factor for morbidity and mortality[7]. Therefore, early diagnosis and treatment of intestinal necrosis caused by incarcerated hernias are critical for reducing morbidity and mortality.

De Ritis ratio (DRR) was first described by Fernando De Ritis in 1957 to differentiate viral hepatitis from other icteric and anicteric liver diseases[8]. Aspartate aminotransferase (AST) is predominantly expressed in mitochondria and is abundantly present in many organs including the liver, kidney, brain, heart, and skeletal musculature, while alanine aminotransferase (ALT) is mainly found in the hepatocyte cytoplasm[9]. These two enzymes play critical roles in biological processes and reflect the link between protein and carbohydrate metabolisms[10]. These enzymes are normally released into plasma at a constant rate in healthy humans depending on the programmed hepatocyte regeneration, with a DRR of approximately 1[11]. In clinical conditions such as intestinal ischemia, where oxidative stress and mitochondrial damage occur, there is an increase in possible hepatocyte damage, altering the ratios of AST and ALT measured in blood[12].

Complete blood count (CBC) and biochemical tests such as white blood cell (WBC), neutrophil count, and C-reactive protein (CRP) have traditionally been used as markers of systemic inflammation. There are recent studies demonstrating the feasibility of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and lymphocyte-to-CRP (LCR) parameters as good markers of systemic inflammation[13-15]. Yildirim et al. reported that LCR could be used as a marker of intestinal necrosis in incarcerated hernias[16], while Xie et al.[17] reported that NLR could be used for the same purpose.

The primary aim of this study was to investigate the efficacy of DRR as an inflammatory marker for detecting intestinal necrosis in IIHs and to compare the efficacy of preoperatively measured systemic inflammatory markers with DRR for predicting intestinal necrosis.

Materials and methods

This single-center retrospective cohort study included patients who underwent an emergency operation for IIH in the General Surgery Clinic between March 11, 2015, and July 25, 2021. Only the data of patients who underwent open surgery were analyzed from the hospital data system. Patients' age, gender, hernia type, whether bowel resection was performed, mesh use, post-operative complications, length of hospital stay, and mortality status were evaluated. Moreover, CBC parameters such as WBC, platelet, neutrophil, and lymphocyte counts and biochemical parameters of AST, ALT, and CRP were recorded at the time of admission to the emergency department. NLR, PLR, LMR, LCR, and DRR were calculated using these parameters. Patients were divided into two groups: those who underwent bowel resection for necrosis (Group 1) and those who did not (Group 2). These groups were statistically compared by calculated systemic inflammatory markers and biochemical parameters to investigate their efficacy for determining intestinal necrosis.

Based on the evaluation of clinical, laboratory, and imaging examinations at emergency admission, patients with IIH who were eligible for TAXIS (a manual reduction of hernia under analgesia/sedation) procedure were attempted to be treated with reduction under analgesia and sedation, and those who achieved reduction were observed in the surgical unit for 24-48 h. Asymptomatic patients were discharged and scheduled for an elective operation. Patients with an unsuccessful TAXIS procedure underwent an emergency operation.

In the operation, bowel resection was performed on patients with intestinal necrosis due to strangulation, and mesh was used for hernia repair depending

upon the surgeon's preference. Patients undergoing laparoscopic surgery, aged < 18 years, having a recurrent inguinal hernia, scheduled for emergency surgery for reasons other than incarceration, and those with missing blood results were excluded from the study.

This study was approved by the Institutional Review Board with the approval number 86/1509. The study has been reported in line with the Strengthening The Reporting of Cohort Studies in Surgery criteria[18].

Statistical analysis

The statistical analyses of the study were carried out using the Statistical Package for the Social Sciences version 25 software. The Chi-square test was used to compare categorical variables between the groups. The Shapiro–Wilk normality test was used to check the normality distribution of continuous variables. The non-parametric Mann–Whitney U test was used to compare non-normally distributed continuous variables. The student's t-test was used if continuous variables were normally distributed.

The cutoff value of inflammatory markers for detecting necrosis was evaluated by the receiver operating characteristic (ROC) analysis. The area under the curve (AUC), ROC curves, and 95% confidence interval (CI) of the AUC were calculated. $p < 0.05$ was considered statistically significant.

Results

The mean age of the 132 patients who were operated for IIH was 61.7 (± 18.3) years. Of the patients, 111 (84.1%) had inguinal hernias and 21 (15.9%) had femoral hernias. Thirty-five patients (26.5%) had developed early post-operative complications, and 10 patients died (7.6%).

There were 45 patients (34.1%) (8 female and 37 male patients) in Group 1 (resection group) and 87 patients (65.9%) (11 female and 76 male patients) in Group 2 (non-resection group). While the mean age of the patients in Group 1 was 66.7 (± 19.4) years, the mean age of the patients in Group 2 was 59.2 (± 17.3). Although there was no statistically significant difference, the mean age and male sex ratio of the patients in Group 1 were higher ($p = 0.346$ and $p = 0.426$, respectively).

There was a statistically significant difference between the two groups in terms of morbidity, mortality, mesh use, and length of hospital stay ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). While the morbidity and mortality rates were higher and the length of hospital stay was longer in Group 1, the rate of mesh use was higher in Group 2. Table 1 illustrates detailed information on the demographic and clinical parameters of the patients.

In Group 1 patients, the morbidity rate was 51.1%. The most common complication was infection with 22.2%, and the mean length of hospital stay was 9.3 (± 8.2) days. In Group 2 patients, the morbidity rate was 14.9%. Pulmonary complications (4.6%) and wound site hematoma (4.6%) were the most common complications, and the mean length of hospital stay was 3.8 (± 3) days.

Of the 10 patients (7.6%) who postoperatively died, 6 were male and 4 were female, with a mean age of 76.7 (± 13.6) years. Nine of these patients were in the resection group, and 3 of them had femoral hernias. One patient had a positive test result for COVID-19 in the post-operative period and died from pulmonary complications on day 13 of hospitalization. One patient in the non-resection group had severe heart failure and died at the third post-operative hour. Table 2 shows the clinical information of the patients who postoperatively died.

The median (± IQRs) values of inflammatory markers at diagnosis were as follows: WBC, 12.05 (8.5-15.5) in Group 1 and 9.3 (7.2-12.5) in Group 2; CRP, 8.4 (1.5-17.9) in Group 1 and 2.1 (0.9-6.5) in Group 2; NLR, 9.25 (6.2-15.7) in Group 1 and 3.9 (2.6-7.9) in Group 2; PLR, 279.37 (145.2-427.4) in Group 1 and 160.5 (118-206.6) in Group 2; LMR, 1.475 (0.8-2.5) in Group 1 and 2.39 (1.5-3.2) in Group 2; LCR, 0.121 (0.05-0.4) in Group 1 and 0.76 (0.2-1.7) in Group 2; and DRR, 1.945 (1.3-2.2) in Group 1 and 1.36 (1.05-1.7) in Group 2. The comparison of these values showed a statistically significant difference between the two groups ($p = 0.027$, $p = 0.04$, $p < 0.0001$, $p < 0.0001$, $p = 0.001$, $p < 0.0001$, and $p = 0.001$, respectively) (Table 3).

The comparison of inflammatory markers by ROC analysis results showed NLR, PLR, and DRR as the most significant markers for predicting bowel necrosis (AUC = 0.767, 0.697, 0.684, and respectively). The ROC analysis results of these three markers are shown in figure 1.

A DRR cutoff value of 1.94 had a sensitivity of 50% and a specificity of 83.9% (AUC, 0.684; 95% CI, 0.588-0.781; $p = 0.001$), an NLR cutoff value of 6.66 had a sensitivity of 71.1% and a specificity of 92%

Table 1. Comparative demographic and clinical characteristics of patients who underwent emergency inguinal hernia surgery

Characteristics	Total n = 132 (%)	Group 1 (with intestinal resection) n = 45 (34.1%)	Group 2 (without intestinal resection) n = 87 (65.9%)	p-value
Age, mean year (± SD)	61.7 (± 18.3)	66.7 (± 19.4)	59.2 (± 17.3)	0.346*
Gender				
Male	113 (85.6)	37 (82.2)	76 (87.4)	0.426†
Female	19 (14.4)	8 (17.8)	11 (12.6)	
Post-operative complications				
Infection	12 (9.1)	10 (22.2)	2 (2.3)	**< 0.0001†**
Pulmonary	10 (7.6)	6 (13.3)	4 (4.6)	
Hematoma	6 (4.5)	2 (4.4)	4 (4.6)	
Seroma	4 (3.0)	2 (4.4)	2 (2.3)	
Cardiac	3 (2.3)	2 (4.4)	1 (1.1)	
Morbidity				
Yes	36 (27.3)	23 (51.1)	13 (14.9)	**< 0.0001†**
No	96 (72.7)	22 (48.9)	74 (85.1)	
Hernia type				
Inguinal	111 (84.1)	36 (80)	75 (86.2)	0.355†
Femoral	21 (15.9)	9 (20)	12 (13.8)	
Mesh				
Yes	81 (61.4)	16 (35.6)	65 (74.7)	**< 0.0001†**
No	51 (38.6)	29 (64.4)	22 (25.3)	
Mortality				
Yes	10 (7.6)	9 (20)	1 (1.1)	**< 0.0001†**
No	122 (92.4)	36 (80)	86 (98.9)	
Length of hospital stay, mean day (± SD)	5.68 (± 6)	9.3 (± 8.2)	3.8 (± 3)	**< 0.0001***

*Mann–Whitney U test.
†Pearson Chi square test.
Bold fonts designate statistical significance.

Table 2. Characteristics of patients who underwent emergency inguinal hernia surgery with post-operative mortality

Patients	Gender	Age (year)	Hernia type	Comorbidity	Surgical Procedure	Morbidity	Length of hospital stay (day)
1.	Male	91	Femoral	Cardiac	SSBRA	Pulmonary (COVID test result positivity)	13
2.	Male	75	İnguinal	Pulmonary	SSBRA	Sepsis	2
3.	Female	89	Femoral	Cardiac	SSBRI	Neurological	42
4.	Male	45	İnguinal	-	SSBRI	Sepsis	2
5.	Male	78	İnguinal	Cardiac	-	Cardiac	3 h
6.	Male	63	İnguinal	-	SSBRI	Sepsis	12
7.	Male	83	Femoral	Diabetes, Cardiac	SSBRA	Cardiac	2
8.	Male	76	İnguinal	Cardiac	SSBRA	Pulmonary	9
9.	Female	84	İnguinal	Cardiac	SSBRA	Pulmonary	18
10.	Female	85	İnguinal	Renal, Cardiac	SSBRA	Pulmonary	11

SSBRA: segmenter small bowel resection and anastomosis; SSBRI: segmenter small bowel resection and ileostomy.

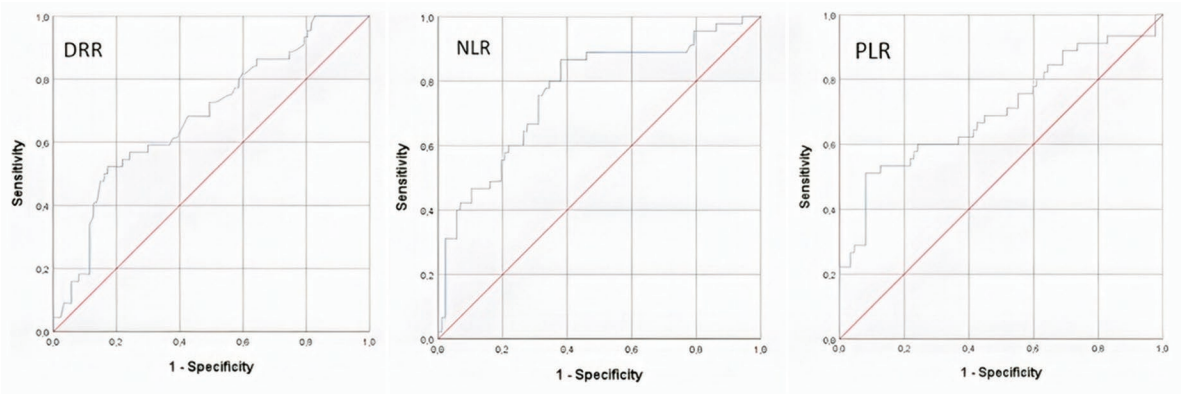

Figure 1. *ROC analysis for De Ritis ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio.*

Table 3. Comparison of the laboratory test results of the groups at the time of diagnosis

Inflammatory marker	Group I (with intestinal resection) n: 45 Median (± IQRs)	Group II (without intestinal resection) n: 87 Median (± IQRs)	p
WBC	12.05 (8.5-15.5)	9.3 (7.2-12.5)	**0.027***
CRP (mg/dL)	8.4 (1.5-17.9)	2.1 (0.9-6.5)	**0.04***
NLR	9.25 (6.2-15.7)	3.9 (2.6-7.9)	**< 0.0001***
PLR	279.37 (145.2-427.4)	160.5 (118-206.6)	**< 0.0001***
LMR	1.475 (0.8-2.5)	2.39 (1.5-3.2)	**0.001***
LCR	0.121 (0.05-0.4)	0.76 (0.2-1.7)	**< 0.0001***
DRR	1.945 (1.3-2.2)	1.36 (1.05-1.7)	**0.001***

Bold fonts designate statistical significance.
*Mann–Whitney U test.
IQRs: interquartile ranges; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; LCR: lymphocyte-to-CRP ratio; DRR: De Ritis ratio.

Table 4. ROC curve results and sensitivity and specificity values

Values	NLR	PLR	DRR
Cutoff	6.66	289.10	1.94
p-value	< 0.0001	< 0.0001	0.001
AUC (95% CI)	0.768 (0.681-0.855)	0.703 (0.602-0.804)	0.684 (0.588-0.781)

CI: confidence interval.

(AUC, 0.768; 95% CI, 0.681-0.855; p < 0.0001), and a PLR cutoff value of 289.1 had a sensitivity of 51.1% and a specificity of 92% (AUC, 0.703; 95% CI, 0.602-0.804; p < 0.0001) for predicting necrosis in patients with IIH undergoing small bowel resection (Table 4).

Discussion

An incarcerated hernia is the entrapment of abdominal tissue within the hernial sac. The risk of strangulation due to incarceration increases as the emergency surgery is delayed. Perforation and sepsis may develop secondary to necrosis, leading to a life-threatening clinical situation[6].

Comorbid diseases and post-operative mortality increase with age[19]. In this study, the mean age of the resection group was higher than that of the non-resection group, while the rate of femoral hernia was lower. Both of these results contradict some reported literature data[16,17]. This is thought to be due to the fact that elective inguinal hernia surgeries may have been postponed due to the number of increased comorbid diseases with age and the COVID-19 pandemic.

Previous studies have reported that emergency hernia surgery was performed more frequently in men and bowel necrosis was higher in women. In the current study, emergency hernia repair and bowel resection were performed more frequently in male patients[20,21]. The rate of mesh use was significantly higher in Group 2 patients who did not undergo bowel

resection ($p < 0.0001$). This can be attributed to not preferring the use of mesh in Group 1 patients due to the risk of infection by the surgeon.

In the present study, the rate of performing bowel resection was 34.1% among patients with IIH who underwent emergency surgery, and the mortality rate was 7.6%, which was higher than those reported in the literature[1,16]. This high mortality rate may be due to the fact that our hospital is a tertiary referral center serving a population of 4.5 million people, where complicated patients are referred for management, and that the study period covers approximately 1.5 years of the COVID-19 pandemic when hospital admissions were delayed[1,22].

In the case of inflammation, an increase in neutrophil count, accordingly associated lymphopenia, and an increase in CRP levels are expected[16]. Most of the previous studies conducted to predict bowel necrosis have focused on acute mesenteric ischemia, reporting that CRP, WBC, and NLR values are significant for prognosis[23,24]. Performing bowel resection for necrosis in incarcerated hernias increases post-operative morbidity and length of hospital stay, as in our study[2].

The present study demonstrates the feasibility of a novel biomarker, DRR, as an inflammatory biomarker for early prediction of bowel necrosis in patients with IIH, unlike the literature data reported so far. In addition to DRR, the resection group had significantly different WBC, CRP, NLR, PLR, LMR, and LCR values, which is consistent with the literature data.

In some studies, an increased DRR has been associated with the prognosis of urothelial carcinoma, cholangiocarcinoma, renal cell carcinoma, gastric adenocarcinoma, and head-and-neck cancer[25-30]. Cancer cells exhibit a higher rate of aerobic glycolysis in order to multiply faster than normal cells[31]. AST plays an essential role in the mitochondrial displacement of nicotinamide adenine dinucleotide hydrogen in aerobic glycolysis via the malate aspartate shuttle[10]. Therefore, an increase is observed in AST activation of fast-growing tissues such as cancer cells[32]. Some studies have also used DRR to predict the risk of liver fibrosis and liver damage secondary to the hepatitis C virus[33,34].

Weng et al. found that an increased DRR was independently associated with the risk of developing cardiovascular disease, especially in men[35]. An elevated serum AST level is also an important marker in systemic conditions such as metabolic syndrome, sarcopenia, and increased oxidative stress, which are risk factors for mortality apart from liver damage[36]. Elinav et al. found a decrease in ALT levels, especially in men over 70 years of age, throughout a 12-year follow-up period, reporting that it was significantly associated with mortality, although multivariate regression analysis revealed that diabetes, chronic renal failure, and malignancy were strong predictors of mortality[37].

We think that the higher male ratio and the higher mean age of patients in the resection group than the non-resection group in the present study may be associated with increased DRR, which is in line with the literature data, indicating that ALT values may be decreased in the male gender and elderly population[37].

Although we cannot clearly reveal the underlying mechanism of increased DRR for predicting intestinal necrosis in light of the literature, we can consider that the development of intestinal necrosis may have triggered the dysfunction of the hepatic inflammatory pathway activated by catecholamines at the mitochondrial level, leading to liver damage with increased oxidative stress[38,39].

This study has some limitations. First, the study has a retrospective design. Second, it was not known whether the patients included in the study had a history of liver disease. However, this study is the first to propose that the DRR can be used as a predictor of bowel necrosis in IIHs. In this sense, we believe that our work is valuable.

Conclusion

Based on all clinical findings, laboratory and radiological imaging results obtained by the examination of patients with IIH, the prognosis can be predicted and a decision can be made. We are of the opinion that in addition to the examination findings to predict bowel necrosis, monitoring the DRR with serial AST and ALT measurements during the follow-up when radiological imaging fails to provide adequate results or after manual reduction of the hernia is successful may shorten the diagnosis time and speed up the surgical intervention in these patients.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

The effects of health belief model-based intervention on nurses' sterilizing practices when moistening surgical instruments

Los efectos de la intervención basada en el modelo de creencias de salud en las prácticas de esterilización de las enfermeras al humedecer los instrumentos quirúrgicos

*Ruixue Hu[1,2], Yanhua Chen[1,2], Ting Hu[1,2], and Liangying Yi[1,2]**

[1]Department of Sterile Processing Nursing, West China Second University Hospital, Sichuan University/West China School of Nursing, Sichuan University; [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education. Chengdu, Sichuan, China

Abstract

Objective: *We investigated the effects of the Health Belief Model (HBM)-based intervention on nurses' behaviors in terms of keeping surgical instruments moist.* **Materials and methods:** *Pre- and post-training surveys about instrument moistening were conducted with the same 356 nurses from a hospital in China. Both of the surveys contained questionnaire concerning general knowledge relating to instrument moistening, perception scale-based questions concerning the same issue, and an inspection form concerning the implementation of moistening procedures. Three months' training was provided for the nurses.* **Results:** *After training, the nurses' knowledge, attitudes, beliefs, and behaviors for instrument moistening were improved.* **Conclusions:** *The HBM-based intervention can bring about a significant improvement in nurses' compliance with surgical instrument moistening requirements, and corresponding improvements in instrument cleanliness and patient safety.*

Keywords: *Surgical instruments. Health belief model. Self-efficacy. Surveys and questionnaires.*

Resumen

Objetivo: *Investigar los efectos de la intervención basada en el modelo de creencias de salud en los comportamientos de las enfermeras en términos de mantener húmedos los instrumentos quirúrgicos.* **Método:** *Se realizaron encuestas previas y posteriores a la capacitación sobre la humectación de instrumentos con las mismas 356 enfermeras de un hospital en China. Ambas encuestas contenían un cuestionario sobre el conocimiento general relacionado con la humectación del instrumento, preguntas basadas en escalas de percepción sobre el mismo tema y un formulario de inspección sobre la implementación de los procedimientos de humectación. Se proporcionó una formación de 3 meses a las enfermeras.* **Resultados:** *Después de la capacitación se mejoraron los conocimientos, las actitudes, las creencias y los comportamientos de las enfermeras para la humectación del instrumento.* **Conclusiones:** *La intervención basada en el modelo de creencias en salud puede generar una mejora significativa en el cumplimiento de los requisitos de humectación del instrumental quirúrgico por parte de las enfermeras, y las correspondientes mejoras en la limpieza del instrumental y la seguridad del paciente.*

Palabras clave: *Instrumental quirúrgico. Modelo de creencias sobre la salud. Autoeficacia. Encuestas y cuestionarios.*

***Correspondence:**
Liangying Yi
E-mail: yiliangying88@163.com

Date of reception: 29-07-2022
Date of acceptance: 19-10-2022
DOI: 10.24875/CIRUE.M22000628

Cir Cir (Eng). 2023;91(4):485-490
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Thorough cleaning of surgical instruments is the key to successful disinfection and sterilization[1]. However, in practice, owing to various reasons, surgical instruments might not always be collected and cleaned timeously after use, resulting in the surfaces of instruments and those of articulation, grooves, slits, and lumen dry and remaining contaminated. The longer these surfaces remain uncleaned, the more difficult it is to remove the contaminants. Dried organic residue such as blood stains, sticky fluids, and proteins adhering to these instruments can easily form a biofilm, which is resistant to disinfection procedures[2]. The guidelines stipulate that the operating room staff using surgical instruments shall decontaminate these instruments and moisten them in a timely manner after use to improve cleaning efficiency and prolong the service life of the instrument[3-5].

The moisturizing methods commonly used by the operating room staff using surgical instruments include soaking the instrument with cleaning solution, rinsing the instrument with normal saline, or spraying a moisturizing agent on the instrument[6-8]. After the instrument is delivered to the central sterile supply department (CSSD) of the hospital, standard cleaning procedures including brushing and ultrasonic cleaning must be carried out[3].

In our study, we examined a sample of instruments, and found that some were not moistened immediately after use or were not moistened properly; residues were especially pronounced around the articulation, grooves, and lumen. The contaminants on the collected instruments were found to have dried severely, making cleaning difficult. Our survey among the nurses in our hospital shows that some of the nurses were not fully aware of the necessity of having the instruments moisturized immediately after use, and were not fully acquainted with the method of moisturizing. The results of this study demonstrate the need for raising nurses' awareness of the importance of keeping surgical instruments moist to increase decontamination efficiency and raise the moistening and cleaning pass rates. The Health Belief Model (HBM) is an important theoretical model based on social psychology designed to explore the influence of individual subjective psychological processes on people's behavior, which has been widely used in behavioral research[9,10]. The aim of this study is to investigate the effects of HBM-based intervention on nurses' behaviors in terms of keeping surgical instruments moist.

Materials and methods

Participants

A total of 356 nurses from the clinical departments of a Tertiary A hospital in Chengdu, Sichuan, China participated in this study between August and December 2019. Inclusion criteria: the nurses who were working in the clinical departments of the hospital and were responsible for moistening the surgical instruments after use. Exclusion criteria: (1) the nurses who were not responsible for moistening the surgical instruments after use; (2) the nurses who did not agree to participate in our study.

Theory

The HBM, first proposed by the US psychologist Hochbaum and revised by Rosenstock[11], consists of five components: perceived severity, perceived susceptibility, perceived benefits, perceived barriers, and self-efficacy. In the analysis of nurses' behaviors for keeping surgical instruments moist, these HBM components can be translated into the following: "perceived susceptibility that surgical instruments were not kept moist," "perceived severity of not keeping surgical instruments moist," "perceived benefits of keeping surgical instruments moist," "perceived barriers for keeping surgical instruments moist," and "increase self-efficacy in keeping surgical instruments moist."

Survey tools

Pre- and post-training surveys about the surgical instrument moistening protocol were distributed among 356 nurses. Both of the surveys contained three parts: (1) questionnaire concerning general knowledge relating to keeping surgical instruments moist; (2) perception scale-based questions concerning the same issue; and (3) an inspection form concerning the implementation of moistening procedures. The pre-training survey was conducted in August 2019. The same 356 nurses then received 3 months' training on keeping surgical instruments moist from September to November 2019, and then completed the post-training survey in December 2019.

The questionnaire concerning general knowledge relating to keeping surgical instruments moist consisted

of 10 questions regarding the definition of biofilm, the optimal time to moisten the instrument, where the moisturizing agent should be sprayed on when adopting spraying method, the ratio of the volume occupied by the instruments in the collection box to the volume of the collection box when adopting spraying method, correct moisturizing method for keeping lumen instruments moist, what operating room staff should do on surgical instruments after surgery, benefits of keeping surgical instruments moist, moisturizing methods, what dried blood on the surface of the instrument will result in if the instrument was not moistened after use, and protection measures for occupation exposure. The questionnaires contained single-choice and multiple-choice questions. A correct answer earned 10 points and an incorrect answer earned 0 point. The full marks of this questionnaire were 100.

The design of our perception scale in terms of keeping surgical instruments moist was based on the HBM, as well as relevant literature, books, and reports. It consists of 5 constructs: perceived severity of not keeping surgical instruments moist (6 questions), perceived susceptibility that surgical instruments were not kept moist (6 questions), perceived benefits of keeping surgical instruments moist (8 questions), perceived barriers for keeping surgical instruments moist (9 questions), and self-efficacy in keeping surgical instruments moist (7 questions) (total 36 questions). The 5-point Likert scale was used for scoring. For the questions about perceived severity, perceived susceptibility, and perceived benefits, 5 = Very good, 4 = Good, 3 = Average, 2 = Poor, and 1 = No knowledge; for the questions about perceived barriers, 5 = Strongly agree, 4 = Agree, 3 = Somewhat agree, 2 = Somewhat disagree, and 1 = Disagree; for the questions about self-efficacy, 5 = Extremely likely, 4 = Likely, 3 = Somewhat likely, 2 = Somewhat unlikely, and 1 = Unlikely. The scale-level content validity index was 0.833, construct validity (Kaiser–Meyer–Olkin index) was 0.933, Bartlett's test of sphericity value was 12136.637, $p < 0.001$, and Cronbach's alpha coefficient of internal consistency reliability was 0.911, indicating a high level of reliability and validity.

The inspection form concerning the implementation of moistening procedures was composed of 2 sections. Section 1 consisted of the questions regarding which campus and which department that the respondent worked in, as well as the respondent's age, length of service, educational background, and job title. Section 2 contained 4 open-ended questions regarding name of the surgical procedure, name of the surgical pack, the end date and end time of the surgery, and time of moistening the instruments, and 11 close-ended questions regarding the place of moistening the instruments, job position of the person responsible for moistening, moistening method, moisturizing liquid, who supplied the moisturizing liquid, whether the moisturizing liquid was prepared in conformity with the manufacturer's instruction, type of the moisturizing liquid for spray, spray methods, and where the moisturizing liquid was sprayed on, the reasons why moistening procedures failed, and the reasons why the instruments were not moistened.

Data collection

The online questionnaires were produced through WJX, a Chinese survey app. A total of 356 pre-training questionnaires were distributed, and 356 pre-training questionnaires were returned, of which 351 pre-training questionnaires were valid; thus, the valid response rate was 98.60%. Health instructors from CSSD delivered the 3 months' training to the 356 nurses. Intervention measures included regular seminars on the rationale behind surgical instrument moistening procedures, optimal time for moistening, moisturizing methods, and on minimizing occupational exposure during moistening. In addition, brochures describing the importance of keeping instruments moist were distributed to the 356 nurses, videos about keeping instruments moist were provided for them, and a follow-up session was carried out every week during the 3-month training period. After the 3 months' training period, the post-training questionnaires were distributed to the 356 nurses, of which 356 valid post-training questionnaires were returned (valid response rate was 100%).

Statistical methods

Data analysis was conducted in SPSS 21.0. The measurement data was expressed as the standard deviation of the mean. t-test and linear regression analyses were conducted on the pre- and post-training effect data. $p < 0.05$ indicates a statistically significant difference.

Results

Since 351 of the 356 completed pre-training questionnaires were valid, even though all 356 completed

post-training questionnaires were valid, the results below are based on a sample size of n = 351.

Demographic data

The 351 nurses' average length of service was (7.60 ± 8.204) years. Of them, 275 (78.35%) had bachelor's degree qualifications, and 169 (48.15%) were nurse practitioners, as shown in table 1.

Change in nurses' knowledge, attitudes, and beliefs after training period

In general, the nurses' knowledge, attitudes, and beliefs concerning surgical instrument moistening improved during the course of the training period, as evidenced by increases in total scores and scores for individual components, as shown in tables 2 and 3.

Influence of job title, educational background, and length of service

The results in table 4 indicate connections between the nurses' degree of knowledge before the training period, and their attitudes and beliefs concerning surgical instrument moistening as well as their educational background. The higher their educational attainment, the more positive their attitude toward moistening, and the higher their knowledge score. The knowledge score after training is mainly a reflection of their attitude toward moistening. The results in table 5 show that the nurses' attitudes toward moistening before training are associated with the length of service, educational background, and knowledge of moistening. The nurses with longer lengths of service, higher educational attainment, and greater knowledge of surgical instrument moistening generally showed a more positive attitude towards moistening. After training, the main determinant of nurses' attitudes towards surgical instrument moistening appears to be their knowledge of moistening.

Change in nurses' behaviors during training

Before training, moistening implementation and pass rates among the nurses were 57.25% and 32.38%, respectively. After training, moistening implementation and pass rates had increased to 96.54% and 92.16%, respectively, which revealed a significant improvement in the nurses' behaviors in keeping surgical instruments moist.

Table 1. Demographic data (n = 351)

Item	Number	Assignment	Percentage
Length of service			
< 1 year	15	1	4.27
1-5 years	185	2	52.71
6-10 years	57	3	16.24
11-15 years	39	4	11.11
16-20 years	25	5	7.12
> 20 years	30	6	8.55
Educational background			
Junior college diploma and below	60	1	17.09
Bachelor	275	2	78.36
Master and above	16	3	4.56
Job title			
Nurse	94	1	26.78
Nurse practitioner	169	2	48.15
Supervisor nurse and above	88	3	25.07

Table 2. Comparison of nurses' knowledge, attitudes, and beliefs before and after training about keeping surgical instruments moist (n = 351, $\bar{x}$ ± S)

Time	Knowledge of keeping surgical instruments moist	Attitudes and beliefs in keeping surgical instruments moist
Before training	67.48 ± 12.805	139.93 ± 15.145
After training	89.27 ± 16.844	151.57 ± 15.264
t-value	−17.046	−10.143
p-value	0.001	0.001

Discussion

Zhang et al.[12] pointed out that modern health education, the purpose of which is to change people's behavior, focuses on integration and union of "knowledge, attitudes, beliefs and behaviours." Knowledge is essential; without it, it is impossible for the reader to exert oneself when they do not know how their exertions are to be directed. Attitude is the driving force for behavior change. Our study demonstrates that the nurses had developed a more comprehensive understanding of the necessity of keeping surgical instruments moist, and that the training period led to an improvement in their attitudes and beliefs regarding the same issue. Regardless of their length of service and educational background, their awareness of the importance of keeping surgical instruments moist had increased noticeably during the 3-month period.

Table 3. Comparison of Scores of the HBM constructs before and after training about keeping surgical instruments moist

Time	Perceived severity	Perceived susceptibility	Perceived benefits	Perceived barrier	Self-efficacy
Before training	26.99 ± 3.446	24.50 ± 1.998	36.54 ± 4.186	22.78 ± 8.509	29.12 ± 4.662
After training	28.14 ± 2.868	27.70 ± 2.901	38.73 ± 2.229	31.22 ± 8.509	32.88 ± 2.643
Glass delta	0.40	1.10	0.98	0.99	1.42
t-value	−2.974	−17.000	−2.429	−13.148	−4.070
p-value	0.003	0.001	0.016	0.002	0.001

Table 4. Multivariate analysis of knowledge score

Variable	Pre-training				Post-training			
	b-value	b-value standard error	t-value	p-value	b-value	b-value standard error	t-value	p-value
Length of service	2.535	1.333	1.902	0.058	−1.199	1.075	−1.115	0.266
Educational background	3.041	1.329	2.288	0.023	1.627	2.491	0.653	0.514
Job title	3.175	2.529	1.255	0.210	−1.012	2.181	−0.464	0.643
Attitude and belief score	3.766	1.385	2.719	0.007	1.557	0.681	2.286	0.023

Table 5. Multivariate analysis of attitude and belief score

Variable	Pre-training				Post-training			
	b-value	b-value standard error	t-value	p-value	b-value	b-value standard error	t-value	p-value
Length of service	2.899	1.434	2.022	0.044	−1.061	0.907	−1.170	0.243
Educational background	3.474	1.733	2.005	0.046	2.931	1.793	1.635	0.103
Job title	3.485	1.819	1.915	0.056	−3.002	1.713	−1.752	0.081
Knowledge score	3.993	1.379	2.896	0.004	1.078	0.503	2.144	0.041

The results in tables 2 and 3 show that many of the nurses lacked the necessary knowledge of surgical instrument moistening before training, and also had poor attitudes and negative beliefs. The shorter the length of service and the lower the educational attainment, the poorer their knowledge and the more negative their attitude. During the study, we established a multidisciplinary team composed of head nurses from in-patient operating rooms, CSSD, and outpatient operating rooms. The team explained to the nurses the importance, benefits, and operating procedures of, and precautions surrounding, surgical instrument moistening[13]. For the practical training sessions, the team developed a standard operating procedure for keeping instruments moist and produced on-site guidance for the nurses responsible for instrument moistening. For theoretical training, the team first provided training for the key nurses of the clinical departments, and then such nurses provided training for other nurses in their respective departments, thus accelerating the dissemination of knowledge of surgical instrument moistening procedures across the nursing pool. For departments with more advanced personnel coordination, such as the department of obstetrics, the CSSD staff members were reassigned to these departments to handle moistening procedures. In summary, this study has shown that HBM intervention can lead to significant improvements in surgical instrument moistening implementation and pass rates among nursing personnel.

Conclusions

The findings of this case study indicate that HBM-based intervention can bring about a significant improvement in nurses' compliance with surgical instrument moistening requirements, and corresponding improvements in instrument cleanliness and patient safety. However, this study has one major limitation: because the intervention lasted only for a short period (3 months), we are unable to determine the long-term effect of the intervention. A follow-up study entailing a longer intervention period is therefore required.

Acknowledgments

The authors would like to thank the 356 nurses who actively participated in this study, and we also express gratitude to the clinical departments of the hospital for their cooperation.

Funding

The authors declare that this study was supported by the Sichuan Provincial Health Department [no. 100374].

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Renal transplant waiting list mortality in COVID era: is it advisable to halt transplant activity?

Mortalidad en lista de espera de trasplante renal en la era COVID: ¿pausar actividad de trasplante?

Jorge Martínez-Ulloa-Torres[1], Paulo Gutiérrez-Torres[1], Pablo Castro-Ruiz[1], Patricia B. Bolado-García[2], Mariano Hernandez-Dominguez[3], Luis F. Aguilar-Castillejos[4], Mauro E. Tun-Abraham[5], and Juan P. Baas-Cruz[6]*

[1]Servicio de Trasplantes, Unidad Médica de Alta Especialidad, "Ignacio García Téllez", Centro Médico Nacional, Instituto Mexicano del Seguro Social (IMSS), Merida, Yucatan; [2]División de Investigación en Salud, Unidad Médica de Alta Especialidad, "Ignacio García Téllez", Centro Médico Nacional, IMSS, Merida, Yucatan; [3]Kidney Transplant Service, Hospital Ángeles Lomas, Mexico City; [4]Kidney Transplant Service, Hospital Star Medica, Merida, Yucatan; [5]Transplant Service, Centro Médico Vossan, Campeche, Campeche; [6]Department of Nephrology in Transplants, Centro Estatal de Trasplantes de Yucatán, Merida, Yucatan. Mexico

Abstract

Introduction: *Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD). Since March 2020, transplant activity in Mexico has been affected due to the COVID-19 pandemic.* **Objective:** *The aim of the study was to determine the impact on mortality of patients on the waiting list (WL) for cadaveric donor kidney transplantation in a referral hospital in Yucatán, due to suspension of activities due to the pandemic.* **Material and methods:** *Patients over 18 years of age on the waiting list for kidney transplantation at this hospital. In the event of a patient's death, the cause was investigated, especially if it was associated with COVID-19. A two-tailed $p \leq 0.05$ was considered significant in all analyzes.* **Results:** *The odds ratio (OR) of death from COVID-19 in a patient with ESRD in the WL in 2020 was OR = 5.04 (95% CI: 1.65-7.14, p = 0.023). The OR of dying with ESRD in the WL with a delay in the follow-up visits was OR = 6.59 (95% CI: 2.7-16.28, p = 0.008).* **Conclusion:** *The probability of death of a patient with ESRD with delayed follow-up visits and transplant retention is statistically higher than the probability of death from COVID-19.*

Keywords: *COVID-19. End stage renal disease. Kidney transplant. Waiting list mortality.*

Resumen

Introducción: *El trasplante renal es el tratamiento de elección de la enfermedad renal en etapa terminal (ERT). Desde marzo de 2020, la actividad de trasplantes en México se ha visto afectada debido a la pandemia de COVID-19.* **Objetivo:** *Determinar el impacto en la mortalidad de pacientes en lista de espera (LE) para trasplante renal de donante cadavérico en un hospital de referencia en Yucatán, por suspensión de actividades debido a la pandemia.* **Material y métodos:** *Pacientes > 18 años en LE para trasplante renal en este hospital. En caso de muerte de un paciente, se investigó la causa, especialmente si estaba asociada a COVID-19. Un valor de p de dos colas ≤ 0.05 se consideró significativo en todos los análisis.* **Resultados:** *La razón de probabilidad de muerte por COVID-19 en un paciente con ERT en la LE en 2020 fue OR = 5.04 (IC 95%: 1.65-7.14, p = 0.023). La razón de probabilidad de morir con ERT en la LE con retraso en las consultas de seguimiento fue de OR = 6.59 (IC 95%: 2.7-16.28, p = 0.008).* **Conclusión:** *La probabilidad de muerte de un paciente con ERT en la LE con retraso en las consultas de seguimiento y retención del trasplante es estadísticamente más alta que la probabilidad de muerte por COVID-19.*

Palabras clave: *COVID-19. Enfermedad renal crónica terminal. Trasplante renal. Mortalidad de lista de espera.*

***Correspondence:**
Jorge Martínez-Ulloa-Torres
E-mail: jorge.martinezu@imss.gob.mx

Date of reception: 17-09-2021
Date of acceptance: 14-01-2022
DOI: 10.24875/CIRUE.M22000629

Cir Cir (Eng). 2023;91(4):491-497
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Transplant activity in Mexico is coordinated centrally and close to 3000 renal transplants that are performed across the country, with over 550 brain-dead organ donors every year[1]. Kidney transplantation represents the treatment of choice for patients with end-stage renal disease (ESRD) but, worldwide, organ availability has decreased significantly, directly, or indirectly associated with the severe acute respiratory syndrome coronavirus pandemic 2 (SARS-CoV-2)[2-4].

The pandemic has limited the access for patients with kidney disease to continue with the transplant protocol; by health policies and the fear of contagion and its consequences, reason why they have stopped going to their medical units. This, together with the level of kidney damage and the crisis derived from the lack of donors, has contributed to ineffective control and monitoring culminating in accelerated organic deterioration leading to death. It should be kept in mind that during outbreaks, medical staff and health-care capacity might be inadequate if massive widespread occurs, and this will adversely affect the quality of patient care[5].

A study conducted in Spain reported that the average number of transplants performed in 2019 decreased considerably in the first months of 2020[6]. In Mexico, organ procurement surgeries have been severely affected as of the second quarter (Q2) of 2020, with zero multi-organ donations throughout the country. On the ongoing months until December (Q2-Q4), 51 multiple organ donations were performed, 88% less than the previous year with 433.

The state of Yucatan was not the exception in this struggle; during 2020, only two brain-dead organ donors procurement surgeries were done, while on a yearly basis are performed 9-20. Regarding living donor kidney transplantation, it has also been halted at almost all centers and a limited number of units have been able to resume some activity[7].

There are different reasons that explain the decrease in donation and transplantation activities during the outbreak. In the context of an overwhelmed health-care system, there has also been a decline in the number of elective admissions to the hospital. The logistical problems are frequent, either associated with restricted mobility of health teams[6] or due to the restriction of outpatient medical control with the consequent delay in medical care.

Nowadays, technological improvements make it easier to reach patients at home through telemedicine practices aided by cellphones, smartphone apps, video calls, and smartwatch apps.

Considering that most ESRD patients are at high risk of developing severe COVID-19, remote follow-up access methods will help patients follow-up[5]. Patients who may not efficiently use these technologies can be followed by phone, and in case of drug changes or laboratory tests, patients should come to the hospital with appropriate precautions.

Managing kidney transplant recipients require a sustainable infrastructure that can provide reliable medical care both before and after transplantation. COVID-19 pandemic has disrupted transplantation processes, leading a decrease in the number of transplant procedures, and resulted in changes in the practice of control and follow-up before and after transplantation[8].

The impact of the pandemic has been noted in patient care, transplant centers, and national and local health policies[8]. The increase in mortality on the waiting list (WL) has become a consequence of the pandemic[6] that will continue to have a negative effect long after the pandemic has subsided. This situation should be an alert that result in the protection of patients more effectively and devise rational policies for transplant decisions and establishing a strong health system[8].

For all of the above, the aim of the study was to determine the mortality of patients on the WL for renal transplantation with a cadaveric donor in a third-level referral hospital of medical care in the state of Yucatan, Mexico. The purpose was to demonstrate the impact derived from the suspension of activities associated with the care of kidney disease, as well as to compare the risk-benefit of accessing a kidney transplant, in the context of the pandemic, with remaining on the WL without medical follow-up.

Materials and methods

A retrospective study was carried out with patients under a kidney transplant protocol from a tertiary hospital in the state of Yucatan, Mexico and who died. Data from February 2019 to March 2021 were analyzed.

Patients ≥ 18 years of age, who were on the national computer system WL and who were contacted by telephone were included in the study. The variables included were sex, age, body mass index (BMI), blood type, duration of renal replacement therapy (RRT),

etiology of chronic kidney disease, and comorbidities. Patients who died in the aforementioned period were considered. As a cause of death, COVID-19, complications typical of kidney disease, acute myocardial infarction (AMI), and other causes were considered.

The information was divided into two periods, from February 2019 to February 2020, and from March 2020 to March 2021. The mortality data from both periods were compared with each other considering those from 2019-2020 as patients with medical care comprehensive and 2020-2021 as patients with delay in their medical care.

Descriptive statistics were performed with measures of central tendency and dispersion. The data were presented in means ± SD and percentages, according to the type of variables. Kaplan-Meier analysis was performed to compare the number of deaths between both periods. $p \leq 0.05$ was considered statistically significant; a systematic error (SE) ≤ 0.05 was considered clinical significance. Odds ratio (OR) between death from COVID-19 and death from complications derived from underlying kidney disease, AMI, and other causes was calculated. In addition, the OR was calculated between deaths before the pandemic (those who underwent medical follow-up, according to the WL protocol) and those that occurred during the pandemic, that is, those who were delayed in their medical care due to the restriction admission to any of the areas of the hospital involved with their comprehensive treatment.

Results

Of the 333 patients included in the National Computer System a total of 144 were excluded because the phone number was incorrect or inactive. Of the 189 patients contacted, 50 deaths were reported, 13 between February 2019 and 2020 and 37 between March 2020 and 2021 (Fig. 1).

Demographic and clinical characteristics are described in table 1. Patients death mean age was 48.5 ± 11.4 years, 66% were men, with a BMI of 26.7 ± 4.8 (Fig. 2), and 76% on blood group 0 list, with diabetes and hypertension as the main cause of ESRD, with 4.6 ± 2.6 years on RRT, most on peritoneal dialysis (64%). Comorbidities were frequent, as shown in table 2.

About 74% of the deaths occurred during COVID-19 pandemic, but only 18% where directly related to SARS-CoV-2 infection; the majority was associated to non-COVID-19 causes. Most deaths occurred during the pandemic, they were attributed in 68% of the cases due to delay in follow-up clinic visits.

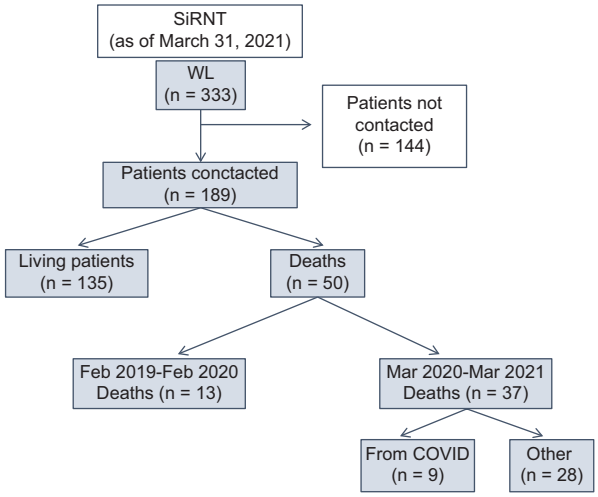

Figure 1. *Flow chart of patients anlyzed from the national computer system.The flow chart shows the selection procedure for patients admitted to the study. Many patients could not be reached by phone, making it difficult to track their outcome.*

Table 1. Baseline characteristics of deceased patients on the kidney transplant waiting list

Variables	Descriptive data
Age (years)	48.56 ± 11.42
Weight (kg)	68.44 ± 16.18
Height (m)	1.57 ± 0.1
Body mass index (kg/m^2)	26.73 ± 4.82
Duration of renal replacement therapy (years)	4.6 ± 2.6
Sex	
Men	66%
Women	34%
Blood Group	
0	76%
A	20%
B	4%
Renal Replacement Therapy modality	
Hemodialysis	36%
Peritoneal dialysis	64%
Cause of chronic kidney disease	
Hypertension	28%
Diabetes mellitus	34%
Nephrolithiasis	2%
Polycystic Kidney Disease	8%

Numerical variables are expressed as means with their standard deviation (± SD); qualitative variables are expressed as a percentage. The data correspond to a sample of 50 deceased patients.

Table 2. Distribution of comorbidities identified in deceased patients on the kidney transplant waiting list

Comorbidities	Percentage
Hypertension	60
Diabetes mellitus	42
Nephrolithiasis	2
Ischemic heart disease	6
Depression	2
Anemia	10
Hyperparathyroidism	8
Dyslipidemia	6
Number of comorbidities	
1	52
2	30
3	14
≥ 4	2

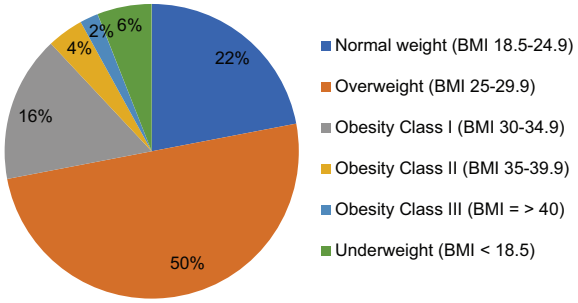

Figure 2. *Distribution by body mass index (BMI). 50% of the patients were classified as overweight; this must be studied to determine as an independent risk factor for developing severe COVID.*

COVID-19-related death risk for an ESRD patient on the WL in 2020 was OR = 5.04 (IC 95%: 1.65-7.14; p = 0.023). The OR between death for an ESRD patient on the WL and delay in follow-up clinic visits was 6.59 (IC 95%: 2.7-16.2; p = 0.008). OR for others variables is shown in table 3.

Finally, figure 3 shows the cumulative survival rate of ESRD patients on WL for kidney transplantation, whether or not they had delayed medical care during the pandemic (Fig. 3).

Discussion

During 1Q 2020, there was a reasonable fear as to whether already immune compromised transplanted population had an increased risk of severe SARS-CoV-2 or death development, which resulted in many transplant societies and regulatory agencies recommended temporary suspension of transplant activity. Mexico published their own on March 17, 2020 with very similar policies[9-11].

However, during the following months and the emerging knowledge regarding the clinical course in transplanted population, where apparently no worse prognosis developed, led to reconsideration of the measures taken. On June 2020, Mexico published a reactivation plan, which included chest CT and PCR screening. Unfortunately, the recovery of donation and transplants programs in the country was poor, unlike those reported in the US or Spain[12-14].

This disparity may correspond to the fact that the reality in emerging countries is very different from that of the first world. Kute et al.[15] mention several possible obstacles that may affect the management of pandemic outbreaks and the reactivation of transplant programs: limitations in protective equipment; high prevalence of asymptomatic infections; availability of reverse transcription polymerase chain reaction tests; isolation rooms and beds in intensive care units; functions duplicity in healthcare workers; the constant changing dynamics and waves of this pandemic; and, ultimately, the pressure on the already overwhelmed health-care system.

Despite these considerations, doubts raised as to whether recommendations for temporary suspensions of transplant activity were the best way to act in our country. The need for scientific evidence to support reactivation became a priority.

The endpoint of this study showed a 19.5% of mortality rate in ESRD patients on the WL for kidney transplantation during the last pandemic year, in comparison with a 6.8% mortality rate noted in 2019. A significant increase on the death risk developed.

One might question whether the deaths were secondary to COVID infection; however, only a quarter of them were directly associated to it. Most deaths were due to delay in medical care because of loss in follow-up clinic visits and lack of access to kidney transplantation.

The most relevant factor revealed that the risk of death because of SARS-CoV-2 infection is lower than the risk of death if the patient remains on the WL and is not transplanted. We suggest reconsidering the adopted measures in our country at the beginning of the pandemic and reactivate all transplantation programs.

Table 3. Comparison of the OR of death from delay in medical care and death from COVID-19

	OR	CI95%		p
		Lower limit	Upper limit	
OR of death from COVID-19	5.04	1.65	7.14	0.023
OR of death due to delay in medical attention*	6.59	2.7	16.28	0.008
OR of death due to complications associated with chronic kidney disease and hypertension	5.78	0.65	51.237	0.086
OR of death due to complications associated with chronic kidney disease and diabetes mellitus	3.81	0.6	24.5	0.067
OR of death due to complications associated with chronic kidney disease and ischemic heart disease	0.93	0.85	1.010	0.446 (SE 0.037)
OR of death due to complications associated with chronic kidney disease and dyslipidemia	0.38	0.39	3.72	0.41
OR of not dying due to anemia	0.89	0.79	0.99	0.313 (SE 0.041)
OR of not dying due to hyperparathyroidism	0.9	0.82	0.99	0.373 (SE 0.039)
OR of dying from the etiology of chronic kidney disease (nephrolithiasis)	0.98	0.93	1.023	0.67 (SE† 0.033)

*The concept of delay in medical care was operationally defined as the period between March 2020 and March 2021 (during the pandemic), which was characterized by the temporary suspension of comprehensive medical care provided to patients with chronic kidney disease who require transplantation, which were on the national computer system waiting list.
†Systemic error.
The ES ≤ 0.05 means that the clinical phenomenon occurs, although statistically it is not possible to confirm it, probably due to the sample size.
OR: odds ratio

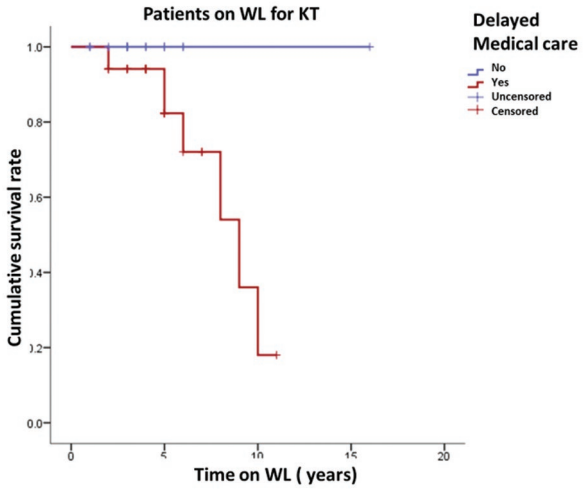

Figure 3. *Survival before and during the pandemic. The figure shows a comparison between the deaths on the waiting list for kidney transplants that occurred before and during the pandemic. (From February 2019 to February 2020, blue line; from March 2020 to March 2021, red line). There was an increase in patients who died during the pandemic due to the temporary suspension of health services because follow-up visits and transplantation were not considered a priority, such as COVID management. This policy was adopted as a measure to prevent infections caused by SARS-CoV-2 in vulnerable patient groups.*

Miller et al.[16] reported a rise in kidney WL mortality in the United States (adjusted hazard ratio [aHR], 1.37; 95% CI: 1.23-1.52), especially during the he first 10 weeks after the declaration of a national emergency. Mortality was not significantly for liver, pancreas, lung, and heart. They also hypothesized that the mortality rate increase may be due to delays in transplants.

Understanding the reasons for higher waitlist mortality among kidney candidates will require continued study. Social distancing may have been more challenging for kidney transplant candidates undergoing in-center dialysis.

Case series published in the United States with more than 400 solid organ transplant recipients have provided information on the clinical presentation of COVID-19 in this population, with mortality in the range of 6-30%[17].

Clarke et al.[18] analyzed a cohort of 1 433 patients with end-stage kidney disease, resulting that COVID-19 infection was more commonly diagnosed in the waitlist patients (p = 0.001), than on transplant population.

Pereira et al.[19] reported a series of 90 solid organ transplant recipients with COVID-19 with the following symptoms: fever (70%), cough (59%), and dyspnea (43%); 76% required hospitalization and 35% mechanical ventilation. Overall mortality was 18%. Mexican

regulatory agencies statistics as of December 21, 2020, reported 232 suspected and or confirmed COVID-19 cases in kidney transplant recipients, with 64 deaths (overall 27%)[20].

The decrease in transplant activity was not only observed in Mexico. Most transplant centers worldwide temporarily reduced the number of procedures early in the pandemic but did not stopped as in Mexico[21-23].

At the end of March 2020, a U.S. survey of 88 transplant institutions reported that 71% had temporarily stopped living donor kidney transplantation and 84% had implemented restrictions on deceased donor kidney transplantation[9].

Another report informed productivity reductions of 51% and 90% in solid organ transplantation procedures in the US and France[24]. However, at the end of 2020, the activity recovered close to that reached in the previous years; organ donation from deceased donors in the United States increased 6% over 2019. Deceased donor transplantation briefly fell approximately 50% in early April before returning to a more consistent baseline in late May. Living donor transplants decreased 22.6%[13].

The negative impact on multi-organ donation in Spain was mostly affected during the March-May 2020 period, coinciding with the worst months of the pandemic. However, according to ONT reports these have recovered to levels close to those registered in 2019[14], based on a staggered recovery, contrary to what was observed in Mexico, where activity came to an abrupt halt in March and so far, the its recovery has been very limited.

Mexico continues to be on the list of countries with high transmissibility for SARS-CoV-2[25]. In addition to this, the vast majority of first and second level care hospitals (donor recruitment centers) as well as third level and high specialty hospitals (transplantation centers) had the need to use their health-care resource converted into COVID units, severely affecting activity in the whole country, in terms of transplantation. It is necessary to review the public policy for the management of the pandemic, so that high specialty hospitals continue their transplantation activity, while other lower-level hospitals continue the care for COVID-19 patients. It is vital to adopt mitigation strategies such as donor screening, resource planning, and a staged approach to transplant volume considerations as local resource issues demand.

The management of immunosuppression in transplant patients with COVID-19 is not well defined. Current recommendations are based on reducing immunosuppression according to the severity, beginning with suspension of antiproliferatives and continue with calcineurin inhibitors, while steroids are not discontinued.

The use of any therapy for COVID-19, such as chloroquine, azithromycin, remdesivir, favipiravir, tocilizumab, convalescent plasma, and among others, should be used cautiously, based on the available evidence at least for the general population and taking into account peculiarities of the transplanted patient and possible drug interactions[26].

Conclusions

This study aims to help quantify the negative impact of the COVID-19 pandemic on ESRD patients on the WL at a hospital in Yucatán, Mexico and serves as a good example of the devastating impact on withholding organ harvesting and renal transplantation activity.

The death OR for an ESRD patient on the WL with delay in follow-up clinic visits and transplantation withhold is statistically higher than COVID-19 death OR.

The risk of dying due to lack of prompt access to transplantation is way much higher than the presumed risk of dying from COVID, so we hope that these findings can help inform new policies and specific service strategies to bring transplant activity back to previous rates.

Funding

This research did not receive any funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Efforts for detection of aortic aneurysms and human resources training for the optimization of their treatment

Esfuerzos en la detección de aneurismas aórticos y la formación de recursos humanos para la optimización de su tratamiento

Carlos A. Hinojosa-Becerril[1], Javier E. Anaya-Ayala[1], Luis Bobadilla-Rosado[1], Juan C. Arámburo-López[1], Luis Barragán-Galindo[1], Rodrigo Lozano-Corona[2], Adriana Torres-Machorro[2], and Hugo Laparra-Escareno[1]*

[1]Dirección de Cirugía, Sección de Angiología, Cirugía Vascular y Terapia Endovascular, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; [2]Dirección de Cirugía, Sección de Angiología, Cirugía Vascular y Terapia Endovascular, Instituto Nacional de Cardiología Ignacio Chávez. Ciudad de México, México

Abstract

Objective: *To review admissions, interventions and in-hospital mortality associated to Abdominal Aortic Aneurysms (AAA), and to analyze the impact of the introduction of a training program and imaging screening at our institution.* **Methods:** *Retrospective study where hospitalizations, procedures and mortality secondary to AAA were recorded. The national databases (ND) from the Secretariat of Health were utilized from 2010 to 2020. In-hospital lethality was calculated and compared with the experience at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). The statistical analysis was completed with the STATA version 17.* **Results:** *According to the ND, 899 (91%) hospital admissions secondary to AAA occurred, while in the INCMNSZ 85 (9%). Most of them belonged to the male gender (68%); 811 (82%) patients underwent open surgical repair, and 173 (18%) to an endovascular exclusion (EVAR), the latter approach was significantly more frequently performed at our institution (p = 0.007). The 30-day hospital mortality was 22.5%; in the ND was 23.9 vs. a 16.4% in the INCMNSZ without significant difference (p = 0.1).* **Conclusions:** *AAA remain unrecognized in our country. The introduction of University programs and imaging screening might impact in the early detection, and to reduce the morbidity and mortality associated to emergency procedures.*

Keywords: *Abdominal Aortic aneurysms. Ultrasonographic screening. Training of human resources.*

Resumen

Objetivo: *Revisar los ingresos, procedimientos y defunciones intrahospitalarias asociadas a aneurismas aórticos abdominales (AAA) y analizar el impacto de la introducción de programas de formación de recursos humanos y tamizaje ultrasonográfico.* **Métodos:** *Estudio retrospectivo, se analizaron las bases de datos nacionales obtenidas del portal datos abiertos de la Dirección General de Información en Salud (DGIS) del año 2010 al 2020. Se calculó la letalidad intrahospitalaria anual y comparamos la experiencia del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). El análisis estadístico se realizó en el programa STATA versión 17.* **Resultados:** *De acuerdo con la base nacional (BN), se registraron 899 (91%) ingresos, mientras que en el INCMNSZ 85 (9%). La mayoría pertenecía al sexo masculino (68%), un total de 811 (82%) pacientes fueron sometidos a cirugía abierta, mientras que 173 (18%) a terapia endovascular (EVAR), siendo este abordaje más frecuente en nuestra institución (p = 0.007). La mortalidad intrahospitalaria fue del 22.5%, en la BN fue del 23.9%, mientras que en el INCMNSZ fue del 16.4%, sin que encontráramos diferencia significativa (p = 0.1).*

***Correspondence:**
Carlos A. Hinojosa-Becerril
E-mail: carlos.a.hinojosa@gmail.com

Date of reception: 01-06-2022
Date of acceptance: 20-07-2022
DOI: 10.24875/CIRUE.M24000557

Cir Cir (Eng). 2023;91(4):498-504
Contents available at PubMed
www.cirugiaycirujanos.com

Conclusiones: *Los AAA continúan siendo poco reconocidos en nuestro país. La introducción de programas universitarios de especialidad y el tamizaje podría impactar en la reducción de la morbimortalidad.*

Palabras clave: *Aneurismas aórticos abdominales. Tamizaje ultrasonográfico. Formación de recursos humanos.*

Introduction

Abdominal aortic aneurysms (AAA) are one of the clinical entities that most frequently develop within the spectrum of conditions and disease affecting the human aorta. They are typically diagnosed when imaging modalities reveal the presence of a focal or localized dilatation with diameters > 50% of the normal diameter of this artery. The most common anatomical location of AAA is the infrarenal part of the abdominal aorta[1-3].

Multiple international studies have demonstrated that the presence of AAA increases proportionally with age, with a higher prevalence being reported in men at, or older than 65 years, and in women older than 70 years. Risk factors associated with this condition include smoking (current or prior), male gender, family history, systemic arterial hypertension, coronary and peripheral artery disease, and chronic obstructive pulmonary disease[2-4]. The prevalence of these lesions has been reported in 1.4% of the patients aged 55 to 84 years in the United States, while frequencies of up to 2% (and even as high as 8%) have been reported in men older than 65 in former studies[1,4]. Nonetheless, controversy surrounds the relatively low prevalence reported among the Latin American population of the United States, particularly Mexican-Americans, while the experience treating this condition in Mexico remains modest[5-7]. Since we launched the ultrasonographic screening program in 2015 at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), Mexico City, Mexico we have detected a prevalence of 3.29% in the at-risk population studied[7]. Subsequently, efforts have continued, and as part of an initiative by the current administration of the Mexican Society of Angiology, Vascular Surgery, and Endovascular Surgery (SMACVE), the first multicenter trial ever conducted on this subject in 9 centers has found a prevalence of AAA of 3.08%[8]. This confirmed that in the 4 metropolitan areas included in this trial, the frequency of this disease does not seem significantly different from that in at-risk populations from other international registries. This has led us to further investigate possible genetic factors in Mexican mestizo individuals at risk of developing AAA[9,10].

Rupture is undoubtedly the most feared complication of AAA and is fatal in most cases, with nearly 200 000 deaths reported worldwide attributed to this cause, and mortality rates between 70% and 80%[1,4].This underscores the importance of timely detection to allow for adequate elective planning and repair. International experience has suggested that early referral can directly impact the reduction of mortality associated with emergently performed procedures[11]. Additionally, one of the most important goals of SMACVE and the Mexican Council of Angiology, Vascular Surgery, and Endovascular Surgery in Mexico has been to promote the expansion of university residency programs with the highest international standards[12].

The objective of this study is to review admissions, procedures, surgical and endovascular techniques, and in-hospital deaths associated with AAA in Mexico and analyze the impact of the introduction of human resource training programs at INCMNSZ and ultrasonographic screening.

Materials and methods

This was an observational, retrospective trial where we first analyzed AAA related mortality nationwide, and investigated the number of hospital admissions, procedures, and AAA related in-hospital mortality among the study population. We used national databases obtained from the 'open data' portal of the General Directorate of Health Information (DGIS). We analyzed all available years in the portal for overall population deaths (from 1998 through 2020) and hospital discharges reported (from 2010 through 2020)[13]. Subsequently, data were filtered according to the ICD-10 code for AAA (I713, I714). Code I713 corresponds to AAA rupture, while I714 corresponds to AAA without mention of rupture. The variable 'medical care,' in the context of national databases, is considered positive when the patient receives any type of health care intervention by a health care professional, without necessarily implying hospital admission.

We used descriptive statistics, represented in percentages, frequencies, and rates. To obtain mortality rates per million inhabitants, we used mid-year population projections as published by the National Population Council (CONAPO)[14]. We calculated the annual in-hospital

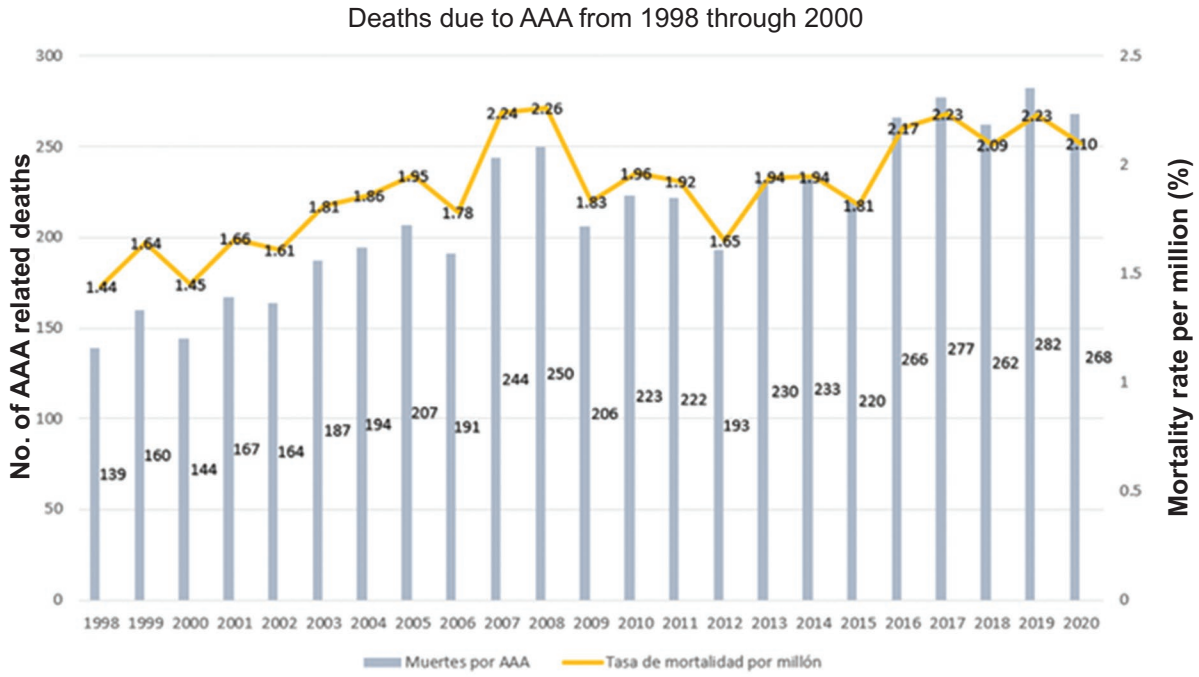

Figure 1. *Graph of mortality due to abdominal aortic aneurysms (AAA) from 1998 through 2020 with an analysis of the mortality rate per million inhabitants.*

lethality, and compared it with the admissions and institutional experience of the Angiology and Vascular Surgery Service of INCMNSZ. Statistical analysis was performed using STATA version 17. The Student's t-test was used for the comparisons of means and the chi-square test was used for the comparison of proportions. The protocol was approved by INCMNSZ research and ethics committee.

Results

According to the national database (NDB), which includes records from 1998 through 2020, a total of 4924 deaths were reported due to complications associated with AAA in Mexico. The mean age of these patients was 74 years, and most of these deaths, totaling 3517 (71%), were reported in men. The number of deaths, mortality, and annual incidence rate are detailed in figure 1. According to the NDB, in 4500 (95%) of these deaths, the patient was contacted or treated from a health care professional (medical care), while in 2963 (60%) of these patients, the cause of death was a ruptured aortic aneurysm, which confirmed the need for specialists for timely diagnosis and management[13].

Regarding hospital admissions with records in the NDB from 2010 through 2020, 899 (91%) out of 984 admissions due to AAA, belonged to the NDB on AAA[13], while 85 (9%) patients were admitted to INCMNSZ. Most individuals studied were men (68%), with a mean age of 69 years and a standard error of 0.4. A total of 811 (82%) of these patients underwent open surgery, while 173 (18%) underwent endovascular aneurysm repair (EVAR), being the latter the most common approach in our center (p = 0.007). Figure 2 presents a graph from the NDB on the annual mortality rate. Figure 3 through 5 present and illustrate cases from the INCMNSZ successfully treated with both open and endovascular approaches. The in-hospital mortality rate, mainly associated with emergency procedures, was 22.5% across the 11 years evaluated; in the NDB, this rate was 23.9%, while at INCMNSZ, it was 16.4% (p = 0.1). We did not see any differences in mortality with respect to gender (men, 23%; and women, 21%; p = 0.6). Table 1 compares demographic variables, types of procedures, and mortality between the NDB and INCMNSZ. Figure 6 graphically represents the overall mortality of the studied populations with respect to gender.

Discussion

In most cases, AAAs remain asymptomatic, and their diagnosis often occurs incidentally in our setting.

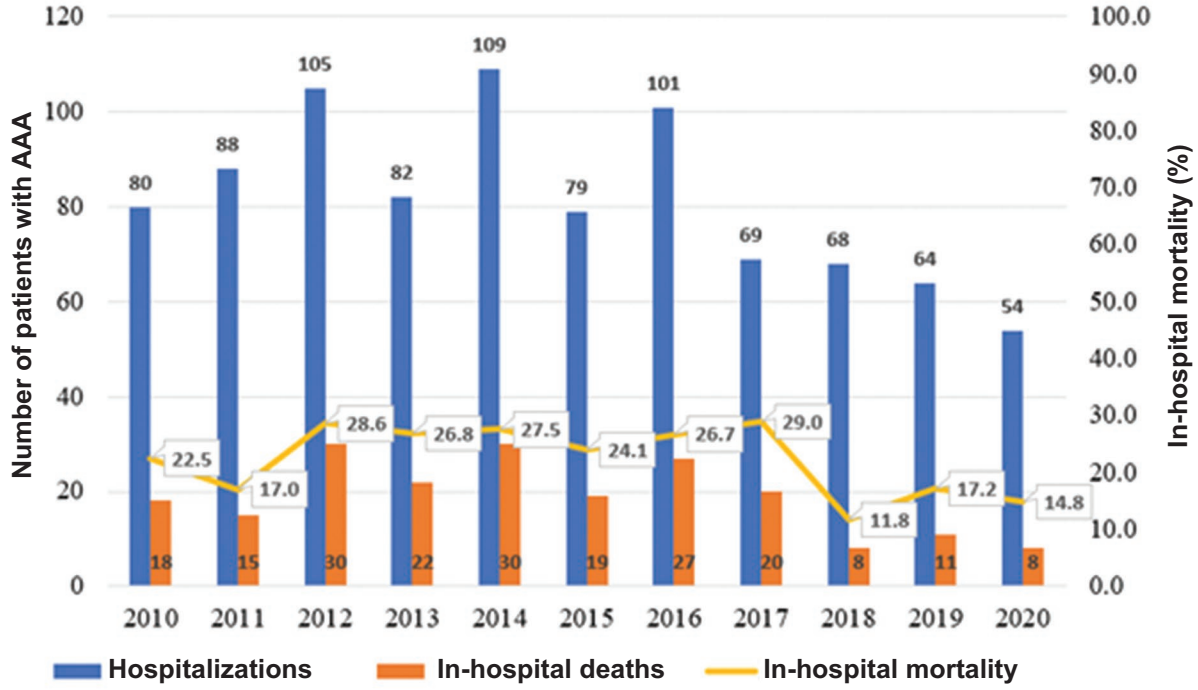

Figure 2. *Graph showing the overall number of hospital admissions according to the National Database and annual mortality from 2010 through 2020. AAA: abdominal aortic aneurysm.*

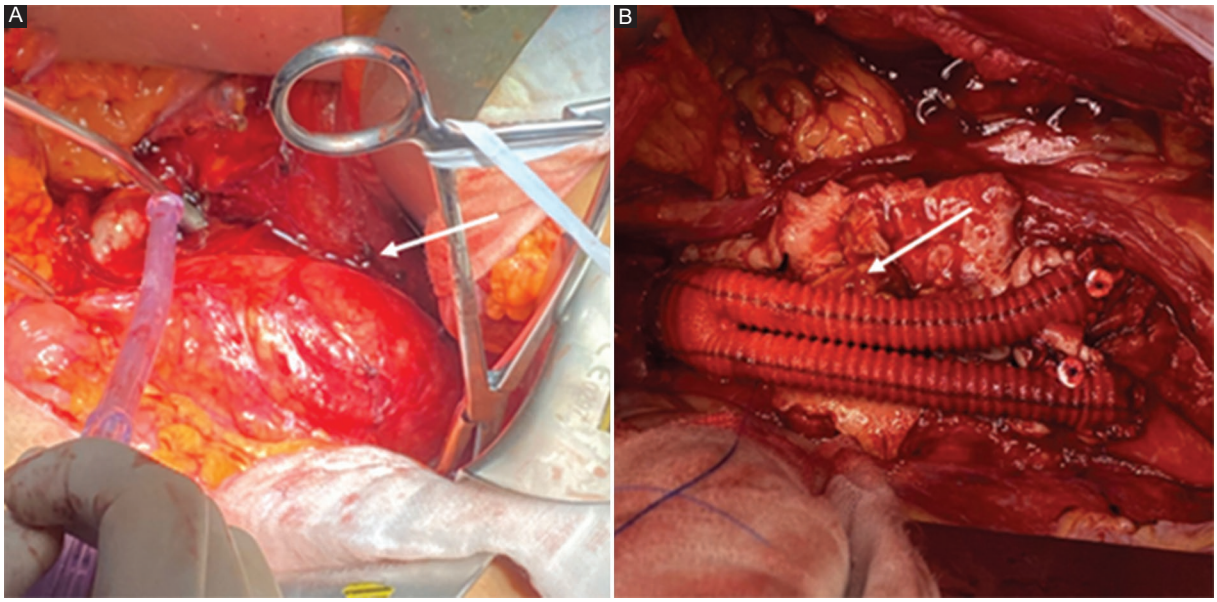

Figure 3. *Intraoperative image of a 74-year-old woman undergoing open repair of an abdominal aortic aneurysm.* **A:** *image of the aneurysm sac.* **B:** *intraoperative image of the repair with a bifurcated aortic bi-iliac Dacron graft.*
EVAR, endovascular aneurysm repair.

When they manifest clinically, as previously mentioned, the most feared complication is rupture, with a mortality rate close to 80%[15]. Invasive treatment aimed at excluding the lesion from circulation is an absolute indication to prevent this risk. AAAs must be evaluated and treated by highly trained and qualified professionals in open and endovascular surgical techniques. Currently, widely disseminated clinical practice

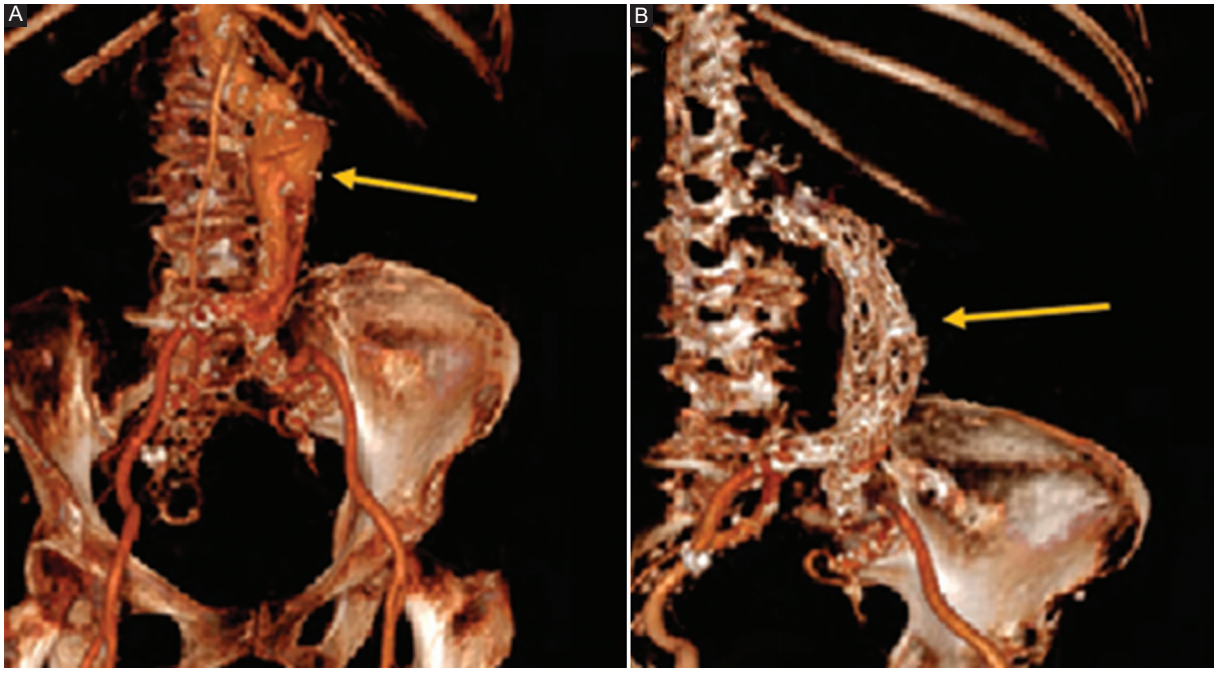

Figure 4. *Coronary computed tomography angiography images with 3D reconstruction of a 28-year-old woman with a history of Marfan syndrome, 25 weeks pregnant.* **A:** *preoperative image where the yellow arrow points to a 6.2 cm abdominal aortic aneurysm (AAA), and the yellow arrow indicates a 25-week gestation product.* **B:** *postoperative image after open repair with aortic bi-iliac Dacron graft and EVAR explantation, with the yellow arrow showing the reconstructed abdominal aorta.*

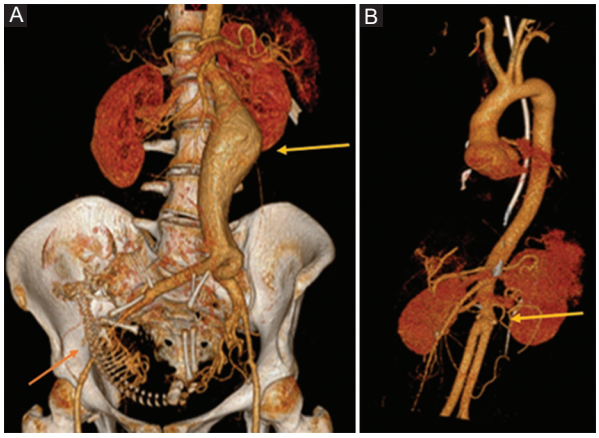

Figure 5. *Coronary computed tomography angiography images with 3D reconstruction of an 80-year-old woman undergoing endovascular repair of an abdominal aortic aneurysm (AAA).* **A:** *preoperative image of a 6 cm in diameter AAA (yellow arrow).* **B:** *postoperative image of the stent-graft at infrarenal abdominal aorta level (yellow arrow).*

Table 1. Comparison between the National Database and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) showing the number of admissions, demographic variables, procedures, and mortality

Variables	National database	INCMNSZ	p
Number of admissions	899	85	NS
Age (years)	69	69	NS
Men	606 (67%)	61 (72%)	NS
Women	293 (33%)	24 (28%)	NS
Open procedure	750 (83%)	61 (72%)	NS
Endovascular procedure	149 (17%)	24 (28%)	0.007
30-day mortality	208 (23%)	14 (16%)	NS

NS: not significant.

guidelines in the field recommend elective AAA repair in asymptomatic patients whose lesions have an anteroposterior diameter ≥ 55 mm in men and > 50 mm in women. Similarly, the type of repair (endovascular or open) should be selected by the vascular surgeon, individualizing this decision based on the patient's clinical characteristics and favorable anatomical features of aneurysmal lesions for the implantation of approved endovascular devices[4,16]. Thanks to the advances made in timely diagnosis, the refinement of techniques, and the expansion of highly advanced training programs, the perioperative mortality reported in patients undergoing elective AAA repair is < 5% in European and American series[4,16]. In Mexico, we still

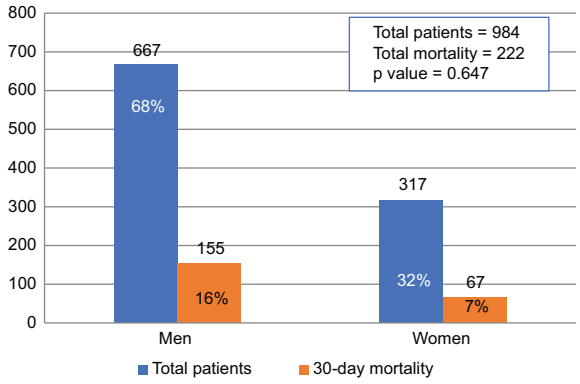

Figure 6. *Graph of gender based 30-day mortality for all patients. Men's mortality rate was 23% compared to women (21%). No significant differences were observed in this variable (p = 0.647).*

have much to do in terms of detection, planning, and execution of these procedures under the best safety conditions possible, as reflected in the still high mortality rate seen in this analysis[15].

In the scientific medical literature currently available, reports from Mexican tertiary referral centers remain scarce, limiting the analysis of variables that have the greatest impact on the outcomes derived from the NDB. Factors determining postoperative evolution and survival of aortic reconstructions are known, including patient comorbidities and anatomical characteristics of the aneurysm. However, postoperative renal function has been one of the most statistically significant predictors of morbidity and mortality in our 10-year retrospective analysis published in *Cirugía y Cirujanos*[17-19] of 80 patients undergoing both open and endovascular procedures for aortic diseases in different locations (thoracic, thoracoabdominal, and abdominal). An impaired postoperative renal function was the most statistically significant predictor of morbidity and mortality[20]. Endovascular reconstructions have been associated with lower 30-day morbidity and mortality rates, and currently, these techniques that have gained global acceptance are the first-choice approach in industrialized countries like the United States, where it has been reported that > 70% of all abdominal aneurysms are repaired this way[4,21,22]. Immediate availability of this technology is another aspect that limits the possibility of offering this treatment to patients in some Mexican health centers. Despite the reduced morbidity reported during endovascular reconstruction procedures, there are still patients in contemporary practice who must undergo open surgery, mainly due to anatomical factors and a younger age. Therefore, teaching and refining open techniques remain relevant and necessary in training programs at the international level.

An interesting aspect regarding gender is the fact that the prevalence of AAA in women is lower compared to men. However, current international information indicates that perioperative morbidity and mortality rates are higher in women considering both approaches[23-25]. Although some authors explain that various variables could play a role in these results, such as anatomical characteristics, socioeconomic factors, and disparities in access to health care services[25], our current analysis confirms a higher prevalence of AAA in men but no gender related difference in mortality among patients who received medical and surgical care.

We emphasize that the prevention of deaths due to aneurysmal ruptures largely depends on timely diagnosis and the initiation of appropriate and timely treatment for these patients. The authors of this work believe that the formation of highly trained specialists in Mexico, along with education and dissemination of related topics directed at other specialties and primary care physicians, could impact the optimization of results in the medium term. SMACVE and university programs continue to work on implementing a national registry that accurately reports the prevalence of this disease and the clinical outcomes reported. We acknowledge that this study has limitations, such as the retrospective nature of the health records and, primarily, possible underdiagnoses of deaths at national level. In any case, as scholars, these data compel us to delve deeper into epidemiological and clinical studies in Mexico.

Conclusions

AAAs and their complications remain poorly recognized among medical-surgical specialties in Mexico. The introduction of university programs in the field of angiology and vascular surgery could impact early detection, referral, and the survival of patients with these conditions.

This study is a regulatory work of the Mexican Academy of Surgery: Current Issues in Abdominal Aortic Aneurysms. Presented on May 24, 2022.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Salivary gland tumor incidence in adult patients in a tertiary hospital in Mexico from 2008 to 2019

Incidencia de tumores de glándulas salivales en pacientes adultos en un hospital de tercer nivel en el Estado de México del año 2008 al 2019

*Anuar Kuri-García[1], Aarón Kuri-García[2], Alberto Guakil-Haber[1], Erasmo González-Arciniega[1], and Benjamín García-Enríquez[1]**

[1]Servicio de Otorrinolaringología y Cirugía de Cabeza y Cuello, Centro Médico Instituto de Seguridad Social del Estado de México y Municipios, Toluca, Edo. de México; [2]Laboratorio de Biología Celular y Molecular, Facultad de Ciencias Naturales, Universidad Autónoma de Querétaro, Qro. México

Abstract

Objective: *To determine the incidence of salivary gland tumors in a population of a tertiary hospital in the State of Mexico, and to describe demographic variables.* **Method:** *An observational, cross-sectional and retrospective study of salivary gland tumors reported in a tertiary hospital in the State of Mexico in the period 2008-2019 is presented.* **Results:** *A prevalence of 0.049% was found. There was no difference between sex in the studied population. Benign salivary gland tumors were the most frequent (86.7%). The age range most affected was 51-60 years. The most frequently found tumor was the pleomorphic adenoma, followed by Warthin's tumor. There was 13.33% of sialolipomas, and one myoepithelioma. There were no cases of sublingual gland tumors or minor salivary glands.* **Conclusion:** *Tumors of the major salivary glands are infrequent tumors; population cases from a central Mexican state and their demographic characteristics are presented to contribute to the information found in local and international literature.*

Keywords: *Salivary glands. Tumor. Incidence. Mexico. Mexicans.*

Resumen

Objetivo: *Determinar la incidencia de los tumores de glándulas salivales en una población de un hospital de tercer nivel en el Estado de México y describir variables demográficas.* **Material y métodos:** *Se presenta un estudio observacional, transversal y retrospectivo de los tumores de glándulas salivales reportados en un hospital de tercer nivel en el Estado de México en el periodo 2008-2019.* **Resultados:** *Se encontró una prevalencia del 0.049%. No hubo diferencia entre sexos en la población afectada. Los tumores de glándulas salivales benignos fueron los más frecuentes (86.7%). El rango de edad mayormente afectado fue el de 51-60 años. El tumor más frecuentemente encontrado fue el adenoma pleomorfo, seguido por tumor de Warthin. Se presentó un 13.33% de sialolipomas y un mioepitelioma. No se presentó ningún caso de tumores de glándulas sublinguales ni glándulas salivales menores.* **Conclusión:** *Los tumores de glándulas salivales mayores son tumores infrecuentes, se exponen casos de población de un Estado del centro de México y sus características demográficas para contribuir a la información encontrada en literatura local e internacional.*

Palabras clave: *Glándulas salivales. Tumor. Incidencia. México. Mexicanos.*

***Correspondence:**
Benjamín García-Enríquez
E-mail: benjaorl@hotmail.com

Date of reception:05-05-2021
Date of acceptance: 03-08-2021
DOI: 10.24875/CIRUE.M21000558

Cir Cir (Eng). 2023;91(4):505-511
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Salivary gland tumors are rare tumors, estimated to represent 3% of all head and neck tumors[1]. The World Health Organization (WHO) created a classification for these tumors in 1982, with the latest updates in 2005 and 2017[2]. These updates included adding soft tissue lesions and other epithelial lesions to the classification of benign tumors[3].

Various global studies from 1999 through 2019 have reported a mean incidence rate of malignant tumors of 0.25% vs a 68.3% incidence rate of benign tumors. When focusing on studies conducted in Mexico, the mean incidence rate of malignant tumors is 0.41%, with benign tumors accounting for 66.0% (Table 1).

Among different types of salivary gland tumors, benign tumors are the most common (Table 1). The most frequent histopathological type of tumor is pleomorphic adenoma[14]. The parotid gland[15] is the most widely affected gland by neoplasms, with a female predominance (2:1), except for Warthin's tumor, which happens to be more common in men[16].

In 19 studies of 8049 cases, the mean number of tumors analyzed per study was 456 (range, 59-2508). The rate of benign tumors was 71.5%, with a male-to-female ratio of 1.0:0.9 and a mean age of 46.9 years. Different incidence rates of involvement in various glands were observed, eg, the parotid gland, submaxillary gland, sublingual gland, minor salivary glands, pleomorphic adenoma, and Warthin's tumor showed incidence rates of 72.9%, 16.5%, 0.5%, 14.3%, 59.8%, and 13.6%, respectively. The parotid gland had the highest incidence rates reported, while the sublingual gland had the lowest ones (Table 2).

Incidence has been reported to vary due to sample size and the period analyzed by each study, even within the same population, as seen in the data from Mexico (Tables 1 and 2). Additionally, due to the rarity of this condition, epidemiological studies are scarce[25]. Therefore, this study aims to report data from a 10-year period to determine the incidence rate of salivary gland tumors in a tertiary referral center from the State of Mexico.

Material and methods

Study design

This is an observational, cross-sectional, and retrospective study.

Table 1. Incidence of major salivary gland tumors

Study	Year of study	Malignant tumors (%)	Benign tumors (%)	Country
Pinkston[4]	1999	0.093	84.3	United States
Ledesma-Montes[5]	2002	1.2	64.2	Mexico
Ansari[6]	2007	0.019	68.4	Iran
Toranzo-Fernández[7]	2008	0.11	55.9	Mexico
Mejía-Velázquez[8]	2012	0.15	67	Mexico
Etit[9]	2012	0.079	62.1	Turkey
Araya[10]	2015	0.002	70.3	Chile
Bobati[11]	2017	0.58	69	India
Sotelo-Gavito[12]	2018	0.16	77.2	Mexico
Reinheimer[13]	2019	0.08	65.3	Brazil

Data mining and analysis

The study reviewed a total of 60 261 pathology records from a tertiary referral center in Mexico, specifically searching for records classified as major salivary gland tumors from 2008 through 2019. Diagnoses were corroborated with results records. Data mined included patient age, gender, affected gland, and tumor histology features.

Statistical analysis

Descriptive statistics were used for data presentation, and data were analyzed using Excel® and SPSS® (version 23.0, SPSS Inc., Chicago, IL, United States).

Results

In a tertiary referral center in Mexico, a total of 60 261 pathology specimens were studied over a 10-year period. Within these specimens, 30 tumors were categorized as major salivary gland tumors, and their histopathological results matched 1 of the classifications provided by the WHO. This accounts for an incidence rate of 0.049%.

The studed included 15 men and 15 women with salivary gland tumors. However, regarding benign tumors, there was a slight male predominance (53.8%) of cases. On the other hand, regarding malignant tumors, there was a female predominance, with 3 cases being reported in women vs only 1 case in men (Table 3).

Table 2. Characteristics of retrospective clinical trials

Author	Population	Year	No. of tumors studied	Benign tumors (%)	Women (%)	Men (%)	Parotid gland involvement (%)	Submandibular gland involvement (%)	Sublingual gland involvement (%)	Minor salivary glands involvement (%)	Pleomorphic adenoma (%)	Warthin tumor (%)	Mean age, or age range
Pinkston[4]	United States	1999	248	84.30	NR	NR	86	14	0	0	65.60	NR	55.4
Ma'aita[17]	Jordan	1999	221	68.40	38.47	61.53	70.13	10.40	0.45	19.00	47	NR	40-49
Vargas[18]	Brazil	2002	124	80	60	40	70.96	24.19	0	4.83	67.70	10.48	48
Ito[19]	Brazil	2005	496	67.50	NR	NR	67.70	9.47	0	22.70	54.20	NR	NR
Ansari[6]	Iran	2007	130	68.40	60	40	63	23	0	14	65.40	NR	39
Toranzo-Fernández[7]	Mexico	2007	106	55.90	53.85	46.15	NR	NR	NR	NR	NR	NR	NR
Subhashraj[20]	India	2008	684	62	48.83	51.17	60.52	16.95	0.58	21.92	53	3	43
Shishegar[21]	Iran	2011	392	68.20	49.50	50.50	58.9	59	NR	NR	58	6	44.57±14.65
Trenkic[22]	Serbia	2012	139	73.38	52.52	47.48	84.70	5.76	0	10.07	49.02	47.06	51.2±13.9
Etit[9]	Turkey	2012	235	62.13	51.06	48.94	82.38	17.62	0	17.87	67.12	21.23	NR
Mejía-Velázquez[8]	Mexico	2012	319	67.04	63.80	36.20	78	20.70	3.60	17.70	65.50	7.30	42
Boza-Mejías[23]	Peru	2012	62	91.94	46.77	53.23	93.55	6.45	0	0	58.06	4.84	41.69
Luksic[24]	Croatia	2012	779	64.20	49.70	50.30	65.30	6.60	0.09	27.20	66.80	22.80	52
Bradley[15]	United Kingdom	2013	1065	86.19	NR	NR	81	9	0	9	71	22	NR
Wang[16]	China	2014	2508	77.11	49.60	50.40	69.70	10.48					
Araya[10]	Chile	2015	279	70.30	58.10	41.90	67	17.60	0	18.70	53.80	8.20	53.3±19.09
Bobati[11]	India	2017	59	69.16	64.40	35.59	84.21	NR	NR	3.39	60.71	5.07	43
Sotelo-Gavito[12]	Mexico	2018	79	77	51%	49	72	18	0	10	72	10	52.13
Reinheimer[13]	Brazil	2019	124	65.30	54.83	45.17	57.20	11.20	2.41	29.00	59.67	3.22	53

NR: not registered.

Table 3. Type of tumor affecting by gender

Sex	Histological type of tumor														
	Benign								Malignant						Total
	Pleomorphic adenoma	%	Warthin tumor	%	Lipoma	%	Mioepithelioma	%	Mucoepidermoid carcinoma	%	Ex pleomorphic carcinoma	%	Hodgkin's lymphoma	%	
Man	7	23.33	3	10	3	10	1	3.33	0	-	1	3.33	0	-	15 (50%)
Woman	5	16.67	6	20	1	3.33	0	-	1	3.33	0	-	2	6.67	15 (50%)
Total	12	40	9	30	4	13.33	1	3.33	1	3.33	1	3.33	2	6.67	30 (100%)

Table 4. Type of tumor affecting by age range

Age ranges	Histological type of tumor														
	Benign								Malignant						Total
	Pleomorphic adenoma	%	Warthin tumor	%	Lipoma	%	Mioepithelioma	%	Mucoepidermoid carcinoma	%	Ex pleomorphic carcinoma	%	Hodgkin's lymphoma	%	
21-30	0	-	0	-	0	-	1	3.33	1	3.33	0	-	0	-	2 (6.67%)
31-40	3	10	0	-	0	-	0	-	0	-	1	3.33	0	-	4 (13.33%)
41-50	5	16.67	1	3.33	1	3.33	0	-	0	-	0	-	1	3.33	8 (26.67%)
51-60	4	13.33	5	16.67	1	3.33	0	-	0	-	0	-	1	3.33	11 (36.67%)
61-70	0	-	3	10	2	6.67	0	-	0	-	0	-	0	-	5 (16.67%)
Total	12	40	9	30	4	13.33	1	3.33	1	3.33	1	3.33	2	6.67	30 (100%)

Regarding the age at which tumors were diagnosed, the most affected age range was 51to 60 years, followed by 41 to 50 years. Most pleomorphic adenomas were diagnosed in the 41 to 50 age group (41.7%), while most Warthin's tumors were diagnosed in the 51 to 60 age group (55.6%). Sialolipomas were found in older age ranges, with 50% (2) occurring in the 61 to 70 age group, and myoepithelioma being diagnosed in the 21 to 30 age group. Malignant tumors and non-Hodgkin lymphomas were diagnosed in patients in their 6th decade of life, while mucoepidermoid carcinoma and carcinoma ex pleomorphic adenoma were diagnosed in the 3rd and 4th decades of life, respectively (Table 4).

Out of the 30 major salivary gland tumors reported, 26 (86.7%) were benign tumors, and 4 (13.3%) were malignant tumors. Among the former, pleomorphic adenoma was the most frequent, accounting for 40% of all tumors, followed by Warthin's tumor, representing 30% of all tumors reported (Table 2). Additionally, 1 myoepithelioma (3.3%) and 4 sialolipomas (13.3%) were reported. Among malignant tumors, 2 non-Hodgkin lymphomas, 1 mucoepidermoid carcinoma, and 1 carcinoma ex pleomorphic adenoma were diagnosed (Table 5).

The parotid gland was the most widely affected major salivary gland (76.7%), followed by the submaxillary gland (23.3%). In this study, no tumors were reported in the sublingual gland or minor salivary glands. The most common tumor in both the parotid and submaxillary glands was the pleomorphic adenoma. Warthin's tumor was predominantly found in the parotid gland, while sialolipomas occurred equally in both the parotid and submaxillary glands. The sole myoepithelioma found was located in the parotid gland. Among malignant tumors, only carcinoma ex pleomorphic adenoma was found in the submaxillary gland, while the rest were found in the parotid gland (Table 5).

Discussion

The present study reported an incidence rate of salivary gland tumors lower compared to former studies reported in the Mexican population, such as

Table 5. Type of tumor affecting each salivary gland

Salivary gland	Histological type of tumor														
	Benign										Malignant				Total
	Pleomorphic adenoma	%	Warthin tumor	%	Lipoma	%	Mioepithelioma	%	Mucoepidermoid carcinoma	%	Ex pleomorphic carcinoma	%	Hodgkin's lymphoma	%	
Parotid	9	30	8	26.67	2	6.67	1	3.33	1	3.33	0	-	2	6.67	23 (76.67%)
Submaxillary	3	10	1	3.33	2	6.67	0	-	0	-	1	3.33	0	-	7 (23.33%)
Total	12	40	9	30	4	13.33	1	3.33	1	3.33	1	3.33	2	6.67	30 (100%)

Ledesma-Montes et al., Mejía-Velázquez et al., Toranzo-Fernández et al., and Sotelo-Gavito et al. who reported incidence rates of 1.2%[5], 0.15%,[8] 0.11%,[7] and 0.08%[12], respectively. However, the incidence rate found is comparable to that of authors from other countries, such as Etit et al. in the Turkish population (0.096%)[9] and Reinheimer et al. in Brazil (0.08%)[13], and it is even higher than that reported by Araya et al. in Chile at 0.002%[10].

The study found no significant differences between sexes regarding salivary gland tumors. In the case of benign tumors, there was a slight male predominance, which differs from most studies that report an overall female predominance for this type of tumor. Some studies do report male predominance (53.3%[23]) or in lower incidence rates[16,20,21,24], while others report female predominance. For instance, Ma'aita et al. reported a male predominance of 61.53%, while Mejía-Velázquez and Bobati reported a female predominance (63.88%[8], and 64.4%[1], respectively).

Differences exist in the reported ages and the way they are presented in the literature. In the current study, the 6th decade of life is the most commonly affected, which is consistent with the findings made by Pinkston et al., Trenkic et al., Araya et al., Sotelo-Gavito et al., and Reinheimer et al., who reported mean ages of 55.4 years[4], 51.2 years[22], 53.3 years[10], 52.13 years[12], and 53 years, respectively[13].

The incidence rate of benign tumors is similar to that found by Bradley et al. in the United Kingdom, Pinkston et al. in the United States, and Vargas et al. in Brazil (> 80%)[4,15,18]. Only 1 study reported a higher incidence rate of benign salivary gland tumors than the present study, with a 91.2% reported by Boza-Mejías et al[23]. The incidence rates reported among the Mexican population vary from 55.9% in Mejía-Velázquez's study up to 77.2% in Sotelo-Gavito's study[7,12].

The salivary gland most commonly affected was the parotid gland, which is consistent with all the studies compared. However, there are different rates of involvement reported in the literature, ranging from 57.2% in the Peruvian population up to 93.5%[13,23] in the Brazilian population. The second salivary gland most widely affected is the submaxillary gland, and the incidence rates also varies widely in the literature. Our value is similar to the one reported by Mejía-Velázquez et al. at 20.7%[8]. However, other studies have reported incidence rates ranging from 5.76%[22] up to 59%[21]. However, most of the studies found report incidence rates of the submaxillary gland between 10% and 20%[4,9,10,17,20]. In the present study, no tumors were found in the sublingual gland or in the minor salivary glands. Former studies have reported incidence rates < 4%, or even < 1% for the involvement of these glands[8,17,20,24].

Pleomorphic adenoma was the most common tumor in all studies, including the present one. The incidence rate found in this study is consistent with that found by Ma'aita et al. (47%[17]), and Trenkic et al. (49%[22]), which are among the lower incidence rates ever reported. The overall incidence rate of pleomorphic adenoma can be up to 72% in other studies, like Sotelo-Gavito et al. reported[12]. Warthin's tumor is often reported as the 2nd most frequent tumor. Trenkic et al. and Etit et al. report incidence rates of 47.06% and 21.23%, respectively[9,22], while other studies report lower incidence rates (≤ 10%) (Table 2).

Mioepitheliomas are rare, with only 1 case presented in this study, which is similar to other studies reporting just 1 case, just like our study[10,18,20]. Other authors report 2 cases[13,22], while only 1 author reports 12 cases in his analysis of 392 salivary gland tumors[21]. As for sialolipomas, which are considered non-epithelial tumors, some studies report 2 cases in men out of

279 tumors[10], 3 cases in the parotid gland out of 62 tumors[23], another study reported 4 cases out of 235 tumors[9], 1 sialolipoma in 106 cases[7], or 1 in 130 tumors[6].

There has also been variability in the presentation of malignant tumors in major salivary glands in various studies, with incidence rates ranging from 8.06%[23] up to 44.1%[7], although the mean incidence rate of the studies presented in table 3 is 29%. In the study conducted by Boza-Mejía et al., which had the highest incidence rate of benign salivary gland tumors, they reported 2 cases of adenocarcinoma and 2 cases of squamous cell carcinoma, each accounting for 3.23%[23]. In Bradley et al.'s study, a lower incidence rate of malignant salivary gland tumors was reported vs the table 3 mean. They reported that the most common malignant tumor was mucoepidermoid carcinoma, being the parotid gland the most widely damaged[15]. Additionally, Pinkston et al. reported a lower incidence rate of malignant salivary gland tumors, and similarly, they reported that mucoepidermoid carcinoma is the most common one accounting for 8.1% of the reported tumors and primarily affecting the parotid gland[4].

However, the presentation of mucoepidermoid carcinoma in the 3rd decade and adenoid cystic carcinoma in the 4th decade of life, as well as the 2 cases of Hodgkin lymphoma in the current study, may be due to the fact that the hospital unit where data was collected is not specialized in the management of cancer patients.

Conclusions

Despite reporting all cases over a 10-year period, this retrospective study found a lower incidence rate of salivary gland tumors vs the medical literature currently available. There was a male predominance in most diagnoses, except for Warthin's tumor, where females predominated. These findings differ from what is generally presented in the literature. Due to the limited number of cases studied, rare histopathological varieties such as mioepithelioma (1) and sialolipomas (4) were identified. Further prospective and cohort studies are needed to identify the risk factors associated with different histopathological types of these tumors. Additionally, investigating the rates of recurrence of salivary gland tumors and the presentation of other tumor types in the same patient may reveal correlations that contribute new information to established diagnoses.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Knowledge of professionals about sexuality of the ostomyzed

Conocimientos del profesional sobre la sexualidad del ostomizado

Yovana Rodríguez-Maldonado[1], Teresa Sánchez-Moreno de Juan[1], Alicia Ruiz-de la Hermosa[1], Inés Naranjo-Peña[2], Virginia de Gea-López[1], and Javier Cambronero-Santos[3]*

[1]Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario Infanta Leonor; [2]Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario Infanta Cristina; [3]Servicio de Urología y Andrología, Hospital Universitario Infanta Leonor. Madrid, España

Abstract

Background: *An ostomy significantly influences a person's life, altering their biopsychosocial and sexual sphere and affecting their interpersonal relationships.* **Materials and methods:** *Through an observational, descriptive, and cross-sectional study, with a questionnaire aimed at professionals from a health area in Madrid, we analyzed: sociodemographic variables, knowledge of the professionals on the subject, referral of the patient according to the professional's assessment and feelings that the subject under study produces in the patient and in professionals.* **Results:** *49% claimed to have no knowledge about sexuality of the ostomyzed patients. 55.9% of those surveyed consider that the healthcare provider is the one who should introduce the topic of sexuality during the clinical interview. 48.5 and 85.2% are unaware of treatments for male and female sexual dysfunction, respectively.* **Conclusions:** *The data show that the training provided in the university centers is insufficient to deal effectively with this issue in the medical consultation. The participants manifest null or minimal knowledge about the sexual sphere in ostomized patients. Knowledge deficiencies are detected in relation to the sexuality of the ostomized patient, difficulty in talking about sex with these patients, and the importance that sanitary professionals give to the patient's sexual sphere, among others.*

Keywords: *Ostomy. Nurses. Physicians. Sexuality. Knowledge.*

Resumen

Antecedentes: *Una ostomía influye significativamente en la vida de la persona, alterando su esfera biopsicosocial y sexual, y afectando a sus relaciones interpersonales.* **Material y método:** *Estudio observacional, descriptivo y transversal. Mediante un cuestionario dirigido a profesionales de un área sanitaria de Madrid, se analizan variables sociodemográficas, conocimientos de los profesionales, derivación del paciente a un especialista según la valoración del profesional encuestado y sentimientos que produce en ellos el tema de estudio.* **Resultados:** *El 49% afirma tener conocimientos nulos sobre la sexualidad del paciente ostomizado. El 55.9% de los encuestados considera que el sanitario es quien debe introducir el tema de la sexualidad durante la entrevista clínica. El 48.5 y el 85.2% desconocen tratamientos para la disfunción sexual, masculina y femenina, respectivamente.* **Conclusión:** *Los datos demuestran que la formación impartida en los centros universitarios es insuficiente para tratar de forma efectiva este tema en la consulta. Los participantes en el estudio muestran nulo o mínimo conocimiento sobre la esfera sexualidad en el paciente ostomizado Se detectan deficiencias de conocimiento en relación con la sexualidad del ostomizado, dificultad para hablar de sexo con el paciente y valor que da el profesional a la esfera sexual en su paciente, entre otras.*

Palabras clave: *Ostomía. Enfermeras. Médicos. Sexualidad. Conocimiento.*

***Correspondence:**
Yovana Rodríguez-Maldonado
E-mail: Virgirm_17@hotmail.com

Date of reception: 04-03-2022
Date of acceptance: 06-04-2022
DOI: 10.24875/CIRUE.M22000562

Cir Cir (Eng). 2023;91(4):512-518
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

There is nearly 70 000 ostomized individuals in Spain, with 15 000 new cases bein reported each year[1]. Worldwide epidemiological data on this topic are not available.

Ostomized patients often experience a loss of the sense of "fullness" related to body image and may experience significant anxiety. Loneliness and isolation exacerbate stress and lead to a loss of sexuality too[2,3].

Psychological reactions to the stress caused by the disease and the ostomy care process are the leading causes of sexual dysfunction in men and dyspareunia in women. Many ostomized individuals try to keep their condition a secret for fear of being stigmatized or rejected, leading to changes in how they express their sexuality, which ends up affecting their interpersonal relationships[4].

Sexuality in ostomized patients is a topic that is rarely addressed by health care professionals, and often considered taboo and laden with prejudices. This may be due to limited knowledge and training in this area[1,5]. Despite the importance of health education aimed at informing and addressing the sexual problems of these patients, health professionals often encounter difficulties in resolving these issues, which can manifest as decreased libido or sexual dysfunction[6-10].

Some authors have found that many patients had never discussed sexuality with health care professionals. Most expressed feelings of self-doubt, shame, and fear too. A significant number of patients experience significant discomfort due to the impact of the ostomy care process on their body image and sexuality[11-13]. Other authors report that most professionals assisting ostomized patients believe that patients will probably feel uncomfortable addressing this issue and they prefer to drop the subject[6].

The objective of the study is to analyze the current best knowledge of health care professionals on the sexuality of ostomized patients in the Salud de Vallecas area, Spain and identify possible deficiencies in the surveyed professionals regarding the sexuality of ostomized patients.

Material and methods

- Design. This was an observational, descriptive, and cross-sectional study that used a questionnaire directed at health care professionals treating ostomized patients at Hospital Universitario Infanta Leonor, and Hospital Virgen de la Torre, both based in Madrid, and affiliated primary and specialized care centers (13 primary and specialized care centers). Inclusion criteria were health care professionals specialized in Family and Community Medicine, General and Digestive System Surgery, Urology, Gynecology, Internal Medicine, primary care nursing, and specialized care nursing. Medical and nursing students and health care professionals who did not wish to voluntarily participate in the study were excluded.

Questionnaires were distributed and collected from April through July 2021.

- Sample size. Convenience sampling was conducted among all health care professionals involved in the above centers treating ostomized patients who correctly completed the questionnaires.
- Procedure. An expert group was created, including 1 colorectal surgeon, 1 urological surgeon specialized in andrology, 2 ostomy nurses, and 2 surgical ward nurses from the surgery and urology departments. An ad hoc cross-sectional questionnaire was created by the expert group regarding this research, consisting of 22 questions with single or multiple-choice answers. The items were developed after consulting the scientific medical literature on this topic and reaching consensus within the group. The sociodemographic variables, professionals' best knowledge on the topic in question, patient referral according to professional assessment, and the feelings that the topic in question evokes in the professional were all collected. Construct and content validation were not considered necessary due to the highly specific nature of the topic, and also because the research's primary goal was to describe health care professionals' best knowledge on the sexuality of ostomized patients.
- Data analysis. Descriptive analysis of variables was performed. Categorical variables were expressed as frequencies and percentages, while the quantitative ones were expressed as mean and standard deviation (SD). The level of confidence for parameter estimation was set at 95%. Differences were considered significant when the *P* value associated with the statistical test of contrast was <. 05. The association of qualitative variables (nominal and ordinal) was assessed using the chi-square test. Data were analyzed using the SPSS-22 software program. Convenience sampling was used, including correctly completed questionnaires in the sample.

– Ethical aspects. Information on the objective of the survey was provided along with the questionnaire, and participants were asked for their prior consent before completing it. Additionally, participants were informed that the data would be used for educational and research purposes only. Data collection was anonymous and followed the principles established in the Organic Law 3/2018, of 5 December, on the Protection of Personal Data and the Guarantee of Digital Rights always in full compliance with the fundamental principles outlined in the current version of the Declaration of Helsinki.

Results

Sociodemographic data

The target population surveyed included 812 professionals, with a participation rate of 41.6% (14.29% physicians, and 27.34% nurses).

Twenty-one out of the 359 surveys received were discarded due to incompleteness, resulting in a total sample of 338 questionnaires for final analysis. The participants' mean age was 41.6 years (SD, 11.8).

Table 1 illustrates the general characteristics of the participants.

Table 1. General characteristics of participants

	n (338)	%
Gender		
woman	275	81.4%
Man	63	18.6%
Professional category		
Medicine in PC	52	15.4%
Medicine in SC	64	18.9%
Nursing in PC	94	27.8%
Nursing in SC	128	37.9%
Health care level		
PC	103	43.2%
SC	135	56.8%
Professional Experience		
< 10 years	110	32.5%
11-20 years	110	32.5%
21-30 years	72	21.4%
> 31 years	46	13.6%

PC: primary care; SC: specialized care.

Best knowledge of health care professionals on sexuality and ostomized patients

The level of knowledge acquired in college on sexuality was minimal for 66% (223) of the surveyed health care professionals, while 59.5% (201) stated that, overall, their best knowledge on ostomized patients was also minimal. When asked specifically on their level of best knowledge on the sexuality of ostomized patients, 95.3% (322) said they had minimal, or no knowledge at all (Fig. 1). There is a significant correlation (p = 0.008) between the overall number years worked and the overall level of best knowledge on ostomized patients.

There is statistical significance (p = 0.001) when assessing the knowledge of sexuality health care professionals have in relation to how the topic is discussed with the patient. A total of 54% (134) of health care professionals claim to openly discuss the topic while reporting not knowing too much on sexuality.

Figure 2 shows the health care professionals' best knowledge on existing treatments for male and female sexual dysfunction. Among those who claim to know the treatments available for men, only 68.4% (119) specify their response, being Viagra® the most frequently mentioned. Other treatments mentioned include sildenafil or tadalafil (phosphodiesterase inhibitors), testosterone-based hormonal therapy, Caverject® (prostaglandin with vasodilatory action), or penile prostheses. In the case of women, only 14.8% (50) claim to know about treatment. Participants who claim to know about therapies vs this issue include specialist physicians at 32.9% (21), while those who know the least are primary care physicians at 9.6% (5). A total of 64% (32) of the 50 respondents who specify treatments for female sexual dysfunction, mention hormonal therapy with androgens and estrogens, lubricants, creams, radiofrequency, psychological treatment, and vitamin complexes that stimulate libido such as Libicare® and Gynfeel®.

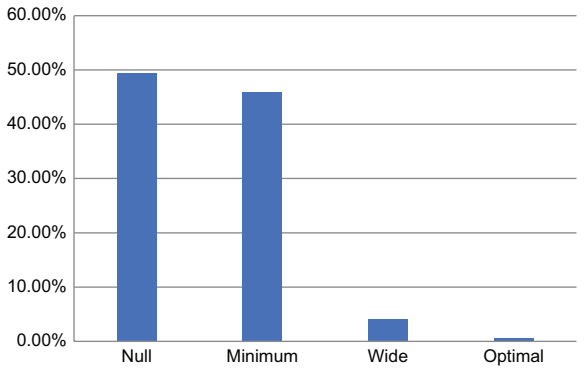

Figure 1. *Best knowledge of health care professionals on ostomized patients, and their sexuality.*

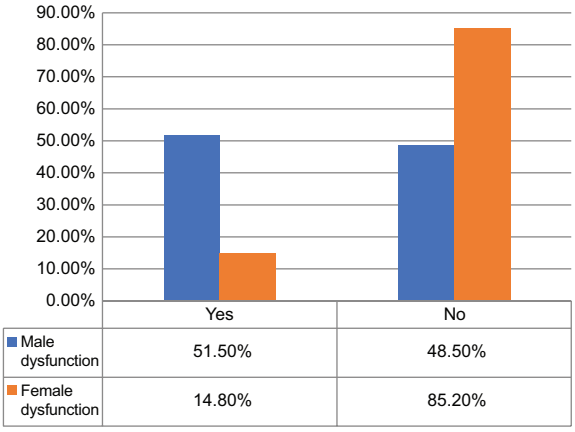

Figure 2. *Best knowledge of treatments vs. sexual dysfunction.*

A total of 96.4% (326) of the entire sample are unaware of the existence of any surveys to assess sexual changes in surgical patients. Only 9 professionals wrote down the surveys they knew: the International Index of Erectile Function (IIEF-5), the Sexual Health Inventory for Men (SHIM), IIEF-5, and the Sexual Function Questionnaire for Men (FSH).

Referral of ostomized patients based on the health care professional's assessment

Table 2 specifies the specialties involved in counseling ostomized patients, both in terms of who should be referred, and the most qualified specialty for it.

In relation to the total years worked by the health care professional regarding whom they would refer ostomized patients to, there is significance ($p = 0.001$) in the case of men. Health care professionals with < 30 years of experience mainly refer patients to urologists. However, 21.1% with over 30 years of work experience would refer patients to a specialist psychologist.

Feelings evoked in health care professionals when discussing the sexuality of ostomized patients

A total of 73.4% (248) of health care professionals would openly discuss the topic if the patient actively requested information on their sexuality.

A total of 55.9% (189) of respondents believe that health care professionals should be the ones to introduce the topic of sexuality during the clinical interview vs 44.1% (149) who think that the patient should initiate the discussion. Regarding when to address the topic of discussion, 79.9% (270) believe that it can be discussed at any time during the process if doubts arise.

Figure 3 illustrates the feelings generated in health care professionals when discussing sex. The feeling of normality is more ingrained among the nursing staff.

Overall, 62.7% (212) consider it important to address sexuality.

Table 2. Specialties involved in advising ostomized patients

	n (338)	%
Specialty for referral		
Coloproctology	19	5.6%
Urology/Gynecology	86	25.4%
PC physician	27	8%
Ostomy nurse	115	34%
Psychology	91	26.9%
Specialty most qualified for resolving questions		
Urology	108	32%
Gynecology	13	3.8%
Coloproctology	33	9.8%
Oncology	3	0.9%
Psychiatry	4	1.2%
Psychology	77	22.8%
PC physician	9	2.7%
Ostomy nurse	75	22.2%
Nursing	16	4.6%
Specialty for referral in case of male changes		
Urology	198	58.6%
Andrology	50	14.8%
Coloproctology	12	3.6%
Oncology	2	0.6%
Psychologist specialized in sexual therapy	76	22.5%
Specialty for referral in case of female changes		
Gynecology	215	63.6%
Andrology	11	3.3%
Coloproctology	11	3.3%
Oncology	5	1.5%
Psychologist specialized in sexual therapy	96	28.4%

PC: primary care.

Discussion

Despite the importance placed on sexuality in ostomized patients, little is known on what health professionals know on this topic.

The response rate to the questionnaire was 41.6% (388 health care professionals), which is similar to the rate reported by other studies of similar characteristics[14-17]. Many of these studies conduct surveys by mail,

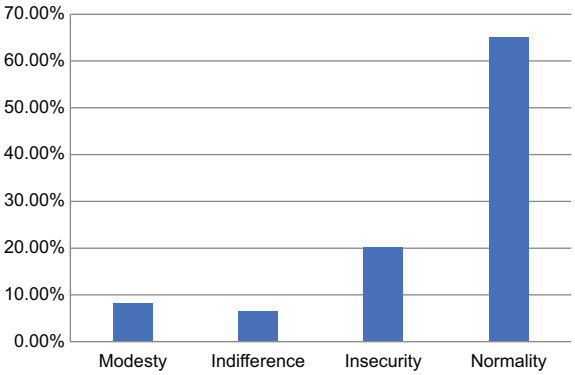

Figure 3. *Feelings of health care professionals when addressing sexuality with their patients.*

while in this study, the survey was personally delivered to the heads of each evaluated unit for subsequent distribution among the target population. This method did not significantly impact the response rate. However, we should mention that the nursing group had a strikingly higher though statistically nonsignificant response rate compared to physicians.

Kaner et al.[18] suggest that one important factor impacting response rates to surveys is the topic of research. If the surveyed individual is interested in the topic in question, the response rate tends to be higher. Based on the results obtained and this theory, we can deduce that sexuality in ostomized patients is an interesting topic of discussion, especially in the field of nursing, as supported by various nursing reports on this subject[19-22]. These reports, however, do not focus on the training or level of acquired knowledge.

Analyzing the population that responded to the surveys, we can conclude that the group of hospital nurses exceeds that of specialized physicians, which can be a bias, as the study originates from hospital nursing professionals, thus making it easier to access professionals within the hospital setting compared to primary care professionals, with whom it is a little more difficult to come into contact.

The surveyed population is consistent with that of studies of similar characteristics[14-23]. An example of this is studies that assess the best knowledge of health care professionals on fecal incontinence. The study topic is considered comparable to the sexuality of ostomized individuals because it is also a taboo topic of discussion. The respondents' mean age was 47.7 years, which is very similar to the 41.6 years, on average, of the surveyed population for the completion of this work. Similarly, the professional experience in the sample of this study is < 20 years in 65% of the cases, while in the study conducted by Ng Kheng-Seong et al.[23] it is 72.5%.

Despite having more and better education in sexuality today, there are no statistically significant differences in terms of best knowledge and total working experience. However, education in ostomies is significantly better.

The participants in this study were, as expected, predominantly women, which is similar to what other contemporary studies have reported. In contrast, the participants of studies conducted in the 1970s[24] on the best knowledge on sexuality in physicians were male participants in 100% of the cases.

The participants included in this study represent a diverse group, and despite having different educational backgrounds during their respective college degrees, they all agree on the lack of knowledge acquired. No significant differences were observed among them.

In Spain, according to the scientific medical literature currently available[25], patients do not openly discuss sexual dysfunction and expect health care professionals to initiate discussions about their sexual issues. While more than half of the respondents believe that it should be the health care professional the one bringing up the topic of discussion, the reality (based on another question asked) is that they only address this topic is requested by the patient.

Urologists are considered the most qualified professionals to respond to the general questions asked by ostomized patients. Regarding the referral process for ostomized patients, the respondents believe that ostomy nurses are the most suitable individuals to address the topic of sexuality, even more so than urologists, or gynecologists. Therefore, the answer to the question "which health care professional would you refer ostomized patients to when not knowing how to approach their new sexuality" is an interesting one because the expectation is to refer the patient to the most qualified health care professional. This response is probably biased because respondents were aware that the study was conducted, among others, by ostomy nurses. When asked about sexual dysfunction, they do mention that they would refer ostomized patients to urologists and gynecologists.

A similar situation arises when asking about the feelings that talking about sex with patients generates in health care professionals. As mentioned earlier, if one lacks sufficient knowledge about a topic, discussing it with a patient will, at least, create insecurity. It is noteworthy that 65% of respondents claim they would

address the topic normally. This response does not seem very logical and suggests that respondents may be trying to hide the feelings of modesty and insecurity created in them while discussing sex with their patients.

The benefit of explaining to the patient, before the procedure, what an ostomy is and the care it requires, has been widely demonstrated[12,26,27]. Most professionals believe it should be addressed when uncertainty arises. Only 18.9% believe it is important to discuss the topic in question in the preoperative phase.

We should mention that primary care physicians are the health care professionals who know more on how to treat male sexual dysfunction. In contrast, they are the ones who know the least on female sexual dysfunction. This may be related to the limited consultation by women about their sexual dysfunctions, causing doctors to be unaware of them[28].

In general, the respondents agree that sexuality will be affected after undergoing an ostomy. Over a quarter of them say sexuality will not recover, and the patient must accept the changes.

Conclusions

It is essential for patients to receive comprehensive care including addressing sexuality, which, in turn, requires the education and training of health care professionals. This study confirms the current shortage of knowledge among health care professionals on sexuality during their college education. The lack of preparation to address patient inquiries, the barrier of modesty, and preconceptions contribute to this underaddressed issue.

There is a need for educational tools that help health care professionals develop knowledge, trust, and comfort when discussing sexuality with ostomized patients.

It would be valuable to establish a referral system for addressing the sexuality of these patients to foster a trustful environment between health care professionals and patients, enabling open discussions on this topic without fear.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Infectious endocarditis without intracardiac devices or underlying structural heart disease

Endocarditis infecciosa sin dispositivos intracardiacos ni cardiopatía estructural subyacente

*Abelardo Flores-Morales[1], Andrés Jacobo-Ruvalcaba[1], Ariana C. Acevedo-Meléndez[1], María J. Fernández-Muñoz[1], Héctor A. Carmona-Ruiz[2], Gabriela Borrayo-Sánchez[3], Alberto Chaparro-Sánchez[4], and Óscar Orihuela-Rodríguez[1]**

[1]Departamento Clínico de Cardiología, Unidad Médica de Alta Especialidad, Hospital de Especialidades "Dr. Bernardo Sepúlveda Gutiérrez", Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social (IMSS), Ciudad de México; [2]Servicio de Cardiología, Hospital General de Zona con Medicina Familiar No. 1 Dr. Alfonso Mejía Schroeder, Pachuca, Hidalgo; [3]Coordinación de Innovación en Salud, IMSS, Ciudad de México; [4]Servicio de Infectología, Hospital de Infectología, Centro Médico Nacional La Raza, Ciudad de México. México

Abstract

Objective: *To describe clinical, microbiological and echocardiographic aspects of endocarditis in a specific group of patients without intracardiac devices or underlying structural heart disease.* **Method:** *Retrospective study, clinical records and echocardiographic reports were reviewed during the period 1997 to 2020. Duke's modified criteria were applied. Statistical analysis: univariate expressed in frequencies, using measures of dispersion and central tendency.* **Results:** *30,000 echocardiographic reports were reviewed, only 1350 had infectious endocarditis as a reason for sending, of which 248 cases were selected. The mean age was 48.1 ± 16.7 years. 140 men (56%) and 108 women (44%). The most frequent echocardiographic sign was vegetation, in 278 (93.60%), and most common location was mitral (35.55%), with a higher number of cases in the right ventricle than expected. The most common systemic disease was kidney disease, in 135 (41.08%). A case of Streptococcus thoraltensis not previously reported in Mexico was identified.* **Conclusions:** *The presence of infectious endocarditis has increased due to invasive in-hospital and drug procedures. Due to their complexity, multidisciplinary teams are indispensable.*

Keywords: *Endocarditis. Infectious endocarditis. Vegetation.*

Resumen

Objetivo: *Describir aspectos clínicos, microbiológicos y ecocardiográficos de endocarditis en un grupo específico de pacientes sin dispositivos intracardiacos ni cardiopatía estructural subyacente.* **Método:** *Estudio retrospectivo en el que se revisaron expedientes clínicos y reportes ecocardiográficos durante el periodo de 1997 a 2020. Se aplicaron los criterios modificados de Duke. Se describió la muestra por edad, sexo, enfermedad sistémica, vegetaciones y agente microbiológico. Se excluyeron pacientes con cardiopatía estructural o Libman-Sacks. Análisis estadístico: univariado expresado en frecuencias, utilizando medidas de dispersión y tendencia central.* **Resultados:** *Se revisaron 30,000 reportes ecocardiográficos, de los cuales solo 1350 tenían como motivo de envío endocarditis infecciosa, y de estos se seleccionaron 248 casos. La edad promedio fue de 48.1 ± 16.7 años. Hubo 140 hombres (56%) y 108 mujeres (44%). El signo ecocardiográfico más frecuente fue la vegetación, en 278 (93.60%), y la ubicación más común fue mitral (35.55%), con un número mayor de casos en el ventrículo derecho de lo esperado. La enfermedad sistémica más común fue la enfermedad renal, en 135 (41.08%). Se identificó un caso de Streptococcus thoraltensis no reportado previamente en México.*

***Correspondence:**
Óscar Orihuela-Rodríguez
E-mail: orihuelao@yahoo.com.mx

Date of reception: 18-08-2021
Date of acceptance: 13-10-2021
DOI: 10.24875/CIRUE.M21000563

Cir Cir (Eng). 2023;91(4):519-524
Contents available at PubMed
www.cirugiaycirujanos.com

Conclusiones: *La presencia de endocarditis infecciosa ha aumentado debido a procedimientos invasivos intrahospitalarios y fármacos. Por su complejidad, los equipos multidisciplinarios son indispensables.*

Palabras clave: *Endocarditis. Endocarditis infecciosa. Vegetación.*

Introduction

Infective endocarditis (IE) is a multisystemic infection that typically results from an infection, often caused by bacteria, on the heart endocardial surface. IE is categorized based on its location, clinical presentation, mode of acquisition, infectious agent, or presence of underlying structural heart disease[1,2]. The mortality rate of IE that can vary between countries but remains consistently over 30% within 30 days. The estimated incidence rate of IE is 3 to 10 cases per 100 000 people per year[2,3]. However, contemporary reviews have indicated a gradual increase in its epidemiology, from 0.32 up to 0.75 cases per 100 000 people in the United States alone[4], being 30% of the cases associated with the health care provided[5].

In 2011, expert consensus in Europe already raised concerns on the predisposing factors for developing IE[6], as demonstrated by other meta-analyses such the one conducted by Rigau et al. [7] who showed variations in clinical presentation, treatment, prognosis, and mortality when patients were stratified based on vegetation location and predisposing factors such as intracardiac devices, use of IV drugs, or underlying structural heart disease (whether rheumatic, degenerative, congenital, or ischemic). Other proposed risk groups include patients on hemodialysis, immunosuppressive therapy, non-cardiac surgery, and elderly patients[8,9].

In Mexico, IE started being reported back in 1976, primarily in native vs prosthetic valves, microbiology, embolic complications, and medical vs surgical therapy[10,11]. However, little is known on the predisposing factors, clinical presentation, microbiological agents, and complications in patients with systemic disease, without intracardiac devices, or underlying structural heart disease[11,12]. This study aimed to identify the clinical aspects and predisposing factors of this group of patients.

Method

This was a retrospective study involving the review of all echocardiographic studies conducted at the Cardiology Department of UMAE "Dr. Bernardo Sepúlveda Gutiérrez" Hospital de Especialidades within Centro Médico Nacional Siglo XXI of the IMSS, Mexico City, Mexico. The study only included patients who met the absolute or possible modified Duke criteria for IE[13]. Patients with IE in prosthetic valves, those with pacemakers, a history of underlying structural heart disease, or non-infectious Libman-Sacks endocarditis were all excluded.

Echocardiographic studies were performed using commercially available echocardiographic equipment (iE33®, Philips Medical System, Andover, MA, United States). Two-dimensional and M-mode images were acquired from parasternal and apical approaches while the patient remained in the left lateral decubitus position. Measurements followed the recommendations established by the American Society of Echocardiography[14]. The echocardiographic criteria for diagnosing IE were based on the European Society of Cardiology clinical practice guidelines, including the definitions for vegetation, abscess, aneurysm, pseudoaneurysm, perforation, fistula, and valvular aneurysm[15].

Descriptive statistics was used and expressed as means and standard deviations for the quantitative variables and percentages for the dichotomous ones. The incidence rate was calculated considering the total number of cases and studies conducted per year. The SPSS Statistics version 22.0 software was utilized for data analysis.

Results

A total of 30 000 patient studies conducted at the Cardiology Department were reviewed from January 1997 through December 2020. Of these, 248 cases met the inclusion criteria for IE with a mean annual incidence of 5 cases of IE per 1000 echocardiographic studies. A 35.9% increase in cases within the last year was reported vs the previous one (12.8 vs 8.2) for a total of 140 men, 108 women, and a mean age of 48.1 ± 16.7 years (Fig. 1).

A total of 207 (83.20%) patients had 1 or more systemic diseases. Chronic kidney disease (CKD) was the most widely reported in 54.43% of the patients (135 cases), followed by endocrine diseases in 27.41% of the patients (diabetes mellitus, 43; hypothyroidism, 18; dyslipidemia, 7), rheumatological diseases in 7.25% (systemic lupus erythematosus, 8; rheumatoid arthritis,

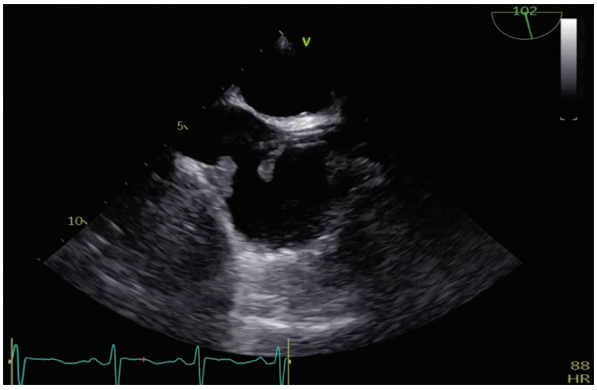

Figure 1. *Right atrial endocarditis. The bicaval view of the transesophageal echocardiogram reveals the presence of a vegetation attached to the distal end of the hemodialysis catheter and another one at the inferior vena cava junction.*

Table 1. Predisposing factors, clinical presentation, and complications of infective endocarditis

	n	%
Systemic disease	248	100
Chronic kidney disease	135	54.43
Systemic arterial hypertension	51	20.56
Diabetes mellitus	43	17.33
Other	99	39.91
Predisposing factors	196	100
Hemodialysis	96	48.95
Immunosuppressive drugs	27	13.78
IV drug use	19	9.69
Central catheter	25	12.76
Organ transplant	9	4.59
Peritoneal dialysis	8	4.08
Dental extraction	6	3.06
Tissue infection	6	3.06
Clinical presentation		
Fever	118	52.54
Purulent secretion	62	15.25
Neurological: delirium, seizures, stroke	18	7.66
Other	9	24.55

4; vasculitis, 3; dermatomyositis, 2; fibromyalgia, 1), solid tumors in 5.18% (17), hematological diseases in 3.62% (leukemias, 6; aplastic anemia, 2; amyloidosis, 1), neurological disorders in 1.20% (multiple sclerosis, 1; Guillain-Barré syndrome, 1; stroke, 1), and GI diseases with only 2 cases reported of ulcerative colitis (0.60%). Predisposing factors were identified in 157 patients (63.30%). Among the 196 cases with predisposing factors, the most common one was the presence of a catheter for hemodialysis in 96 patients, while only 6 cases with a past medical history of dental extraction within the 12 months prior to developing IE were reported (Table 1).

The most common clinical sign at hospital admission was fever (52.54%), followed by hypotension (6.77%), dyspnea (5.93%), and weight loss (4.23%). Splinter hemorrhages, pharyngeal abscess, and bradycardia were less common, accounting for 7.61% of the cases. Complications occurred in 23 patients (9.23%): 12 cerebral embolisms (52.7%), 6 pulmonary embolisms (26.06%), 4 osteomyelitis (17.39%), and 1 mycotic pseudoaneurysm (4.34%).

Echocardiography was the most widely used imaging modality (100%) for diagnosing IE. Transesophageal echocardiography was used in 36% of the cases of persistent IE. Other imaging modalities included computed tomography in 12 patients and scintigraphy with ciprofloxacin in 9 (3.62%).

A total of 301 images consistent with IE were identified, including 282 vegetations (93.60%), 7 cases (2.35%) of valve perforation, 7 cases (2.35%) of aneurysm/pseudoaneurysm, and 5 cases (1.68%) suggestive of abscess on the echocardiogram. The mean maximum diameter of vegetations was 16.81 mm ± 11 mm, with a minimum mean of 10 mm ± 8.9 mm. Regarding transplant recipients (8 renal and 1 marrow), the mean vegetation size was 10 mm, with no differences being reported compared to the general mean (Table 2).

The most frequent location of IE was the left heart in 175 cases (58.13%), with the mitral valve as the most commonly damaged one in 107 cases (35.55%), followed by the aortic valve in 65 (21.59%), the left atrium in 2 (0.66%), and the left ventricle in 1. Right heart IE was described in 126 (41.86%) echocardiograms, being the right atrium the most common location in 61 (20.27%) cases, followed by the tricuspid valve in 46 (15.28%), the superior vena cava in 11 (3.65%), the pulmonary valve in 5 (1.66%), and the right ventricle in 3 (Fig. 2).

Regarding blood cultures, a total of 113 results (45.56%) tested positive, being *Staphylococcus aureus* the most frequently isolated agent in 49 cases (42.61%), followed by *Staphylococcus epidermidis* in 19 cases (16.52%). *Streptococcus thoraltensis* isolation was confirmed through histopathological examination. Fungal agents (5.26%) included 1 case of *Histoplasma capsulatum* and 5 cases of *Candida albicans*, but they were rare findings. The antibiogram reported 26.53% of oxacillin-resistant *S. aureus* isolates, and only 1 case of vancomycin-resistant *Enterococcus gallinarum* (Fig. 3).

Discussion

IE without pre-existing structural heart disease ranges from 2% up to 58% in the case series reported[16].

Table 2. Echocardiographic findings and location of infective endocarditis

Echocardiographic findings of IE	No. of images suggesting IE (n = 301)	%
Vegetations	282	93.68
1	215	71.42
2	58	19.26
3	9	2.99
Perforation	7	2.32
Pseudoaneurysm	7	2.32
Abscess	5	1.66
Location of echocardiographic findings	**No. of images suggesting IE (n = 301)**	**%**
Left heart chambers	175	58.13
Mitral valve	107	35.54
Aortic valve	65	21.59
Left atrium	2	0.66
Left ventricle	1	0.33
Right heart chambers	126	41.86
Right atrium	61	20.26
Tricuspid valve	46	15.28
Inferior vena cava	11	3.65
Pulmonary valve	5	1.66
Right ventricle	3	0.99

IE: infective endocarditis.

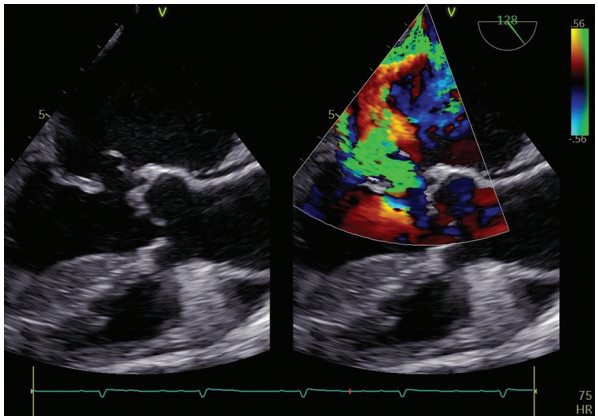

Figure 2. *Mitral valve endocarditis. Long-axis view of the left ventricle on the transesophageal echocardiogram. A perforation of the mitral valve A2 segment can be seen (left image), resulting in regurgitant flow (right image). The mechanism of regurgitation is consistent with type I in Carpentier's functional classification.*

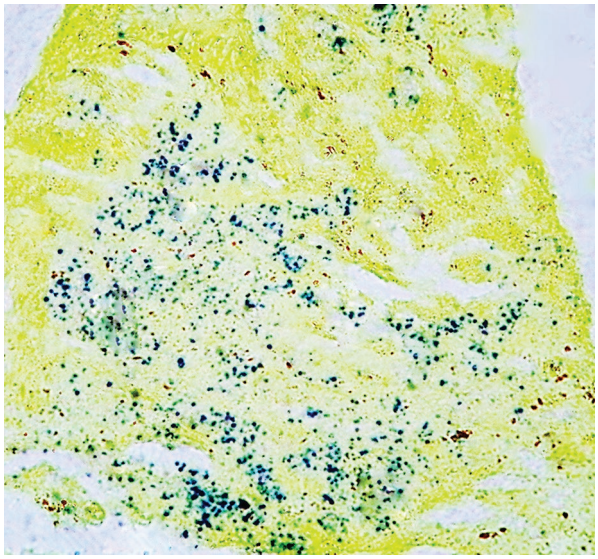

Figure 3. *Aortic valve endocarditis. Gram staining revealed gram-positive cocci (blue dots), which was consistent with the presence of S. thoraltensis in blood cultures.*

Our study represents the largest reported case series of IE in patients with systemic disease and without pre-existing structural heart disease, or intracardiac devices in Mexico. The mean annual incidence in this cardiology unit was 5 cases for every 1000, with a peak of 27 cases back in 2017, which, compared to other published case series, indicates a higher incidence (10.4 vs 6-9/100 000 inhabitants)[17]. Over the past 5 years, a 45.5% increase vs the previous 5 years (2001-2005) was reported. This increase is consistent with the current trend observed in high-income countries, such as Germany, where Zahn et al.[18] reported more cases and a high in-hospital mortality rate (21.96%), which does not seem to drop despite advances made in diagnostic and surgical treatment.

The mean age of our study population was 48.1 ± 16.7 years, which is similar to the findings made by Wu et al. in their study[19] One possible explanation is the exclusion of cases with degenerative valvular heart disease, which is associated with older age[20]. Unlike other series reported, IE was more common in men vs women, with a male-to-female ratio of 1.33:1, which is quite different to other reports with ratios as high as 9:1[21].

The risk of developing IE depends on various factors related to the host as well as external factors, such as surgical or therapeutic procedures causing transient bacteremia. Factors such as poor oral hygiene, chronic alcoholism, systemic lupus erythematosus, diabetes

mellitus, and chronic kidney disease (CKD) can increase the risk[22]. At least 1 systemic disease was present in 207 (83.20%) patients, being CKD the most widely reported, which is similar to reports coming from various studies. The most significant predisposing factor was hemodialysis in 96 patients, which was higher vs other series[23]. However, we should mention that our hospital serves as a tertiary referral center for patients with CKD, meaning that there can be a bias of overrepresentation. Nonetheless, our case review spanned 23 years, which is longer compared to other studies of patients with CKD with only 4 years of income observation and fewer patients[24]. Another strength of our study was the ability to identify multiple predisposing factors, as patients without, at least, 1 predisposing factor accounted for only 36.7% (91 out of 248 patients), which is a much lower rate that the one reported by Castillo et al.[25] at 68% (33 out of 49 patients).

Regarding clinical presentation, fever was present in 52.54% of the population, which was a less common finding vs other studies (80% to 94%). One possible explanation is the immunosuppression observed in some patients, as suggested by DeSimone et al.[26], where 46% of the patients with IE did not exhibit fever associated with immunosuppresion.

Among the systemic complications associated with IE, the neurological ones were the most frequent, occurring in over 30% of the cases. However, we cannot rule out that they occur more frequently due to limited screening with tomographic or magnetic resonance imaging studies in our setting, as other reviews have found rates > 30%, even up to 60%[27,28]. In our study, the mean size of vegetations was 13.2 mm, which is a smaller size compared to other reported cases (14.2 mm), possibly due to the low frequency of this complication (4.8%)[28]. Another embolic complication in the study associated with left-sided IE was 1 mycotic pseudoaneurysm and 1 case of osteomyelitis.

Left-sided heart involvement is the most frequent location for IE, with incidence rates of up to 80%. In our study, the mitral valve was the most impacted one (50% of the cases), followed by the aortic valve (both valves with incidence rates from 10% to 25%).[29] The most common site of left-sided IE was the mitral valve (64%), followed by the aortic valve (37%), which similar to other cohorts[29,30].

Right-sided IE represents between 5% and 10% of the general population but it can be as high as 90% in IV drug users. According to former studies, only 10% occur in patients with intravascular catheters for hemodialysis, chemotherapy, vascular or intracardiac devices[30]. However, in our study, 3 times more echocardiographic images were found in the right heart, with 107 (35.54%) non-IV drug users. Therefore, in our setting, invasive treatments could play a more relevant role in the development of IE than previously described[31]. Also, right heart lesions were more present in the right atrium vs the tricuspid valve (20.27% vs 15.28%), as expected by the research group, since the latter has been reported in up to 90% of right heart lesions found, which may be associated with the invasive nature of hemodialysis[32].

S. aureus was the most widely isolated agent, which is similar to what former studies have reported in this regard. Streptococci were less commonly isolated compared to the study conducted by Castillo et al.[33] (4.38% vs 34%). However, we should mention the isolation of *S. thoraltensis*, a rare agent for IE (reported in Vietnam in 2020 in 1 patient with mechanical valve IE). Therefore, compared to the medical literature currently available, this would be the very first case of IE in a native valve, and the very first case ever reported Mexico caused by this agent, which was associated with aortic valve perforation and septic embolism to the central nervous system[34]. A case of *Histoplasma capsulatum* was identified in the fungal group, which had previously been reported by researchers from this hospital[35]. Unfortunately, no follow-up of these EI cases was possible.

Conclusions

In this 23-year case review conducted in our hospital, the presence of IE associated with systemic disease was found in 248 patients, with an incidence of 5 cases for every 1000. The most widely reported systemic disease was CKD (in 135 patients), and the most common predisposing factor was the presence of hemodialysis catheters in 96 patients. The most common location for the IE was the mitral valve in 107 patients, but the frequency of right-sided IE was 3 times higher than the one reported in the literature. The most common complication was embolism to the central nervous system (4.8%). *S. thoraltensis* was isolated in 1 case. The most frequently isolated agent was *S. aureus*.

Acknowledgments

The authors wish to thank C. Nayeli América Mares Téllez (head of clinical archives UMAE HE), QFB María

de Jesús García Parra, and QFB Eduardo Ureña Reyes (head of clinical laboratory UMAE HE).

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Procalcitonin and C-reactive protein: markers in the early diagnosis of anastomotic leak

Procalcitonina y proteína C reactiva: marcadores en el diagnóstico temprano de fuga anastomótica

Isadora G. Maldonado-Hernández[1,2], Eduardo Vega-Chavarría[1], Yamir A. Nacud-Bezies[1], Hid F. Cordero-Franco[3], and Gerardo C. Palacios-Saucedo[4]*

[1]Departamento de Cirugía Digestiva, Unidad Médica de Alta Especialidad No. 25, Instituto Mexicano del Seguro Social (IMSS); [2]División de Ciencias de la Salud, Universidad de Monterrey; [3]Unidad de Investigación Epidemiológica y en Servicios de Salud, Centro de Investigación Biomédica del Noreste (CIBIN), Delegación Nuevo León, IMSS; [4]División de Investigación en Salud, Unidad Médica de Alta Especialidad No. 25, IMSS. Monterrey, Nuevo León, México

Abstract

Objective: *To determine the efficacy of serum procalcitonin (PCT) and C-reactive protein (CRP) in the early diagnosis of anastomotic leak (AL) in patients undergoing colorectal surgery.* **Method:** *Diagnostic test in a tertiary care hospital. Patients who did not have preoperative measurements of PCT and CRP were excluded. Those with postoperative infection not related to AL were eliminated. The diagnostic efficacy measures were sensitivity (Sn), specificity (Sp), positive (PPV) and negative (NPV) predictive values, positive (LR+) and negative (LR–) likelihood ratios, and area under the receiver operating characteristic curve (AUROC).* **Results:** *Thirty-nine patients were analyzed; six had AL (15.4%). PCT and CRP increased on the second postoperative day, only in patients with AL. The cut-off points at the second postoperative day were 1.55 ng/mL for PCT and 11.25 mg/L for CRP. The most efficacious test was CRP at second postoperative day (AUROC: 1.00; Sn: 100%; Sp: 96.7%; PPV: 85.7%; NPV: 100%; LR+: 33.0).* **Conclusions:** *CRP at second postoperative day was the most effective test in the early diagnosis of AL in patients undergoing colorectal surgery, with a cut-off point lower than that reported in the international literature.*

Keywords: *Anastomotic leak. Sensitivity and specificity. ROC curve. Predictive value of tests. Procalcitonin. C-reactive protein.*

Resumen

Objetivo: *Determinar la eficacia de la procalcitonina (PCT) y la proteína C reactiva (PCR) séricas en el diagnóstico de fuga anastomótica (FA) en los pacientes sometidos a cirugía colorrectal.* **Método:** *Prueba diagnóstica en un hospital de tercer nivel. Se excluyeron los pacientes que no tuvieron mediciones preoperatorias de PCT y PCR. Se eliminaron los que cursaron con infección posoperatoria no relacionada con FA. Las medidas de eficacia diagnóstica fueron sensibilidad (S), especificidad (E), valores predictivos positivo (VPP) y negativo (VPN), razones de verosimilitud positiva (RV+) y negativa (RV–), y área bajo la curva característica operativa del receptor (AUROC).* **Resultados:** *Se analizaron 39 pacientes, de los cuales 6 (15.4%) tuvieron FA. La PCT y la PCR aumentaron al segundo día posoperatorio solo en los pacientes con FA. Los puntos de corte al día 2 fueron 1.55 ng/ml para PCT y 11.25 mg/l para PCR. La prueba más eficaz fue la PCR al día 2 (AUROC: 1.00; S: 100%; E: 96.7%; VPP: 85.7%; VPN: 100%; RV+: 33.0).* **Conclusiones:** *La PCR en el segundo día posoperatorio fue la prueba más eficaz en el diagnóstico temprano de FA en los pacientes sometidos a cirugía colorrectal, con un punto de corte inferior a lo reportado en la literatura internacional.*

Palabras clave: *Fuga anastomótica. Sensibilidad y especificidad. Curva ROC. Valor predictivo de las pruebas. Procalcitonina. Proteína C reactiva.*

***Correspondence:**
Isadora G. Maldonado-Hernández
E-mail: maldonadoisa05@gmail.com

Date of reception: 15-02-2022
Date of acceptance: 04-05-2022
DOI: 10.24875/CIRUE.M22000564

Cir Cir (Eng). 2023;91(4):525-531
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Dehiscence or anastomotic leak (AL) is one of the most serious complications of digestive surgery due to the increased risk of severe complications and death[1]. The incidence of AL ranges between 0.3% and 33%[2-7], with associated mortality rates ranging from 0.5% to 45.5%[2-4,6]. Known risk factors for AL include male sex, arterial hypertension, perioperative transfusions, a Charlson comorbidity index score > 3, distal location of the anastomosis, malnutrition, immunosuppression, diabetes, chronic use of non-steroidal anti-inflammatory drugs, and radiation therapy[1,4,7,8].

Early diagnosis of AL is crucial for favorable patient outcomes. However, it is challenging in the early postoperative period in the absence of clinical signs[9]. Therefore, auxiliary laboratory and imaging modalities to enhance diagnostic efficacy are of paramount importance. The decision to perform a computed tomography scan to refine diagnosis is a common thing, which has shown a 69% sensitivity rate[6]. This stresses the need for a faster, accurate, and cost-effective diagnostic tool.

For several years, laboratory parameters measured in venous blood samples in the postoperative period have been used being 2 of these parameters procalcitonin (PCT) and the C-reactive protein (CRP). The former is a peptide prohormone whose precursor—preprocalcitonin—is initially synthesized in thyroid C cells. Under physiological conditions, serum levels are usually very low (p < 0.05 ng/ml). However, its extrathyroidal synthesis increases 100 to 1000 times due to the presence of endotoxins and cytokines such as interleukin-6, tumor necrosis factor-alpha, and interleukin-1β[10]. Therefore, PCT has been successfully used in various diagnostic contexts related to bacteremia, such as infectious complications of burns and polytrauma, bacterial meningitis, septicemia, and pancreatitis, among others[11]. CRP is a pentameric protein synthesized by the liver, and its levels increase in response to inflammation due to its proinflammatory and anti-inflammatory properties[12]. CRP has been extensively studied to differentiate bacterial from non-bacterial infections in febrile patients and can be a cost-effective alternative in settings with limited resources as part of the diagnostic algorithm for each particular clinical situation[13]. Therefore, despite extensive research on the diagnostic efficacy of PCT and CRP for AL, the cutoff points for these markers vary ranging from 50 mg/L up to 245 mg/L for CRP[14-20], and 0.27 ng/mL up to 5.27 ng/mL for PCT[15,18,19,21,22]. This variability in the cutoff points complicates the early diagnosis of AL, and no related studies have ever been conducted in the Mexican population. The objective of this study was to determine the effectiveness of serum PCT and CRP in the early diagnosis of AL in patients undergoing colorectal surgery.

Method

This was an ambispective diagnostic test study in patients undergoing elective colorectal surgery at a tertiary referral center that serves patients from northeast Mexico. Using non-probabilistic consecutive case sampling, we included patients who underwent conventional or laparoscopic anastomosis surgery from May through December 2021. Patients without preoperative PCT or CRP determinations and those who, at the time of the preoperative assessment, showed clinical or laboratory evidence of an active infection (which could elevate PCT and CRP levels) were excluded. Patients who developed concurrent postoperative infections unrelated to AL (urinary tract infection and pneumonia) were also excluded.

Procedures

Once the protocol was approved by the hospital research ethics committee, the health records of patients who underwent colorectal anastomosis surgery from May through October 2021 were retrospectively reviewed. Patients were included in the study if they met the selection criteria and had preoperative and postoperative measurements of PCT, CRP, and total leukocyte counts. Subsequently, the prospective inclusion of preoperative patients who met the criteria was considered. These patients were informed about the study objective and then invited to participate by signing an informed consent form. Overall, 4 measurements of each inflammatory marker were taken: the first one the day prior to the surgery and the following 3 on postoperative days 1, 2, and 3, all from venous blood samples. Serum PCT and CRP determinations were performed using the absorbance method with Alinity Hc (Abbott, IL, United States, 2016). Similarly, leukocyte counts were performed using an automatic cell counter with KX-21N (Sysmex Corporation, United States, 2015). To document or rule out the presence of AL, patients were monitored from the 1st postoperative day until discharge. AL was defined by findings made during reoperation, such as fecal drainage from

the wound, contrast extravasation on an enema, or the presence of air or fluid at the anastomotic site visualized by computed tomography. Hospital discharge was left to the treating physician›s criterion.

Ethical aspects

The project was submitted to the local research committee 1901 of the Mexican Social Security Institute and later approved with no. R-2021-1901-084. Data confidentiality and patient anonymity were guaranteed at all times. From the moment the protocol was approved onward, the patients who met the inclusion criteria signed a valid informed consent form to participate in the study. Similarly, the health records of patients operated on before the protocol was approved were consulted once the protocol was approved and handled with absolute discretion, respecting their anonymity.

Statistical analysis

Measures of central tendency and dispersion were estimated for quantitative variables, and proportions for categorical ones. The Mann-Whitney U test was used to compare age ranges and hospitalization days between patients with and without AL. Rates of categorical variables were compared using the chi-square test. *P* values <.05 were considered statistically significant.

The efficacy of PCT and CRP tests was evaluated using sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), area under the receiver operating characteristic curve (AUROC), positive likelihood ratio (LR+), and negative likelihood ratio (LR-), all with 95% confidence intervals. The cutoff points for PCT, CRP, and leukocyte count were determined by calculating the Youden index (S + E - 1). Estimates of such diagnostic indicators were made using the free statistical package Epidat 3.1[23]. Diagnostic efficacy indicators were considered unacceptable, acceptable, or ideal based on the following criteria[24-27]: Sn, PPV, and NPV, ideal ≥ 80%, acceptable 60% to 79.9%, and unacceptable < 60%; Sp, ideal ≥ 95%, acceptable 90% to 94.9%, and unacceptable < 90%; LR+, ideal ≥ 10, acceptable 5 to10, and unacceptable < 5; and AUROC, ideal > 0.90, acceptable 0.70 to 0.90, and unacceptable < 0.70.

Results

Laboratory determinations were conducted on 42 patients, 3 of whom were excluded (without AL) (2 with pneumonia, and 2 with urinary tract infections on the first after surgery). The 3 patients excluded from the study did not differ from the rest of the sample. Finally, a total of 39 patients were included, with a mean age of 51.9 ± 13.2 years (43.6% were women). The most widely reported comorbidity was arterial hypertension (30.8%). The most common preoperative diagnosis was cancer in 38.5% of the patients, while colorectal anastomosis was the most common type. Among the clinical and surgical variables analyzed, only age and the length of stay were significantly higher in patients with AL ($p < 0.05$ and $p < 0.0001$, respectively) (Table 1).

Postoperative course of PCT, CRP, and leukocyte count

Blood concentrations of PCT and CRP increased on the 2nd and 3rd postoperative days in patients with AL, while in those without AL, these concentrations remained at values similar to preoperative levels (Figs. 1 and 2). Total leukocyte counts increased the 1st day after surgery in patients with and without AL, remaining stable with no inter-group difference being reported on the 2nd and 3rd postoperative days (Fig. 3).

Diagnostic efficacy of PCT, CRP, and total leukocyte counts

In the search for optimal cutoff values, PCT and CRP showed ideal AUROCs, whereas for total leukocyte counts, the AUROC was only acceptable on the 3rd postoperative day. The Sn of all 3 markers was ideal on all 3 postoperative days, while the Sp was optimal only on the 2nd postoperative day for CRP. Furthermore, CRP reached the highest PPV on days 2 and 3 (85.7% and 75%, respectively) and the highest LR+ (33 and 16.5, respectively). PCT showed unacceptable Sp and PPV. All NPVs were optimal. Given the consistent increase in PCT and CRP from the 2nd postoperative day onwards, the cutoff values at that time were 1.55 ng/mL and 11.25 mg/L, respectively. Finally, most diagnostic efficacy indicators for total leukocyte counts were unacceptable (Table 2).

Discussion

In this study, CRP demonstrated superior diagnostic performance vs PCT and total leukocyte counts on the 2nd postoperative day. This result is of paramount

Table 1. Clinical and surgical characteristics of patients treated with intestinal anastomosis

	Total n = 39 (%)	Anastomotic leak Yes, n = 6 (%)	Anastomotic leak No, n = 6 (%)	*P*
Age, years (mean ± SD)	51.9 ± 13.2	63.7 ± 7.9	49.8 ± 12.8	0.011
Gender				
Woman	17 (43.6)	4 (66.7)	13 (39.4)	0.374
Man	22 (56.4)	2 (33.3)	20 (60.6)	
Comorbidities				
None	12 (30.8)	2 (33.3)	10 (30.3)	0.266
Hypertension	12 (30.8)	1 (16.7)	11 (33.3)	
Diabetes	8 (20.5)	2 (33.3)	6 (18.2)	
Other	7 (17.9)	1 (3.0)	6 (18.2)	
Preoperative diagnoses				
Cancer	15 (38.5)	4 (66.7)	11 (33.3)	0.130
Diverticular disease	7 (17.9)	0 (0)	7 (21.2)	
Intestinal perforation	7 (17.9)	1 (16.7)	6 (18.2)	
Crohn's disease	4 (10.3)	0 (0)	4 (12.1)	
NSUC	4 (10.3)	1 (16.7)	4 (12.1)	
Other	3 (7.7)	0 (0)	4 (12.1)	
Types of anastomoses				
Colon-rectum	22 (56.4)	2 (33.3)	20 (60.6)	0.321
Ileum-rectum	8 (20.5)	1 (16.7)	7 (21.2)	
Ileum-transverse	7 (17.9)	2 (33.3)	5 (15.2)	
Ileum-anus	2 (5.1)	1 (16.7)	1 (3.0)	
Suture type				
Manual	15 (38.5)	2 (33.3)	13 (39.4)	1.000
Mechanical	24 (61.5)	4 (66.7)	20 (60.6)	
Surgical approach				
Laparotomy	18 (46.2)	4 (66.7)	14 (42.4)	0.387
Laparoscopy	21 (53.8)	2 (33.3)	19 (57.6)	
Type of resection				
Right colon	14 (35.9)	2 (33.3)	12 (36.4)	0.520
Sigmoid colon	13 (33.3)	1 (16.7)	11 (33.3)	
Rectum	6 (15.4)	0 (0)	6 (18.2)	
Partial colectomy	4 (10.3)	1 (16.7)	3 (9.1)	
Total colectomy	2 (5.1)	0 (0)	3 (9.1)	< 0.0001
Length of stay, days (mean ± SD)	4.9 ± 1.8	8.5 ± 1.0	4.3 ± 0.9	

NSUC: nonspecific ulcerative colitis; SD: standard deviation.

importance in the in-hospital follow-up of patients, as it may lead to reconsidering the decision for early discharge[19]. One important aspect of this study is the cutoff value for the CRP. In this work, it was found to be 11.25 mg/L on day 2, while in international studies, it varies widely, ranging from 44.32 mg/L in Turkey[28] up to 245.64 mg/L in Poland.[18] Additionally, the postoperative days on which the best cutoff values were reported are also controversial in the literature, ranging from day 2 in Croatia[15] up to day 6 in Portugal[16]. These discrepancies also apply to PCT. For example, this study determined a cutoff value of 1.55 ng/mL on day 2, while levels ranging from 0.24 ng/mL in Poland[21] up to 5.27 ng/mL in Malaysia[22] have been reported. Similarly, the postoperative days for the best cutoff values are also variable ranging from day 3 in Poland and Malaysia[18,21,22] up to day 5 in Spain[29]. Therefore, we can see that cutoff values for both inflammatory markers are relatively variable among populations. It is worth considering that no similar studies were found in the Mexican population, making this study necessary to strengthen the scientific evidence available for Mexican surgical practice.

Patients in this study had lower diagnostic levels for both markers vs other populations, suggesting that, with values lower than those internationally published,

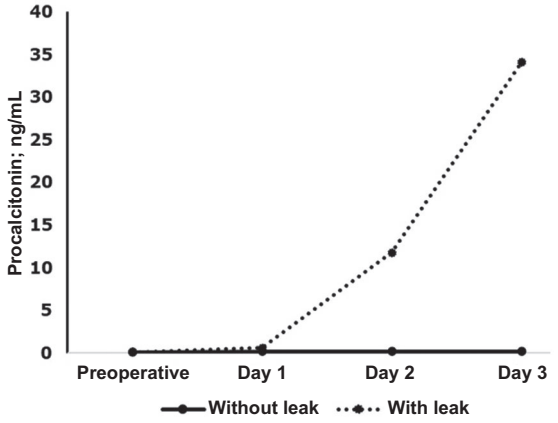

Figure 1. *Median preoperative and postoperative concentrations of procalcitonin in 6 patients with anastomotic leak vs 33 patients without anastomotic leak.*

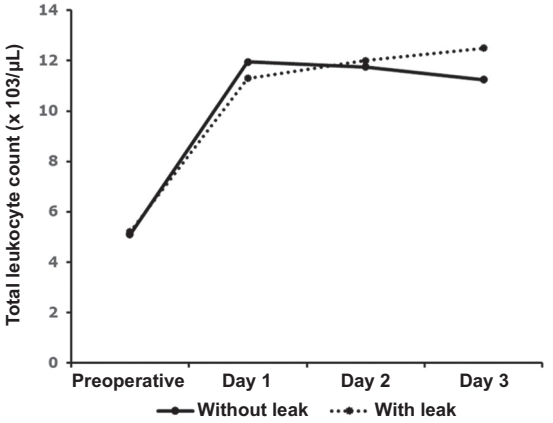

Figure 3. *Median preoperative and postoperative total leukocyte count in 6 patients with anastomotic leak vs 33 patients without it.*

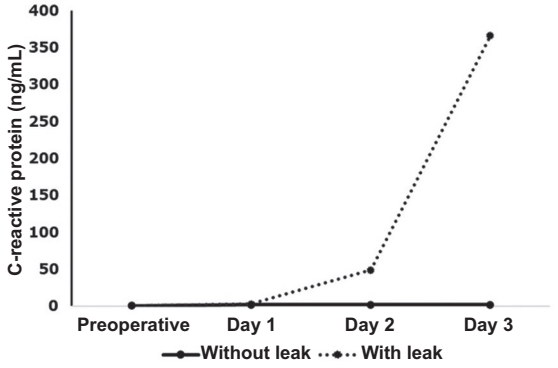

Figure 2. *Median preoperative and postoperative C-reactive protein concentrations in 6 patients with anastomotic leak vs 33 patients without it.*

a high degree of suspicion of AL can be warranted. Based on this, it seems reasonable to postpone the discharge of a postoperative patient with such CRP values (the inflammatory marker that achieved the highest diagnostic efficacy indices) while the diagnosis is being confirmed. Additionally, this study demonstrated the postoperative progression of circulating concentrations of both inflammatory markers along with the total leukocyte count. On this topic, we should mention that although the leukocyte count is a routine laboratory test, it showed poor diagnostic efficacy compared to CRP and PCT.

Based on the results of this study, it is recommended to monitor CRP or, for the lack of it, PCT levels daily, as they showed a consistent increase from the 2nd postoperative day onwards, at least, in this population. Similarly, we saw that both markers offered very high Sn but with different Sp. In many of the studies consulted, a lower Sn for CRP vs this study was evident, even with higher diagnostic cutoff values. For example, a study conducted in France by Benoit et al.[30] achieved a Sn rate of 63.6%[30]. Other studies conducted in Spain[29], Portugal[16], and Brazil[14,20] reported slightly higher results, but none reached rates close to 100%, while 2 studies conducted in Poland found Sn rates of 92%[21], and 100%[18]. The Sp rate of this protein ranged from 66.1% in Turkey[28] up to 98% in Poland[18].

For PCT, international variability is even more evident, with Sn rates as low as 69% in Croatia,[15] and up to 100% in Malaysia.[22] The Sp rate of this marker also ranged from 68%[21] up to 100%[18] in Poland. These discrepancies in the diagnostic efficacy of both tests represent a challenge for surgeons using scientific literature, especially in Mexico, where no records of any articles related to these markers were found. Based on these results, we should mention that the role of CRP as a useful and accurate test for the early diagnosis of AL is evident. As previously mentioned in the theoretical framework of this study, the physiological importance of this marker lies in its proinflammatory and anti-inflammatory properties[12]. In fact, the CRP may very well become a cost-effective option among the auxiliary diagnostic resources available to surgeons in settings with limited resources[13].

Limitations

We should acknowledge the small sample size, which is likely due to the limited number of intestinal anastomoses performed, most likely due to the restrictions

Table 2. Diagnostic efficacy of postoperative serum measurements of procalcitonin, C-reactive protein, and total leukocyte counts in the early diagnosis of anastomotic leaks

Marker	AUROC (95%CI)	Cutoff value	Sn (95%CI)	Sp (95%CI)
PCT Day 1	0.94 (0.85-1.00)	0.35 ng/mL	100% (91.7-100)	69.7% (52.5-86.9)
PCT Day 2	1.00 (1.00-1.00)	1.55 ng/mL	100% (91.7-100)	81.8% (67.1-96.5)
PCT Day 3	1.00 (1.00-1.00)	13.4 ng/mL	100% (91.7-100)	84.9% (71.1-98.6)
CRP Day 1	0.83 (0.66-0.99)	2.1 mg/L	100% (91.7-100)	51.5% (33.0-70.1)
CRP Day 2	1.00 (1.00-1.00)	11.25 mg/L	100% (91.7-100)	96.7% (89.6-100)
CRP Day 3	1.00 (1.00-1.00)	63.85 mg/L	100% (91.7-100)	93.9% (84.3-100)
Leukocyte count Day 1	0.43 (0.24-0.63)	10.8 mil/µL	100% (91.7-100)	27.3% (10.6-44.0)
Leukocyte count Day 2	0.52 (0.33-0.71)	11.7 mil/µL	83.3% (45.2-100)	45.5% (27.0-64.0)
Leukocyte count Day 3	0.86 (0.76-1.00)	11.6 mil/µL	100% (91.7-100)	57.6% (39.2-76.0)
Marker	**PPV (95% CI)**	**NPV (95%CI)**	**LR+ (95%CI)**	**LR- (95%CI)**
PCT Day 1	37.5% (10.7-64.4)	100% (97.8-100)	3.30 (1.97-5.54)	*
PCT Day 2	50.0% (17.5-82.4)	100% (98.2-100)	5.50 (2.67-11.34)	*
PCT Day 3	54.5% (20.6-88.5)	100% (98.2-100)	6.60 (2.94-14.80)	*
CRP Day 1	27.3% (6.4-48.2)	100% (97.1-100)	2.06 (1.45-2.93)	*
CRP Day 2	85.7% (52.7-100)	100% (98.4-100)	33.0 (4.79-227.36)	*
CRP Day 3	75.0% (38.7-100)	100% (98.4-100)	16.50 (4.31-63.22)	*
Leukocyte count Day 1	20.0% (4.0-36.0)	100% (94.4-100)	1.38 (1.12-1.69)	*
Leukocyte count Day 2	21.7% (2.7-40.8)	93.8% (78.8-100)	1.53 (0.95-2.46)	0.37 (0.06-2.28)
Leukocyte count Day 3	30.0% (7.4-52.6)	100% (97.4-100)	1.38 (1.12-1.69)	*

*Impossible to estimate as no false negative results were reported.
95%CI: 95% confidence interval; AUROC: area under the Receiver Operating Characteristic curve; LR-: negative likelihood ratio; LR+: positive likelihood patio; NPV: negative predictive value; CRP: C-reactive protein; PCT: procalcitonin; PPV: positive predictive value; Sn: sensitivity; Sp: specificity.

imposed by the COVID-19 pandemic. This could have impacted the estimation of diagnostic efficacy indicators, which means that these results should be interpreted with caution and further multicenter studies in the Mexican population should go on. A strength of this study is the inclusion of different measures of diagnostic efficacy, which could provide a comprehensive view of the diagnostic performance of each test.

Conclusions

CRP on the 2nd postoperative day was the test with the highest efficacy in the early diagnosis of AL in patients undergoing colorectal surgery, with a cutoff value lower than the one reported in the international literature. It is recommended to continue this line of research to obtain more precise estimates of both cutoff values and diagnostic efficacy indicators. This will allow surgeons to have timely evidence to support their clinical decisions, whether for early discharge or closer in-hospital monitoring.

Acknowledgments

The authors wish to thank the clinical laboratory staff at the High Specialty Medical Unit No. 25 of the Mexican Social Security Institute in Monterrey, Nuevo León, Mexico for their assistance in conducting the tests.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Application of artificial neural networks in assigned leadership and academic success in medical graduates

Aplicación de redes neuronales artificiales en el liderazgo asignado y el éxito académico en egresados de medicina

Efrén R. Ponce-Rosas[1], Rocío Dávila-Mendoza[1], Irma Jiménez-Galván[1], Miguel A. Fernández-Ortega[2], Armando Ortiz-Montalvo[3], and Guillermo Fajardo-Ortiz[4]*

[1]Subdivisión de Medicina Familiar, División de Estudios de Posgrado, Facultad de Medicina; [2]Centro de Investigación en Políticas, Población y Salud; [3]Secretaría de Educación Médica, Facultad de Medicina; [4]Subdivisión de Educación Continua, División de Estudios de Posgrado, Facultad de Medicina. Universidad Nacional Autónoma de México, Ciudad de México, México

Abstract

Objective: *To apply an artificial neural networks analysis (ANN) model to identify variables that predict assigned leadership and academic success in graduates of six generations of medical school.* **Method:** *Analytical, retrospective, comparative study. A total of 1434 graduates participated. A questionnaire was sent to them by e-mail including a voluntary participation consent. A multivariate statistical analysis using multi-layer perceptron ANN, decision trees and driver analysis was performed.* **Results:** *The ANN identified seven independent variables that predicted professional success and eight for leadership in medical graduates. The decision trees identified significant differences in the variables professional performance (p = 0.000), age (p = 0.005) and continuing education activities (p = 0.034) related to professional success, and for leadership the variables gender (p = 0.000), high school grades (p = 0.042), performing clinical practice during the social service year (p = 0.002) and continuing education activities (p = 0.011).* **Conclusions:** *The ANN identified the main independent predictor variables of professional success and leadership of the graduates. This study opens up two new lines of research little studied with the techniques of in the area of medicine.*

Keywords: *Medical career. Graduate follow-up. Leadership. Academic success. Artificial neural networks.*

Resumen

Objetivo: *Aplicar un modelo de análisis de redes neuronales artificiales (RNA) para identificar las variables que predicen el liderazgo asignado y el éxito académico en egresados de seis generaciones de la carrera de Medicina.* **Método:** *Estudio analítico, retrospectivo y comparativo. Participaron 1434 egresados. Se envió un cuestionario por correo electrónico que incluyó el consentimiento de participación voluntaria. Se realizó análisis estadístico multivariado mediante RNA del tipo perceptrón multicapa, árboles de decisión y análisis de impulsores.* **Resultados:** *Las RNA identificaron siete variables independientes que predijeron el éxito profesional y ocho para el liderazgo en los médicos egresados. Los árboles de decisión identificaron diferencias significativas en las variables desempeño profesional (p = 0.000), edad (p = 0.005) y actividades de educación continua (p = 0.034) relacionadas con el éxito profesional, y para el liderazgo las variables sexo (p = 0.000), promedio en el bachillerato (p = 0.042), realizar práctica clínica en el servicio social (p = 0.002) y actividades de educación continua (p = 0.011).* **Conclusiones:** *Las RNA identificaron las principales variables independientes predictoras del éxito profesional y el liderazgo de los egresados. El estudio abre dos líneas de investigación poco estudiadas con las técnicas de RNA en el área de la medicina.*

Palabras clave: *Carrera de Medicina. Seguimiento de egresados. Liderazgo. Éxito académico. Redes neuronales artificiales.*

***Correspondence:**
Efrén R. Ponce-Rosas
E-mail: ipr@unam.mx

Date of reception: 14-06-2022
Date of acceptance: 29-07-2022
DOI: 10.24875/CIRUE.M22000565

Cir Cir (Eng). 2023;91(4):532-542
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

For Universidad Nacional Autónoma de México (UNAM), and particularly its School of Medicine, follow-up studies of graduates represent a very important area thanks to the information obtained from students who graduate from their study programs, and their potential impact on the professional, educational, and social practice in Mexico. In UNAM School of Medicine current study plan (plan 2010), follow-up studies of graduates are included to obtain information on the following general areas: job market, professional profile, access to the national medical residency system, and academic and professional performance. The same study plan emphasizes the need to conduct comparative studies of its graduates in their professional performance. Technically, follow-up studies are not easy to conduct due to the geographical dispersion of graduates and their various workplaces, whether in the public or private sector, medical administration, and management, among other factors. For these reasons, this follow-up study aimed at investigating 2 important areas on the Medical School: leadership and academic success. The approach to studying these 2 aspects is predictive, using multivariate techniques that have been increasingly used in medical education research: artificial neural networks (ANN).

ANNs are information processing systems whose structure and function are inspired by biological neural networks[1]. The term "neural network" is applied to a family of models characterized by a large parameter space and flexible structure, derived from studies on the functioning of the brain[2].

A neural network is defined as a set of simple processing elements called nodes or neurons, which are interconnected by connections with modifiable numeric values, called weights[1]. Depending on the relationship model, there can be 1 or more layers, or nodes that are hidden or not visible, which communicate with each other, making synaptic weights not easily to interpret.

In a neural network with a set of variables, it is important to understand the general architecture of the network. There are 2 main types: the multi-layer perceptron network and the radial basis function network. Both are predictor functions, also called inputs or independent variables, which minimize the prediction error of the target variables (dependent or output variables).

Unlike linear regression, characterized by a rigid model and assumptions, neural networks are flexible. Also, they do not make a priori assumptions on the type of relationships that exist between independent and dependent variables or require theoretical assumptions on data distribution either. Instead, the shape of the relationships between variables is determined during the learning process of the neural network itself, meanig that neural networks learn by themselves.

Figure 1 illustrates the basic architecture of an ANN. The inputs are predictors, or independent variables, and the output layer consists of all categories of response for the dependent variable. The hidden layer are the nodes, or units not observable in the relationships between variables, which are formed by the forces or interconnection weights between neurons (arrows in Fig. 1). An example of this, a few dotted lines in a lighter color are shown, which are interpreted as having lower weights, i.e., lower predictive value.

Therefore, a neural network is a massively parallel distributed processor with a natural propensity to store experimental knowledge and make it available for use. It resembles the brain in 2 aspects: 1) knowledge is acquired by the network through a learning process, and 2) interneuronal connection strengths, known as synaptic weights, are used to store knowledge[2].

In medicine and education, studies have been reported in which ANNs have been applied as a multivariate prediction technique. In medicine, various studies have been conducted on this topic[1,3-10], and in education, ANNs have mainly been used to predict student performance, academic success, and the selection of medical residency candidates[11-23]. However, no studies have ever been conducted of ANNs used to predict leadership in students.

In the present study, since we aimed at using the ANN technique, no in-depth review of the concepts related to leadership and the success of graduates in the field of Medicine was ever conducted. In any case, readers are referred to the consulted works on success and leadership for further reference[24-31]. Notably, the study conducted by Sánchez[25] in 2015 stands out, who conducted a literature narrative review on leadership (which is complex to define and has multiple definitions in the literature) and highlighted the characteristics of leadership as a trait vs process or assigned vs emergent leadership. In the present study, the type of leadership under consideration is assigned leadership. On the other hand, Gatica et al.[24] analyzed the variables associated with academic success in undergraduate students at UNAM Medical School.

The objective of this study was to apply an ANN analysis model to identify the variables that predict

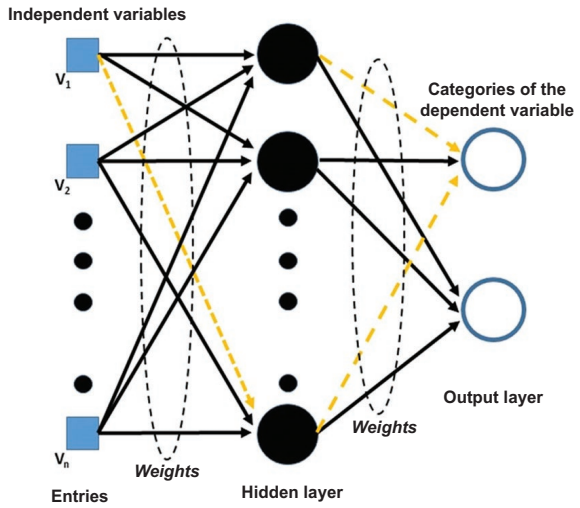

Figure 1. *Basic architecture of an artificial neural network.*

assigned leadership and academic success in graduates from 6 generations of the medical degree program at UNAM Medical School.

Method

This was a multivariate, analytical, retrospective, and comparative study of 1434 graduate students from the medical degree from the 2004-2009 generations graduated at UNAM Medical School. A questionnaire with 62 variables was sent, with 29 independent variables distributed across 8 different areas: demographics, family, student's educational background in middle and high school, failure in subjects, suspension of studies, opinions on the curriculum of the medical program, admission to medical postgraduate programs, the job market, and professional performance in the public or private sector. The dependent variables were academic (professional) success and assigned leadership activities.

Operational definitions

In the study, assigned leadership was regarded as having served as a student technical advisor at the Medical School, a group leader or representative, or a student leader in academic events during the medical degree. Academic (professional) success was regarded as holding managerial or middle management positions, professional recognition by peers, and satisfaction with the economic income received after graduating. The questionnaire content was validated by 8 faculty members from the Medical School with over 10 years of teaching experience.

It was deemed relevant that for the follow-up studies of the graduates, at least, 5 years should have gone by since graduation to assess the professional development achieved with some stability in their careers. For this reason, the generations of graduates who obtained their medical degree from 2004 through 2009 were selected. Therefore, the latest generation (2009) had graduated, at least, 6.5 years ago.

Data curation method

An e-mail was sent to all graduates inviting them to participate in the study voluntarily and answer an electronic questionnaire. The e-mail addresses of the graduates were provided by the Medical School Office of Academic Services. The invitation included the objective of the study, its academic importance, and voluntary consent form to respond to the attached questionnaire. A period of 2 to 10 months (from August 2017 through April 2018) was given to obtain responses. Questionnaires were administered in person to those graduates who did not wish to respond electronically, but who were willing to participate.

Statistical analysis

The information obtained was stored in the statistical program SPSS v.25. Multivariate statistical analysis was performed using data mining techniques: multilayer perceptron neural networks (ANN), decision trees (DT), and boosted trees (BT). These 3 analysis techniques combined were used to determine the most important variables which, in their combined and synergistic interaction, predicted (ANN), classified and compared the response categories (DT), and determined the performance coefficients (BT). These techniques were applied to the response categories of assigned leadership during the undergraduate program and academic success during the graduates' professional performance and practice. Due to its technical and methodological importance,[2] to reproduce the ANN model used, table 1 describes the parameters and specifications used to calculate the neural network model.

Ethical considerations

The project was approved by UNAM Medical School Research Division Research and Ethics Committee, with registration no. 04-2013. A consent form for voluntary

Table 1. Parameters and specifications of the calculated neural network model

Parameter	Specifications
Type of neural network	Multilayer perceptron
Independent variables (Factors)	29 variables
Dependent variables	Assigned leadership and academic success
Initial model point	Fixed random
No. of processed and calculated models	10 models (selection of the model with the lowest entropy error)
Sample partitions	Training 70%, testing 30%, and reserved 0%
Architecture	Automatic selection
Hidden layers	1
Training	Supervised, batch
Optimization algorithm	Scaled conjugate gradient
Initial lambda	0.0000005
Initial sigma	0.00005

participation in the study was e-mailed to the 1434 graduate students. The study fully complied with the ethical research recommendations in education, including the Ethical Standards of the American Educational Research Association[32], the Code of Professional Responsibilities in Educational Measurement by the National Council of Measurement in Education[33], the Code of Fair Testing Practices in Education[34], and the Universal Declaration on Bioethics and Human Rights[35].

Results

Information was obtained from 1434 graduates from UNAM Medical School, spanning 6 generations (2004-2009). Two former works were conducted with the same graduate students: the first one was a descriptive study[36] including the overall profile of the 1434 graduates, educational backgrounds, career aspects, and satisfaction with professional training. The second study analyzed phenomena related to subject failure and discontinuous trajectories through multivariate discriminant analysis[37].

Table 2 illustrates the results of entropy error, incorrect forecasts, and the area under the ROC (Receiver Operating Characteristic) curve obtained from the calculated ANN, both for academic success and assigned leadership. This table 2 also illustrates that Model 1 was the best suited for professional success (entropy error, 176.5 in the training sample), while Model 6 was the best suited one for assigned leadership (entropy error, 527.5 in the same type of sample).

To identify the most important independent variables and their correlation with the dependent variable of professional success, performance coefficients of the chosen ANN model (no. 1 in table 2) were calculated. For this purpose, a BT analysis was performed, assigning values to variables (in standardized z-units) based on their level of importance and performance. Table 3 shows the performance coefficients of the most important and well-evaluated independent variables that predicted academic (professional) success, as obtained in figure 2 (upper right quadrant).

Additionally, a CHAID (Chi-Squared Automatic Interaction Detector) type DT analysis was conducted, comparing the categories of all independent variables, and selecting only those where significant differences were found. Figure 3 illustrates the DT with the CHAID analysis calculated for the independent variables that showed statistically significant differences in the graduates' academic success.

The most important variables with statistically significant differences regarding academic success included good professional performance (p = 0.000), being 34 years of age or younger (p = 0.005) and participating in 1 or more activities of continuous medical education per year (p = 0.034). The correct classification of predicted cases according to the observed cases in the DT was 100%.

Similarly, to identify the most important independent variables and their correlation with the dependent variable "assigned leadership," performance coefficients of the chosen model (no. 6 in table 2) were calculated. Table 4 shows the performance coefficients of the most important and well-evaluated independent variables that predicted assigned leadership, as shown in figure 4.

Figure 5 illustrates the CHAID and DT analysis calculated for the independent variables that showed statistically significant differences in assigned leadership among graduates. The most important variables in which statistically significant differences related to assigned leadership were found included gender (p = 0.000), in women, performing clinical practice activities during social service (p = 0.000) and having a mean high school GPA of 9 to 10 (p = 0.042). In men, performing clinical practice activities during social

Table 2. Calculated models of ANNs and their values obtained for entropy error, incorrect predictions, and areas under the ROC curve

Academic success (professional)						
ANN	**Entropy error**		**Incorrect prognosis (%)**		**Area under the ROC curve* (%)**	
Model	**Training**	**Test**	**Training**	**Test**	**Managerial position and better income**	**Professional recognition and enjoying the work done**
M1	176.5	80.5	5.0	4.9	72.1	72.1
M2	193.0	78.1	5.0	4.8	65.8	65.8
M3	196.7	72.1	5.1	4.5	66.8	66.8
M4	195.4	74.8	5.1	4.5	66.3	66.3
M5	195.2	80.7	5.1	4.6	63.5	63.5
M6	200.0	68.0	5.4	3.9	68.2	68.2
M7	197.2	82.3	5.0	4.8	60.7	60.7
M8	183.5	83.6	4.9	5.1	68.6	68.6
M9	209.5	53.1	5.5	3.6	70.0	70.0
M10	180.0	87.5	4.9	5.1	68.8	68.8
Assigned leadership						
Model	**Entropy error**		**Incorrect prognosis (%)**		**Area under the ROC curve * (%)**	
	Training	**Test**	**Training**	**Test**	**Technical advisor, team leader**	**None**
M1	565.5	236.5	28.4	25.9	67.4	67.4
M2	554.3	252.6	27.8	27.3	67.0	67.0
M3	559.1	237.1	26.2	28.1	68.6	68.6
M4	553.6	248.1	28.9	26.4	67.8	67.8
M5	577.2	216.0	29.5	25.0	69.7	69.7
M6	527.5	264.8	26.9	28.5	69.0	69.0
M7	549.6	261.8	28.1	27.6	65.8	65.8
M8	677.3	227.6	27.3	27.7	67.4	67.4
M9	561.3	239.6	27.6	27.1	68.2	68.2
M10	552.1	241.8	27.8	27.0	69.3	69.3

*The ROC curve provides the level of performance of the ANN model.
ANN: artificial neural network.

service (p = 0.002) and participating in 1 or more activities of continuous medical education per year (p = 0.011) were significant. In this CHAID analysis, the correct classification of predicted vs observed cases in DT was 71.9%.

Discussion

In the field of medicine, ANN techniques have been used for various purposes: Montaño[1] used them in his doctoral thesis for survival analysis and addictive behaviors; Trujillano et al.[3,6,7] reported on their use primarily to predict quantitative measurements of patients in medical practice (mortality, survival, diagnosis, image processing, electrocardiograms, electroencephalograms, optimal drug dosages, intensive care medicine, and hospital mortality); Hernández and Lorente,[8] and Ortiz et al.[9] used ANN techniques for predictive studies of factors associated with breast cancer; Palmer et al.,[10] used ANN techniques to predict ecstasy consumption;

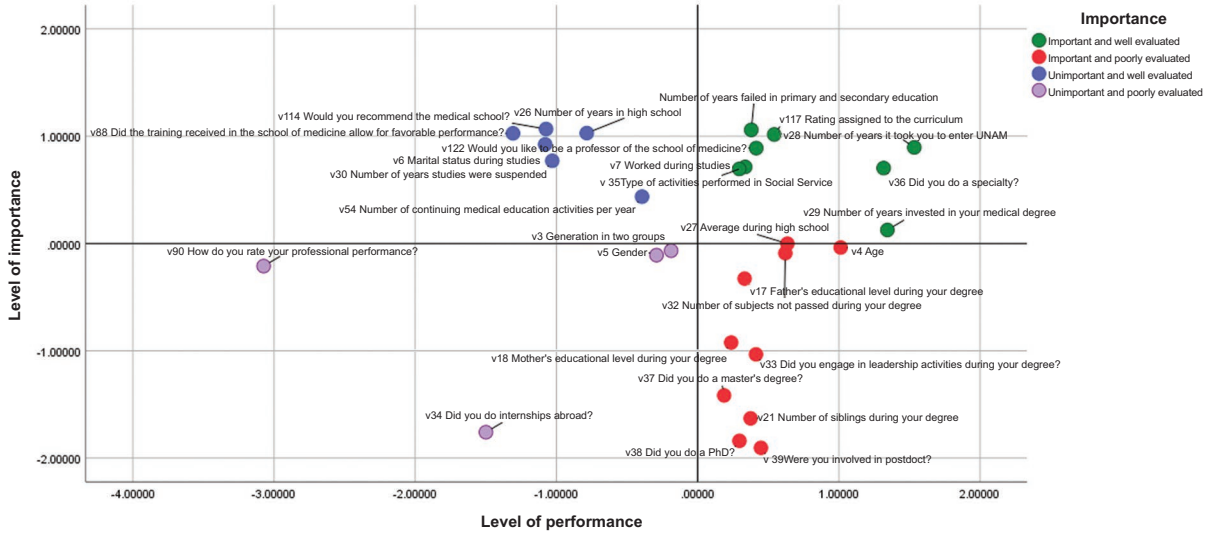

Figure 2. *Independent variables based on their level of importance and performance in predicting professional success.*

Table 3. Coefficients of performance of predictor variables for academic success

Performance coefficients (Boosted tree)	Most important and well-assessed independent variables that predicted academic success	Performance coefficients (Boosted tree)
0.98	Would you recommend this Medical School?	0.98
0.97	No. of years of high school attendance	0.97
0.97	Did the training received at the Medical School allow favorable professional performance?	0.97
0.93	Marital status during studies	0.93
0.92	Would you like to become a professor at the Medical School?	0.92
0.88	No. of years of suspension of studies in the medical program	0.88
0.77	No. of continuing medical education activities per year	0.77

Table 4. Coefficients of performance of predictor variables for assigned leadership

Performance coefficients (Boosted tree)	Most important and well-assessed independent variables that predicted assigned leadership
0.98	Would you recommend the Medical School?
0.97	No. of years of high school attendance
0.97	Rating assigned to the curriculum you studied at the Medical School
0.93	Marital status during studies
0.93	Years it took you to enter UNAM
0.92	Would you like to become a professor at the Medical School?
0.88	No. of years of suspension of studies in the medical degree
0.77	No. of continuing medical education activities per year

and Menacho[38] to predict academic performance. Additionally, Basogain[39] mentions various applications of ANN in medicine (image processing, medical diagnosis, robotics, and classification of data from sensors). These referenced works used ANNs for aspects of medical practice, with a relatively small no. of variables, primarily quantitative, on a continuous or ratio scale.

With the development of both open-source and proprietary software in the current century, ANNs have ventured into the social sciences. In the field of education, particularly in medicine, few works have been published on ANNs. Menacho[38] used ANNs to predict the academic performance of medical students using school-related variables. Other authors have also used them, primarily to forecast academic performance in various areas: Cataldi et al.[11] used ANNs to predict academic performance in a sample of 450 undergraduate students; Zacharis[12] studied the academic

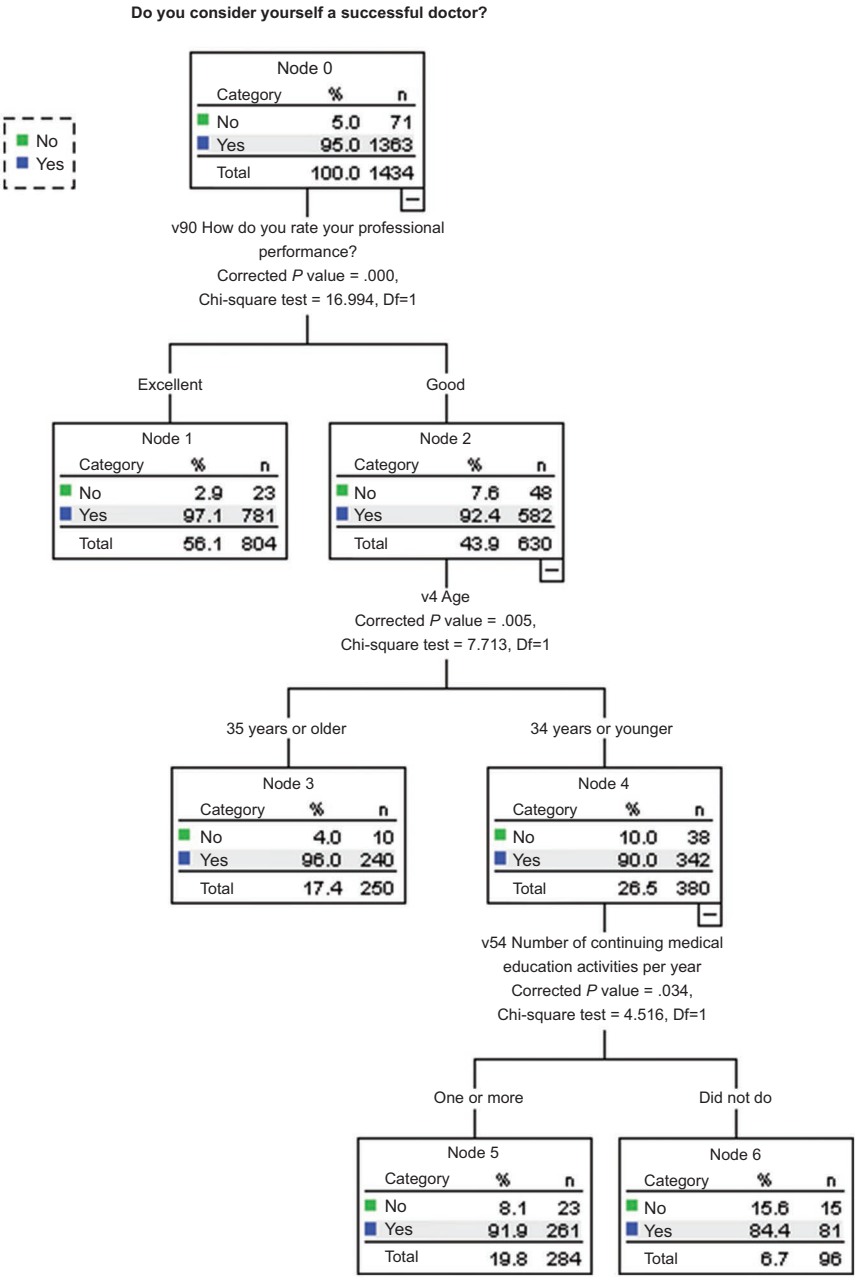

Figure 3. *Decision tree of independent variables that showed significant differences associated with professional success.*

performance of 265 college students of mechanical engineering; and Salgueiro et al.[13] reported on their progress using ANNs to predict the abilities of college students. Apparently, studies using ANNs have a certain preference for predicting academic performance or achievement as confirmed in the research from Ahmad and Shahzadi [15], Bahadir[16], and Baashar et al.[17] We should mention that most of these authors consider the grades obtained in the subjects taken by the students as the main independent variables in their ANN models. Our study examined 29 variables distributed across 8 different areas described in the section "Method" above.

Regarding academic success, Agdelen et al.[14] studied a total of 154 first-grade students of engineering and architecture at college level. They included 20 independent variables (social, economic conditions, and environmental factors) in their ANN model, and the dependent variable was categorized into 5 levels of academic success, without specifying the names of

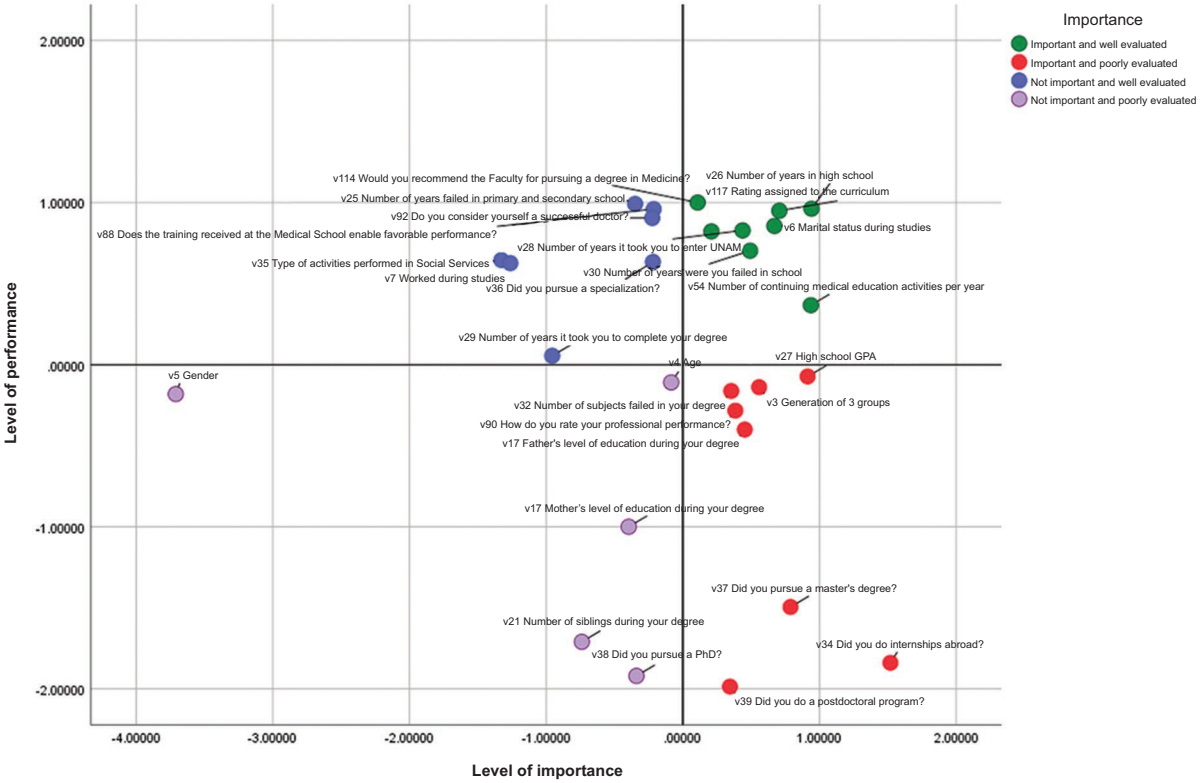

Figure 4. *Independent variables based on their level of importance and performance in predicting assigned leadership.*

these predictive categories. These authors used a radial basis function type ANN model; our study used the multilayer perceptron type because it is supervised and provided a better interpretation of the results. The mentioned authors[14] only calculated one ANN model, but with different rates of the training and test samples. In the present research, a total of 10 random models were calculated with the same fixed rates of training (70%) and test (30%), as mentioned in the "Statistical analysis" section above. These same authors[14] cite Büyüköztürk and Deryakulu (2002), Begik (1997), Parke and Welsh (1998), and Perçin (1998) as other researchers who studied academic success; however, they did not use the ANN technique but primarily resorted to linear regression.

López et al.[19] conducted a study among 1614 college students majoring in biochemistry, in which they analyzed 8 independent variables to predict academic performance. The authors used both types of ANNs (multilayer perceptron and radial basis function) with the same variables and concluded that while both types had good predictive capacity, the adjustments provided by the multilayer perceptron networks were superior to those obtained with the radial basis function networks. Borracci and Arribalzaga[18] used ANNs for the classification and selection of candidates for medical residencies, while Porcel et al.[20] and Acosta and Pizarro[23] used ANNs to predict academic performance.

Regarding assigned leadership in the field of medicine, no publications were found using ANNs. The consulted works mainly focused on the conceptualization, types, importance, teaching in medical school, and other characteristics related to leadership training in the medical field[24,25,27-31].

As for the limitations of the present study, we should mention that the results obtained cannot be generalized since, although the sample of graduates was large (1434 medical graduates from 6 generations), it was not random or voluntary. Another bias inherent to retrospective surveys is the possibility of obtaining information that cannot be verified, but which is acknowledged to have existed. Another limitation was the operational definition of the 2 dependent variables (assigned leadership and academic success); graduates gave their responses based on events or facts through their own opinions or personal perceptions.

Regarding the limitations of the ANN technique used, the results depend on several elements: the number and order of input (independent) variables, the random

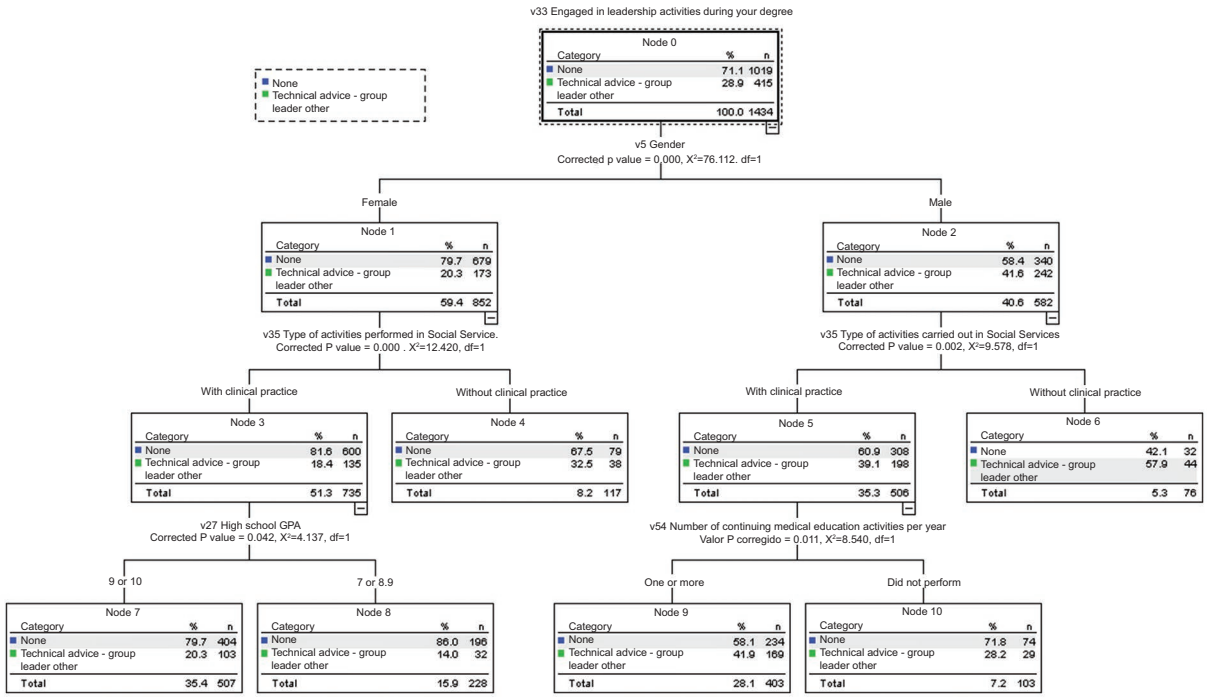

Figure 5. *Decision tree of independent variables that showed significant differences associated with assigned leadership.*

starting point of the model, and the order of the categories introduced into the independent variables. Another limitation is that ANNs assign pseudo-probability values[40] to variables that are predictors of the dependent variable, which means that they need to be complemented with more robust methods that do quantify the value of the performance coefficients seen in Figs. 2 and 4, such as CHAID-type DT[41] (Figs. 3 and 5) and BT[42].

Among the strengths of this study, we should mention that 10 random ANN models were calculated, and the best model was selected based on the lowest entropy error. The rationale for this decision is that the calculated network learns by itself by examining individual records (70% of the sample in this study), generating a prediction for each record, and making weight adjustments when it gets a prediction wrong[40]. This process is repeated many times, and the network continues to improve its predictions until it reaches 1 or more stop criteria considering the values of the lambda and sigma optimization algorithm specified in table 1.

To verify and validate the results of the 10 calculated models and ensure the consistency of the values obtained, a fixed random starting number in the statistical program was selected. Although these aspects were not mentioned in the consulted articles, they are considered important and necessary to verify the results obtained from the calculated models and make sure that readers understand the parameters used in the study, whose design and neural network architecture are described in the "Method" section above and specified in table 1.

Another strength is the size of the study sample, which we consider large (1434 graduates). This characteristic increases the predictive capacity of the ANN technique since 70% of the sample was used to "train" the ANN and "learn" to predict the relationships between independent and dependent variables. The supplementary analysis on the importance and performance of the independent variables (BT) allowed us to obtain performance coefficients; their highest values clearly identified the main independent predictor variables (7 variables for success and 8 for leadership).

Calculating 10 ANN models allowed us to choose the one with the lowest entropy error, which is shown in the ROC curves that explain the expected performance of a classifier according to the areas under the curve, always ranging between 0 and 1; the higher the value, the better the classifier, and the higher the rate of correctly classified individuals (Table 2).

Another strength is having complemented the ANN with a CHAID-type DT analysis[41] to identify significant nested variables, and BT[41] to determine performance coefficients. These techniques allowed for a better understanding and interpretation of the ANN results.

Finally, an additional strength is having followed the general guidelines recommended by the National Association of Universities and Higher Education Institutions[43] on the waiting period for graduates from the program (at least 5 years) before conducting follow-up studies.

Conclusions

This study is consistent with the current curriculum guidelines of UNAM School of Medicine, which emphasizes the importance of conducting follow-up research on its graduates to strengthen and make curricular adjustments[44].

The ANN identified the main variables that predicted academic success and assigned leadership roles among the medical graduates. The ANN technique is straightforward and statistically favorable as it does not require the robust theoretical assumptions of linear regression analysis. However, it is advisable to have theoretical training in neural networks for its use. Additionally, ANN analysis should be complemented with other statistical techniques, such as BT to measure performance coefficients and DT (nested significant independent variables) to identify the specific weight and statistical significance of predictor variables in more detail and depth.

The use of the multilayer perceptron-type ANN technique in this study identified the main independent predictor variables (7 for success and 8 for leadership). Furthermore, the study delved into 2 less-studied research areas in the field of medicine using ANN techniques.

Acknowledgments

The authors would like to thank Omar Rodríguez Mendoza for his assistance in translating the abstract into English.

Funding

The authors declare that the project was evaluated and registered at UNAM Medical School Research Division with registration no. 041/2013, which provided the corresponding funding to support the research project.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Prevalence of risk factors associated with development of capsular contracture after placement of breast implants

Prevalencia de factores de riesgo asociados al desarrollo de contractura capsular posterior a la colocación de implantes de mama

Yazmin Sánchez-Delgado, José B. Mendoza-Ramírez, Brenda Gómez-Calva, Beatriz H. Kushida-Contreras, Juan A. Ugalde-Vitelly, José A. García-García, and Jorge A. Gómez-Navarro*

Departamento de Cirugía Plástica, Estética y Reconstructiva, Hospital General de México Dr. Eduardo Liceaga, Ciudad de México, México

Abstract

Objective: *To determinate the prevalence of the main risk factors associated with development of capsular contracture after placement of breast implants in a referral center.* **Method:** *Retrospect study on 210 patients where sociodemographic variables, Baker's clinical scale and histopathological results were recorded.* **Results:** *Statistical analysis of 210 patients was performed; 98.1% were women. The average age was 47 years (± 11), body mass index 25 (± 10) and onset of symptoms 13 years (± 8.5). Sociodemographic factors: domestic work 63.3%. Alcoholism 70% and smoking 65.7%. The main reason for consultation was pain plus deformity in 81.6%. The risk factors with statistical significance were the history of trauma, with 83.3% (p = 0.004), and the subglandular plane, with 73.8% (p = 0.0115). Histopathology: fibrous capsule 81.4%.* **Conclusions:** *The prevalence of the risk factors described are similar to those reported in the literature. Only for the history of trauma and the subglandular plane there was statistical significance.*

Keywords: *Capsular contracture. Epidemiology. Risk factors. Backer's classification.*

Resumen

Objetivo: *Determinar la prevalencia de los principales factores de riesgo asociados a contractura capsular posterior a mamoplastia de aumento en un centro de referencia.* **Método:** *Estudio retrospectivo de 210 pacientes en el que se registraron variables sociodemográficas, escala clínica de Baker y resultados histopatológicos.* **Resultados:** *Se realizó el análisis estadístico de 210 pacientes; el 98.1% fueron mujeres. La edad promedio fue de 47 años (± 11), el índice de masa corporal 25 kg/m^2 (± 10) y el inicio de los síntomas 13 años (± 8.5). Factores sociodemográficos: labores domésticas 63.3%. Alcoholismo 70% y tabaquismo 65.7%. El principal motivo de consulta fue dolor más deformidad, en el 81.6%. Los factores de riesgo con significancia estadística fueron el antecedente de traumatismo, con un 83.3% (p = 0.004), y el plano subglandular, con un 73.8% (p = 0.0115). Histopatología: cápsula fibrosa 81.4%.* **Conclusiones:** *La prevalencia de los factores de riesgo descritos es similar a lo reportado en la literatura. Solo para el antecedente de traumatismo y el plano subglandular hubo significancia estadística.*

Palabras clave: *Contractura capsular. Epidemiología. Factores de riesgo. Clasificación de Baker.*

***Correspondence:**
Brenda Gómez-Calva
E-mail: brendagomezc95@hotmail.com

Date of reception: 06-06-2022
Date of acceptance: 26-08-2022
DOI: 10.24875/CIRUE.M22000566

Cir Cir (Eng). 2023;91(4):543-548
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Since their appearance in 1962, the use of breast implants for breast augmentation and reconstruction has increased dramatically[1]. According to the latest report from the International Society of Aesthetic Plastic Surgery, breast augmentation was the most common operation performed 2018, with nearly 2 million procedures performed[2]. In Mexico alone, nearly 45 570 surgeries are performed, making it the 2nd most widely performed procedure in our country after liposuction[3]. Capsular contracture is a hyperreactive response to a foreign body that can result in pain and distortion of the breast[4,5].

Capsular contracture is the most widely reported complication, and holds the highest rates of morbidity and reintervention[3,4]. Its prevalence ranges from 3% up to 18.9% between 5 and 10 years after breast augmentation, and up to 30% at 3 years after reconstruction[1]. This prevalence depends on multiple factors, such as bacterial contamination, absence of antibiotic prophylaxis during surgery, silicone implants, rupture of silicone breast implants, history of radiation therapy, and postoperative hematomas[6-8]. Regardless of the exact triggering factor, chronic inflammation and dysregulation of the immune system seem to play a central role in its pathogenesis[7,9]. In 1978, Baker introduced a clinical classification of capsular contracture for the very first time, which to this date is still the most widely used one and generally accepted[10,11] (Table 1).

Capsular contracture is one of the most unpredictable and problematic complications that occur after breast augmentation. Despite extensive study, the exact etiology for its development and associated risk factors remains elusive[12]. There are still no encouraging results with the different interventions described, and prevention of recurrences remains uncertain[13].

The aim of this study was to determine the prevalence of the most common risk factors associated with capsular contracture in patients undergoing breast implantation and determine which are statistically significant.

Method

In March 2021, after approval by the center research committee, the healths records of patients diagnosed with capsular contracture (older than 18 years old) from 2016 through 2020 were retrospectively reviewed. Patients with a history of uncontrolled collagen disease were excluded since they exhibit a clinical picture of generalized inflammation that complicates differential diagnosis with capsular contracture. Both the clinical and sociodemographic data were extracted from the health records of patients who met the inclusion criteria. The variables included were age, body mass index (BMI), occupation, chronic degenerative diseases, substance abuse, time from implantation to symptom onset, reason for consultation, history of trauma, surgical approach, and histopathology. Descriptive and inferential statistical analysis of a database of 210 observations was performed, using R and Excel software, and for qualitative variables, the chi-square test was used, comparing the 4 Baker grades with risk factors. Prevalence was estimated for each risk factor detected in the sample. p values ≤ 0.05 were considered statistical significant.

Table 1. Baker scale

Grade I	Breast with normal appearance and touch
Grade II	Hardened touch without visible deformity
Grade III	Firm breast with visible deformation without causing pain
Grade IV	Hard breast with visible deformation causing pain

Results

Regarding the results obtained, the health records of 210 patients were included; 98.1% were women and 1.9% were men. The mean age was 47 years (± 11), the BMI was 20 kg/m^2 (± 10), and the mean time elapsed since breast implantation until symptom onset was 13 years (± 8.5). The risk factors associated with capsular contracture with the highest prevalence are listed in table 2. The most common occupation of patients with Baker III and IV capsular contracture was housework (20.5% and 21.9%), totaling 63.3%. The main chronic degenerative diseases associated with grades III and IV were arterial hypertension and type 2 diabetes mellitus (31.4% and 37.1%), totaling 96.7%. Substance abuse associated with patients with Baker IV grade was alcoholism in 29% and smoking in 25.7%, while in those with Baker III grade, rates were 21% and 20.5%, respectively; overall, the rates of alcoholism and smoking were 70% and 65.7%, but they were statistically nonsignificant. Regarding implant-related aspects, the main reason for implantation was aesthetic (90%), followed by reconstructive (10%). The surgical approach site was periareolar in 73.3% and

Table 2. Prevalence of the main risk factors identified

Risk factors	Baker scale				Total according to variable
	Grade I	Grade II	Grade III	Grade IV	
Domestic chores	8.1%	12.9%	20.5%	21.9%	63.3%
Arterial hypertension and type 2 diabetes mellitus	11.0%	17.1%	31.4%	37.1%	96.7%
Alcoholism	6.7%	13.3%	21.0%	29.0%	70.0%
Smoking	7.6%	11.9%	20.5%	25.7%	65.7%
History of trauma	7.6%	16.2%	28.6%	31.0%	83.3%
Periareolar	10.0%	16.2%	21.0%	26.2%	73.3%
Submammary	4.5%	20%	19%	27.2%	70.7%
Submuscular	6.06%	18.1%	33.3%	39.3%	96.76%
Subglandular	8.6%	11.9%	25.2%	28.1%	73.8%
Fibrous capsule	10.0%	15.2%	26.2%	30.0%	81.4%

submammary in 70.7%, without statistical significance (p = 0.98) vs the implantation plane, which was submuscular in 73.8% and subglandular in 96.76%, with statistical significance (p = 0.0115). The type of implant was smooth in 90% of cases, while it was textured in the remaining 10% of the cases.

History of trauma occurred in 28.6% for grade III and 31% for grade IV, totaling 83.3%, with statistical significance (p = 0.004). The degree of involvement according to the Baker classification was grade I, 11.43%; grade II, 18.1%; grade III, 32.38%; and grade IV, 38.10%. Regarding histopathological results, the fibrous capsule was reported as grade III in 26.2% and grade IV in 30%, totaling 81.4% (Fig. 1).

No statistically significant differences were found across the different levels of the Baker classification regarding age, occupation, diabetes mellitus, arterial hypertension, BMI, and time of clinical presentation. The only statistically significant data were the history of trauma (p = 0.004) and the subglandular plane (p = 0.0115) (Table 3).

Baker grades correlate with statistically significant data in our study supporting that, with a higher degree of capsular contracture, the rates of previous traumas and subglandular approach were higher in grades III and IV (Fig. 2).

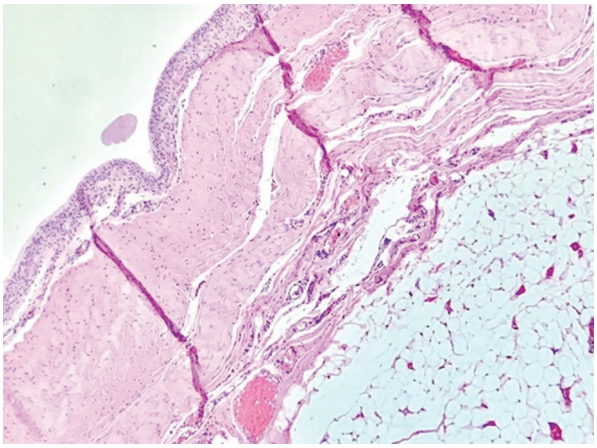

Figure 1. *Capsular tissue composed of granulomatous tissue with hypocellular fibrous stroma and residual adipose tissue.*

Discussion

Capsular contracture is a serious complication following breast implantation. Various risk factors have been described in the literature, such as age, textured implants, presentation time, implant volume, hematomas, and postoperative injuries; however, only radiation therapy has been documented[14]. In our study, the risk factors associated with capsular contracture were occupation (housework) in 63.3%, BMI of 20 kg/m^2 (± 10), smoking in 65.7%, alcoholism in 70%, and arterial hypertension and type 2 diabetes mellitus in 96.7%. The only statistically significant factors were a history of trauma, 83.3% (p = 0.004), and the subglandular plane, 73.8% (p = 0.0115).

Regarding the results obtained, the age range was 47 years (± 11), which is consistent with the literature, and there is evidence that age is a particularly

Table 3. Risk factors and statistical significance

Risk factors	Results	*P*
Mean age	47 years (± 11)	0.6257
Body mass index	20 (± 10)	0.2744
Time to clinical presentation	13 years (± 8.5)	
Domestic chores	63.3%	0.6204
Arterial hypertension and type 2 diabetes mellitus	96.7%	0.6435
Substance abuse		
Alcoholism	70.0%	0.5097
Smoking	65.7%	0.687
History of trauma	83.3%	0.004
Periareolar	73.3%	0.98
Submammary	70.7%	0.98
Submuscular	96.76%	0.1136
Subglandular	73.8%	0.0115

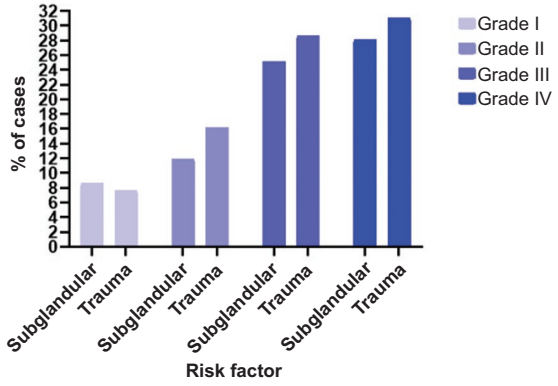

Figure 2. *Baker grades correlate with statistically significant data; higher grades of capsular contracture show a higher percentage of previous traumas and subglandular approach in grades III and IV.*

significant factor when the patient is older than 54 years ($p < 0.001$). Therefore, the age of the patients has an impact on the formation of capsular contracture associated with more than 10 years after implantation[15]. The most common occupation in patients with Baker III and IV capsular contracture was housework (20.5% and 21.9%), totaling 63.3%; however, there are no current studies in the literature supporting this data.

We identified that the main conditions related to capsular contracture in Baker grades III and IV were arterial hypertension and type 2 diabetes mellitus (31.4% and 37.1%), totaling 96.7%. In patients with uncontrolled diseases, an interaction among inflammatory cells, the extracellular matrix, and fibroblasts has been reported, leading to an abnormal fibroblast response within the capsules surrounding the implants statically, creating more capacity to contract[8]. Substance abuse associated with patients with Baker IV grade was alcoholism in 29% and smoking in 25.7%, while in patients with Baker III grade, these rates were 21% and 20.5%, respectively; overall, the rates of alcoholism and smoking were 70% and 65.7%, respectively, but not statistically significant. Smoking causes a chronic inflammatory process that triggers the progressive formation of fibrotic tissue in the periprosthetic space, and elevated serum fibrosis indices (e.g., hyaluronate, N-terminal propeptide of type III procollagen, matrix metalloproteinases, and tissue inhibitors of metalloproteinases), causing progressive thickening and contraction, and eventually leading to asymmetry and symptoms from local hypersensitivity to severe pain[7-9]. In the study reported by Dancey[16], no association was ever found between alcohol and capsular contracture ($p = 0.413$). Although the BMI of 20 kg/m^2 (± 10) reported in our study is consistent with the one reported by Dancey[16], it disagrees with the one reported by Largent et al.[17], who found an adjusted relative risk of 1.02 (95% confidence interval [CI95%], 0.98-1.07), while Dancey[16] found no significant differences ($p = 0.83$) in patients with BMI < 30 kg/m^2 vs those with BMI > 30 kg/m^2. The main reasons for implantation were aesthetic (90%) and reconstructive (10%). The cause of capsular contracture is different for reconstruction patients, in whom radiation therapy plays a key role by inducing capsule and pectoral muscle fibrosis (in retropectoral reconstructions), resulting in contracture and cephalic displacement of the implant[16,18].

The surgical approach site with the highest rate of reported capsular contracture in our study was periareolar, 73.3%, followed by submammary, 70.7%, with no statistical significance. Wiener[18] relates the periareolar incision approach to capsular contracture due to the potential for implant contamination by bacteria colonizing mammary ducts. In contrast, the implantation plane showed statistical significance, with 96.76% for the submuscular plane and 73.8% for the subglandular one ($p = 0.0115$). A randomized controlled clinical trial found fewer capsular contracture symptoms with the use of textured implants in the submuscular plane[3]. However, when smooth implants were placed in the subfascial plane, their capsular contracture rate was significantly higher than that of textured implants[18].

The most widely reported type of implant in our study was textured in 90% of the cases; in the

remaining 10%, the type of implant was the smooth one. The literature available reports that textured implants result in thicker and in the formation of more inflammatory capsule than smooth surface implants. Microtextured implants have been reported to reduce the rates of capsular contracture due to diversion force vectors around the implant[19,20]. In their study, Filiciani et al.[20] reported that smooth implants had a higher rate of capsular contracture rate 1 year after surgery vs textured implants, although with borderline statistical significance (p = 0.06). Smooth-surfaced breast implants in the subfascial plane had a 4-fold higher risk of capsular contracture vs textured-surfaced implants in the same plane (OR, 4.4; 95%CI, 1.6-12.4). However, when implanted in the submuscular plane, both textures had a similar risk of contracture. The rate of contracture was similar 2 years after implantation (p = 0.21).

Regarding clinical presentation and the degree of capsular contracture, our study is consistent with what has been reported in the scientific medical literature currently available[21]. The history of trauma was presented by 83.3%, which was statistically significant (p = 0.004). This data is crucial, as the current literature reports it as a potentiator of the inflammatory process related to biofilm, bleeding, and silicone gel irrigation following the rupture of the implant[11].

The capsule is initially thin and soft, with little or no effect on breast appearance; however, over time, it undergoes progressive thickening, contraction, and compression, causing asymmetry and producing symptoms that can go from local hypersensitivity to acute pain[7,9]. The diagnosis was clinical according to the Baker classification, being the highest percentages grades III (32.38%) and IV (38.10%). However, there is still no evidence that this scale is the most reliable for the diagnosis of capsular contracture. One study found that the inter-observer reliability of Baker's classification was poor (95%CI, 0.37-0.72) for the clinical parameters of firmness (0.64; 95%CI, 0.49-0.79), displacement (0.49; 95%CI, 0.26-0.73), and symmetry (0.61; 95%CI, 0.34-0.88). The inter-observer agreement reliability using Baker's classification for capsular contracture performed poorly[22]. There is a lack of consensus on how to appropriately assess and grade the symptoms and signs presented by patients as early signs of capsular contracture to avoid subjective values may underdiagnose this condition.

Regarding the limitations of our study, the implant volume > 355 mL is a factor reported in the literature as a risk factor for developing capsular contracture. However, in our study, the precise data could not be collected as most patients did not have this information accurately recorded, or the implant warranties to corroborate it.

Within the histopathological results obtained, the fibrous capsule was reported as grade III in 26.2% and grade IV in 30%, totaling 81.4%; findings that are consistent with what is reported in the literature. By fluorescence microscopy, populations of fibroblasts associated with severe contractures were oriented perpendicular to the long axis, suggesting a spiral orientation in the compaction of these cable-like structures. These findings were absent in less severe contractures[23]. In the study conducted by Schreml et al.[23] they obtained samples from 45 patients with unilateral capsular fibrosis after breast augmentation with silicone implants and found no colonization for Baker grades I or II contractures vs a 67.7% colonization for grades III or IV contractures.

Another interesting aspect that should be investigated in future studies is the biofilm, as it is one of the theories described for the development of capsular contracture. There are few studies in the literature available on these histopathological findings in breast implant capsules, the biological mechanisms involved in the reorganization of collagen fiber bundles leading to capsular contracture, which are critical steps in developing therapeutic strategies to control the pathophysiology of this disease.

Conclusions

The prevalence of the most common risk factors associated with capsular contracture in patients undergoing breast implantation was determined. Only for the history of trauma and the subglandular plane, there was statistical significance, so these 2 factors can be safely studied when diagnosing capsular contracture.

Funding

None declared

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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CLINICAL CASE

Peritoneal sarcoidosis that simulates peritoneal carcinomatosis: a case report

Sarcoidosis peritoneal que simula carcinomatosis peritoneal: a propósito de un caso

Julieta Zanatta-Scattolini[1], Cecilia I. Rodríguez-Oses[1], José G. Yaryura-Montero[1], Juan A. Albiero[2], Jorge O. Flores[3], and Carlos I. Ferrero[1]*

[1]Department of General Surgery; [2]Department of Rheumatology; [3]Department of Pathology. Sanatorio Allende, Córdoba, Argentina

Abstract

Sarcoidosis is a multisystem inflammatory disorder of unknown cause characterized by the formation of pleomorphic, non-caseating granulomas with predominantly pulmonary involvement. Although abdominal sarcoidosis represents 30% of extrapulmonary manifestations, peritoneal involvement is extremely rare. We will describe a rare case of peritoneal sarcoidosis simulating carcinomatosis in a young patient with abdominal pain who underwent laparoscopic examination.

Keywords: *Peritoneal diseases. Sarcoidosis. Laparoscopy. Abdomen acute.*

Resumen

La sarcoidosis es un trastorno inflamatorio multisistémico de causa desconocida que se caracteriza por la formación de granulomas pleomórficos, no caseificantes, con afectación predominantemente pulmonar. Aunque la sarcoidosis abdominal representa el 30% de las manifestaciones extrapulmonares, la afectación peritoneal es extremadamente rara. Describiremos un caso poco frecuente de sarcoidosis peritoneal simulando carcinomatosis en una paciente joven con dolor abdominal sometida a exploración laparoscópica.

Palabras clave**:** *Enfermedades peritoneales. Sarcoidosis. Laparoscopía. Abdomen agudo.*

Introduction

Sarcoidosis is a multisystem, inflammatory disorder of unknown cause characterized by the formation of epithelioid, non-caseating granulomas[1]. The presence of granulomas in the absence of other granulomatous diseases is characteristic of sarcoidosis[2]. It is usually diagnosed in patients between 20 and 40 years of age, with a greater incidence in female patients[3]. The lungs and lymphoid system are the most commonly involved sites, with a frequency of 90% and 30%, respectively[4]. Extrapulmonary involvement is observed in 30% of patients, with the abdomen being the most frequent site. However, peritoneal involvement is extremely rare[5]. Abdominal sarcoidosis can occur in the absence of lymphatic or pulmonary disease[6]. The lesions are uncharacteristic, mimicking more common neoplastic or infectious diseases such as lymphoma, peritoneal carcinomatosis, granulomatous, or mycobacterial infections[7]. Although usually asymptomatic, the presence of symptomatic abdominal involvement can affect prognosis and treatment options. Symptomatic abdominal sarcoidosis requires treatment with immunosuppressant agents[1]. We will describe a rare case of peritoneal sarcoidosis mimicking carcinomatosis in a young patient.

***Correspondence:**
Julieta Zanatta-Scattolini
E-mail: julietazanatta93@gmail.com

Date of reception: 16-09-2021
Date of acceptance: 12-10-2021
DOI: 10.24875/CIRUE.M21000630

Cir Cir (Eng). 2023;91(4):549-552
Contents available at PubMed
www.cirugiaycirujanos.com

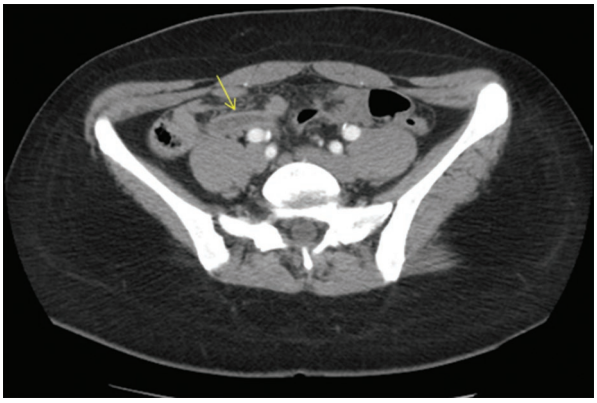

Figure 1. *Axial computed tomography scan where diffuse thickening of the appendix can be seen (yellow arrow).*

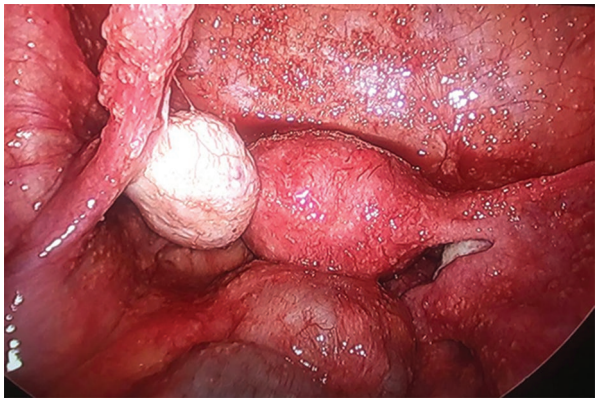

Figure 3. *Intraoperative findings: uterine tubes with punctate lesions and serous free fluid at the pouch of Douglas.*

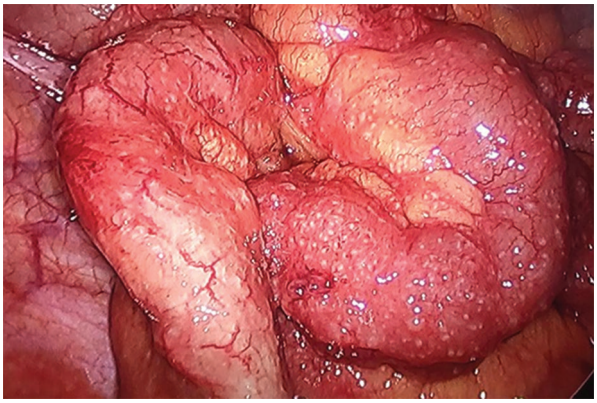

Figure 2. *Intraoperative findings: small bowel with multiple punctate lesions.*

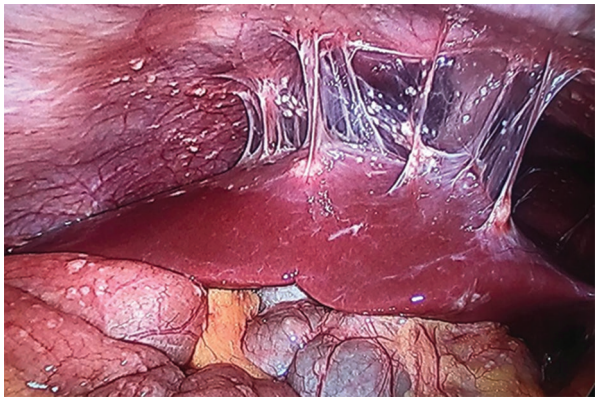

Figure 4. *Intraoperative findings: hepatic adhesions with seeding of lesions from which samples were taken.*

Case report

A 29-year-old female patient, with a history of slowly resolving pneumonia associated with pleural effusion 3 years earlier, attended at the Emergency Room with a moderate intensity generalized abdominal pain starting 3 h ago, predominantly located in the hypogastrium, continuous with colic exacerbations, associated with episodes of vomiting of gastro-bilious content. On physical examination, she was clinically and hemodynamically stable, with preserved vital signs and a soft lax abdomen with mild tenderness and guarding over the right iliac quadrant and hypogastric region without definite rigidity as in peritonitis. Laboratory tests showed 7300 white blood cells/dL, with 74% neutrophils and 0% eosinophils, CRP 0.49 mg/dL, erythrocyte sedimentation rate 25 mm/h, negative human chorionic gonadotropin, and normal urine test results. Abdominal and transvaginal ultrasounds were requested, both normal, and because she continued with symptoms, a CT scan of the abdomen and pelvis with intravenous contrast was requested, which showed diffuse thickening of the appendix with concentric reinforcement, homogeneous post-contrast, and inflammatory edematous appearance (Fig. 1). In addition, minimal thickening was visualized with increased density of the greater omentum on the left margin (non-specific) and a 3-mm calcification in the lower sector of segment 8 of the right hepatic lobe. The patient was admitted and underwent laparoscopic exploration, where multiple punctate lesions were observed throughout the peritoneum, proximal, and distal small intestine and in the colon (Fig. 2). The appendix presented the same characteristics. At the pelvis, both fallopian tubes were found with lesions of the same characteristics and serous free fluid was visualized at the bottom of the pouch of Douglas (Fig. 3). Samples were taken from the peritoneal right flank and from the hepatic adhesions, with seeding of lesions (Fig. 4), and the decision was not to perform

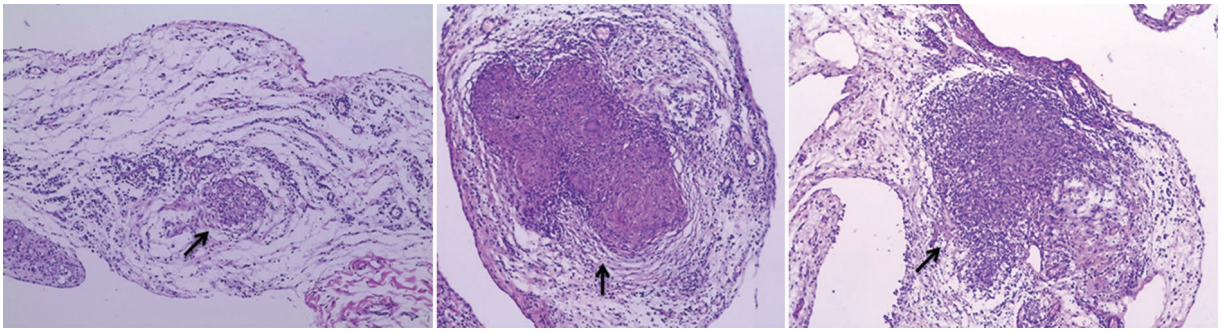

Figure 5. *Histopathological examination: granulomas with multinucleated giant cells. Hematoxylin-eosin stain. ×10 (black arrows).*

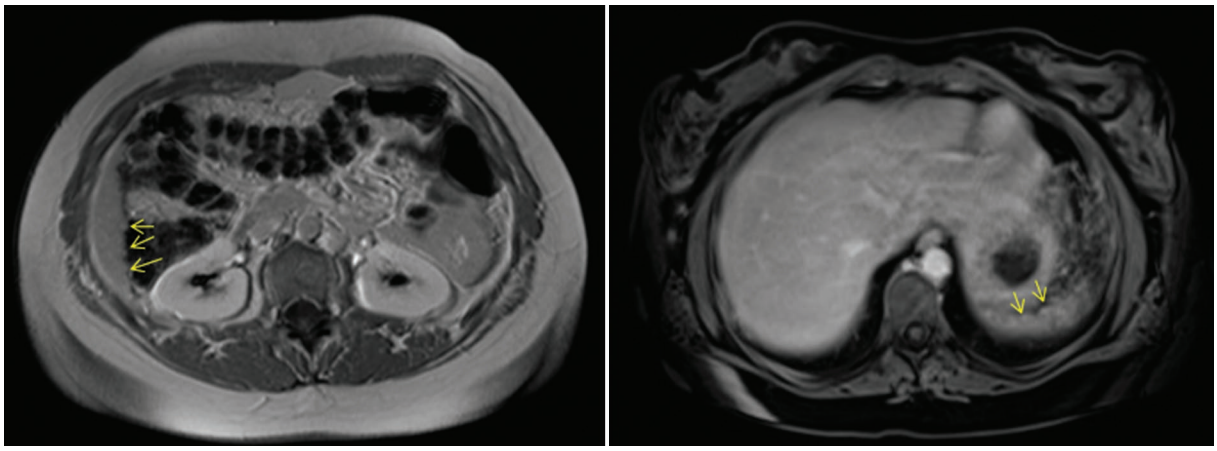

Figure 6. *Axial abdominal MRI where small hypointense nodules in the right hepatic lobe and the subcapsular splenic medial border can be seen (yellow arrows).*

appendectomy. The histopathological study revealed granulomatous peritonitis with non-necrotizing sarcoid granulomas, PAS, and ZN negative; and the cytological smear of the abdominal fluid showed mesothelial cells, lymphocytes, and neutrophils (Fig. 5). The post-operative period was uneventful without complications and the patient was discharged from the hospital 48 h after surgery. Evaluated by the Rheumatology Department, an immunological laboratory test was requested showing negative ANA, ENA, anti-DNA, ANCA, normal complement, Beta-2 microglobulin 1.7 mg/dL (normal range: 0.8-2.2), ECA 24.2 UI (normal range: 8-52), and normal proteinogram by electrophoresis with 1.5 g% of gamma globulin, normal both serum and urinary calcium levels. In addition, IgG4 was normal, and an MRI of the abdomen showed small hypointense nodules in very small numbers, visible in the right hepatic lobe and the subcapsular splenic medial border, associated with a small amount of laminar perihepatic and perisplenic fluid (Fig. 6). The patient started treatment with methotrexate 20 mg/week, folic acid 10 mg/week, and colchicine 1 mg/day, with clinical improvement.

Discussion

Sarcoidosis is a granulomatous disease with predominant pulmonary involvement. Although abdominal sarcoidosis represents 30% of extrapulmonary manifestations, peritoneal involvement is rare, and the exclusive presence of peritoneal sarcoidosis without pulmonary involvement is exceptional[8]. Extrapulmonary involvement depends on gender, age at diagnosis, and ethnicity[9].

Most cases occur in women between the second and fourth decades of life[10]. A literature search was performed in PubMed, where it was found that there are only 33 cases of peritoneal sarcoidosis reported to date, with the first case reported by Robinson and Ernest in 1954[11].

The most frequent clinical presentation is abdominal pain, but it is often asymptomatic[12]. It most commonly presents as ascites or granulomatous peritoneal nodules,

requiring pathological examination by a biopsy to rule out peritoneal carcinomatosis or tuberculous peritonitis[13].

In general, the diagnosis of peritoneal sarcoidosis is established when clinical and imaging findings are supported by typical histopathological findings in the peritoneum. Non-caseating granulomatous inflammation and other causes of granulomas, such as infectious diseases (tuberculosis, histoplasmosis, brucellosis, and toxoplasmosis), autoimmune disorders (granulomatosis with polyangiitis, primary biliary cholangitis, and Crohn's disease), occupational and environmental exposures (beryllium, talc, and fungi), delayed-type hypersensitivity to foreign agents, and neoplasms should be excluded[14].

As the differential diagnoses of this granulomatous process are extensive, diagnostic laparoscopy is often required to reveal the involvement of granulomatous disease in the visceral and parietal peritoneum since imaging studies such as tomographies are often unable to detect them due to their small size[15].

Laboratory studies are often unrevealing, and peripheral lymphopenia with CD4 depletion, hypercalcemia, and hypercalciuria may be found. Elevated CA 125 levels have been observed in some cases of peritoneal sarcoidosis, but it is still uncertain whether it would be a reliable marker of sarcoidosis activity[5,16] since it is also present in other causes of benign and malignant peritoneal diseases[16]. Although elevated ACE levels have been repeatedly observed in patients with sarcoidosis, increased concentrations have not been directly correlated with peritoneal involvement[15].

Most cases of peritoneal sarcoidosis have a benign course, resolving spontaneously or with a short course of corticosteroids[17], sometimes with the addition of methotrexate[18], as in the case of our patient.

Conclusion

Sarcoidosis is a multisystem, inflammatory disorder of unknown cause. Although peritoneal involvement is extremely rare, it may mimic peritoneal carcinomatosis and should be suspected as a differential diagnosis, especially in young women. The diagnosis is established when clinical and imaging findings are supported by typical histopathological findings. Most cases have a benign course.

Funding

No financial support was provided for this investigation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Aortoenteric fistulae and their multidisciplinary approach

Fístula aortoentérica y su manejo multidisciplinary

Haydée Calvo-García[1], Johnn H. Herrera-Kok[1], Antonio Álvarez-Martínez[1], Silvia Maqueda-Ara[2], José M. Ortega-Martín[2], Tomás Elosua-González[1], and María V. Diago-Santamaría[1]*

[1]Servicio de Cirugía General y del Aparato Digestivo; [2]Servicio de Angiología y Cirugía Vascular. Complejo Asistencial Universitario de León, León, España

Abstract

Aortoenteric fistula is an uncommun life-threatening condition which remains associated with significant morbidity and mortality. It can be primary (aneurysm, neoplasms, radiation therapy, infection) or secondary to vascular prosthesis. Early diagnosis and aggressive surgical treatment are very important to achieve optimal outcomes in these patients. The aim of this article is to highlight the importance of early diagnosis and multidisciplinary approach of aortoenteric fistula through the presentation of a clinical case.

Keywords: *Aortoenteric fistula. Enteroparaprosthetic fistula. Vascular prosthesis. Gastrointestinal bleeding. Sepsis.*

Resumen

La fístula aortoentérica es una patología poco frecuente, pero de riesgo vital, asociada a alta morbimortalidad. Puede ser primaria (aneurisma, neoplasia, radioterapia, infección) o secundaria a prótesis vascular. El diagnóstico precoz y el tratamiento quirúrgico agresivo son los pilares fundamentales para lograr buenos resultados en estos pacientes. El objetivo de este trabajo es destacar la importancia del diagnóstico precoz de la fístula aortoentérica y su manejo multidisciplinar, mediante la presentación de un caso clínico.

Palabras clave: *Fístula aortoentérica. Fístula enteroparaprotésica. Prótesis vascular. Hemorragia digestiva. Sepsis.*

Introduction

Aortoenteric fistula (AEF) is a rare but life-threatening condition characterized by an abnormal connection between the aorta and the GI tract. It can be primary if it arises de novo due to compression from an aneurysm, a neoplasm, previous radiation therapy, or infection, resulting from mechanical or inflammatory factors, or it can be due to vascular device implantation after an aortic reconstructive procedure.

Secondary fistula can present in 2 forms: as an anastomotic communication between the aortic lumen and the intestine (true enteroprosthetic fistula), and less frequently as aortoenteric erosion (enteroparaprosthetic fistula) due to direct contact between the vascular device and the intestine.

***Correspondence:**
Haydée Calvo-García
E-mail: hcalvog@saludcastillayleon.es

Date of reception: 12-09-2021
Date of acceptance: 13-10-2021
DOI: 10.24875/CIRUE.M21000567

Cir Cir (Eng). 2023;91(4):553-557
Contents available at PubMed
www.cirugiaycirujanos.com

The objective of this study is to emphasize the importance of the early diagnosis of AEF and its multidisciplinary management.

Case report

This is the case of an 80-year-old woman with a past medical history of hypertension, smoking, stage IIIb chronic kidney disease, who underwent aortobifemoral bypass surgery and subsequent femoro-femoral bypass due to right graft branch thrombosis, who presented with sepsis of probable abdominal origin, anemia, and lower back pain.

The esophagogastroduodenoscopy performed due to GI bleeding (Fig. 1) revealed the presence of a foreign body consistent with a partially emergent device from the duodenal lumen with adherent clots, but without active bleeding. The coronary computed tomography angiography (CCTA) (Fig. 2) confirmed the decubitus ulceration of the duodenal wall due to the prosthetic material of the aortobifemoral bypass, probable hematoma, or infectious process in the right psoas, and right ureterohydronephrosis.

With a diagnosis of enteroparaprosthetic fistula, surgical intervention was scheduled (Figs. 3-5), involving left axillofemoral bypass, section of the infrarenal aorta, suturing of the proximal stump, and ligation of the device left branch. During the procedure, perforation of the posterior side of the third-fourth portion of the duodenum due to intrusion of the aortic prosthesis was reported; Cattell-Braasch maneuver, duodenal section, pyloric exclusion, and Roux-en-Y reconstruction were performed.

The patient experienced a postoperative complication (Clavien-Dindo IIIa) in the form of an abdominal collection, which was resolved with percutaneous drainage and antibiotic therapy. She was eventually discharged 29 days after surgery.

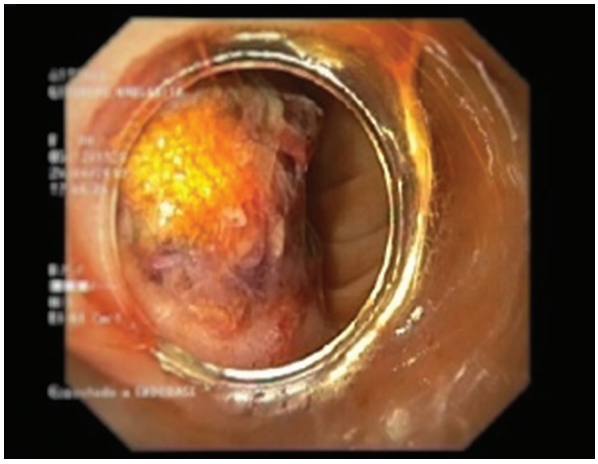

Figure 1. *Gastroscopy: yellowish material consistent with a prosthesis emerging into the lumen in the 3rd portion of the duodenum.*

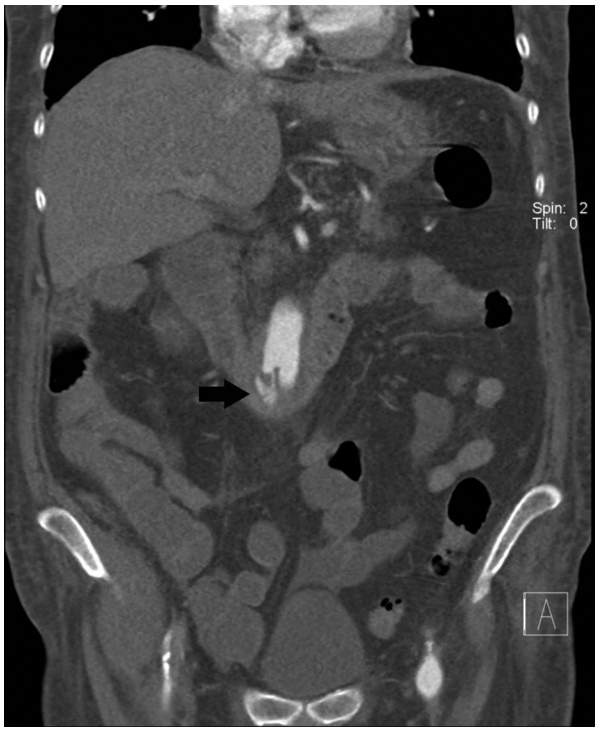

Figure 2. *Coronary computed tomography angiography, coronal section, showing contrast extravasation from the aortic lumen to the duodenum (arrow).*

Discussion

Concept

AEF is an uncommon but highly morbid and mortal condition[1-3]. It is defined as an abnormal connection between the aorta and the GI tract, being the duodenum the most frequent location. There are 2 types: primary and secondary. The former occurs de novo as a result of compression of an abdominal aortic aneurysm (AAA) against the intestine, with mechanical, inflammatory, and infectious factors being involved in its pathophysiology[4-6]. The latter, more common, results from surgical reconstruction[7,8], through erosion of aortic prosthetic material onto the adjacent intestine, which can also occur in endovascular procedures[9,10].

AAA is the most important risk factor for developing AEF, either as a cause of primary fistula or as subsequent repair leading to secondary fistula[11]. Fistulas are more common in men, parallel to the incidence of AAA and aortic surgery.

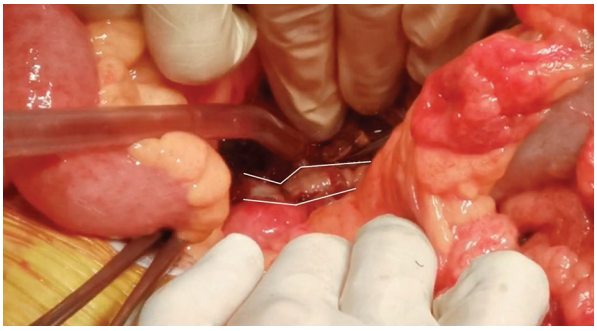

Figure 3. *Surgical intervention: aortobifemoral prosthesis intimately adhered to the duodenum (white contour).*

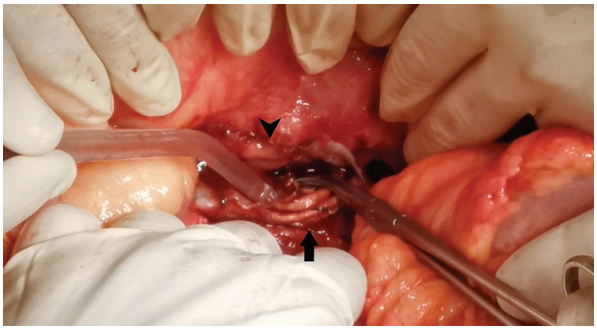

Figure 4. *Surgical intervention: duodenal mucosa (arrowhead) and aortobifemoral prosthesis (arrow).*

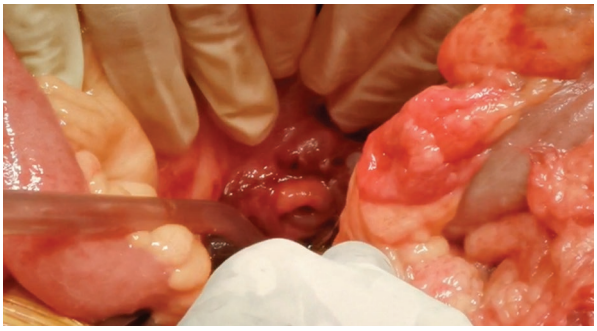

Figure 5. *Surgical intervention: duodenal mucosa after release of adhesions to the aortobifemoral prosthesis.*

Clinical signs

The most common clinical presentation of AEF is GI bleeding[12] in patients with known or unknown AAA, or previous vascular surgery. GI bleeding can vary in severity due to rupture of the aorta into an intimately adhered portion of the intestine, leading to rapid exsanguination of the patient. Other signs include discomfort, weight loss, sepsis, graft thrombosis with lower limb ischemia, or nonspecific symptoms.

Diagnosis

The classic triad described consists of bleeding, abdominal pain, and palpable mass. However, in practice, diagnosis requires a high clinical suspicion and is often delayed, especially if the aneurysm is unknown, the etiology is different (e.g., aortitis), or idiopathic.

Hemodynamically unstable patients with massive hemorrhage and a known AAA (whether repaired or not) should be taken directly to the operating room for bleeding control and surgical repair. In case of suspected AAA due to risk factors, an emergency ultrasound is required to identify it, although it may not reveal the fistula.

Hemodynamically stable patients with acute GI bleeding generally require gastroscopy, although its sensitivity rate for diagnosing fistulas is only 50%[13]. Therefore, in cases of high suspicion, a CCTA should be performed, and if the CCTA turns out negative, gastroscopy should be considered to visualize the distal duodenum. Thrombus and impacted prosthetic material in this location should not be removed initially[14].

In patients with suspected GI bleeding and possible AEF, a CT scan is advised as a non-invasive imaging modality of choice[15,16], although radiological characteristics of the fistula and peri-graft infection may be difficult to differentiate and require additional supplementary studies. Specific radiological findings on the CT suggesting the presence of AEF include ectopic gas adjacent to or within the aorta, focal thickening of the intestinal wall, aortic wall discontinuity, and contrast extravasation into the intestinal lumen[17,18]. Any tomographic feature of peri-graft infection should raise the possibility of a secondary fistula.

Treatment

Treatment includes initial resuscitation and hemodynamic support, antibiotic therapy, and aortic repair, considering removal of prosthetic material if present. The type and timing of repair should be individualized, while considering the clinical presentation (severity of bleeding or infection), type of fistula (primary or secondary), patient comorbidities, aortic anatomy, etc. Therapeutic options include open and endovascular repair.

Open surgical management includes vascular control, debridement of necrotic and infected tissue

(intestine and aorta), restoration of GI continuity, and revascularization (local repair, in-situ reconstruction, extra-anatomic, etc.) [19].

Endovascular methods, either alone or in combination with open repair, include aortic balloon occlusion[20], endovascular coiling[21], endovascular plug[22], fibrin glue[23], and stent graft repair[24]. These techniques are often performed as temporary measures for hemorrhage control and provide a window period to resuscitate the patient and plan definitive treatment[25]. In some cases, endovascular procedures can be used as palliative therapy for high surgical risk patients[26]. In the presence of systemic infection, standalone endovascular repair leads to recurrent infection[27-29].

Conclusions

AEF is an uncommon condition associated with high morbidity and mortality. Prognosis depends on the speed of diagnosis, patient baseline status, level of infection, and affected aortic portion.[30] Therefore, early diagnosis and aggressive surgical treatment are fundamental pillars to achieve good outcomes in patients with this condition.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Anesthetic management of a child with Loeys-Dietz syndrome undergoing complete aortic arch replacement

Manejo anestésico en una niña con síndrome de Loeys-Dietz sometida a recambio completo de arco aórtico

*Unai Olabarrieta-Zarain[1], Leire Martínez-Santos[1], Alex Alberdi-Enríquez[1], Ane Guereca-Gala[1], Blanca Bravo-Sevilla[1], and Alberto Martínez-Ruiz[1,2]**

[1]Servicio de Anestesiología, Reanimación y Terapia de Dolor, Hospital Universitario de Cruces, Osakidetza; [2]Facultad de Medicina, Universidad País Vasco, EHU/UPV. Vizcaya, España

Abstract

Loeys-Dietz syndrome (LDS) is a connective tissue disease related to β-transforming growth factor mutations, which causes aneurysms formation, vascular tortuosity and skeletal manifestations. The prognosis is very poor, and mortality occurs at the age of 27 in patients without surgical treatment. Despite being diagnosed in childhood, is not usual surgical aortic replacement in children. We report a case of 12 years old child with LDS and multiple aneurysms in thoracic aorta, undergoing complete aortic arch replacement and our proposal for the anesthetic management, due to surgical complexity and implications in pediatric population.

Keywords: *Loeys Dietz Syndrome. Aortic arch surgery. Marfan like syndrome. Cervical subluxation. Brain injury neuroprotection.*

Resumen

El síndrome de Loeys-Dietz (SDL) es una enfermedad del tejido conectivo debida a mutaciones del factor de crecimiento transformador beta que provocan formación de aneurismas, malformaciones vasculares y esqueléticas. Tiene mal pronóstico y el fallecimiento sobreviene de media a los 27 años sin tratamiento quirúrgico. A pesar de diagnosticarse en la infancia, es infrecuente la cirugía en niños. Presentamos el caso de una niña de 12 años con SDL y aneurisma múltiple en aorta torácica, programada para recambio completo de arco aórtico, proponiendo estrategias para el manejo anestésico, dada la complejidad y las implicaciones de esta cirugía en la población pediátrica.

Palabras clave: *Síndrome de Loeys-Dietz. Cirugía de arco aórtico. Síndromes marfanoides. Subluxación cervical. Neuroprotección cerebral.*

Introduction

Loeys-Dietz syndrome (LDS) is an autosomal dominant genetic connective tissue disorder caused by mutations in the transforming growth factor beta (TGF-β) gene that was first described back in 2005. It is a rare entity whose incidence rate is 1 for every 100 000 inhabitants. LDS is related to 6 different mutations of TGF-β. Type 1 and 2 (TGFBR1 and TGFBR2 genes), which have an earlier and more severe onset, are the most common mutations (25% and 60%, respectively). Types 3 (SMAD3), 4 (TGFB2), and 5 (TGFB3) are less severe, with frequencies ranging from 10% up to 25%.

***Correspondence:**
Alberto Martínez-Ruiz
E-mail: Alberto.martinezruiz@osakidetza.eus

Date of reception: 25-10-2021
Date of acceptance: 07-01-2022
DOI: 10.24875/CIRUE.M22000568

Cir Cir (Eng). 2023;91(4):558-562
Contents available at PubMed
www.cirugiaycirujanos.com

Variant 6 (SMAD2), recently described, accounts for < 5% of the cases reported (table 1)[1,2]. It predisposes to early development of aortic aneurysms and vascular malformations, with greater aggressiveness compared to other Marfan-like syndromes.

The most serious clinical aspect is cardiovascular involvement, more common in types 1, 2, and 3. Thoracic aortic aneurysms are typical, with rapid growth and risk of rupture at smaller diameters vs other syndromes (3.9 cm vs 5 cm in Marfan syndrome). Unlike Marfan syndrome, the entire thoracic aorta is involved in LDS. In LDS types 1 and 2, up to 95% of the patients have a dilated aortic root, which leads, in most patients, to aortic regurgitation, mitral valve prolapse, and pulmonary artery elongation. A total of 50% of the patients exhibit aneurysms which are distal to the aortic root, and most have vascular tortuosity in the head and neck[2]. Aortic dissections, even in 3-month-old infants, abdominal, iliac, and popliteal aneurysms in up to 20% of the patients, and cerebral vascular malformations have been reported too. Additionally, in LDS type 3, up to 24% of the patients develop atrial fibrillation and left ventricular hypertrophy, and less frequently, patent ductus arteriosus and septal defects, among other disorders[3].

Craniofacial and skeletal abnormalities are also a common finding. Cleft palate and hypertelorism are most common, present in virtually all patients with the types 1 and 2 variants, allowing for early diagnosis. Craniosynostosis is also common in severe forms. Less frequently, retrognathia, dental malocclusion, and bifid uvula have been reported. In LDS type 3, craniofacial abnormalities are mild or absent. In LDS types 1 and 2, arachnodactyly has been reported in 33% of the patients. Also, ligamentous hyperlaxity, clubfoot, cervical subluxations, dorsal kyphosis, and bone fractures. Joint abnormalities and early-onset arthrosis are common findings in LDS type 3[3].

Less commonly reported findings are immunological, and allergic disorders, bronchial hyperreactivity, restrictive lung disease, sleep apnea-hypopnea syndrome, atrophic skin, retinal detachment, and blue scleral among others.

Early diagnosis is essential due to the aggressive course of the disease. It is based on clinical suspicion, family history, presence of a dilated aortic root, or type A dissection, and confirmed by genetic testing. Differential diagnosis with Marfan syndrome and other syndromes such as Ehler Danlos, Shprintzen-Goldberg, and Turner is required too. *Cutis laxa* and Noonan syndrome, as well as non-familial causes of aortic dilatation and dissection, valvular heart diseases, or fibromuscular dysplasia also need to be ruled out.

Table 1. LDS classification based on the clinical spectrum

LDS variant	Genetic disorder	Frequency	Predominant clinical signs
LDS, type 1	*TGFBR1*	25%	TAA, TAD, hypertelorism, cleft palate, craniosynostosis, AA
LDS, type 2	*TGFBR2*	60%	TAA, TAD, hypertelorism, cleft palate
LDS, type 3	*SMAD 3*	10% to 25%	TAA, premature arthrosis, AF, LVH
LDS, type 4	*TGFB2*	5% to 10%	Tortuosity and cerebral vascular malformations. Skeletal abnormalities

AA: abdominal aneurysm; AF: atrial fibrillation; LDS: Loeys-Dietz syndrome; LVH: left ventricular hypertrophy; TAA: thoracic aortic aneurysm; TAD: thoracic aortic dissection. *Adapted from Meester et al., 2017[1] and MacCarrick et al., 2014[2].*

Treatment is essential to increase survival. Angiotensin-converting enzyme inhibitors (ACEIs), and/or beta-blockers are advised for hemodynamic control and early surgical intervention.

Prognosis is grim and mortality rate is high. The main causes of death are rupture, aortic dissection, and cerebral hemorrhage.

Case report

A 12-year-old girl weighing 33 kg with LDS type 2 and multiple aneurysmal dilatations in the thoracic aorta was scheduled for aneurysm resection in the ascending aorta and replacement of the valve and complete aortic arch.

The patient's past medical history included a normal pregnancy and eutocic delivery. The patient presented with a dysmorphic phenotype with clubfoot, joint hyperlaxity, arachnodactyly, camptodactyly, and bifid uvula. At the age of 8, genetic testing confirmed the presence of heterozygosity for the pathogenic variant *de novo* c.1639 G > C in the TGFBR2 gene. Associated findings included dilated aortic root, patent ductus arteriosus, patent foramen ovale, and tortuosity in the thoracoabdominal aorta, both internal carotid arteries, and the right vertebral artery. Atenolol and losartan were prescribed, and the surgical intervention involved aortic root replacement. Over the past year, there was rapid aneurysmal growth distal to the prosthesis (47 mm diameter), with damage to the brachiocephalic trunk and moderate-to-severe aortic regurgitation. Both the arch

and the descending aorta were normal. A new surgical procedure was scheduled for aortic valve repair and aortic arch replacement.

Anesthesia evaluation found the patient asymptomatic. Airway examination revealed the presence of a high-arched palate and Mallampati I/IV with a bifid uvula, but without any other craniofacial malformations. Both the lab test results, and the electrocardiogram were normal. Cervical x-ray revealed the presence of atlanto-axial subluxation with a 9 mm distance between C1 and the odontoid. The patient was classified as ASA III, losartan discontinuation was advised 24 hours before the procedure, and the patient remained on atenolol.

During pre-anesthesia, a peripheral 18 G IV line was established in the right forearm, and midazolam (2.5 mg IV) was administered. In the operating room, non-invasive blood pressure, electrocardiogram, oxygen saturation, bispectral index (BIS), and regional oxygen saturation (NIRS) were monitored. Before induction, lidocaine (1 mg/kg) and tranexamic acid (50 mg/kg) were administered. General anesthesia was induced with propofol (4 mg/kg), fentanyl (5 μg/kg), and cisatracurium (0.2 mg/kg). Endotracheal intubation was performed with the head in a neutral position, avoiding cervical hyperextension and mandibular subluxation. A size 6.5 endotracheal tube was placed using an Airtraq® device (Prodol Meditec, Vizcaya, Spain). Another peripheral 18 G line, a central internal jugular line, and a femoral artery line were established. A transesophageal echocardiography (TEE) probe was inserted. For maintenance, a balanced technique with sevoflurane (CAM 0.8-1), cisatracurium (0.1 mg/kg/h), and fentanyl (2-4 μg/kg/h) was used. After sternotomy, 2 new aneurysms in the aortic arch and descending aorta, not diagnosed preoperatively, were identified, which required complete thoracic aortic repair.

The surgical team decided to proceed with peripheral cannulation for extracorporeal circulation (ECC), with cannulas placed in the right axillary artery and ipsilateral femoral vein. During the first part of ECC, after an unsuccessful attempt to repair the aortic valve, the valve was replaced, and the ascending aortic aneurysm was resected. Subsequently, under deep hypothermia (22 ºC), in total circulatory arrest (TCA) and antegrade selective cerebral perfusion (SCP), the aortic arch was replaced. Neuroprotective measures were implemented with sodium thiopental (5 mg/kg), methylprednisolone (30 mg/kg), magnesium sulfate (25 mg/kg), local ice helmet, and insulin infusion. A hybrid device with a covered stent distal to the left subclavian artery was deployed in the descending aorta, with reimplantation of both supra-aortic trunks. Thirty out of 153 minutes went by in hypothermia and SCP. After ECC was restarted, the device was anastomosed to the proximal aorta. The total ECC time was 200 minutes, with 136 minutes of aortic clamping. ECC termination was uneventful after confirming adequate contractility, valvular function, and volume status through TEE. Vasoplegia and profuse bleeding both require noradrenaline (0.1 to 0.3 μg/kg/min), fluid therapy, blood and plasma transfusion, and fibrinogen (2 g).

After a 6-hour procedure, the intubated child was transferred to the intensive care unit, where she remained for 8 days before being discharged from our center 1 week later.

Discussion

LDS type 2 is more aggressive than other connective tissue disorders such as Marfan syndrome. The mean age of death is 27 years in unoperated patients vs 50 years for the Marfan syndrome[2-5]. Replacement of the aortic root is advised for diameters ≥ 99th percentile, or aortic annulus > 1.8 cm² in children[2]. Its recent description and the rarity of aortic arch surgery in the pediatric population limit experience regarding management. Some authors suggest adopting aspects of Marfan patients' management. However, there are particularities addressed in this article.

Management is challenging, and complications are frequent and severe. Risk factors include severity of vasculopathy, duration and invasiveness of surgery, difficult airway, adrenergic discharge from laryngoscopy, ECC with hypothermia, interruption of cerebral blood flow (CBF), and hemorrhage, among others.

- We suggest paying special attention to allergy history, airway assessment, and drug adjustment in the pre-anesthetic evaluation, which is mandatory. The high incidence of immunological disorders triggers many allergies, which should be noted. ACEIs and beta-blockers may delay surgical indication in diameters of 2 cm to 2.2 cm. Beta-blockers will be maintained by discontinuing ACEI/angiotensin receptor blockers (ARB) II 24 hours prior to avoid refractory hypotension. Transverse atlanto-axial ligament hyperlaxity causes cervical subluxation and instability. Cervical flexion-extension x-rays will be requested to avoid neurological injury during ventilation and

orotracheal intubation (OTI). A distance between the atlas and odontoid > 5 mm is diagnostic vs 3 mm in adults[6]. Airway examination will reveal those craniofacial anomalies impeding ventilation and OTI. In our case, a high-arched palate and bifid uvula did not cause any problems in the previous surgery. The Mallampati grade is only valid for older children.

- We suggest monitoring with invasive blood pressure (BP), TEE, NIRS, and EEG or BIS. In addition to the standard recommendations of the American Society of Anesthesiologists (ASA), invasive BP and central venous pressure should be monitored. Wilkey et al.[7] advocate for invasive arterial monitoring prior to anesthetic induction. TEE is advised for all patients, and a pulmonary artery catheter is recommended in the presence of pulmonary hypertension. Neurological complications are common following ECC, TCA, embolization, aortic clamping, and interruption of CBF. Keenan and Hughes[8] recommend combined monitoring of NIRS and electroencephalography in aortic arch surgery to detect ischemia. In some cases, somatosensory evoked potentials or jugular venous saturation may be useful. Due to the complexity of EEG, BIS has been proposed to determine anesthetic depth and electrical silence during TCA, and NIRS to detect changes in regional cerebral oxygen saturation (pre-induction baseline of 60% to 70%). According to Svyates et al., the degree and duration of desaturation are predictive of postoperative neurological complications. Levels < 55% kept for > 5 minutes are associated with neurological impairment.
- We propose induction with lidocaine. Anesthetic induction should be gentle with strict hemodynamic control, as arterial hypertension could trigger aortic ruptures. Adequate premedication is necessary. A midazolam-type anxiolytic associated with an opioid and a drug minimizing adrenergic discharge, such as esmolol, urapidil, or lidocaine, as in our case, are advised. The appropriate anesthetic depth and relaxation prior to OTI are advised. According to Postaci et al.[9], short-acting opioids at high doses such as remifentanil 0.5-1 μg/kg as a bolus for induction in pediatrics may be useful; however, the advantage of using this over other drugs has not been demonstrated. Therefore, in our case, we opted for fentanyl as a valid alternative, considering our limited experience with the IV bolus administration of remifentanil in children.
- We propose intubation with a fiberoptic bronchoscope or videolaryngoscope. Cervical subluxation increases the risk of neurological injury during OTI. Airway structures are very close to the cervical spine in children, causing displacement during positioning, manipulation, mandibular traction, and insertion of ventilation and OTI devices. Therefore, it seems reasonable to avoid aggressive maneuvers, as no ventilation devices is risk-free. Naola et al.[10] recommend a neutral head position and avoiding cervical hyperextension or the "sniffing" position, which would cause maximum extension and atlantoaxial instability. In this case, we intubated with Airtraq® (Prodol Meditec, Vizcaya, Spain), as the use of videolaryngoscopes for OTI is prioritized, as they require less force to expose the airway. However, direct laryngoscopy may be safe in experienced hands.
- We propose the use of moderate hypothermia (22°C) with antegrade SCP and pharmacological neuroprotection. There is no evidence on the superiority of one maintenance technique over the other. We prefer balanced techniques in the pediatric population. Complete replacement of the aortic arch requires interruption of CBF. The balance between oxygen supply and demand to the brain should be guaranteed, avoiding factors that worsen neurological damage. Among protective measures, deep hypothermia allows prolonged interruption of CBF, reducing the cerebral metabolic rate (CMR) by 50% for every 6° to 10°C. However, it causes longer ECC, edema, coagulopathy, and organ dysfunction[11]. In our case, we opted for moderate hypothermia (22°C) with antegrade SCP, as there are fewer complications, and pharmacological neuroprotection. Corticosteroids have been proposed to reduce ischemic brain damage, inflammation, and reperfusion ischemia; barbiturates reduce CMR and protect vs focal ischemia; mannitol and furosemide reduce cerebral edema, and calcium channel blockers, magnesium sulfate, and lidocaine block calcium channels[12]. Local cooling with ice may be effective and, although controversial, we used it due to its low rate of complications. Hyperglycemia should be avoided, as it worsens cerebral ischemia; levels > 180 mg/dL are harmful, and > 250 mg/dL are associated with poor neurological outcomes.

Insulin infusion therapy is protective. The impact of anesthetics is varied; halogenated ones increase CBF and reduce CMR, while propofol, etomidate, and benzodiazepines decrease CBF and CMR alike. Relaxants reduce CMR.

- We propose the use of tranexamic acid. Post-ECC hemorrhage is common and particularly severe in children. Hypothermia inhibits platelet function, and prolonged ECC dilutes coagulation factors. Thrombin consumption triggers hypofibrinogenemia, thrombocytopenia, and hyperfibrinolysis, a situation similar to disseminated intravascular coagulation (DIC). Bleeding is often profuse due to multiple vascular sutures. Prophylactic use of antifibrinolytics is advised. We use tranexamic acid for its proven efficacy over others[12].

In conclusion, LDS is a serious condition. It poses an anesthetic challenge in the pediatric population due to 3 factors: potentially difficult airway due to craniofacial malformations, high rate of intraoperative and postoperative neurological complications, and difficult hemodynamic management due to the risk of aneurysmal rupture before surgical control. Additionally, aortic arch surgery is uncommon in children, and experience is limited. It is essential to develop a plan considering all these variables for the appropriate anesthetic management of these patients.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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LETTER TO THE EDITOR

Usefulness of immunohistochemical markers of myoepithelial cells in the diagnosis of invasive carcinoma of the breast

Utilidad de los marcadores inmunohistoquímicos de células mioepiteliales en el diagnóstico de carcinoma invasor de la mama

Pablo S. Montes-Arcón

Postgrado de Patología, Universidad de Cartagena, Cartagena, Colombia

Breast cancer is the most common type of cancer worldwide according to statistical analyses by GLOBOCAN (2018), with an incidence rate of > 45 cases per 100 000 inhabitants, followed by prostate and lung cancer. In Mexico, it is the 2nd most common type of cancer among the population only second to prostate cancer. However, this type of cancer has the highest incidence rate among the female population, accounting for 25% of the cases, and has an estimated mortality rate of 16 cases per 100 000 women older than 20 years, meaning that it is the leading cause of cancer death among women in Mexico, being those between 50 and 59 years old the most affected of all[1].

In the interesting article "Predictive factors of invasion in ductal carcinoma in situ diagnosed by core-needle biopsy"[2], the authors present a series of factors determining the risk of invasion for patients with ductal carcinoma in situ (DCIS), among which they evaluated the results of immunohistochemical studies for estrogen receptor markers, progestogen receptors, HER-2, and Ki-67 proliferation index, without finding a statistical association between the results of these studies and the risk of presenting invasive carcinoma. In this study, immunohistochemical staining for myoepithelial cells was not considered a determining factor for the disruption of intralobular stroma and the subsequent development of invasive carcinoma[2].

Myoepithelial cells are a normal component of the acini and ducts of exocrine glands, where they are located between secretory epithelial cells and the basal membrane. Morphologically, they are thin and spindle-shaped, similar to smooth muscle cells, with an irregular cellular nucleus, adjacent to the basal membrane, and display a stellate appearance cytoplasm, with numerous extensions interdigitating with similar extensions of adjacent myoepithelial cells[3].

These cells have multiple functions, including assisting in secretion progression through their contractions, serving as a barrier between connective tissue and epithelium by forming the basal membrane, performing support functions, as well as paracrine functions of organization and polarity. They are present in sweat glands, salivary glands, mammary glands, lacrimal glands, and the prostate[4].

Invasive breast carcinoma is defined as a histopathological lesion in which neoplastic breast tissue penetrates the basal membrane of the ductal lobular unit, spreading into the adjacent stroma with a higher risk of generating disseminated disease through lymphatic or neural routes[3].

The immunohistochemical markers that allow delineation of the basal membrane of the acinar structures of the breast are mainly p40, p63, the heavy chain of smooth muscle myosin, calponin, CK5/6, and CK5, which highlight the intact surrounding layer of myoepithelial cells but may be attenuated vs normal ductolobular mammary structures, especially in patients with high-grade DCIS, thus confirming the diagnosis of invasive carcinoma[5].

Considering the ability of these immunohistochemical markers to determine invasion of mammary stroma, their application in the study to determine the

Correspondence:
Pablo S. Montes-Arcón
E-mail: pmontesarcon@gmail.com

Date of reception: 15-03-2022
Date of acceptance: 22-03-2022
DOI: 10.24875/CIRUE.M22000569

Cir Cir (Eng). 2023;91(4):563-564
Contents available at PubMed
www.cirugiaycirujanos.com

development of invasive carcinoma would have been useful. Therefore, these variables should be analyzed in subsequent studies to determine the risk for patients.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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LETTER TO THE EDITOR

Do prolonged syndrome of COVID-19 and variants of SARS-COV-2 cause hepatitis of unknown origin in Oaxaca?

¿Síndrome COVID-19 prolongada y las variantes de SARS-COV-2 causa de la hepatitis de origen desconocido en Oaxaca?

Sergio A. Ramírez-García

Facultad de Ciencias Químicas de la Universidad Autónoma Benito Juárez, Oaxaca, México

To the Editor,

I resume with great interest Rojo del Moral's article. Indeed, long COVID-19 represents a high percentage of current medical consultations and has high social importance[1]. Faced with the increase in hepatitis of unknown origin, the possibility of post-COVID hepatopathy, or coronavirus 2-induced hepatitis due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be ruled out. Since SARS-CoV-2 can bind to heparan sulfate, apoE, and the angiotensin-converting enzyme 2 (ACE2) at the endothelial level, its internalization becomes possible by activating vascular endothelial growth factor and cathepsin E, even being stored in cells or tissues in syncytia[2].

This is the case of a 4-year-old girl, non-jaundiced. General urine examination revealed urobilinogenuria and positive urobilinogen. Elevated lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), and bilirubin levels were noted (Table 1). Ultrasound revealed decreased bile flow in the intrahepatic ducts. Viral hepatitis tests turned out negative (Table 1). As a relevant history, 4 months prior, she had a SARS-CoV-2 infection. Currently, only real-time quantitative polymerase chain reaction (qRT-PCR) for SARS-CoV-2 in stool has tested positive. She was put on ivermectin at a dose of 150 μg/kg every 24 hours for 3 days and OM-85 infant granules for 30 days.

Case #2 is a 3.7-year-old woman who presented with a fever of 38.9 ºC, urobilinogenuria, and mild jaundice on her skin and conjunctiva. Pharyngeal enanthema was observed upon examination[3]. Elevated bilirubin and transaminases levels were noted, with negative viral hepatitis tests, qRT-PCR for SARS-CoV-2 in nasopharyngeal, oropharyngeal, and stool samples all turned out positive. As a relevant history, her parents had contracted the BA.1/BA.2 combined variant of Omicron in Los Angeles, CA, United States. She was treated with ivermectin at a dose of 150 μg/kg every 24 hours for 3 days, Vita Deyon® One Shot, and a single dose of pirfenidone LP® 50 mg, and OM-85 (Broncho-Vaxom®) infant granules for 30 days. Both patients improved 21 days into treatment (Table 1). Thus, case #1 was an intrahepatic cholestasis in the context of long COVID-19, and case #2 was a SARS-CoV-2-induced acute hepatitis.

For the management of COVID-19 related hepatopathy, early diagnosis is crucial to inhibit viral replication and reverse liver damage. In this regard, in rural areas, we have ivermectin and OM-85 as well as Vita Deyon® One Shot and pirfenidone LP® for their triple antiviral effect vs COVID-19, reducing the expression of ACE2, anti-cytokine storm, and antioxidants, attenuating the mitochondrial stress associated with COVID-19[4,5]. In conclusion, we provide population-based evidence of COVID-19 related hepatopathy in Mexico, both in the acute phase and in the context of

Correspondence:
Sergio A. Ramírez-García
E-mail: sergio7genetica@hotmail.com

Date of reception: 20-01-2021
Date of acceptance: 19-05-2021
DOI: 10.24875/CIRUE.M21000570

Cir Cir (Eng). 2023;91(4):565-567
Contents available at PubMed
www.cirugiaycirujanos.com

Table 1. Sociodemographic and clinical data of patients with COVID-19 related hepatitis

Socio-demographic data	Case #1	Case #2		21 days after admission
Socio-demographic Data	At admission	21 days after admission		
Gender	Woman	Woman		
Age	4 years	3.7 years		
Social status	Middle class	Lower class		
Ancestry	Zapotec/Afro-Mexican	Zapotec		
City of origin	Miahutlán de Porfirio Díaz	Putla de Guerro		
Type of housing	Semi-urban	Rural without soil		
History of COVID-19	DeltaAY.4/OmicronBA.1	No		
Family history of COVID-19	Yes, variant unknown	Yes, BA.1/BA.2 variant		
SARS-CoV-2 tests				
Nasopharyngeal and oropharyngeal qRT-PCR	Negative	Negative	Positive	Negative
Stool qRT-PCR	Positive	Negative	Positive	Negative
Liver function tests				
AST	22 UI/L	25 UI/L	1234 UI/L	33 UI/L
ALT	47 UI/L	34 UI/L	634 UI/L	26 UI/L
LDH	916 UI/L	146 UI/L	803 UI/L	174 UI/L
GGT	435 UI/L	201 UI/L	286 UI/L	155 UI/L
Total bilirubin	1.4 mg/dL	0.9 mg/dL	1.5 mg/dL	1.1 mg/dL
Direct bilirubin	1.0 mg/dL	0.5 mg/dL	0.9 mg/dL	0.6 mg/dL
Indirect bilirubin	0.4 mg/dL	0.4 mg/dL	0.6 mg/dL	0.5 mg/dL
Viral hepatitis panel				
HAV qRT-PCR	Negative	Negative	Negative	Negative
HBV qRT-PCR	Negative	Negative	Negative	Negative
HCV qRT-PCR	Negative	Negative	Negative	Negative
HDV qRT-PCR	Negative	Negative	Negative	Negative
HEV qRT-PCR	Negative	Negative	Negative	Negative
Herpes simplex 1 and 2 qRT-PCR	Negative	Negative	Negative	Negative
Cytomegalovirus qRT-PCR	Negative	Negative	Negative	Negative
Autoimmunity markers				
Anti-TAPO antibodies	Negative	Negative	Positive	Negative
Anti-citrullinated peptide antibodies	Negative	Negative	Positive	Negative
Anti-ANA antibodies	Negative	Negative	Positive	Negative
Anti-SMA antibodies	Negative	Negative	Positive	Negative

ALT: alanine aminotransferase; ANA: antinuclear antibodies; AST: aspartate aminotransferase; HV: hepatitis virus; LDH: lactate dehydrogenase; GGT: gamma-glutamyl transpeptidase; qRT-PCR: real-time quantitative polymerase chain reaction; SMA: smooth muscle antibodies; TAPO: thyroperoxidase.

long COVID-19. We introduced a new test for COVID-19 monitoring—qRT-PCR in stool—which reinforces the theory of the GI transmission route through enterohaptic circulation, considering that we found SARS-CoV-2 in stool.

Acknowledgments

The author wishes to thank CB-Xpert Clinical Pathology Laboratory, Miahuatlán de Porfirio Díaz, Oaxaca, Mexico, Professional Medical Services Particular A.C, Alfa-Unit-Ultrasound, Miahuatlán de Porfirio Díaz, Oaxaca, Mexico, for their support in conducting paraclinical and cabinet studies.

Funding

The author declares that his work was funded by the Mexican Foundation of Genetic Diseases and Genomic Medicine A. C.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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