ÓRGANO DE DIFUSIÓN CIENTÍFICA DE LA ACADEMIA MEXICANA DE CIRUGÍA

FUNDADA EN 1933

ISSN: 2444-0507

CIRUGÍA Y CIRUJANOS

Content

Original articles

PERMANYER MÉXICO
www.permanyer.com

Volume 91, No. 1, January-February 2023

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

7571AX221

ORIGINAL ARTICLE

Prognostic value of KI-67 proliferation index in luminal breast cancers

Valor pronóstico del índice de proliferación KI-67 en cánceres de mama luminales

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Abstract

Objective: *This study aimed to examine the prognostic significance of the KI-67 proliferation index, especially in breast cancer (BC) patients without HER-2 expression and no nodal involvement.* **Material and methods:** *The database of hormone-receptor-positive patients who underwent surgery for BC in our Surgical Oncology Clinic between 2008 and 2020 was retrospectively reviewed and recorded. Patients were categorized based on their KI-67 level, considering the cutoff value of 20%.* **Results:** *Our study revealed that tumors with high KI-67 levels were more likely to have a more advanced histological grade (p = 0.00) and size (p = 0.038). In the univariant analysis, KI-67 level was effective on overall survival (p = 0.044) and disease-free survival (p = 0.048). However, we found that there was no independent prognostic factor in the multivariant analysis.* **Conclusion:** *Although the Ki-67 proliferation index does not yet have an agreed threshold value and scoring methodology, it can also be used to determine prognosis and evaluate treatment response in some patients.*

Keywords: *Breast cancer. KI-67 index. Molecular subtypes. Prognostic factor.*

Resumen

Objetivo: *Este estudio tuvo como objetivo examinar la importancia pronóstica del índice de proliferación KI-67, especialmente en pacientes con cáncer de mama sin expresión de HER-2 y sin compromiso ganglionar.* **Material y métodos:** *Se revisó y registró retrospectivamente la base de datos de pacientes con receptores hormonales positivos intervenidas de cáncer de mama en nuestra Clínica de Oncología Quirúrgica entre 2008 y 2020. Las pacientes fueron categorizadas de acuerdo con su nivel de KI-67, considerando el valor de corte del 20%.* **Resultados:** *Nuestro estudio reveló que los tumores con valores elevados de KI-67 eran más propensos a tener un grado histológico (p = 0.00) y un tamaño (p = 0.038) más avanzados. En el análisis univariado, el nivel de KI-67 fue efectivo sobre la supervivencia global (p = 0.044) y la supervivencia libre de enfermedad (p = 0.048). Sin embargo, encontramos que no había ningún factor pronóstico independiente en el análisis multivariante.* **Conclusiones:** *Aunque el índice de proliferación Ki-67 aún no tiene un valor de umbral acordado ni una metodología de puntuación, también se puede utilizar para determinar el pronóstico y evaluar la respuesta al tratamiento en algunas pacientes.*

Palabras clave: *Cáncer de mama. Índice KI-67. Subtipos moleculares. Factor pronóstico.*

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Date of reception: 19-01-2022
Date of acceptance: 17-09-2022
DOI: 10.24875/CIRUE.M22000520

Cir Cir (Eng). 2023;91(1):1-8
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Prognostic factors are clinicopathological variables associated with outcomes (usually disease-free survival [DFS] and overall survival [OS]) used to predict the risk of death in post-surgical early breast cancer (BC). The KI-67 proliferation index has now been shown to be associated with poor clinical outcomes[1,2].

KI-67 is a non-histone type nuclear protein associated with cellular proliferation. It was first found by Gerdes et al. in the early 1980s using rat monoclonal antibodies in a cell line originating from Hodgkin lymphoma. Its function remains unclear, but it is thought to be involved in RNA synthesis. The most common analysis method of KI-67 antigen is detection by immunohistochemical (IHC) evaluation[3].

While KI-67 is expressed in the G1, S, G2, and M phases of the cell cycle, it is not detected in the G0 phase. MIB-1 is a monoclonal antibody developed against recombinant portions of the KI-67 antigen[1].

Proliferation is an important indicator used to predict BC prognosis and treatment response. The comparison of proliferation between uncontrolled growing tumor samples has become the most widely used method. Its potential uses include predicting resistance to chemotherapy or endocrine therapy, estimating residual risk in patients during standard therapy, and as a dynamic biomarker of treatment efficacy in samples taken at each stage in the neoadjuvant therapy process (especially neoadjuvant endocrine therapy). International researchers with significant expertise in evaluating KI-67 and the development of biomarker guidelines organize panels to make comprehensive recommendations on the interpretation and scoring of KI-67 based on the available evidence. Thus, they aim to achieve a consensus methodology, increase interlaboratory and interstudy comparability, and assist in its effective usability in clinical practice[4-6]. However, no consensus has been established on the issues listed yet. Expression of KI-67 has been associated with the luminal B phenotype, a high risk of recurrence, and a good response to neoadjuvant chemotherapy. Several guidelines emphasize the importance of KI-67 expression level in choosing those with early-stage BC and 1-3 positive axillary nodes not to administer adjuvant chemotherapy[7].

Although there is no standard threshold value for the KI-67 proliferation index and is not a standard in evaluation and scoring methodology, it is used to determine prognosis and other clinicopathological prognostic indicators.

In a meta-analysis of approximately 65,000 cases (41 studies), Petrelli et al. found that KI-67 had an independent prognostic value for OS in BC patients, for which only a cutoff value of > 25% was higher compared to lower rates and that it was associated with an increased risk of death[8].

It is now accepted that BC is not a single disease but a heterogeneous disease with biological diversity and molecular subtypes with different behaviors. One of the reasons for this heterogeneity is HER2 amplification[9]. Gene expression profiling has contributed significantly to our understanding of disease occurrence, progression, and recurrence. Therefore, it can be said that most of the clinical presentations of BC are determined within the molecular subtype profile[10].

Molecular subtypes are classified as luminal A, luminal B/HER2-, luminal B/HER2+, HER-2, and triple-negative according to the recommendations of the Gallen International Expert Consensus Report (2013)[11]. They approve a cutoff value of 14% KI-67 index in distinguishing luminal A and B subtypes. Cheang et al. found the best Ki-67 index cutoff point to be 13.25%[12].

The identification of BC molecular subtypes also helps us determine treatment options. While luminal tumors most likely respond to endocrine treatments such as tamoxifen, they are added to chemotherapy in addition to this treatment by their KI-67 levels. Tumors overexpressing HER2 respond favorably to treatment with trastuzumab in combination with an anthracycline taxane. On the other hand, triple-negative tumors have high genomic instability with an aggressive clinical course; therefore, treatment options are limited and non-specific[13-15].

There are significant differences in BC molecular subtypes in age, histological grade, lymph node status, and staging. Luminal type A BC is associated with the smallest tumor and the best prognosis. The HER2+ subtype is more commonly associated with a large tumor, positive lymph node metastasis, and poor grade[16]. Therefore, tumors with HER-2+ and axillary nodal metastases were not included in this study. We only aimed to determine the prognostic significance of the KI-67 index in luminal A and luminal B/HER2- tumors.

Material and method

Participants

Our study was initiated with the Medical Faculty Ethics Committee's approval (Decree number: İ2-123-21).

Patients with estrogen receptor (ER) and progesterone receptor (PR) positivity, no HER-2 expression, and no axillary lymph node involvement who were operated for BC in our Surgical Oncology Clinic between 2008 and 2020 were included in the study. Out of a total of 370 patients, 168 met the inclusion criteria. The hospital database was scanned retrospectively in a digital environment. Patients' age, menopausal status, and type of surgical procedure were extracted from the file contents and recorded. Besides, the following parameters were excluded from the histopathological reports: information such as receptor status (ER, PR, and HER-2), KI-67 percentage, histopathological subtype, size, Scarff-Bloom-Richardson (SBR) grade, lymphovascular invasion (LVI) status, and recurrence status were also recorded. Patients were categorized as over 14 and below according to their KI-67 percentage. For patients with recurrence, distant recurrences were defined as those occurring beyond the boundaries of the ipsilateral breast, chest wall, or regional lymph nodes. Distant recurrence sites were categorized as bone, brain, liver, lung, distant nodal, and multiple organ recurrence.

ER and PR status were determined using IHC staining. A positive ER or PR was considered when ≥ 1% of invading malignant cells display nuclear staining or immunoreactivity. Tumors were considered HER2-positive only if they showed 3+ staining with IHC staining or HER2 amplification (ratio > 2) using fluorescent *in situ* hybridization. ER, PR, and HER2 tests were scored per the American College of Pathologists Guidelines[17].

Histological grade was evaluated according to the Nottingham modification of the Bloom-Richardson system. Accordingly, grading was performed based on the Elston-Ellis modification by histochemical features such as tubular differentiation percentage, presence of nuclear atypia/pleomorphism, and the number of mitoses[17].

The patients were categorized into two groups by molecular BC subtypes according to the recommendations of the St. Gallen International Expert Consensus Report (2013) by molecular BC subtypes: According to the receptor status of their primary tumors, patients were categorized as follows: Luminal A (ER + and/or PR + and HER2-, Ki-67 < 14%); and luminal B/HER2- (ER + and/or PR +, HER2-, and Ki-67 ≥ 14%)[11].

DFS was determined as the time from diagnosis until the development of recurrence/metastasis or until the last follow-up date, and OS was the time from the date of diagnosis until death due to any cause. The follow-up period was the time from the date of diagnosis to the last follow-up date of the patient.

Post-operative adjuvant treatments of all patients were arranged according to NCCN guidelines. Radiotherapy was applied to the whole breast and tumor bed in patients who underwent breast-conserving surgery. Adjuvant chemotherapy with adjuvant endocrine therapy was applied to all pre-menopausal patients, Ki-67 > 10, tumor diameter > 5 mm, and high-grade tumors (Grade 2 and 3). Chemotherapy was neglected in postmenopausal patients with Ki-67 < 10, Grade 1, and ≤ 5 mm tumors.

Statistical analysis

Descriptive statistical analyzes of quantitative variables were performed and expressed as mean ± standard deviation, number, percentage, maximum and minimum values. Categorical variables were presented as frequency and percentage values. Survival curves were estimated using the Kaplan–Meier method, and the significance of the differences between these curves was determined using the log-rank test.

The relationship between categorical variables was analyzed using the chi-square (χ^2 test) test. Accordingly, KI-67 levels were compared with the following variables: status with menopause at diagnosis, operating tube, tumor size (T), histopathological subtype, histological grade, LVI status, and receptor status (ER and PR). Statistical analysis was performed at a 95% confidence interval. Univariant and multivariant analyzes were performed to identify independent prognostic factors affecting OS and DFS. The results were considered statistically significant if $p < 0.05$ (reported p-values were two-way.)

Results

All 168 patients included in the study were women. The mean age of the patients was 53.9 ± 12.4 years (30-92), and the mean follow-up period was 53 ± 31.8 months (1-117). By the menopausal status, 43.5% (n = 73) of the patients were pre-menopausal and 56.5% (n = 95) were post-menopausal. The affected breast was the right side in 53% (n = 89) of the patients and left in 47% (n = 79). The mean tumor size at the time of diagnosis was 17.5 ± 12.5 mm (2-80). Approximately ¾ of the patients had a tumor size of < 2 cm (n = 124.74%), while the remaining, except for five patients, had a tumor size of 2-5 cm.

Of the patients, 41% were luminal A (n = 69) and 59% luminal B HER- (p = 99). Most cases (n = 118, 70.2%) were ductal by histopathological subtypes, a few (n = 12, 20%) were lobular, and the remaining cases were of other histological types such as medullary tubular, metaplastic, adenoid, and papillary carcinoma. Most cancer cases determined were mildly differentiated (n = 65.39%), followed by moderately differentiated (n = 55.33%) and highly differentiated (n = 46.28%). The mean number of total lymph nodes excised was 9.2 ± 7 (1-30). Recurrence occurred in 4.8% of the patients (n = 8). Nine patients (5.4%) died. The Chi-square analysis p values showing that the clinicopathological features of the patients and their relationship with KI-67 levels are shown in table 1. The 1-, 2-, and 5-year OS and DFS rates determined with the survival analysis performed through the Kaplan–Meier method by the KI-67 levels are presented in table 2.

DFS in the group with Ki-67 < 20 (p = 0.048, 144.56 ± 1.64 months, 95% CI: 111.34-117.78) compared to the group with KI-67 ≥ 20 (p = 0.048, 101.03 ± 2.94 months, 95% CI: 95.26-106.80) it was long. Similarly, in the Ki-67 < 20 group, OS (p = 0.044, 114.25 ± 1.91 month, 95% CI: 110.50-117.99) KI-67 ≥ 20 (p = 0.044, 98.65 ± 3.27 month, 95% CI: 92.24-105.05) was also longer than the group with DFS and OS curves according to KI-67 levels are shown in figures 1 and 2.

The most common sites of metastases were isolated bone (n = 4, 44%), mixed type multiorgan metastases (n = 3, 34%), and local recurrence (n = 1, 12%), respectively. All of the mixed type metastases were liver metastases accompanied by bone metastases. The distribution of other clinicopathological features of the patients is shown in table 1. In the chi-square analysis between KI-67 levels and categorical variables, there was a significant correlation with tumor T stage (p = 0.038) and histological grade (p = 0.00). In contrast, no statistically significant relationship was found between LVI status, receptor status (ER, PR), histopathological subtype, the surgery type, and menopausal status (p < 0.05), (Table 1).

In the univariant analysis, PR (p = 0.047), grade (p = 0.02), and KI-67 levels (p = 0.048) were effective on DFS, while grade (p = 0.011), TNM stage (p = 0.024), and KI-67 levels were effective on OS. We found that the 67 level was effective (Table 3). However, in the multivariant analysis with these variables, we found that none of them were independent prognostic factors for PFS and OS (Table 4).

Table 1. Clinicopathological characteristics of 168 breast cancer patients by groups and p values of Chi-square analyzes of categorical variables

Variables	KI-67 < 20%	KI-67 ≥ 20%	Total	p value
	n = 92 (%)	n = 76 (%)	n = 168 (%)	
Surgery type				0.156
BCS	63 (68.5)	44 (57.9)	107 (63.7)	
Mastectomy	29 (31.5)	32 (42.1)	61 (36.3)	
Histology				0.985
Ductal	65 (70.7)	53 (69.7)	118 (70.2)	
Lobular	11 (12)	9 (11.8)	20 (12)	
Other	16 (17.3)	14 (18.4)	30 (17.8)	
T stage				0.038
T1 (< 2 cm)	73 (79.3)	51 (67.1)	124 (73.8)	
T2 (2-5 cm)	19 (20.7)	21 (27.6)	40 (23.8)	
T3 (> 5 cm)	0 (0)	4 (5.3)	4 (2.4)	
T4	0 (0)	0 (0)	0 (0)	
LVI status				0.462
Negative	80 (87)	63 (83)	143 (85)	
Positive	12 (13)	13 (17)	25 (15)	
Grade				0.00
Grade 1	42 (45.7)	14 (18.4)	56 (33.3)	
Grade 2	43 (46.7)	28 (36.8)	71 (42.3)	
Grade 3	7 (7.6)	34 (44.7)	41 (24.4)	
PR				0.145
Positive	86 (93.5)	66 (86.6)	152 (90.5)	
Negative	6 (6.5)	10 (13.2)	16 (9.5)	
ER				0.118
Positive	89 (96.7)	74 (97.4)	161 (95.8)	
Negative	3 (3.3)	2 (2.6)	5 (4.2)	
Menopause				0.537
No	38 (41.3)	35 (46.1)	73 (43.5)	
Yes	54 (58.7)	41 (53.9)	95 (56.5)	

BCS: breast conserving surgery; LVI: lymphovascular invasion.

Table 2. 1-2-5 year OS and DFS rates of the groups

Survival	KI-67 < 20% (%)			KI-67 ≥ 20% (%)		
	1	2	5	1	2	5
OS	98.8	97.4	95.7	96.9	95.3	93.4
DFS	100	98.5	96.1	98.5	95.5	93.4

DFS: disease free survival; OS: overall survival.

Adjuvant endocrine therapy was given to all patients who were scheduled for post-operative adjuvant therapy in accordance with the NCCN 2017 guideline. Only four of these patients received concomitant adjuvant chemotherapy. Therefore, univariant was not included in the analysis. Radiotherapy was applied to the entire breast and tumor bed in 107 patients who

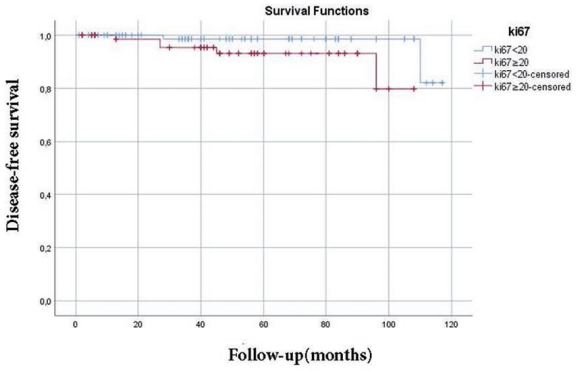

Figure 1. *Kaplan–Meier curve disease-free survival of KI-67 level (months).*

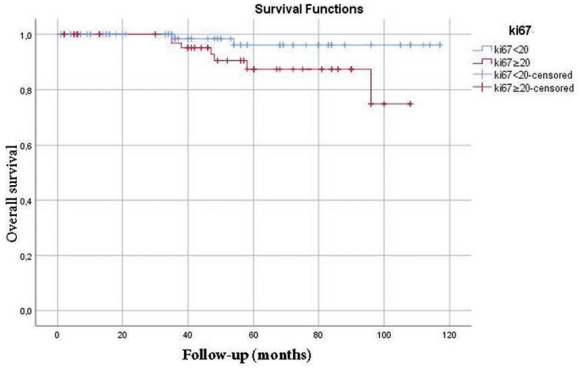

Figure 2. *Kaplan–Meier curve overall survival of KI-67 level (months).*

underwent breast-conserving surgery. In the univariant analysis, it was found that radiotherapy had no effect on OS (p = 0.319).

Discussion

In this study, the prognostic value of the KI-67 index and its relationship with other clinicopathological variables in luminal breast tumors (lumA, lumB HER-) without HER-2 negative and axillary lymph node involvement were examined. It was aimed to make the effect of the KI-67 index more evident by excluding patients with axillary nodal involvement and HER2 positive, which are considered to be one of the critical poor prognostic factors[18]. Our study revealed that tumors with high KI-67 levels were more likely to have more advanced histological grades and sizes (Table 1). In the survival analysis, we found that the 1-, 2-, and 5-year OS and DFS rates were better in the group with low KI-67 levels,

Table 3. Univariant analysis OS and DFS

	OS				DFS			
	p value	OR	95.0% CI		p value	OR	95.0% CI	
			Lower	Upper			Lower	Upper
Menopause	0.775	0.825	0.220	3.091	0.493	0.695	0.246	1.965
Age	0.425	0.973	0.911	1.040	0.274	0.955	0.880	1.037
Surgery type	0.324	1.384	0.726	2.637	0.170	1.861	0.767	4.514
Side	0.799	0.843	0.226	3.143	0.833	0.851	0.190	3.809
Histology	0.533	0.737	0.282	1.924	0.884	0.930	0.351	2.464
Tumor size	0.147	1.043	0.985	1.103	0.867	1.005	0.944	1.070
ER	0.334	0.355	0.044	2.897	0.762	21.414	0.000	-
PR	0.211	0.363	0.074	1.775	0.047	0.177	0.032	0.981
Luminal type	0.252	2.521	0.519	12.252	0.360	2.191	0.408	11.758
Grade	0.011	3.947	1.364	11.422	0.020	4.607	1.275	16.644
LVI	0.335	2.200	0.443	10.931	0.144	3.797	0.634	22.744
TLN	0.644	0.979	0.895	1,071	0.617	0.973	0.873	1.084
TNM stage	0.024	2.242	1.114	4,514	0.265	1.531	0.724	3.240
Radiotherapy	0.319	0.448	0.092	2.176	0.241	0.279	0.033	2.352
KI-67 level	0.044	4.207	10.37	20.395	0.048	6.456	1.013	55.856

CI: confidence interval; ER: estrogen receptor; LVI: lymphovascular invasion; OR: odds ratio; PR: progesterone receptor; DFS: disease free survival; OS: overall survival.

Table 4. Multivariant analysis OS and DFS

	OS				DFS			
	p value	OR	95.0% CI		p value	OR	95.0% CI	
			Lower	Upper			Lower	Upper
Grade	0.090	2.829	0.850	9.418	0.097	3.338	0.805	13.836
TNM stage	0.087	1.889	0.913	3.910	-	-	-	-
KI-67 level	0.630	1.573	0.249	9.921	0.466	2.432	0.223	26.484
PG	-	-	-	-	0.137	0.269	0.048	1.520

CI: confidence interval; LVI: lymphovascular invasion; OR: odds ratio; PR: progesterone receptor; DFS: disease free survival; OS: overall survival.

and histological grade was vital among the factors affecting DFS (Table 2). In the univariant analysis, we found that grade, tumor size, and if the KI-67 level was above DFS, PR, grade, and KI-67 levels were effective on OS, but none of them were independent prognostic factors for OS and DFS in the multivariant analysis.

There is still no consensus on a standard cutoff value for KI-67. While a 14% cutoff point was recommended in the St Gallen consensus 2011 report, the 2015 report emphasized the labs' median values[11,19]. Various authors have researched this subject and expressed their opinions about the importance of different breakpoints. Petrelli et al. found a cutoff value of > 25% associated with a higher risk of death than lower expression rates, while a 10% value was associated with poor prognosis[8]. In two critical studies, the 20% cutoff point was more closely associated with poor outcomes[20,21]. In this study, the results were evaluated based on the 20% cut-off point.

St. Gallen International Consensus Guidelines 2021 panel discussed strategies for early BC treatment. According to the survey, the panel was unable to define a consistent Ki67 threshold of 10% to 25% to recommend chemotherapy in ER-positive, node-negative BC. Overall, the panel supported the recent working group recommendations that 5% of tumors with Ki67 did not receive chemotherapy, whereas tumors with Ki67 received 30% chemotherapy[22]. Panelists preferred that genomic signature testing be considered in the vast majority of cases in which chemotherapy is considered. In this, they referred to the importance of mature data to be collected from prospective studies (MINDACT, ADAPT, TAILORx, RxPonder, etc.) in which patients were classified based on well-established genomic signatures[23].

In clinical practice, early-stage BCs are classified into three subgroups according to their receptor expression status: ER- and/or PR-positive and HER2-negative, HER2-positive or triple-negative breast cancer (TNBC). The implications of these classifications for systemic therapy are as follows: almost all ER-positive tumors warrant adjuvant endocrine therapy, the majority of TNBCs warrant adjuvant chemotherapy, and most HER2-positive cancers warrant anti-HER2 therapy in combination with chemotherapy. Adjuvant endocrine therapy was given to all patients in the study due to ER expression. Adjuvant chemotherapy was given to the postmenopausal risk group (Grade2-3, Ki-67 > 10, tumor diameter > 5 mm) together with all premenopausal patients. Accordingly, only four patients were candidates for chemotherapy.

ER positive cancers are sometimes classified as 'luminal A-like' (low grade, low Ki-67, strong ER/PR expression) or 'luminal B-like' (high grade, higher Ki67, and lower levels of ER/PR expression)[11]. There is persistent debate about exact thresholds for Ki-67 to justify chemotherapy treatment. Because in reality, most of the early stage, ER-positive tumors fall between these accepted extremes (5-30%)[24].

While adjuvant treatments are being planned, we are in favor of approaching the threshold values of Ki-67 with care, especially in patients with a long life expectancy, until the heterogeneous nature of BC with many genomic signatures is clarified and its implications for treatment are revealed. In these patients, lower threshold values such as 5% should be preferred for the justification of chemotherapy. In elderly patients, the 20% cutoff value can be used to recommend chemotherapy. Because our study revealed that the aggressive features of BC become evident at Ki-67 levels above this value.

Voduc et al. identified a total of 325 local recurrences and 227 regional lymph node recurrences in their study, which included nearly 3000 tumors followed for 12 years. They found that luminal A tumors (ER or PR positive, HER2 negative, Ki-67-14%) had the best prognosis and the lowest local or regional recurrence rate[25].

A meta-analysis of 46 studies indicated that KI-67/MIB-1 positivity confers a higher risk of relapse and worse survival in patients with early BC[1].

In a study conducted, histological Grade I was associated with Luminal A, while Grade III was associated with Luminal B, and other subtypes[26]. Another study showed a significant association between KI-67 values above 20% and histological Grade 3, and these were associated with poor prognosis in early-stage BC patients without nodal involvement[27]. Similarly, in our study, Grade 1 tumors mainly were associated with luminal A subtype with KI-67 < 20%, reaching statistical significance, while others were more associated with Grade 2-3 tumors.

Centralized assessment of KI-67 in 10 collaborative studies (8088 patients) by Abubakar et al. was performed using an automated scoring protocol. The relationship between KI-67 levels and 10-year BC-specific survival (BCSS) was investigated. The KI-67 is divided into quarters with specific breakpoints. They found that patients in the highest quartile of KI-67 (> 12% positive KI-67 cells) had worse 10-year BCSS than patients in the lower three quartiles. This relationship was also statistically significant for ER-positive patients[28]. Small, low-grade tumors with low rates of axillary involvement are more likely to belong to the ER + PR ± HER2- group.[29] Bolat Küçükzeybek et al. reported a positive correlation of KI-67 proliferation index with histological grade and tumor size, as well as a poor effect at 7-year OS[30].

Luminal A subtype BC has also been associated with the smallest tumor and the best prognosis[16]. In this study, we found that in patients with CI-67 < 20%, tumors were mostly T1 (79.3%), and their association was significant, and OS and DFS rates were better than the others (Table 2 and Figs. 1 and 2).

Many studies in the literature have determined that the KI-67 proliferation index is associated with OS and DFS regardless of nodal status[1,20,31].

Metastases identified in our study were the most commonly isolated bone, followed by liver metastases accompanying bone involvement. Except for patients with widespread metastases, two main disease patterns in recurrent BC have been reported. Patients with ER +/PR + (luminal) tumors tend to develop more bone metastases but no brain metastases. The situation is the opposite in patients with ER−/PR−tnonluminal) tumors[32]. Clinically, the most common metastasis sites are organs such as bone, lung, central nervous system, and liver[33,34].

Conclusion

Besides the absence of a specific threshold value agreed on for the KI-67 proliferation index, a certain standard could not be determined in the evaluation and scoring methodology by the laboratories. Although the same antibodies are used in IHC staining, different laboratories may report different results that reach a statistically significant size due to this method difference. Even in the same patient sample, up to 25%, different results can be obtained[35]. Despite all these, it can be used to determine prognosis together with other prognostic indicators and evaluate treatment response in patients with HR-positive, HER-2 negative, and nodal involvement. There is a need for new classification methods based on IHC, genetic and molecular findings, as well as more randomized prospective studies for the standardization of evidence that will form the basis of these studies.

Acknowledgments

The authors thank the members of the surgical oncology department for their collaboration so that this work has been possible.

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 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 relationship between bile reflux and common bile duct diameter after cholecystectomy: a clinical case-control study

La relación entre el reflujo biliar y el diámetro del conducto biliar común después de la colecistectomía: un estudio clínico de casos y controles

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Abstract

Objective: *The present study aims to investigate the relationship between bile reflux (BR) and diameter of the common bile duct (CBD) in patients after cholecystectomy.* **Materials and methods:** *In our case series analysis, according to the endoscopy results, the patients who underwent cholecystectomy were divided into two groups as those with BR and those non-BR. Age, sex, CBD diameter measured on ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, and endoscopic biopsy results of the patients were statistically analyzed.* **Results:** *In a total of 188 patients included in the study, BR was detected in 93 patients, it was not observed in 95 patients. The CBD diameter of the patients was observed to be 7 mm or less in 70.9% (n = 66) in the BR group, and 23% (n = 22) in the non-BR group. The statistical analysis revealed that while there was a significant difference between the two groups in terms of CBD diameter and intestinal metaplasia, the results were similar in both groups in terms of inflammation, activity, atrophy, and Helicobacter pylori.* **Conclusion:** *We believe that CBD diameter may be a predictive factor in the detection of BR after cholecystectomy.*

Keywords: *Cholecystectomy. Common bile duct diameter. Bile reflux. Intestinal metaplasia. Helicobacter pylori.*

Resumen

Objetivo: *Investigar la relación entre el reflujo biliar y el diámetro del colédoco después de la colecistectomía.* **Método:** *Estudio retrospectivo en el que, de acuerdo con los resultados de la endoscopia, los pacientes que se sometieron a colecistectomía se dividieron en dos grupos: con reflujo biliar y sin reflujo biliar. Se analizaron estadísticamente la edad, el sexo, el diámetro del conducto biliar común medido por ultrasonografía, tomografía computarizada y colangiopancreatografía por resonancia magnética, y los resultados de la biopsia endoscópica.* **Resultados:** *En un total de 188 pacientes incluidos en el estudio, se detectó reflujo biliar en 93 pacientes y no se observó en 95 pacientes. Se vio que el diámetro del conducto biliar común de los pacientes era de 7 mm o menos en el 70.9% (n = 66) del grupo con reflujo biliar y en el 23% (n = 22) del grupo sin reflujo biliar. El análisis estadístico reveló que, si bien hubo una diferencia significativa entre los dos grupos en términos de diámetro del conducto biliar común y metaplasia intestinal, los resultados fueron similares en ambos grupos en términos de inflamación, actividad, atrofia y presencia de Helicobacter pylori.* **Conclusiones:** *Creemos que el diámetro del colédoco puede ser un factor predictivo en la detección de reflujo biliar después de la colecistectomía.*

Palabras clave: *Colecistectomía. Diámetro del conducto biliar común. Reflujo biliar. Metaplasia intestinal. Helicobacter pylori.*

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Date of reception: 30-09-2022
Date of acceptance: 20-10-2022
DOI: 10.24875/CIRUE.M22000521

Cir Cir (Eng). 2023;91(1):9-14
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Cholecystectomy is one of the most commonly performed surgeries worldwide. Complaints such as nausea, bilious vomiting, and dyspeptic symptoms occur in some patients after cholecystectomy. These findings are described as in post-cholecystectomy syndrome. It has been reported that 15-20% of patients after cholecystectomy had new-onset or ongoing symptoms[1].

It has been revealed by many studies that there is a physiological bile reflux (BR) in humans. Various studies have shown that the rate of BR can increase up to 60-78% in patients who have undergone cholecystectomy[2-4]. BR has harmful effects that start 2-6 months after cholecystectomy on gastric mucosa[4-6]. Moreover, there are some studies in the literature stating that histological changes caused by BR are a predisposing factor for gastric cancer[7,8].

The underlying causes of BR still remain unclear. The previous therapeutic biliary procedures and gastric diversion surgeries are proven reasons that increase BR. In addition, procedures defunctioning the sphincter of Oddi such as sphincterotomy, stent, and choledochoduodenostomy also increase the development of BR[3]. Since there is no pressure barrier in front of the bile released from the liver as a result of these procedures, it is not expected the common bile duct (CBD) to enlarge.

The upper limit of the CBD diameter is generally accepted to be 7 mm[9,10]. Different results have been obtained in various studies about changes in CBD diameter of patients after cholecystectomy. Some of these studies indicated that CBD diameter has significantly increased following cholecystectomy[11,12]. However, there are also studies in the literature reporting that CBD diameter does not increase significantly after cholecystectomy[13,14].

Most of the studies in the literature investigating the cause of BR have evaluated the findings after operations including sphincterotomy, stent, choledochoduodenostomy, and gastric diversion. Thus, we planned this case series analysis to reveal the relationship between CBD diameter and BR in patients who had cholecystectomy only.

Methods

An ethical approval was obtained from the Clinical Studies Ethics Committee of Tokat Gaziosmanpasa University Faculty of Medicine (Ethics Committee Approval No: 21-KAEK-164). The data of 10,128 patients who underwent upper gastrointestinal system (GIS) endoscopy in the Medical Faculty Hospital of Tokat Gaziosmanpasa University between 2012 and 2020 were retrospectively reviewed. The patients proven to have had cholecystectomy during upper GIS endoscopy were included in the study. For this purpose, the pre-procedural radiological examination reports of the patients as well as their previous surgical history were examined. The patients whose pre-procedural radiological examination reports had the phrase “gallbladder not observed-operated” were included in the study. The endoscopy images of the patients were also examined, and the fact that the gastric mucosa was stained with bile and the presence of bile residues in the stomach during the procedure was evaluated as pathological BR. The patients’ age, sex, endoscopic biopsy results, and the CBD diameter measured from the widest section were recorded.

The patients with a history of therapeutic biliary procedures (sphincterotomy, stent, choledocoduodenostomy, and hepaticojejunostomy) before radiological examination, in which CBD diameter was measured were excluded from the study. In addition, those with signs of subtotal/total gastrectomy and gastric diversion, which remove or bypass the pylorus in their upper GIS endoscopy and surgical history, were also excluded from the study. The absence of sufficient data for quantitative measurement of CBD diameter was also an exclusion criteria. Through these criteria, the patients that were included and excluded have been shown in flow chart (Fig. 1).

In line with these criteria, a total of 189 patients were included in the study. The patients were categorized into two groups as BR group (those with BR,n = 93) and NBR group (those without BR, n = 96) according to endoscopy reports. As is generally accepted, CBD diameter measured above 7 mm was considered to be wide. The CBD diameter was measured from computed tomography (CT) images in 168 (89%) of 189 patients. It was measured by magnetic resonance cholangiopancreatography (MR/MR-CP) in 17 of the remaining 21 patients. All measurements were performed by a single author. The CBD diameter measured by abdominal ultrasonography (USG) reports was taken into account in only four patients. Endoscopic biopsy results were recorded as none, mild, moderate, and severe.

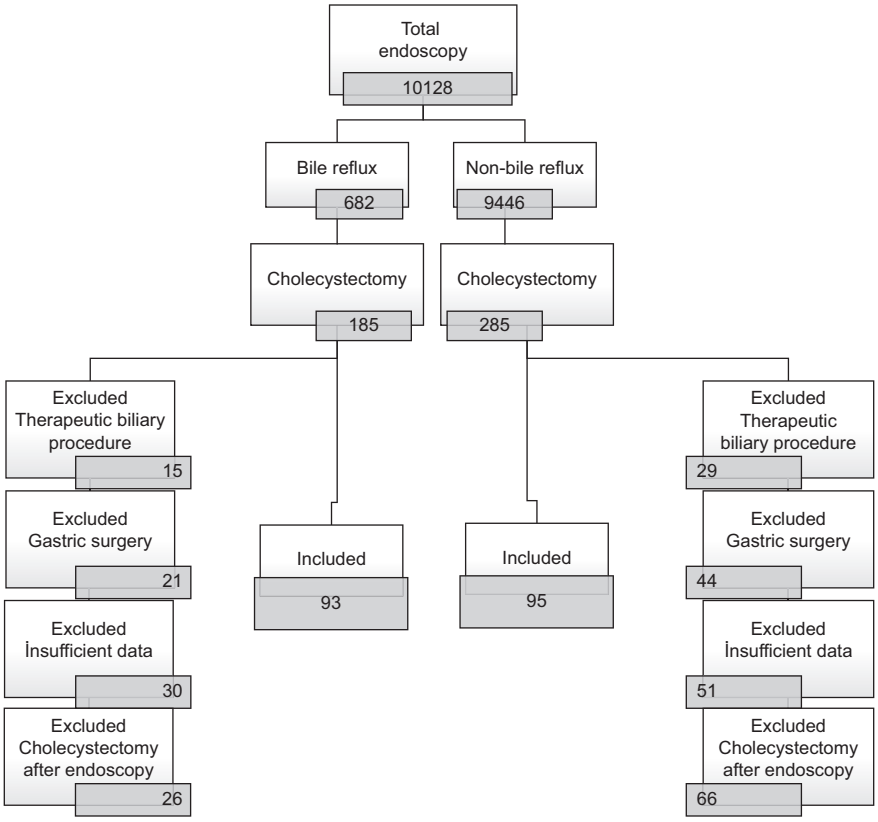

Figure 1. *Flow chart of patients.*

Statistical analysis

The data were recorded using the SPSS software (the Statistical Package for the Social Sciences, version 15). The student t-test was used to compare the difference between the two groups in terms of the mean age, sex, and the mean CBD diameter. The Pearson's Chi-square test was applied to determine the differences between the two groups in endoscopic biopsy results (inflammation, activity, atrophy, *Helicobacter pylori*, and intestinal metaplasia). $p < 0.05$ was regarded as statistically significant.

Results

Of the 189 patients included in the study, one patient was observed to have a CBD diameter of 11 mm, which was measured by USG only. Due to the low sensitivity of USG in evaluating the mass and obstruction causes in the distal CBD, the patient was excluded from the study. All patients included in the study underwent upper GIS endoscopy at least 6 months after cholecystectomy. The CBD diameters were measured from radiologic images that were performed at least 6 months after cholecystectomy. While BR was detected in 93 patients (49.6%), it was not detected in 95 patients (50.6%).

Of the patients included in the study, 80.8% (n = 152) were women, 19.2% (n = 36) were men. The mean age was detected to be 58.64 SD 13.9 years in the BR group and 59.15 SD 12.2 years in the NBR group. While a significant difference was observed between the two groups in terms of sex ($p = 0.038$), the mean ages of groups were statistically similar ($p = 0.199$). The comparison of demographic and clinical characteristics is given in table 1. The CBD diameter was observed to be 7 mm or less in 70.9% (n = 66) of the patients in the BR group and in 23.1% (n = 22) of those in the NBR group. The mean CBD diameter was 6.94 SD 2.1 (3-13 mm) in the BR group, and 9.07 SD 2.3 (4-15 mm) in the NBR group. In our study, the CBD diameter was found to be statistically significantly higher in the NBR group ($p < 0.001$). The comparison of the two groups for biopsy results obtained during endoscopy revealed that intestinal metaplasia was significantly higher in the BR group ($p = 0.001$). On the other hand, no significant differences were observed in terms of inflammation ($p = 0.146$), activity ($p = 0.217$), *H. pylori* ($p = 0.311$), and atrophy ($p = 0.221$) (Table 2).

Table 1. Demographic and clinical characteristics of study patients

	Bile reflux	Non-bile reflux	p value
Population	93	95	
Mean age ± SD, years	59.15 ± 12.2	58.64 ± 13.9	NS
Sex (female/male)	78/15	74/21	0.038
Mean CBD diameter ± SD, mm	6.9 ± 2.1	9.07 ± 2.3	< 0.001
Range	3-13	4-15	
CBD diameter ≤ 7 mm (n)	66	22	< 0.001

CBD: common bile duct; n: population; SD: standard deviation.

Discussion

We investigated the relationship between CBD diameter and BR in patients with cholecystectomy in the present study. We observed that the CBD diameter was 7 mm or less in the group with BR. It was found that the CBD diameter was statistically significantly larger in the non-BR group compared to the BR group.

When the demographic characteristics of patients in both groups were compared, it was found that the mean age of both groups was statistically similar. On the other hand, a significant difference between groups was detected in terms of sex of the patients. However, we are of the opinion that this difference did not clinically affect the results of our study.

The comparison of endoscopic biopsy results revealed that severe intestinal metaplasia was observed in seven patients (13%) in the BR group, while it was not detected in any patients in the NBR group. Intestinal metaplasia was statistically higher in the BR group than in the NBR group. There were no significant differences between two groups in terms of inflammation, activity, atrophy, and *H. pylori.*

BR is defined as reflux of duodenal contents into the stomach, esophagus, or even larynx. The mechanism of BR formation is not clear. The motility of the stomach and duodenum and the prolongation of gastric emptying time are among the factors blamed. In addition, as shown in recent studies, BR is known to develop after operations involving gastric diversion[15,16]. Following the studies showing that BR increased as a result of therapeutic biliary procedures, including cholecystectomy, attention was turned to the sphincter of Oddi. After cholecystectomy, the reservoir function of the gallbladder is removed. The sphincter of Oddi is the first barrier in front of the bile. The bile released from the liver waits in the extrahepatic bile ducts. In cases where the pressure in the bile ducts exceeds the pressure of the sphincter or postprandial opening of the sphincter, bile passes to the duodenum with certain periods. This causes enlargement of the extrahepatic bile ducts. On the other hand, when the sphincter barrier is removed, enlargement of the bile ducts is not expected, since the bile continuously passes into the duodenum without waiting.

There are studies showing that post-operative BR occurs in patients who underwent cholecystectomy only[2,3]. In a study, in which 20 of the 131 patients included in the study underwent cholecystectomy only, BR was detected in 60% of the patients undergoing cholecystectomy alone[3]. Another study investigating BR before and after cholecystectomy revealed that there was an increase in BR in terms of both quantity and incidence after surgery in 66% of patients[2]. In our study, on the other hand, the incidence of BR after cholecystectomy was 49.6%.

As a result of BR, a number of changes occur in the gastric and esophageal mucosa. Endoscopies performed after a certain period of cholecystectomy revealed the development of gastritis due to BR[4,5]. In a multicenter study including 2283 patients, it was shown that especially high-concentration BR caused significantly more intestinal metaplasia than the other groups[17]. The study examining gastric and esophageal biopsies indicated that antral intestinal metaplasia was detected in 10% of the patients, while the presence of intestinal metaplasia was found in the gastroesophageal junction in 33% of patients[18]. There are studies in the literature showing that gastric, esophageal, and even laryngopharyngeal malignancies develop as a result of mucosal changes due to BR[7,19,20]. BR has been determined to be an independent factor in the development of precancerous lesions and gastric cancer[21].

While age and the conditions causing obstruction have been shown among the factors that increase CBD diameter, there are studies revealing that cholecystectomy also increased CBD diameter. In a study conducted in individuals without biliary pathology, it was shown that CBD diameter increases with age, especially in advanced age[22]. In a study that examined the diameter of CBD in similar age groups, it was found that in 80% of patients with cholecystectomy, the diameter of CBD was 6 mm and above at proximal, while this ratio was 28% in the group that did not undergo cholecystectomy[11]. In our study, the CBD diameter was found to be 6 mm and above in 83% of

Table 2. Endoscopic biopsy results of patients

	Non n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total* n (%)	p value
Inflammation bile reflux	1 (1%)	25 (33%)	41 (55%)	8 (11%)	75 (100%)	NS
Non-bile reflux	0 (0%)	20 (48%)	14 (34%)	7 (18%)	41 (100%)	
Activity bile reflux	36 (48%)	20 (27%)	16 (22%)	2 (3%)	74 (100%)	NS
Non-bile reflux	20 (49%)	9 (22%)	7 (17%)	5 (12%)	41 (100%)	
Atrophybile reflux	54 (77%)	10 (14%)	5 (7%)	1 (2%)	70 (100%)	NS
Non-bile reflux	32 (78%)	9 (22%)	0 (0%)	0 (0%)	41 (100%)	
H. pylori bile reflux	60 (77%)	5 (6%)	10 (13%)	3 (4%)	78 (100%)	NS
Non-bile reflux	37 (80%)	4 (8%)	2 (4%)	4 (8%)	47 (100%)	
IM bile reflux	39 (70%)	3 (6%)	6 (11%)	7 (13%)	55 (100%)	0.001
Non-bile reflux	25 (70%)	8 (22%)	3 (8%)	0 (0%)	36 (100%)	

*Endoscopic biopsies were taken from 124 of 188 patients.
IM: intestinal metaplasia; *H. pylori: Helicobacter pylori.*

patients with cholecystectomy. However, in our study, we accepted CBD diameter above 7 mm to be wide, as is generally regarded. We detected that the CBD diameter of 34 patients (18%) was above 10 mm. Of these patients, the CBD diameter was measured by only CT in 28 patients, CT and MR/MR-CP in two patients, only MR/MR-CP in three patients, and only USG in one patient. It is known that CT and MR/MR-CP are superior to USG in the diagnosis of extrahepatic biliary tract diseases[23-25]. In addition, USG is a person-specific examination method. Therefore, this patient, whose CBD diameter was measured by USG, was excluded from the study. We found that 17 of the patients with a CBD diameter of above 10 mm were over 65 years of age and five patients were 80 years of age or older. On the other hand, we did not observe any biliary pathology or elevated liver function tests on CT and MR/MR-CP performed in patients with very large CBD diameters. In our study, the facts that the two groups were similar in terms of age and that most of the CBD diameters (99%) were measured by CT and MR/MR-CP strengthen the results of our study.

There are some limitations in our study due to its retrospective nature. In the patient records, we observed that the CBD diameters of some patients could not be measured quantitatively; thus, we excluded these patients from the study. In this case, the number of the patients included in the study reduced. In addition, the Oddi sphincter pressure of the patients included in the study was not measured. The fact that no biopsy was taken in some patients during endoscopy is also another limitation of the study. In the literature review, we have not come across a study investigating the relationship between CBD diameter and BR. We believe that the issue will be better clarified with prospective and larger population studies.

We observed in our study that BR was less common in cholecystectomy patients with increased CBD diameter. At the same time, we revealed that BR was significantly higher in the patients whose CBD diameter was found 7 mm or below. For this reason, we recommend that patients whose CBD diameter is detected to be 7 mm or below after cholecystectomy be closely monitored for BR. We anticipate that these patients can be protected from malignancies, in which BR plays a predisposing role with appropriate treatment.

Conclusion

We are of the opinion that CBD diameter found 7 mm or below after cholecystectomy may be a predictive factor in the detection of BR. However, we think that this issue should be further investigated with prospective, larger population studies.

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 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

Association between radiographic findings and knee bone tumors

Asociación entre las características radiográficas y los tumores óseos de rodilla

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Abstract

Background: *Bone neoplasms require an adequate clinical-radiographic evaluation for their diagnosis. Plain radiographs are the usual method to establish the diagnosis and evaluate differential diagnoses in the study of bone tumor pathology.* **Objective:** *To recognize the frequency of radiographic characteristics and associate them with bone tumor pathology.* **Method:** *Radiographic data were collected from 132 patients with tumor pathology confirmed by biopsy from bone tumors service of the Traumatology and Orthopedics Hospital Unidades Médicas de Alta Especialidad Dr. Victorio de la Fuente Narváez, Instituto Mexicano del Seguro Social, Ciudad de México, during 2019.* **Results:** *132 patients were registered. The most frequent benign tumor was osteochondroma (27.3%), and malignant was osteosarcoma (9.8%). Active lytic lesions (odds ratio [OR]: 6.9; 95% confidence interval [95%CI]: 2.83-16.85) or aggressive (OR: 26.85; 95%CI: 3.21-224) were associated with giant cells tumors. Poorly differentiated intraosseous blast lesions of bone lineage (OR: 36.15; 95%CI: 4.4-295.5) were associated with osteosarcoma. The periosteal reaction (OR: 36.15; 95%CI: 4.4-295.5), the moth-eaten or permeative pattern (OR: 11.75; 95%CI: 1.26-109) and the central location of the lesion (OR: 3.03; 95%CI: 1.37-6.69) were associated with malignant tumor lesions.* **Conclusions:** *Poorly defined intraosseous blast lesions of bone lineage, periosteal reaction, and moth-eaten or permeative pattern of destruction are associated with malignant lesions.*

Keywords: *Bone neoplasms. Knee. Radiography. Diagnosis. Risk assessment.*

Resumen

Antecedentes: *Los tumores óseos requieren una adecuada evaluación clínico-radiográfica para su diagnóstico. Las radiografías simples son el método incruento usual para establecer el diagnóstico y evaluar diagnósticos diferenciales en el estudio de la patología tumoral ósea.* **Objetivo:** *Reconocer la frecuencia de las características radiográficas y asociarlas con patología tumoral ósea.* **Método:** *Se recolectaron datos radiográficos de 132 pacientes con patología tumoral confirmada mediante biopsia del servicio de tumores óseos del Hospital de Traumatología y Ortopedia Unidades Médicas de Alta Especialidad Dr. Victorio de la Fuente Narváez, Instituto Mexicano del Seguro Social, en Ciudad de México, durante el año 2019.* **Resultados:** *Integraron la muestra 132 pacientes. El tumor benigno más frecuente fue el osteocondroma (27.3%), y el maligno, el osteosarcoma (9.8%). Las lesiones líticas activas (odds ratio [OR]: 6.9; intervalo de confianza del 95% [IC95%]: 2.83-16.85) o agresivas (OR: 26.85; IC95%: 3.21-224) se asociaron a tumor de células gigantes. Las lesiones blásticas de estirpe ósea mal diferenciadas intraóseas (OR: 36.15; IC95%: 4.4-295.5) se asociaron a osteosarcoma. La reacción perióstica (OR: 36.15; IC95%: 4.4-295.5), el patrón apolillado o permeativo (OR: 11.75; IC95%: 1.26-109) y la ubicación central*

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Date of reception: 01-12-2021
Date of acceptance: 29-07-2022
DOI: 10.24875/CIRUE.M23000422

Cir Cir (Eng). 2023;91(1):15-20
Contents available at PubMed
www.cirugiaycirujanos.com

(OR: 3.03; IC95%: 1.37-6.69) se asociaron a lesiones tumorales malignas. **Conclusiones:** *Las lesiones blásticas de estirpe ósea mal definidas intraóseas, la reacción perióstica y el patrón de destrucción apolillado o permeativo se asocian a lesiones malignas.*

Palabras clave: *Tumores óseos. Rodilla. Radiografía. Diagnóstico. Asociación de riesgo.*

Introduction

Several factors complicate the characterization and categorization of bone tumor lesions into specific diagnoses. After the physical examination of a patient with suspected bone tumor, imaging studies of the lesion are advised to proceed with the diagnostic method. The least invasive and most specific method to achieve the differential diagnosis of primary bone tumors is plain x-rays.

Radiology provides detailed images of human diseases, and is essential to see the multiple details associated with visualized anomalies, including bone tumors. Also, in most cases, multiple characteristics related to these lesions allow us to distinguish between malignant and benign tumors. Therefore, radiology is crucial to conduct thorough reviews and specify the various findings associated with different bone tumor lesions to enable a more accurate approach to the definitive diagnosis.

Plain radiography provides more information than any other imaging modality in the study of bone tumor lesions and remains the cornerstone of the differential diagnosis of musculoskeletal tumors and tumor-like lesions, thanks to its specificity when it comes to detecting morphological tumor features[1].

The radiographic characteristics that help us diagnose bone tumors or, at least, narrow down all diagnostic possibilities, include patterns of bone destruction (geographic, moth-eaten, permeative), lesion margins (sclerotic, active, or aggressive borders), internal lesion features (blastic or lytic lesions), type of bone response (medullary or periosteal), location, site (metaphysis, diaphysis, or epiphysis), position of the lesion in the body and bone damaged (central, eccentric, or periosteal), soft tissue involvement, and whether we're dealing with a single or multiple lesions[1-3].

Simple x-rays of the bones damaged are also useful to detect bone metastases, although their sensitivity to detect these effects is lower[4-5].

While current research focuses on innovative imaging modalities that show increasing advancements in the detection of bone tumors and bone metastases and is backed by studies such as bone scintigraphy, computed tomography, magnetic resonance imaging, angiography, or positron emission tomography[6-9], the value of clinical assessment and simple radiography remains irreplaceable when it comes to conducting low-cost differential diagnoses with proper results.

Unfortunately, although the radiographic features of bone tumor lesions have been described under certain diagnostic criteria[2,3,10], deficiencies have been found in the quantitative approaches to the presentation of radiographic features and their association with final diagnosis. Characteristics of aneurysmal bone cysts have been described, as well as the frequencies of each characteristic found[11]. There is also literature available analyzing the radiographic features of chondrosarcomas[12], non-ossifying fibromas[13], eosinophilic granulomas[14], and unicameral bone cysts[15].

We believe we should analyze the frequency of presentation of radiographic features to associate the risk of these features with the final diagnosis of bone tumor pathology.

Method

Data for this research were collected at the outpatient clinic of the bone tumor unit at Hospital de Ortopedia de la Unidad Médica de Alta Especialidad Dr. Victorio de la Fuente Narváez, part of the Instituto Mexicano del Seguro Social, Mexico City, Mexico throughout 2019. Information was obtained from the initial plain x-rays of patients with a previously established histopathological diagnosis through various types of procedures (incisional, excisional, and Trucut biopsies, etc.) performed at this hospital unit. All health records were collected through the hospital's electronic record system and image viewer. The plain x-rays were analyzed, and the features of the findings of each condition recorded. The present study included a total of 133 patients with knee tumor pathology. To be considered eligible for the study, participants should have early radiographic studies and a histopathological diagnosis performed at the hospital, or else, in the absence of histopathological diagnosis documents (considered non-essential due to ethical considerations), a previous clinical and radiographic diagnosis.

Table 1. Demographic characteristics of the different diagnoses of the sample

Type of tumor (n = 132)	Age	Sex		Side		Bone damaged		
	Mean (SD)	Man n (%)	Woman n (%)	Right n (%)	Left n (%)	Femur n (%)	Tibia n (%)	Fibula n (%)
Osteochondroma	22.5 ± 13.9	21 (15.9)	15 (11.4)	18 (13.6)	18 (13.6)	22 (16.7)	11 (8.33)	3 (2.3)
Non-ossifying fibroma	18.17 ± 11.4	14 (10.6)	14 (10.6)	17 (12.8)	11 (8.33)	16 (12.1)	12 (9.09)	-
Enchondroma	59.87 ± 8.9	1 (0.75)	14 (10.6)	11 (8.33)	4 (3.03)	13 (9.84)	2 (1.51)	-
1-chamber bone cyst	19.1 ± 17.4	2 (1.51)	9 (6.81)	5 (3.78)	6 (4.54)	3 (2.3)	4 (3.03)	4 (3.03)
Chondroblastoma	15.7 ± 0.6	2 (1.51)	1 (0.75)	-	3 (2.3)	-	3 (2.3)	-
Cavernous hemangioma	32	-	1 (0.75)	1 (0.75)	-	-	1 (0.75)	-
Fibrous dysplasia	3	1 (0.75)	-	-	1 (0.75)	-	1 (0.75)	-
Osteoid osteoma	27	-	1 (0.75)	1 (0.75)	-	-	1 (0.75)	-
Osteosarcoma	17.6 ± 6.8	7 (5.03)	6 (4.54)	5 (3.78)	8 (6.06)	10 (7.57)	3 (2.3)	-
Chondrosarcoma	25.7 ± 15.5	3 (2.3)	1 (0.75)	3 (2.3)	1 (0.75)	1 (0.75)	3 (2.3)	-
Malignant fibrous histiocytoma	9	-	1 (0.75)	1 (0.75)	-	-	-	1 (0.75)
Fusocellular mesenchymal presentation	67	1 (0.75)	-	1 (0.75)	-	-	1 (0.75)	-
Plasmocytoma	8	-	1 (0.75)	-	1 (0.75)	1 (0.75)	-	-

SD: standard deviation.

Data collected included epidemiological characteristics (age and sex), the bone damaged, lytic lesions (inactive, active, or aggressive, and with ground-glass appearance), amorphous calcifications, extra- and intraosseous cartilaginous blastic lesions, intra- and extraosseous bone lineage lesions (with well-demarcated and poorly defined borders), the periosteal reaction (laminated, sunburst-like, Codman triangle), the lesion site (metaphysis, diaphysis, epiphysis, metaepiphysis), position inside the bone (central, eccentric, parosteal, periosteal), and the pattern of bone destruction (geographic, moth-eaten, or permeative) (Table 1).

Data of the characteristics were entered into the statistical software package SPSS, version 21.0 (Demo), for Windows for statistical analysis. A descriptive analysis of the data was conducted, and the independence of binomial data (presence or absence of a specific characteristic) was assessed using the chi-square test. Odds ratios (OR) were extracted to determine any possible associations between the presence of a characteristic and the final pathology determined by the histopathological analysis.

Results

A total of 133 eligible patients were included in the present study. However, complete data from one patient were missing in the medical records. A total of 55.6% of the sample obtained were men (n = 74) and 43.6% women (n = 58). The sample mean age was 26.03 ± 17.7 years (minimum age, 3 years; maximum age, 78 years).

The most common benign diagnosis was osteochondroma (27.1% of cases (n = 36]), followed by non-ossifying fibroma (21.1% of the cases [n = 28]) and giant cell tumor (12% [n = 16]). The most common malignant diagnosis in the sample was osteosarcoma (9.8% of the cases [n = 3]), followed by chondrosarcoma (3% [n = 4]).

The bones most frequently damaged were femur (54.1% of the cases [n = 72]), tibia (37.6% [n = 50]), and fibula (7.5% [n = 10]). The right side was most often affected (68 cases [51.1%]) compared to the left side (64 cases [48.5%]). None of the cases studied were associated with fractures of the bone damaged.

Inactive lytic lesions appeared in 25.6% of the cases (n = 34), active lytic lesions in 22.65% (n = 30), and aggressive lytic lesions in 6.8% of the cases (n = 9).

Cartilaginous extraosseous blastic lesions and intraosseous cartilaginous blastic lesions were present in 34 cases (25.6%) and 17 cases (12.8%), respectively. Poorly demarcated intraosseous blastic bone

lesions were found in 12 patients (9.0%), while poorly demarcated extraosseous blastic bone lesions were found in 3 (2.3%). Periosteal reaction in the form of Codman triangle occurred in 9 patients (6.8%), and the sunburst pattern in 11 (8.3%).

The most frequently damaged site was the bone metaphysis (33 cases [24.8%]), followed by the epiphyseal region (20 cases [15.0%]), the meta-diaphysis (12 cases [9.0%]), and finally, the diaphyseal region (3 cases [2.3%]). The most common location of the lesion was central (51 cases (38.3%]), eccentric (40 cases [30.1%]), parosteal (38 cases [28.6%]), and periosteal (3 cases [2.3%]).

The geographic pattern of bone destruction was seen in 61 cases (45.9%), moth-eaten in 7 (5.3%), and permeative in 5 (3.8%).

Lesions with inactive borders did not show a statistically significant association with malignant tumor lesions compared to benign lesions (OR, 0.18; 95% confidence interval [CI], 0.05-0.66). Similarly, cartilaginous extra- and intraosseous blastic lesions were not associated with malignant lesions compared to benign lesions (OR, 0.04 and 0.03, respectively; 95%CI, 0.006-0.37 and 0.06-1.44, respectively).

Active or aggressive lytic lesions (OR, 6.9 and 26.85, respectively; 95%CI, 2.83-16.85 and 3.21-224, respectively) were associated with giant cell tumors. Poorly demarcated intraosseous blastic bone lesions (OR, 36.15; 95%CI, 4.4-295.5) were associated with the presence of osteosarcoma. Periosteal reaction (OR, 36.15; 95%CI, 4.4-295.5), the moth-eaten or permeative patterns (OR, 11.75; 95%CI, 1.26-109), and central lesion location (OR, 3.03; 95%CI, 1.37-6.69) were associated with malignant tumor lesions.

In the data reported, statistical power > 80% was found, while the remaining characteristics that were not significant or whose statistical power > 80% are shown on table 2.

Discussion

The analysis of the plain x-rays of 132 patients from Hospital de Ortopedia del Servicio de Tumores Óseos at Unidad Médica de Alta Especialidad Dr. Victorio de la Fuente Narváez, Mexico City, Mexico revealed a predominance of men compared to women. The sample mean age was 26.03 ± 17.7 years, indicative of a higher rate of bone tumors within the first 3 decades of life, which is consistent with former studies that locate the occurrence of primary bone tumors within the second decade of life, corresponding to the peak growth period in humans. The most common malignant conditions in the sample studied was osteosarcoma, which overall, is known as the most common primary malignant bone neoplasm of all.[16-18] Similarly, the most common benign condition was osteochondroma, which is consistent with what other local series have reported[19].

The analysis of radiographic features correlated lesions with inactive borders with benign lesions and radiographic lesions of cartilaginous lineage characterized by “rings and splashes,” both intra- and extraosseous, with benign lesions. Giant cell tumor was associated with lytic lesions with active borders, especially with lesions considered aggressive. Given the potential for metastasis of this type of tumor, the presence of lytic lesions with active borders and aggressive growth requires careful monitoring. Blastic lesions with poorly demarcated borders, both intra- and extraosseous, were significantly associated with primary malignant tumor lesions. Periosteal reactions, in any presentation, were consistently associated with primary malignant bone tumors. The site of the radiographic lesion presentation, whether epiphyseal, metaphyseal, diaphyseal or metadiaphyseal was not associated with any specific benign or malignant condition. Central lesion location with respect to the bone axis was associated with malignant tumor lesions, while other locations (eccentric, parosteal, or periosteal) were not associated any specific type of tumor. The geographic pattern was associated with benign tumor lesions, while moth-eaten or permeative destructive patterns were strongly associated with malignant bone tumor disease.

These descriptive data of radiographic presentations of bone tumors are crucial to achieve more timely diagnoses using clinical assessments and plain x-rays. However, there are no studies correlating radiographic features and clinical findings. The frequency of presentation of tumor features has not been reported previously. The lack of knowledge among primary care physicians on these radiological features and how it delays neoplastic diagnoses is an undisputed fact to this date[20]. That is why the present study includes such features that should be taken into consideration, at least, regarding their frequency of presentation related to a definitive histopathological diagnosis of bone neoplasm.

Due to the nature and type of study conducted, caution is advised when interpreting the association measures used. Further studies with more robust methodologies are needed to consolidate the

Table 2. Table of association between multiple radiographic features and malignant lesions

Feature (n = 132)	c2*	OR	95%CI	Statistical power (1-β)†
Lytic				
Inactive	0.009	0.18	0.05-0.66	> 80
Active	< 0.001	6.91	2.83-16.85	> 80
Aggressive	< 0.001	26.85	3.21-224	> 80
Amorphous calcification	0.612	-	-	-
Blastic				
Extraosseous cartilaginous	< 0.001	0.04	0.006-0.37	> 80
Intraosseous cartilaginous	0.205	0.3	0.06-1.44	73.53
Intraosseous well demarcated	0.612	-	-	-
Intraosseous poorly demarcated	< 0.001	36.15	4.4-295	> 80
Extraosseous well demarcated	0.612	-	-	-
Extraosseous poorly demarcated	0.37	5.52	0.48-62.95	> 80
Periosteal reaction				
Codman triangle	< 0.001	31.66	3.84-261	> 80
Sunburst-like	< 0.001	36.15	4.4-295	> 80
Laminated	-	-	-	-
Site				
Epiphysis	0.275	1.97	0.73-5.32	48.29
Metaphysis	0.09	0.44	0.18-1.03	60.71
Diaphysis	0.37	5.52	0.48-62.95	> 80
Metadiaphysis	0.29	2.39	0.68-8.39	68.09
Location				
Central	0.009	3.03	1.37-6.69	> 80
Eccentric	0.92	0.87	0.37-2.04	9.34
Parosteal	0.01	0.22	0.07-0.68	> 80
Periosteal	0.67	-	-	-
Destructive pattern				
Geographic	0.77	1.2	0.56-2.60	10.74
Moth-eaten	< 0.001	22.93	2.7-194	> 80
Permeative	0.02	11.75	1.2-109	> 80

*c2 ($\alpha = 0.05$).
†$\beta = 0.20$.
95%CI: 95% confidence interval; OR: odds ratio.

radiographic features into a diagnostic tool. Additionally, increasing the feature sample size with a statistical power < 80% is also deemed necessary to improve the statistical conclusions of this research study.

Conclusions

- Inactive border lesions were associated with benign bone tumors.
- Cartilaginous extra- and intraosseous blastic lesions were associated with benign lesions.
- Active or aggressive lytic lesions are radiographic features associated with bone tumors such as giant cell tumor.
- Poorly demarcated intraosseous blastic bone lesions, along with the presence of periosteal reaction and moth-eaten or permeative destructive patterns, are associated with malignant bone lesions, in both cases, of predominant central location.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Evolution of acute care surgery in a general surgery department during the COVID-19 pandemic and comparison with a historical cohort

Evolución de la cirugía urgente en un servicio de cirugía general durante la pandemia de COVID-19 y comparación con una cohorte histórica

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Abstract

Background: *Acute care surgery decreased during the first wave of the COVID-19 pandemic.* **Objective:** *To study the evolution of acute care surgery and its relationship with the pandemic severity.* **Method:** *Retrospective cohort study which compared patients who underwent acute care surgery during the pandemic to a control group.* **Results:** *A total of 660 patients were included (253 in the control group, 67 in the first-wave, 193 in the valley, and 147 in the second wave). The median daily number of acute care surgery procedures was 2 during the control period. This activity decreased during the first wave (1/day), increased during the valley (2/day), and didn't change in the second wave (2/day). Serious complications were more common during the first wave (22.4%). A negative linear correlation was found between the daily number of acute care surgery procedures, number of patients being admitted to the hospital each day and daily number of patients dying because of COVID-19.* **Conclusions:** *Acute care surgery was reduced during the first wave of the COVID-19 pandemic, increased during the valley, and returned to the pre-pandemic level during the second wave. Thus, acute care surgery was related to pandemic severity, with fewer surgeries being performed when the pandemic was more severe.*

Keywords: *Acute care surgery. COVID-19. SARS-CoV-2. Pandemic.*

Resumen

Antecedentes: *La cirugía urgente disminuyó durante la primera ola de la pandemia de COVID-19.* **Objetivo:** *Estudiar la evolución de la cirugía urgente y su relación con la gravedad de la pandemia.* **Método:** *Estudio de cohortes retrospectivo que compara los pacientes intervenidos de forma urgente durante la pandemia con un grupo control.* **Resultados:** *Se incluyeron 660 pacientes (253 en el grupo control, 67 en primera ola de la pandemia, 193 en el periodo valle y 147 en la segunda ola). La mediana del número de cirugías urgentes fue de 2 (intervalo intercuartílico: 1-3) durante el periodo control, disminuyó durante la primera ola (1/día), aumentó durante el valle (2/día) y no se modificó en la segunda ola (2/día). Las complicaciones mayores fueron más comunes durante la primera ola (22.4%). Se encontró una correlación lineal negativa entre el número de procedimientos quirúrgicos urgentes diarios y el número de ingresos hospitalarios y fallecimientos diarios por COVID-19.* **Conclusiones:** *La cirugía urgente se redujo durante la primera ola,*

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Date of reception: 13-12-2021
Date of acceptance: 02-04-2022
DOI: 10.24875/CIRUE.M23000423

Cir Cir (Eng). 2023;91(1):21-27
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aumentó durante el periodo valle y volvió a niveles prepandémicos durante la segunda ola. Además, la cirugía urgente se relaciona con la gravedad de la pandemia, ya que se realizaron menos cirugías urgentes durante el periodo de mayor gravedad de la pandemia.

Palabras clave: *Cirugía urgente. COVID-19. SARS-CoV-2. Pandemia.*

Introduction

During the COVID-19 pandemic, hospitals had to prioritize resources to treat patients infected with SARS-CoV-2, leading to the cancellation or postponement of numerous elective surgical procedures[1,2]. However, the situation was different when considering urgent surgical activity (USA). Urgent surgeries can sometimes be delayed or avoided using alternative treatments such as antibiotic therapy or percutaneous drainage[3-5]. However, some patients require procedures that cannot be postponed, regardless of the pressure hospitals may have gone through during the pandemic.

The impact COVID-19 had on urgent surgical procedures has been analyzed by numerous authors[1,4,6-8]. Some studies have also examined the reduced USA described during the first wave of the pandemic compared to a control period[9-12]. However, the evolution of USA during the pandemic, including the number of surgeries performed, the characteristics of the patients undergoing surgery, and postoperative complications, has not been studied yet. Additionally, there are no data on the possible relationship between the severity of the pandemic throughout different stages and the number of urgent surgical procedures performed.

Therefore, the objective of this study was to analyze the evolution of USA during the COVID-19 pandemic. We examined the number of daily surgical procedures, the main characteristics of the patients, and all complications recorded across different periods of the pandemic. We also explored the potential relationship between USA and the severity of the pandemic.

Method

We conducted a retrospective cohort study of patients who underwent urgent surgery in a tertiary-level general surgery unit of a Spanish hospital. Procedures performed as a complication of elective surgeries were excluded from the study. Four different study periods were defined based on the evolution of the pandemic: a pre-pandemic control period (Period C: from March 1 through July 1, 2019), first wave (Period 1W: from March 13 through April 4, 2020), second wave (Period 2W: from October 7 through December 5, 2020), and a valley period between the 2 waves (Period V: from April 30 through July 22, 2020). The periods of the first and second waves were defined based on the higher incidence rate of SARS-CoV-2 infection, while the valley period was defined by the lower rate of COVID-19 after the first wave, based on data from our region.

Data on the demographic characteristics, clinical variables, details of the surgical procedure, length of stay, postoperative morbidity (grouped according to the Clavien-Dindo classification)[13], and mortality were obtained from the patients' electronic health records. Information on the pandemic (daily diagnoses, deaths, and hospital admissions due to COVID-19) was obtained from hospital and regional government records[14]. Data were recorded in a Microsoft Excel® database and analyzed using Stata® statistical software (version 13.1, StataCorp, TX, United States).

The Shapiro-Wilk test was used to analyze the normality of quantitative variables. Quantitative variables were expressed as median and interquartile range (IQR), and the qualitative ones as absolute numbers and percentages. The Kruskal-Wallis range or the Mann-Whitney U test were used to compare quantitative variables, while the chi-square test or Fisher's exact test were used, as appropriate, to compare the qualitative ones. P values < 0.05 were considered statistically significant. To analyze the relationship between the severity of the pandemic (daily number of diagnosed patients, deaths, or hospital admissions due to COVID-19) and the daily number of urgent surgical procedures, Pearson's correlation coefficient was used.

All procedures were performed in full compliance with the ethical standards of our center, the National Research Committee, and the 1964 Declaration of Helsinki and further amendments. Written informed consent was not deemed necessary for this type of study. The study was approved by our Institutional Review Board (Code 2021/173) and conducted in full compliance with STROCCS criteria[15]. The study was registered in the Chinese Clinical Trials Registry (Code: ChiCTR2100047785).

Results

A total of 660 patients were included in the study, 253 of whom (38.33%) underwent surgery during Period C, 67 (10.15%) during Period 1W, 193 (29.24%) during Period V, and 147 (22.27%) during Period 2W. The median daily number of urgent surgical procedures performed was 2 (IQR, 1-3) during the Period C, 1 (IQR, 0-2; p = 0.003) during Period 1W, 2 (IQR, 2-4; p = 0.047) during the Period V, and 2 (IQR, 1-4; p = 0.172) during Period 2W (Fig. 1).

Among the patients, 371 (56.2%) were men, and the median age was 58.1 years (IQR, 40.3-72.5). According to the American Society of Anesthesiologists (ASA) classification, 303 (45.8%) fell into ASA I, 162 (24.6%) into ASA II, 162 (24.6%) into ASA III, and 33 (5.0%) into ASA IV. Arterial hypertension, diabetes mellitus, dyslipidemia, and ischemic heart disease were diagnosed in 189 (28.6%), 68 (10.3%), 135 (20.4%), and 99 (15.0%) patients, respectively. Patients were slightly healthier (ASA I and II) during Periods 1W (70.1%) and V (77.2%) compared to Periods C (66.4%) and 2W (68.7%), although the differences reported were not statistically significant (p = 0.092).

The most common diagnoses requiring surgery were acute appendicitis (337 patients, 51.1%), acute cholecystitis (155 patients, 23.5%), and intestinal obstruction (43 patients, 6.5%). The median surgical time was 65.0 min (IQR, 35.0-90.0). A total of 395 (59.9%), 250 (37.9%), and 15 (2.3%) patients required laparoscopic approach, open surgeries, and conversion from laparoscopic to open procedures, respectively.

The patients' main characteristics from each period are shown on table 1. Figure 2 compares the most common diagnoses requiring surgery in each period. The median length of stay was 5 days (IQR, 3-9). Shorter lengths of stay were reported during Periods 2W and V (5 days [IQR, 3-11] in the Period C, 4 days [IQR, 2-11] during Period 2W, 4 days [IQR, 2.5-7] during Period V, and 4 days [IQR, 2-8] during Period 2W, respectively; p = 0.069).

As shown on figure 3, major complications (Clavien-Dindo grades III-V) were reported in 92 patients (13.9%). Table 2 compares the complications observed across the different study periods. Morbidity was higher during the first wave with a higher rate of major complications: 37 (14.6%), 15 (22.4%), 16 (8.3%), and 24 (16.3%) patients experienced major complications during Periods C, 1W, V, and 2W, respectively (p = 0.019).

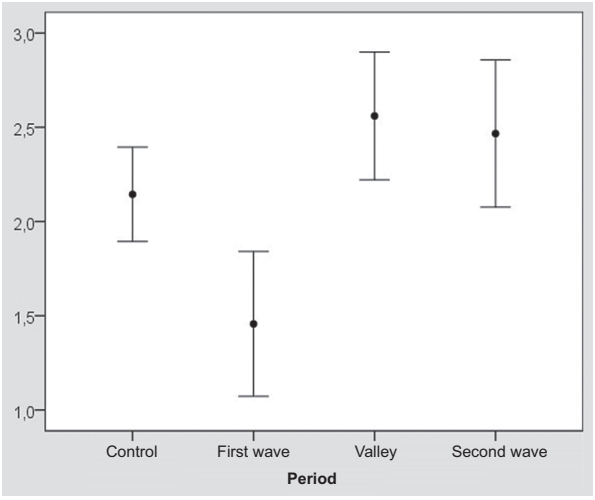

Figure 1. *Mean and 95% confidence interval of the daily number of urgent surgeries performed during each study period.*

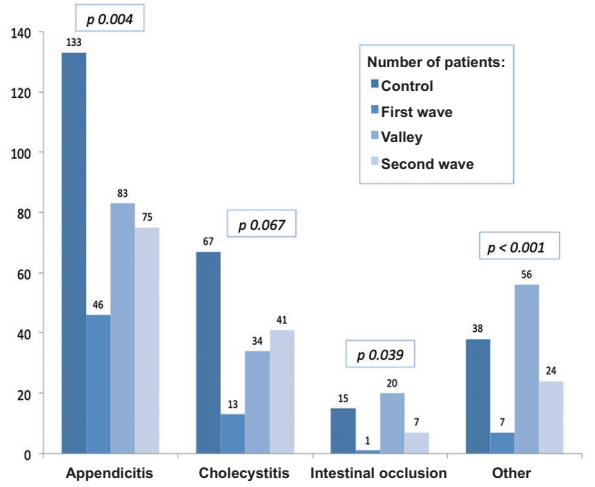

Figure 2. *Comparison of the most common diagnoses requiring surgery in each study period.*

Over the 30-day postoperative period, 24 patients (3.6%) died, 16 of these (2.4%) did so during the first postoperative week. No statistically significant differences were seen in the 30-day mortality rate among the 4 study periods (Table 2) (p = 0.827). Additionally, 110 patients (16.7%) were admitted to the intensive care unit (ICU) after surgery, with a mean ICU stay of 3 days (IQR, 2-7). No statistically significant differences were reported in the percentage of patients admitted to the ICU (p = 0.675) or in the duration of the ICU stay (p = 0.485) among the study periods.

Table 1. Comparison of the main characteristics of patients included in each study period

	Control (n = 253)	1st wave (n = 67)	Valley (n = 193)	2nd wave (n = 147)	p
Sex (n, % men)	151 (59.7%)	34 (50.8%)	101 (52.3%)	85 (57.8%)	0.336
Age (median, IQR)	58.4 (40.4-74.7)	58.5 (40.7-71.5)	53.1 (35.4-69.7)	59.9 (45.8-72.4)	0.045
ASA (n, % III-IV)	85 (33.6%)	20 (29.9%)	44 (22.8%)	46 (31.3%)	0.092
Hypertension (n, %)	75 (29.6%)	13 (19.4%)	49 (25.4%)	52 (35.4%)	0.066
Diabetes (n, %)	19 (7.5%)	6 (9.0%)	16 (8.3%)	27 (18.4%)	0.004
Ischemic heart disease (n, %)	48 (19.0%)	2 (3.0%)	25 (12.9%)	24 (16.3%)	0.009
Dyslipidemia (n, %)	56 (22.1%)	8 (11.9%)	36 (18.7%)	35 (23.8%)	0.185
Laparoscopic approach (n, %)	142 (56.1%)	37 (55.2%)	123 (63.7%)	93 (63.3%)	0.403

ASA: Classification of the American Society of Anesthesiologists; IQR: interquartile range.

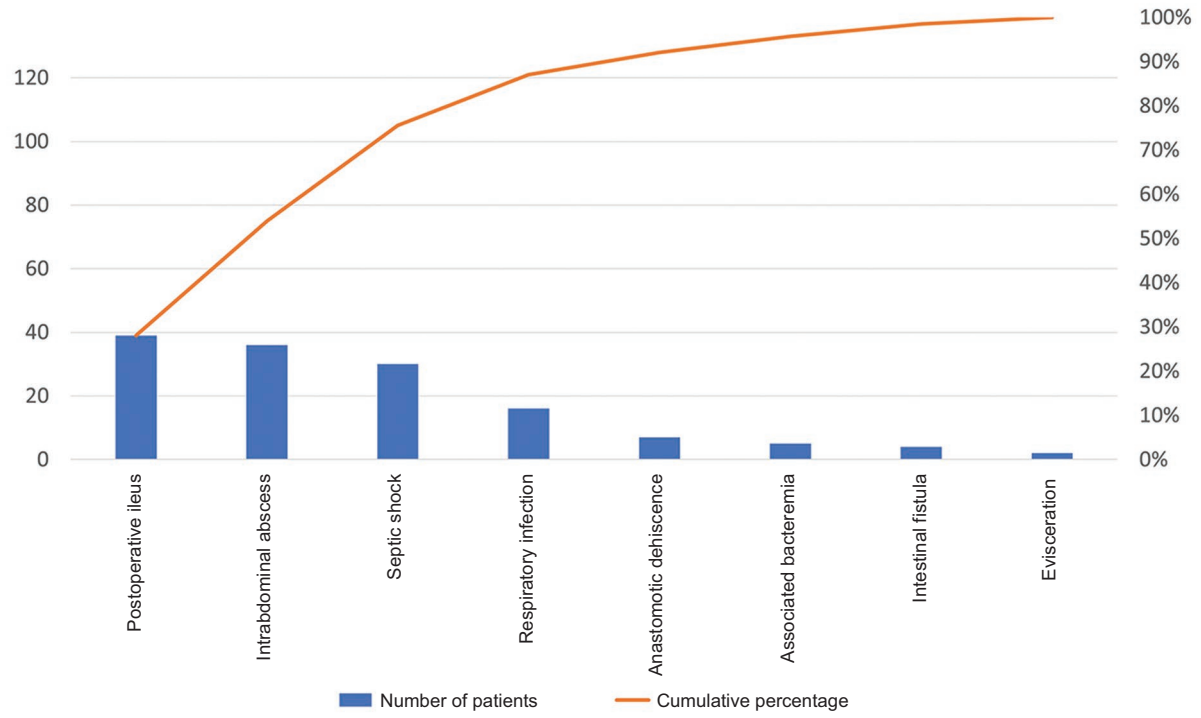

Figure 3. *Pareto diagram showing the number of patients and the cumulative percentage of the most frequent complications.*

The median daily number of patients diagnosed with COVID-19 was 28.5 (IQR, 15.8-43.5) during Period 1W, 0 (IQR, 0-1) during Period V, and 113.0 (IQR, 65.8-150.8) during Period 2W ($p < 0.001$). Also, the median number of daily COVID-19-related deaths was different among the study periods: 2 during Period 1W (IQR, 0-4.3), 0 during Period V (IQR, 0-0), and 1 in during Period 2W (IQR, 0-4) ($p < 0.001$). Finally, the median daily number of hospital admissions due to COVID-19 was 5 during Period 1W (IQR, 2.3-13), 0 during Period V (IQR, 0-1), and 7 during Period 2W (IQR, 5-9) ($p < 0.001$).

There was a negative linear correlation between the daily number of urgent surgeries and the number of daily COVID-19 hospital admissions (Pearson's correlation coefficient, −0.17; 95% confidence interval [CI], −0.31 to −0.02; $p = 0.024$) and the number of daily COVID-19-related deaths (Pearson correlation coefficient: −0.13; 95%CI, −0.27 to 0.01; $p = 0.067$).

Table 2. Comparison of the different postoperative complications diagnosed during each study period

	Control (n = 253)	1st wave (n = 67)	Valley (n = 193)	2nd wave (n = 147)	p
Length of stay (median, IQR)	5 (3-11)	4 (2-11)	4 (2.5-7)	4 (2-8)	0.069
Some complication (n, %)	69 (27.3%)	23 (34.3%)	34 (17.6%)	39 (26.5%)	0.022
Major complications (n, %)	37 (14.6%)	15 (22.4%)	16 (8.3%)	24 (16.3%)	0.019
Postoperative mortality (n, %)	10 (4.0%)	3 (4.5%)	5 (2.6%)	6 (4.1%)	0.827
ICU admission (n, %)	45 (17.8%)	11 (16.4%)	27 (14.0%)	27 (18.4%)	0.675
Intra-abdominal infection (n, %)	12 (4.7%)	7 (10.5%)	7 (3.7%)	10 (6.8%)	0.154
Evisceration (n, %)	1 (0.4%)	1 (1.5%)	0 (0%)	0 (0%)	0.236
Bacteremia (n, %)	2 (0.8%)	0 (0%)	3 (1.6%)	0 (0%)	0.352
Paralytic ileus (%)	16 (6.3%)	6 (9.0%)	5 (2.6%)	12 (8.2%)	0.095
Respiratory infection (n, %)	7 (2.8%)	3 (4.5%)	4 (2.1%)	2 (1.4%)	0.547
Septic shock	9 (3.6%)	5 (7.5%)	7 (3.6%)	9 (6.1%)	0.376

IQR: interquartile range; ICU: intensive care unit.

However, no significant correlation was seen between the number of urgent surgeries performed and the daily number of COVID-19 diagnoses (Pearson's correlation coefficient, 0.02; 95%CI, –0.13 to 0.16; p = 0.830).

Discussion

The main finding of our study was that the number of urgent surgical procedures decreased during the first wave of the COVID-19 pandemic, increased during the valley period, and remained unchanged during the second wave. This confirms that USA changed throughout the pandemic. Across the first wave, we saw a significant increase in the number of appendectomies performed, but fewer cholecystectomies, with the latter trend continuing during the valley period. Also, more complications were seen during the first wave likely because patients delayed visiting the ER, thus leading to developing more severe conditions. We also found an inverse relationship between the severity of the pandemic and the number of urgent surgical procedures eventually performed.

Several authors have already demonstrated that USA dropped during the first wave of the pandemic[9-12]. However, the impact the second wave and the valley period had on the USA is still to be elucidate. The main finding of our study is that the median daily number of urgent surgical procedures dropped from 2 procedures during the control period to just 1 during the first wave (p = 0.003). However, this reduction was not seen during Periods V or 2W.

The reasons for this drop in USA during the pandemic have not been studied extensively. Most authors suggest that patients may have been afraid of getting COVID-19 while visiting the ER, thus leading to delayed visits. This delay could explain the decreased USA reported in case some of these patients improved without surgical treatment[9-12,16]. Over time, patients may lose that fear of the virus, which would explain the increased number of procedures performed during the valley period and the return to higher levels during the second wave of the pandemic. Another possible explanation for the USA evolution could have been the different way of life occurred during the pandemic, especially during the strict lockdown of the first wave. This hard lockdown may explain the reduced incidence rate of certain lifestyle-related urgent surgeries performed during the first wave, such as high-fat intake-related acute cholecystitis[17]. However, these changes were not observed during the second wave of a more relaxed confinement.

When we analyzed the most common diagnoses requiring surgery throughout the different periods, we saw a significant increase in the number of appendectomies performed during the first wave (66.7% of all procedures performed during this period) and a decrease in other conditions. We also found a decline in the number of cholecystectomies performed, a trend that went on during the valley period. However, no changes were reported in the number of cholecystectomies performed during the second wave of the pandemic. Two factors could explain this finding: firstly, as discussed before,

the lifestyle changes occurred during the first wave may have reduced the rate of acute cholecystitis; secondly, it could very well be that numerous patients with cholecystitis were managed non-surgically, as observed by Ielpo et al.[18] in a survey conducted in Spain.

Also, patients operated during the first wave and valley period were generally healthier than those operated during the second wave and the control period. This may be because patients with comorbidities tried to avoid visiting hospitals out on fear of COVID-19 infection. The severity of the pandemic was also related to the evolution of USA. The daily number of urgent surgical procedures kept a close correlation with the severity of the pandemic. Therefore, more patients being admitted to the hospital or died due to COVID-19 equaled fewer urgent surgeries were being performed. However, no association was found between USA and the daily number of COVID-19 diagnoses, likely due to the lack of diagnostic testing performed during the first wave of the pandemic.

Major complications were more common during the first wave of the pandemic ($p = 0.019$). Considering the reduced USA during the first wave, this growth in the number of major complications could be explained by delayed diagnoses following the patients' fear of seeking emergency care during the pandemic[10,19]. Health authorities conducted information campaigns to encourage people to seek medical help when necessary[20]. Therefore, these campaigns were probably effective, and patients probably became aware of the importance of seeking professional care if they had a health issue. Therefore, the absence of a reduced USA during the second wave of the pandemic could be attributed to the effectiveness of these campaigns and the development and implementation of safe health care pathways in emergency services. No significant mortality differences were found throughout the pandemic.

The main limitation of this study is its retrospective design, which may add information biases. However, most of the variables analyzed are objective and properly recorded in electronic health records. Another possible limitation is that the pandemic was still ongoing at the time of the study. Additionally, assessing the severity of the pandemic is challenging. We tried to analyze the number of patients diagnosed with COVID-19, but changes in diagnostic testing availability made it impossible to compare the incidence rate of COVID-19 during the first and second waves. Therefore, we studied the severity of the pandemic using more objective data, such as the number of patients who died or were hospitalized with the virus. Finally, another limitation is that we chose a pre-pandemic period to compare the characteristics of urgent procedures, and it may not correspond exactly with the same seasons as the different periods of the pandemic. This could add bias due to seasonal variation in urgent surgeries. Nevertheless, urgent activity at our center remains relatively stable throughout the year, and the control period selected adequately represents the yearly trend. Hence, we deemed it unnecessary to collect a control period for each pandemic study period.

Conclusions

USA decreased during the first wave of the COVID-19 pandemic, increased during the valley period, and returned to pre-pandemic levels during the second wave. Additionally, we saw that USA was associated with the severity of the pandemic, with fewer surgeries being performed when pandemic severity increased. The main diagnoses requiring urgent surgery changed across the different periods of the pandemic. Finally, complications were more common during the first wave, although no mortality differences were reported.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Analysis of the direct cost of medical and surgical care for breast cancer. Comparative study between early and advanced stages in the third level medical facility

Análisis del coste directo de la atención médica y quirúrgica del cáncer de mama. Estudio comparativo entre etapas temprana y tardía en tercer nivel de atención

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Abstract

Background: *Management of breast cancer is increased by late diagnoses.* **Objective:** *To analyse direct costs of breast cancer in early and advanced stage in a third level medical facility at Mexican Social Security Institute.* **Method:** *Observational study, direct costs of care in breast cancer in initial and advanced clinical stages are compared. Variables analysed were laboratory and diagnostic imaging studies, drugs, as well as hospitalization costs. The evaluated period included from the first care to the completion of the treatment. Costs were determined according to the table of Unit Costs by Level of Medical Care for the year 2019 of the Mexican Social Security Institute. Student's t test was used to determinate differences between groups, as well as descriptive statistics.* **Results:** *The advanced stage compared to the initial stage, causes a greater number of laboratory-cabinet studies, surgeries, day/bed and interconsultations. The average cost of breast cancer care per patient is $99,280.36 (US$5,230.78) and $148,023.60 (US$7,789.92) for the initial and advanced stages, respectively (p = 0.024).* **Conclusions:** *Cost of medical attention in the initial stage is lower than that of the advanced stage.*

Keywords: *Breast cancer. Direct cost. Medical attention. Late diagnosis.*

Resumen

Antecedentes: *Los diagnósticos tardíos elevan los costes de atención del cáncer de mama.* **Objetivo:** *Analizar los costes directos de la atención del cáncer de mama en etapa temprana y avanzada en el tercer nivel de atención en el Instituto Mexicano del Seguro Social (IMSS).* **Método:** *Estudio observacional que compara los costes directos de atención en cáncer de mama en estadios clínicos inicial y avanzado. Los datos analizados fueron estudios de laboratorio, gabinete, tratamiento y hospitalización. El tiempo evaluado incluyó desde la primera atención hasta la finalización del primer tratamiento. Se determinaron los costes de acuerdo con la tabla de Costes Unitarios por Nivel de Atención Médica para el año 2019 del IMSS. Se utilizó la prueba t de Student para diferencias entre grupos, así como estadística descriptiva.* **Resultados:** *El estadio avanzado, comparado con el estadio inicial, ocasiona un número mayor de estudios de laboratorio-gabinete, cirugías, día/cama e interconsultas.*

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Date of reception: 29-07-2021
Date of acceptance: 07-01-2022
DOI: 10.24875/CIRUE.M23000424

Cir Cir (Eng). 2023;91(1):28-33
Contents available at PubMed
www.cirugiaycirujanos.com

El coste promedio de la atención del cáncer de mama por paciente es $99,280,36 (US$5,230.78) y $148,023.60 (US$7,789.92) para los estadios inicial y avanzado, respectivamente (p = 0.024). **Conclusiones:** *El coste de la atención médica del estadio inicial es menor que el del estadio avanzado.*

Palabras clave: *Cáncer de mama. Coste directo. Atención médica. Diagnóstico tardío.*

Introduction

Breast cancer is a problem of public health worldwide[1]. In the Americas, it is the most common type of cancer and the second leading cause of cancer death in women. Each year, over 462,000 women are diagnosed, and almost 100,000 die from this disease[2,3]. By the year 2030, we could be experiencing a 34% rise in the number of cases reported[4].

According to the National Cancer Institute, in 2020, projected medical spending for the management of breast cancer reached $16.5 billion, followed by colorectal cancer ($14 billion), lymphoma, lung cancer, and prostate cancer, each with $12 billion[5].

In Mexico, in 2017, 24 out of every 100 hospital discharges due to cancer in individuals younger than 20 years old, were due to breast cancer, making it the leading cause of hospital discharge for malignant tumors. Based on sex, 1 out of every 100 men and 37 out of every 100 women were discharged after diagnosis of malignant breast tumors[6]. In 2019 and 2020, a total of 88,683 and 60,421 deaths were reported due to malignant tumors, respectively.

There are very few of studies worldwide on breast cancer-related spending. Back in 2006, in the United States alone, the annual spending on treatment was $13.9 billion. In Europe, the annual spending was $8.7 billion in 2009[7]. In Colombia, Latin America, a study on breast cancer spending conducted in 2016 revealed spending of $65,603,537 for regional cancer and $144,400,865 for metastatic cancer[8].

The Mexican Institute of Social Security (IMSS) is a Mexican and Latin American health care institution of paramount importance. At the end of 2018, it had a total of 2910 operative units under the Regular Regime and 4386 medical care units at all levels[9] under the IMSS-BIENESTAR, providing coverage to 53,533,650 beneficiaries, which is representative of nearly 50% of the entire Mexican population[9,10]. This institution was the basis on which this study was conducted to compare the direct medical spending associated with breast cancer in its early and advanced stages at Hospital de Especialidades de Puebla of IMSS, Puebla, Mexico.

Method

This was an observational cost study that compared direct medical spending in patients with breast cancer in the early and advanced stages of the disease. The study included health records of breast cancer patients of any age and sex who were beneficiaries of the Mexican Institute of Social Security (IMSS) and treated at Hospital de Especialidades de Puebla, Centro Médico Nacional General de División Manuel Ávila Camacho, a third-level center with complete health records, confirmed histopathological reports, who had received medical and surgical treatment. Patients who required emergency surgery were excluded, and those who died prior to hospital discharge were removed from the study.

The variables of interest were sex, socioeconomic level, age, lab test results and imaging modalities, hospitalization days per patient, medical and surgical treatments performed, and number of inter-consultations to determine the direct spending per patient.

Data were collected from the patients' health records. The sample included health records from patients from the participant medical unit who met the inclusion criteria from 2017 through 2018.

The sample size was estimated considering that the incidence rate of breast cancer is 3.5% in first-time consultations at this hospital for a total of 960 patients per year, 80% precision, 95% confidence interval, 5% tolerated error, and accounting for a probable 10% loss per group. A total of 23 patients per group were included in the sample.

A total of 30 health records were revised per group. The patients were divided into 2 groups to audit spending:

- Early stage: including operable patients.
- Advanced stage: including patients with locally advanced— inoperable—and advanced stages.

For definition purposes, groups were divided into early and advanced stages based on the classification established by the Spanish Society of Medical Oncology (SEOM)[11].

Spending was studied based on the IMSS Unit Costs of Health and Social Care table for 2019 as published in the *Gaceta Oficial de la Federación*[10].

In the two groups, follow-up started from the moment the patients started treatment at the third-level center until they were discharged after completing their first cycle of medical treatment.

The patients' socioeconomic status was determined using data from the Asociación Mexicana de Agencias de Inteligencia de Mercado y Opinión (2018), including 7 levels from highest to lowest: A/B, C+, C, C-, D+, D, and E[12]. For study purposes, these 7 levels were grouped into 3: A/B and C+ (high socioeconomic level); C, C-, and D+ (medium level); and D and E (low level).

Descriptive statistics with measures of central tendency and dispersion were performed. All variables showed a normal distribution according to the Shapiro-Wilk test. To compare inter-group spending, the Student t test was used. P values ≤ 0.05 were considered statistically significant. IBM Statistical software Package for Social Sciences, version 23 for Windows was used for data analysis.

The study received proper authorization from the ethics and research committee with no. R-2019-2101-022. Additionally, the study complies with the ethical guidelines on health research. It did not require any funding or prior written informed consent, and the participants' anonymity was preserved at all times. The results were used solely for scientific purposes.

Results

A total of 60 patients were included in the study, 30 (50%) in group #1 and another 30 (50%) in group #2.

In group #1, all 30 patients (100%) were women, with a mean age of 57.7 years (range, 40-78; standard deviation, 9.72). Nine patients (30%) were of low socioeconomic level, and 21 (70%) of medium socioeconomic level. The mean numbers of lab and imaging tests performed, hospitalization days per patient, surgeries, medical treatments, and inter-consultations were 9.7, 3.23, 2.77, 1, 10.7, and 3.43, respectively.

In group #2, 29 patients (96.7%) were women, and 1 (3.3%) was a man, with a mean age of 59.3 years (range, 36-95; standard deviation, 14.07). Eight patients (26.7%) were of low socioeconomic level, 21 (70%) of medium socioeconomic level, and 1 (3.3%) of high socioeconomic level (Table 1). The mean numbers of lab and imaging tests performed, hospitalization days per patient, surgeries, medical treatments, and inter-consultations were 19.03, 3.56, 6-73, 1.13, 10.43, and 3.53, respectively.

Regarding the patients' clinical stage, patients from group #2 were older than those from group #1, more lab and imaging tests were performed, longer hospital stays were reported based on the number of hospitalization days per patient, and more medical and surgical acts, and inter-consultations occurred, yet without any statistically significant differences being reported ($p \geq 0.05$) (Table 2).

Regarding the direct health care spending, group #2 presented a significant increase compared to group #1, with statistically significant differences being reported in lab ($p = 0.018$) and imaging tests performed ($p = 0.05$), and hospitalization days per patient ($p = 0.006$) (Fig. 1).

Table 1. Sex and socioeconomic level of the population included

	Early stage	Advanced stage	p
Sex			
Men	0	1	0.313
Women	30	29	
Socioeconomic level			
High	0	1	0.589
Medium	21	21	
Low	9	8	

Table 2. Number of studies, therapies, days/bed, and inter-consultations of the patients included

	Mean	Min.	Máx.	SD	p*
Age (years)					
ES	57.7	40	78	9.72	0.407
AS	59.33	36	95	14.07	
Lab tests					
ES	9.7	0	35	7.14	0.517
AS	19.03	0	62	15.89	
Imaging tests					
ES	3.23	0	8	2.06	0.614
AS	3.57	0	12	2.43	
Days/bed					
ES	2.77	0	9	2.23	0.311
AS	6.73	0	35	7.41	
Surgical therapy					
ES	1	0	3	0.78	1
AS	1.13	0	2	0.43	
Medical therapy					
ES	10.77	0	40	13.44	0.832
AS	10.43	0	58	15.07	
Inter-consultation					
ES	3.43	0	10	2.04	0.314
AS	3.53	0	16	3.8	

AS: advanced stage; ES: Early stage; max.: maximum; min.: minimum; SD: standard deviation.
*Student t test.

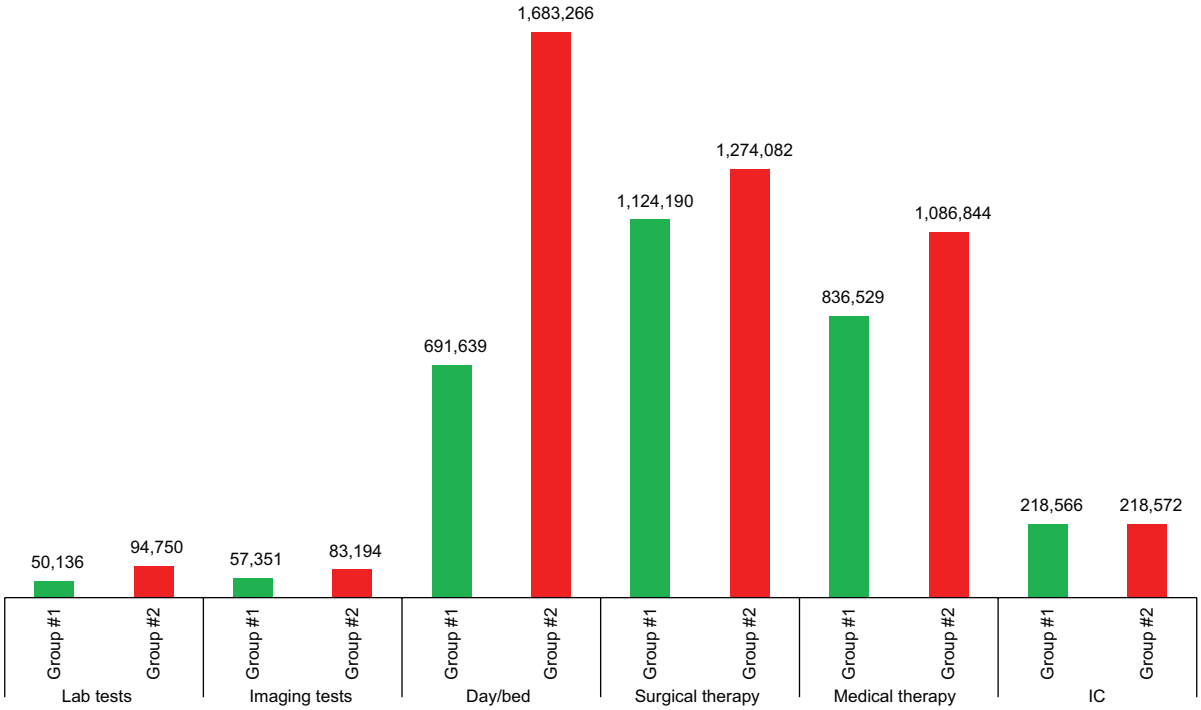

Figure 1. *Spending on lab and imaging tests, hospitalization (days/care), medical therapies (Med Tx), surgical therapies (Surg Tx), and inter-consultations (IC).*

The average spending of breast cancer care per patient was $99,280.36 and $148,023.60 for early and advanced stages, respectively, in 2019, at third-level IMSS centers, with an exchange rate in October 18, 2019, of $18.98 per US dollar and $21.35 per euro. These data are supported by the total direct spending associated with the health care provided to both patient groups (p = 0.024) as shown on figure 2.

We should mention that this study only evaluates direct health care spending, not indirect spending (disability, transportation expenses, psychological implications, etc.).

Breast cancer is a global issue of public health. The impact of late-stage diagnosis affects prognosis, quality of life, and health care spending for these patients[13-15].

When looking at the study results, we should mention that non-medical spending (such as transportation, trips from home to the hospital, among others) were not taken into consideration. The economic impact caused by managing this disease in its advanced stages is clearly identified compared to management in the early stages.

The analysis of direct health care spending gives us a panoramic view on the efficiency of policies and programs related to breast cancer care in different stages.4 Staging breast cancer allows for a simple

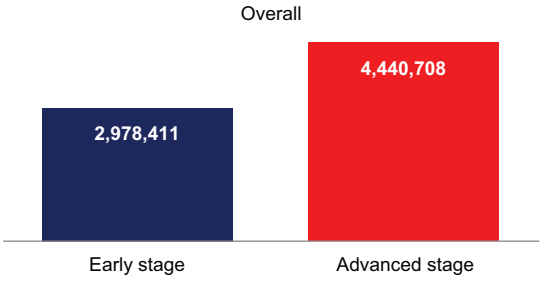

Figure 2. *Difference in overall spending (in Mexican pesos) of direct medical care provided to both groups of patients (p = 0.024).*

presentation of spending because it divides the classification according to SEOM staging, which is based on the treatment used[11].

Regarding the age of breast cancer presentation, both groups had similar mean ages (57.7 and 59.3 years) with no statistically significant differences being reported (p = 0.40). While low socioeconomic level can be considered a factor for delayed diagnosis, the analysis showed a similarity in both groups, with a predominance of the medium socioeconomic level, followed by the low one, once again without statistically significant differences being reported (p > 0.05).

Patients in advanced breast cancer stages required more lab and imaging tests, which ends up increasing spending. These results are consistent with a study published in *The Lancet Oncology* in 2013 that claimed breast cancer was the disease associated with the highest health care spending of all, €6-73,000 million (representative of 13% of all cancer-related spending)[16].

Statistically significant differences were found in spending regarding lab and imaging tests, and hospitalization days per patient between both groups, with more spending associated with group #2 (advanced stage). However, no statistically significant differences in surgical treatment, medical treatment, and interconsultation spending were reported between the two groups.

The results obtained in this study—based on SEOM classification—prove that spending increases when breast cancer is diagnosed in advanced compared to early stages[17].

Within the IMSS, the average annual spending per patient was estimated at $110,459 in 2006. Stage I breast cancer diagnosed in 2002 amounted to $74,522, compared to $102,042 for stage II, $154,018 for stage III, and $199,274 for stage IV[14].

Similarly, in Colombia, the spending estimated for the management of breast cancer was higher in regional and metastatic stages (65,603,637 and 144,400,865 Colombian pesos, respectively), while the in situ stage was associated with the lowest spending of all (8,996,987 Colombian pesos)[8].

In Spain, in 2015, spending according to the Basque Health System was €9838 for stage 0, €17,237 for stage I, €22,145 for stage II, and €28,776 for stage III[18].

In the present study that evaluated breast cancer spending in the IMSS, spending for the management of early-stage care was $99,280.36 ($148,023.60 for advance-stage care). We should mention that exchange rate back in October 18, 2019, was 18.98 pesos per US dollar and 21.35 pesos per euro for a total of $5230.78 and €4650.13, respectively for early stage cancer and $7798.92 and €6933.18 for advanced stage cancer.

In economic terms, we should consider the significant increase in spending due to permanent disabilities resulting from neoplastic diseases. For example, in Madrid, Spain, in 2012, 42.28% (31,554) out of a total of 74,631 permanent disability pensions were absolute pensions, with average pension amounts of €1211.94[19]. In Mexico, breast cancer is the leading cause of disability due to malignant diseases (16%), followed by colon and brain cancer[20].

Based on these results, there is a clear need for early and timely diagnosis in these patients to reduce the economic impact caused by health care when diagnosed in advanced stages.

Regarding health care at the early stages of the disease, from an economic perspective, there would be fewer hospitalization days, medical, and surgical therapies. As a matter of fact, this could be achieved through a training program for the personnel taking care of these patients at the primary level of medical care.

This study on the direct costs associated with breast cancer care can lay the foundations for future research, including the costs of preventing this disease, which would impact health care programs and policies in Mexico and across the world.

One limitation of this study is that it only evaluates the direct costs associated with breast cancer care at the IMSS and in no other public and private centers. It would have been interesting to compare health care spending in other public (Secretaría de Salud, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Petróleos Mexicanos, etc.) and private institutions (Grupo Hospital Ángeles or Christus Muguerza, among others).

We should also mention that IMSS provides medical care to 50% of the Mexican population, which is one of the strengths of the study[11].

In addition, we should track down patients with recurrences, control and reconstruction therapies that are crucial for the patient's social reintegration.

Conclusions

Health care spending for the management of early-stage breast cancer is lower compared to advanced stages of the disease, thus stressing the need for implementing preventive measures for early breast cancer care.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Incidence and factors associated with early and late adverse reactions after the first dose of Pfizer-BioNTech vaccine among healthcare workers

Incidencia y factores asociados con las reacciones adversas tras la primera dosis de la vacuna Pfizer-BioNTech en trabajadores de la salud

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Abstract

Objective: *To determine the incidence of adverse reactions (AR) after the first dose of Pfizer-BioNTech vaccine, and to identify some factors associated with AR.* **Method:** *A retrospective cohort study was conducted. Data were obtained through an epidemio- logical survey answered online. Multivariate analyses were performed to identify factors associated with early (< 2 h) and late (≥ 2 h) AR.* **Results:** *A total of 2295 health care workers were included; in them, the cumulative incidence of AR was 18.2% (95% confidence interval: 16.6-19.8), where the majority were late (78.2%). The associated factors that increased the risk of early AR were being female (odds ratio [OR]: 2.23, p = 0.002) and belonging to the medical staff (OR: 1.56; p = 0.041). In late AR were being female (OR: 1.94; p < 0.0001); on the other hand, diabetes (OR: 0.46; p = 0.021), asthma (OR: 0.53; p = 0.040) and smoking (OR: 0.44, p = 0.002) were inversely associated factors. Interestingly, history of COVID-19 was not associated with either early or late AR.* **Conclusions:** *The risk of presenting some type of AR due to the Pfizer-BioNTech vaccine in health care workers is < 20%.*

Keywords: *Adverse reactions. BNT162b2 vaccine. COVID-19. Health care workers.*

Resumen

Objetivo: *Determinar la incidencia de reacciones adversas (RA) tras la primera dosis de la vacuna Pfizer-BioNTech e identificar algunos factores asociados con ellas.* **Método:** *Se realizó un estudio de cohorte retrospectiva. Los datos fueron obtenidos median- te una encuesta epidemiológica contestada en línea. Se realizaron análisis multivariados para identificar factores asociados con las RA tempranas (< 2 h) y tardías (≥ 2 h).* **Resultados:** *Se incluyeron 2295 trabajadores de la salud; en ellos, la incidencia acumu- lada de RA fue del 18.2% (intervalo de confianza del 95%: 16.6-19.8%) y la mayoría fueron tardías (78.2%). Las RA tempranas más frecuentes fueron dolor local, cefalea y mareo; en las tardías fueron dolor local, cefalea y fatiga. No se documentaron casos de anafilaxia; sin embargo, en el grupo de RA tempranas y tardías hubo un caso y tres casos, respectivamente, con síntomas sistémicos que afectaron a dos órganos diferentes. Los factores asociados que incrementaron el riesgo de RA tempranas fueron ser mujer (odds ratio [OR]: 2.23; p = 0.002) y pertenecer al personal médico (OR: 1.56; p = 0.041). En las RA tardías fue ser mujer (OR: 1.94; p < 0.0001); por su parte, la diabetes (OR: 0.46; p = 0.021), el asma (OR: 0.53; p = 0.040) y el tabaquismo (OR: 0.44; p = 0.002) fueron factores asociados inversamente.*

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Date of reception: 05-10-2021
Date of acceptance: 23-03-2022
DOI: 10.24875/CIRUE.M23000425

Cir Cir (Eng). 2023;91(1):34-40
Contents available at PubMed
www.cirugiaycirujanos.com

Es interesante que la historia de COVID-19 no se asoció con RA tempranas ni tardías. **Conclusiones:** *El riesgo de presentar algún tipo de RA debido a la vacuna Pfizer-BioNTech en trabajadores de la salud es < 20%.*

Palabras clave: *Reacciones adversas. Vacuna BNT162. COVID-19. Personal de salud.*

Introduction

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it triggers (COVID-19) have caused significant disruptions to our way of life. Additionally, numerous cases and deaths have been reported around the world. As of September 5, 2021, over 220 million cases had been detected worldwide, with the death toll exceeding 4.5 million people for a fatality rate of 2.1%[1]. By that same date, in our country, the number of COVID-19 cases reached nearly 3.5 million, with over 260,000 deaths and an estimated fatality rate of 7.7%[2]. To constrain the pandemic, the emergence and use of COVID-19 vaccines have become increasingly popular worldwide. Among them, messenger RNA vaccines have gained importance due to their high efficacy in reducing symptomatic infections caused by SARS-CoV-2 and low rate of severe adverse events (AE)[3,4].

In Mexico, same as in other parts of the world, the vaccination strategy against COVID-19 focused primarily on health care workers responsible for assisting COVID-19 patients. The institutional policy at the hospital where this study was conducted was to administer the Pfizer BioNTech vaccine to all health care workers. This vaccine is based on lipid nanoparticles containing messenger RNA that induces the formation of spike proteins of SARS-CoV-2. The vaccine 2-dose regimen provides 95% protection[3]. The vaccination campaign with the Pfizer-BioNTech vaccine started in Mexico back in December 11, 2020. The immunization schedule consists of a first 30 μg dose in 0.3 mL5 administered intramuscularly in the deltoid muscle of the non-dominant arm. The second dose is administered 21 to 42 days after the first one[5]. Since the beginning of the vaccination campaign with the Pfizer-BioNTech vaccine, there were concerns among medical and non-medical personnel on the possibility of severe systemic AE being reported. Safety studies conducted on this vaccine were scarce when it started to be administered massively to the population, raising concerns on its potential for AE. Additionally, clinical trials may not fully identify the true size of AE among the population because they are often conducted in subgroups with specific inclusion criteria, and results might just not be entirely applicable to the rest of the population. With these concerns in mind, the objectives of our study were to determine the rate of early and late AE after the first dose of the Pfizer-BioNTech vaccine, using an online survey sent to the health care workers of a hospital located in Western Mexico. Also, to explore the rate of events consistent with anaphylactic reactions and identify factors associated with AE.

Method

Design

This was a retrospective cohort study conducted of a single group based on the census of health care workers at a second-level teaching hospital from Western Mexico. The study focused on those who voluntarily received the Pfizer-BioNTech vaccine. The recruitment period spanned from January through April 2021. Health care workers aged ≥ 18 years were included in the study. Those with the following conditions were excluded: age ≥ 65 years, uncontrolled diabetes, uncontrolled arterial hypertension, morbid obesity, neoplastic diseases, use of immunosuppressive medications, pregnant women, uncontrolled chronic obstructive pulmonary disease (COPD), or uncontrolled cardiovascular diseases. Health care workers on whom there was no information available or who remained confined at the time of vaccination and, therefore, could not be vaccinated were also excluded.

Follow-up

Follow-up of all study subjects began from the date the Pfizer-BioNTech vaccine started being administered and extended until 30 days after vaccination. During this time, all AE were recorded.

Measuring tool

Data were collected using an epidemiological survey that was answered online to limit physical contact between individuals. The survey included questions on age, sex, history of COVID-19, and comorbidities such as diabetes, systemic arterial hypertension, cardiovascular disease,

COPD, asthma, current smoking status, and history of allergies. In our study, health care workers were categorized as either medical personnel (physicians and nurses) or non-medical personnel.

Variables

Operatively, variables for the study were collected through the online survey based on self-reporting by all participants. Possible factors associated with AE included gender (female), medical personnel status, diabetes, systemic arterial hypertension, asthma, smoking, and history of COVID-19. All these factors were categorized as present (yes) or absent (no) based on the participant's response.

Adverse events

The outcome variables were classified according to the time they occurred during the post-vaccination follow-up: 1) no AE, 2) early AE (< 2 hours), and 3) delayed AE (≥ 2 hours). The discomfort caused by the vaccine was categorized as local (pain, swelling, redness, cellulitis, among others) or systemic (added to the presence of a local reaction, affecting a different organ or system) and depending on the organs or systems damaged. To identify anaphylactic reactions associated with the Pfizer-BioNTech vaccine, the definitions of anaphylaxis proposed by different international organizations were adapted to our study[6-8].

The history of COVID-19 was defined as the presence of symptoms of the disease plus confirmation of SARS-CoV-2 infection with a positive result in a real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2.

Analysis

Data analysis was performed using IBM SPSS Statistics Version 23.0. The rate of AE following vaccination was expressed as cumulative incidence (number of new events among subjects at risk or vaccinated). The confidence interval was obtained using Wald or Wilson Score Interval as necessary. Categorical variables were expressed as frequency and percentage, and quantitative ones as mean and standard deviation. The chi-square test or Fisher's exact test were used to compare percentages between groups as necessary. The ANOVA formula with Sheffé correction was used to compare means in two or more groups. Finally, to identify variables associated with early or late AE (dependent variables), different multivariate logistic regression models were used, one for each category. The independent variables entered into the models were gender (female or male), medical personnel (yes or no), diabetes (yes or no), systemic arterial hypertension (yes or no), asthma (yes or no), smoking (yes or no), and COVID-19 (yes or no). P values < 0.05 were considered statistically significant.

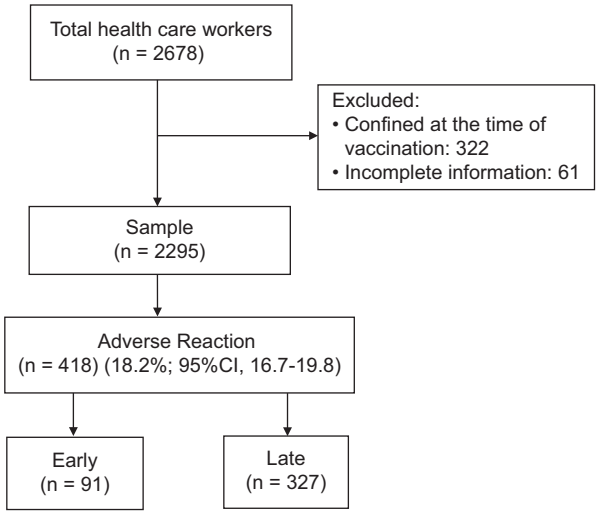

Figure 1. *Flowchart of health care workers with AE to the Pfizer-BioNTech vaccine.*

Ethics

The research was approved by the Ethics Committee of Nuevo Hospital Civil de Guadalajara, Jalisco, Mexico while the epidemiological survey responded by each participant was considered as willingness to participate in the study.

Results

From an overall population of 2678 health care workers, 322 were excluded as they remained confined at the time of vaccination, plus 61 due to incomplete information. The final sample included a total of 2295 health care workers (86% of the overall population) who had received the first dose of the Pfizer-BioNTech vaccine (Fig. 1).

Table 1 shows the characteristics of the population studied. A total of 63.1% of the total were women, and the mean age was 38.1 ± 11.3 years. Overall, 418 out of 2295 health care workers experienced some type of AE (cumulative incidence, 18.2%; 95% confidence interval [CI]: 16.6-19.8), with the majority being late AE

Table 1. Characteristics of healthcare workers based on the type of AE to the Pfizer-BioNTech vaccine

	Total (n = 2295)	No (n = 1877)	Adverse event		p
			Early (n = 91)	Late (n = 327)	
Age, years, mean ± SD	38.1 ± 11.3	39.2 ± 11.0	37.3 ± 12.0	38.9 ± 11.4	0.258
Sex, woman, n (%)	1449 (63.1)	1133 (60.4)	70 (76.9)	246 (75.2)	< 0.0001
Healh care worker, n (%)					
Medical personnel	1550 (67.5)	1269 (67.6)	53 (58.2)	228 (69.7)	0.116
Non-medical personnel	745 (32.5)	608 (32.4)	38 (41.8)	99 (30.3)	
Comorbidity, n (%)					
Diabetes	135 (5.9)	123 (6.6)	2 (2.2)	10 (3.1)	0.014
Systemic arterial hypertension	170 (7.4)	149 (7.9)	2 (2.2)	19 (5.8)	0.061
Cardiovascular disease	46 (2.0)	42 (2.2)	1 (1.1)	3 (0.9)	0.239
COPD	16 (0.7)	13 (0.7)	1 (1.1)	2 (0.6)	0.884
Asthma	138 (6.0)	120 (6.4)	6 (6.6)	12 (3.7)	0.156
Current smoker, n (%)	247 (10.8)	225 (12.0)	5 (5.5)	17 (5.2)	< 0.0001
COVID-19, n (%)	529 (23.1)	435 (23.2)	20 (22.0)	74 (22.6)	0.947

COPD: chronic obstructive pulmonary disease; SD: standard deviation.
Proportions compared using a Chi-square test for 2 degrees of freedom.
Means compared using the ANOVA test.

(78.2%) and the rest, early AE (21.8%). The early AE group mainly included local pain, headache, and dizziness, while the late AE group included local pain, headache, and fatigue. The early AE group had significantly more dizziness and xerostomia compared to the late AE group ($p < 0.05$). On the other hand, the late AE group had significantly more fever, headache, fatigue, local pain, diarrhea, pharyngeal pain, and myalgia compared to the early AE group ($p < 0.05$) (Table 2). Out of the 17 subjects with hives, 5 had early presentation (29.4%) compared to 12 late presentations. The ratio of AE with systemic manifestations was 4 out of 2295 participants (0.17%; 95%CI 0.07-0.45), 1 occurring in the early AE group characterized by hives, body itching, and rhinorrhea (0.04%), and 3 in the late AE group (0.13%) with the same symptoms. In the latter group, a case of wheezing and dyspnea was reported in a 43-year-old woman with a history of smoking.

The factors associated with early AE were being a woman and a member of the medical personnel. Regarding late AE, being a woman increased the chances of early AE by 94%, while having diabetes, asthma, or being a current smoking were inversely associated factors. We should mention that, interestingly enough, the history of COVID-19 was not associated with the presence of early or late AE (Table 3).

Discussion

This study has multiple important findings. First, it shows that little over one fifth of all health care workers experienced some type of AE after receiving the first dose of the Pfizer-BioNTech vaccine. Local pain and headache were the most common clinical signs reported in both the early and late AE groups. Second, as far as we know, this study is the first one ever conducted to report AE related factors associated with the Pfizer-BioNTech vaccine based on when these reactions appeared. Among other things, we saw that women had more chances of experiencing both early and late AE compared to men. Also, the personal history of asthma did not increase the risk of late AE. Third, the history of COVID-19 was also not associated with vaccine-related AE. Finally, the study found that allergic reactions were rare, and specific anaphylactic reactions could not be fully identified.

In the first landmark study ever conducted to assess the efficacy and safety profile of the Pfizer-BioNTech vaccine of over 43,000 subjects, the overall rate of any AE was 27% despite the vaccine 95% efficacy profile. This contrasted significantly with the placebo group, where the rate of any AE was 12%[3]. Similarly, a different study found similar findings, with a 25.4% rate of AE[9]. However, other studies have also shown different results; for example, in Poland, the rate of AE was 94%[10], in Malta, 73% in men and 82% in women[11]; while in Iraq, it was 67%[12]. Probably, the perception of symptoms among participants is a relevant factor in the different AE frequencies reported among the studies. Another explanation could be the manner and timing of data collection. In our case, since the population analyzed were health

Table 2. Comparison of signs and symptoms based on the type of AE to the Pfizer-BioNTech vaccine

	Rate of AE in 2295 participants	AE		p
		Early (n = 91)	Late (n = 327)	
Local symptoms, n (%)				
Local pain	374 (16.3)	68 (74.7)	306 (93.6)	< 0.0001
Local edema	81 (3.5)	18 (19.8)	63 (19.3)	0.913
Local erythema	15 (0.7)	2 (2.2)	13 (4.0)	0.540
Systemic signs, n (%)				
Musculoskeletal	260 (11.3)	35 (38.5)	225 (68.8)	< 0.0001
Fatigue	218 (9.5)	28 (30.8)	190 (58.1)	< 0.0001
Myalgias	190 (8.3)	23 (25.3)	167 (51.1)	< 0.0001
Adynamia	47 (2.0)	6 (6.6)	41 (12.5)	0.112
Arthralgias	23 (1.0)	3 (3.3)	20 (6.1)	0.436
GI	185 (8.1)	52 (57.1)	133 (40.7)	0.005
Dizziness	119 (5.2)	37 (40.7)	82 (25.1)	0.004
Nausea	80 (3.5)	22 (24.2)	58 (17.7)	0.167
Diarrhea	50 (2.2)	4 (4.4)	46 (14.1)	0.010
Abdominal pain	32 (1.4)	4 (4.4)	28 (8.6)	0.264
Vomiting	17 (0.7)	3 (3.3)	14 (4.3)	0.999
Xerostomia	6 (0.3)	5 (5.5)	1 (0.3)	0.002
Respiratory	156 (6.8)	26 (28.6)	130 (39.8)	0.051
Rhinorrhea	91 (4.0)	13 (14.3)	78 (23.9)	0.050
Pharyngeal pain	88 (3.8)	12 (13.2)	76 (23.2)	0.037
Cough	61 (2.7)	10 (11.0)	51 (15.6)	0.271
Dyspnea	22 (1.0)	9 (9.9)	13 (4.0)	0.034
Wheezing	1 (0)	0 (0)	1 (0.3)	0.999
Cutaneous	137 (6.0)	26 (28.6)	111 (33.9)	0.334
Chills	118 (5.1)	21 (23.1)	97 (29.7)	0.217
Body itching	18 (0.8)	5 (5.5)	13 (4.0)	0.528
Hives	17 (0.7)	5 (5.5)	12 (3.7)	0.436
Cellulitis	2 (0.1)	0 (0)	2 (0.6)	0.999
Cardiovascular	28 (1.2)	13 (14.3)	15 (4.6)	0.001
Tachycardia	18 (0.8)	8 (8.8)	10 (3.1)	0.017
Hypertension	14 (0.6)	8 (8.8)	6 (1.8)	0.001
Other	310 (13.5)	56 (61.5)	254 (77.7)	0.002
Headache	294 (3.9)	56 (61.5)	238 (72.8)	0.038
Fever	90 (3.9)	7 (7.7)	83 (25.4)	< 0.0001

P-values were obtained using the Chi-square test or Fisher's exact test, as necessary (early AE or late AE).

care workers, some discomforts may not have been given proper importance, and consequently, when filling out the online survey, they may have been misrepresented. On the other hand, since the vaccine was applied to the deltoid region of the arm, the most common AE were local, among them, pain was the most significant one. In our study population, this discomfort was more frequently observed in a delayed manner. Other local discomforts, although not as common, were erythema and edema. Similar findings have been reported in previous studies[3,9-12]. Regarding systemic AE, in our study, the most common ones were fatigue and muscular pain, which is consistent with previous studies[9,11-13].

Notably, no cases of anaphylaxis were documented among health care workers in this study. However, in the group of both early and late AE, 1 and 3 cases were reported, respectively, with systemic symptoms affecting 2 different organs. According to the classification system for systemic allergic reactions proposed by the World Allergy Organization, these cases would qualify as grade 2 AE[6]. Using the definition of anaphylaxis established by the Brighton Collaboration, these same subjects would fall under level 2 of diagnostic certainty for anaphylaxis[7]. Finally, based on the severity scale of anaphylaxis proposed by the German Working Group of Anaphylaxis Training and Education, these subjects had grade II AE[8]. In conclusion, individuals

Table 3. Multivariate analysis of factors associated with AE to the Pfizer-BioNTech vaccine

Dependent variable: early adverse event			
	aOR	**95%CI**	**p**
Woman	2.23	1.35-3.67	0.002
Medical personnel	1.56	1.02-2.41	0.041
Diabetes	-	-	0.183
Systemic arterial hypertension	0.26	0.06-1.06	0.060
Asthma	-	-	0.988
Smoking	-	-	0.089
COVID-19	-	-	0.714
Dependent variable: late AE			
	aOR	**95%CI**	**p**
Woman	1.94	1.48-2.54	< 0.0001
Medical personnel	-	-	0.70
Diabetes	0.46	0.24-0.89	0.021
Systemic arterial hypertension	-	-	0.629
Asthma	0.53	0.29-0.97	0.040
Smoking	0.44	0.26-0.74	0.002
COVID-19	-	-	0.132

aOR: adjusted odds ratio; 95%CI: 95% confidence interval. Adjusted ORs were obtained through binary logistic regression. Covariates were introduced dichotomously using the forward method: conditional. ORs are not calculated for variables that were removed from the model due to the lack of a significant association.

receiving the Pfizer-BioNTech vaccine who experience hives as a primary symptom, either early or late, should be closely monitored to make sure that their symptoms do not progress into overt anaphylaxis.

The results of this study show an association between AE and certain factors such as sex and a personal history of asthma, among others. Regarding sex and the rate of AE, Menni et al[9]. also showed that the number of local and systemic AE is higher in women compared to men, both with the Pfizer-BioNTech and the ChAdOx1 nCoV-19 vaccines. Similar results have been documented across the world[11,12,14,15]. Probably, differences in innate and acquired immune responses between women and men, higher inflammatory responses in women or information biases could be contributing factors to the higher rate of AE reported in women[16,17].

One relevant finding in this study is the inverse association between asthma and the presence of AE, specifically late AE. Several meta-analyses conducted during the pandemic showed that asthma is related to a lower severity of COVID-19[18,19]. The proposed mechanisms to explain this lack of association could be related to a predominance of the Th2 type inflammatory response over the Th1 type[20], which is primarily responsible for COVID-19 symptoms. Finally, former studies have shown that having a history of COVID-19 is associated with a higher rate of AE following the use of vaccines against this virus[9,12,21]. The arguments that have been put forward to explain this association are related to an improved immune response following the use of the vaccine[22,23]. However, in this study, neither early nor late AE were associated with a history of previous COVID-19.

Another noteworthy finding is the inverse relationship found between diabetes, smoking, and AE. It is possible that some individuals with diabetes may not have initially gone to vaccination centers, which could explain why the rate of diabetes found in the study was relatively lower than the national rate. This could have artificially resulted in a higher rate of AE in people without diabetes. Regarding smoking, one possible explanation could be how health care workers perceive and report their smoking habits. The rate of this addiction might be higher in this population than reported. In both situations, it is suggested to approach these associations with caution and wait for further epidemiological studies to confirm the findings.

Limitations

The study has several limitations. The epidemiological survey did not inquire about the intensity of AE, the duration of discomfort or the need for treatment to control them. Additionally, although the participation rate of health care workers in responding to the survey after the first dose of the vaccine was very good, it decreased notably after the second dose. Therefore, the study is limited regarding whether the rate of AE was higher or lower in relation to the first dose. We have the perception that, once the fears that existed in the survey participants due to the information circulating regarding the side effects of a new vaccine were overcome, the participation to complete the survey decreased significantly. As a result, the follow-up of late AE was limited until the time of the second dose of the vaccine was reached. Furthermore, individuals with a personal history of anaphylaxis may not have gone to vaccination centers as scheduled, which may have influenced the lack of observation of this type of discomfort. As mentioned

earlier, we should consider that the type of population studied (health care workers) may have perceived and reported on the occurrence of vaccine-associated AE differently, as well as some of the factors investigated (asthma, diabetes, or smoking). Therefore, caution should be exercised when extrapolating the results to the general population.

Conclusions

The risk of experiencing any type of AE to the Pfizer-BioNTech vaccine in health care workers was < 20%, which is similar to what has been reported in previous clinical trials. Early and late AE were more frequent in women than in men. Notably, asthma, diabetes, and smoking showed an inverse association with late AE, a finding that requires further epidemiological studies for confirmation purposes. Finally, the risk of AE with systemic sign was very low (< 1%). Also, no cases of anaphylaxis were ever documented in this study.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Staging accuracy in resecable esophageal cancer. Observational retrospective study

Exactitud diagnóstica en el cáncer de esófago localizado. Estudio observacional retrospectivo

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Abstract

Objective: *To assess the accuracy of the diagnostic tests for a correct clinical tumor staging in localized esophageal cancer (EC).* **Method:** *Retrospective observational study of patients who underwent esophagectomy for cancer in a referral hospital between January 2003 and September 2019. Those patients who received neoadjuvant treatment were excluded in order to avoid bias from downstaging effects. The preoperative stage was compared with the pathological stage of the surgical specimen. Computed tomography (CT), endoscopic ultrasound (EUS) and positron emission tomography (PET) were evaluated. The pT stage was correlated with the tumor length described in the esophagram (EG).* **Results:** *Among the 63 patients included, the clinical staging was correct in 16 (global accuracy 25.4%), it was overstaged in 21 (33.2%) and understaged in 26 (41.3%). For cT staging, the accuracy of EUS was higher than that of CT (46.6% and 34.9%, respectively), specially for early stages. EG tumor length correlated with pT stage ($p < 0.05$). For cN staging, PET had the highest sensitivity (50.0%) and negative predictive value (75.0%).* **Conclusions:** *Despite the multiple diagnostic tools used, the global accuracy of clinical staging in localized EC is still a challenge. The lack of a test that stands out significantly from the others reinforces the need to use them in a complementary way.*

Keywords: *Esophageal cancer. Tumor staging. Diagnostic accuracy.*

Resumen

Objetivo: *Evaluar la exactitud diagnóstica para el estadiaje clínico del cáncer de esófago (CE) localizado.* **Método:** *Estudio observacional retrospectivo de los pacientes esofagectomizados por CE en un hospital de referencia entre enero de 2003 y septiembre de 2019. Se excluyeron aquellos que recibieron neoadyuvancia para evitar sesgos de infraestadiaje. Se comparó el estadio preoperatorio con el estadio patológico de la pieza quirúrgica. Se evaluaron la tomografía computarizada (TC), la ecoendoscopia (EUS) y la tomografía por emisión de positrones (PET). El estadio pT se correlacionó con la longitud tumoral descrita en el esofagograma (EG).* **Resultados:** *De los 63 pacientes incluidos, el estadiaje clínico fue correcto en 16 (exactitud 25.4%), con sobreestadiaje en 21 (33.2%) e infraestadiaje en 26 (41.3%). Para el estadiaje cT, la EUS fue superior a la TC (exactitud 46.6% y 34.9%, respectivamente), en especial para estadios precoces. La longitud tumoral del EG se correlacionó con el estadio pT ($p < 0.05$). Para el estadiaje cN, la PET tuvo la mayor sensibilidad (50.0%) y el mayor valor predictivo negativo (75.0%).* **Conclusiones:** *A pesar de las múltiples herramientas diagnósticas empleadas, la exactitud diagnóstica en el CE localizado es limitada. La ausencia de una prueba que destaque de manera significativa refuerza la necesidad de emplearlas de forma complementaria.*

Palabras clave: *Cáncer de esófago. Estadificación tumoral. Exactitud diagnóstica.*

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Date of reception: 19-09-2021
Date of acceptance: 30-11-2021
DOI: 10.24875/CIRUE.M23000426

Cir Cir (Eng). 2023;91(1):41-47
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

The survival of patients with esophageal cancer correlates with the degree of tumor spread at the time of diagnosis. Therefore, to offer optimal treatment and make a reasonable use of health care resources, it is essential to perform accurate clinical staging[1].

Typically, tumor diagnosis is established through upper digestive endoscopy with biopsy. Clinical staging is achieved by combining several diagnostic imaging modalities, such as thoraco-abdominopelvic (TAP) computed tomography (CT) (cervical in case of cervical tumor involvement), esophagogram (EG), positron emission tomography (PET), and ultrasound (US)[1].

Once distant dissemination (cM) has been ruled out, it is important to determine the tumor (cT) and lymph node (cN) stages because these patients will likely be eligible for curative intent treatment. Patients with early tumor stages without lymph node involvement may be eligible for endoscopic or surgical treatment alone, while those with suspected lymph node involvement or more advanced stages of the disease will benefit from a multidisciplinary approach with neoadjuvant treatment (chemotherapy-radiation therapy) and further surgery[1-4].

The T staging is mainly evaluated using CT and US. CT measures the thickness of the esophageal wall (pathological if > 5 mm) and its asymmetry, as well as possible infiltrations of adjacent structures. On the other hand, the US provides a more precise assessment of tumor infiltration into the different layers of the esophageal wall[5,6]. Lymph node involvement is also evaluated by these two imaging modalities, mainly based on the size of the lymph nodes (pathological if > 10 mm), but also on their shape or formation of adenopathy clusters.1 The main objective of PET is to rule out lymph node or metastatic dissemination.

Former studies have already analyzed the performance of various diagnostic tests for the clinical staging of esophageal cancer[7-10]. However there are no studies comparing TAP CT, PET, EG, and US all together.

The objective of this study is to evaluate diagnostic accuracy in the clinical staging of localized esophageal cancer. For this purpose, clinical staging was compared with the anatomopathological staging (8th edition of the TNM classification)[11].

Method

This was a retrospective observational study of patients treated with esophagectomy due to neoplasm at a tertiary referral hospital from January 2003 through September 2019.

The study included patients with localized stages of cancer who underwent surgery as the initial treatment. Patients who received neoadjuvant therapy were excluded to avoid under-staging bias (Fig. 1).

Tumor staging of the patients

All patients with esophageal cancer underwent several diagnostic tests, including TAP CT, upper digestive endoscopy with biopsy, EG, and a full blood test with tumor markers. Also, an US was performed in non-stenotic lesions without distant disease, and a PET in cases where distant disease was suspected. The cytology of lymph nodes through fine-needle aspiration (FNA) was not performed systematically. In case of discrepancies among different imaging modalities, the more advanced stage was considered.

The US was not always performed by the same endoscopist. Nonetheless, they all followed the same diagnostic criteria: for T staging, visualization of a 5-line structure of hypo- and hyperechoic alternations corresponding to the 5 histological layers of the esophageal wall. For N staging, identification of lymph nodes > 10 mm, round, well-demarcated, heterogeneous or hypoechogenic suggestive of malignancy[12].

Patients with stages > cT3 or cN+ were eligible for neoadjuvant therapy with chemotherapy-radiation therapy according to the CROSS scheme. After finishing treatment, a CT was performed to assess the response, and surgery was performed 6-8 weeks later. Tumors staged as cT1-2 cN0 were generally considered eligible for surgery as first-line therapy.

Staging was performed according to the current TNM classification at each time, and later according to the 8th edition for proper comparability.

Surgical technique

A 3-stage esophagectomy (McKeown procedure) was performed for tumors located in the upper and middle thirds of the esophagus, a 2-stage esophagectomy (Ivor-Lewis procedure) for tumors located in the lower third or at the gastroesophageal junction (Siewert I and II), and a two-stage transhiatal esophagectomy (Orringer procedure) in cases of significant cardiac or respiratory comorbidity. A standard two-field lymphadenectomy was performed according to the International Society for Diseases of the Esophagus classification (1994)[13-15], with a requirement of resecting, at least,

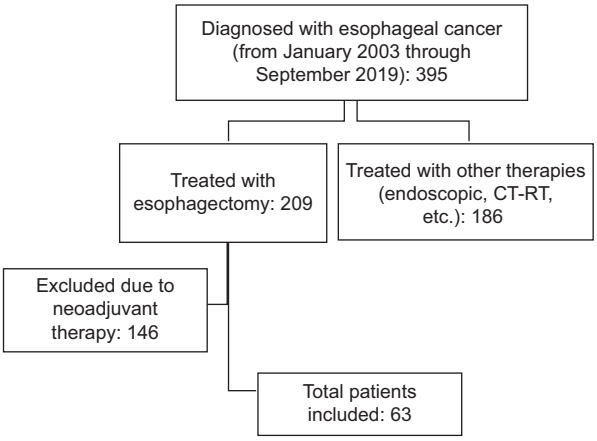

Figure 1. *Flowchart of the patient selection process for the studied group. CT: chemotherapy; RT: radiation therapy.*

12 lymph nodes for the two-field lymphadenectomy to be considered optimal. Reconstruction was performed using gastroplasty or coloplasty in cases of previous gastric surgery.

Surgical approach was minimally invasive, open, or hybrid, with a clear trend towards minimally invasive techniques across the entire study period.

Statistical analysis

Variables were described using the most appropriate statistical measures based on the nature and scale of measurement for each variable: mean and standard deviation for quantitative variables, and absolute and relative frequencies in percentage for qualitative variables.

The preoperative stages cT and cN, as well as their combination (cTNM), were compared to the pathological stage of the surgical specimen (pT, pN, pTNM), which was considered the reference method. CT and US were evaluated for cT and cN, respectively, while PET was only used for cN. Additionally, the pT stage was correlated with the tumor length described in the EG.

Correct staging was considered when cT, cN, or both were confirmed in the surgical specimen (pT, pN), reflected by the accuracy of each test. Over- or understaging was considered when cT or cN were higher or lower than pT or pN, respectively.

To conduct certain analyses, data were grouped. Specifically, pT1a and pT1b stages were grouped as pT1, and pT4a stages as pT4 to be able to compare them with cT stages, which do not consider these subdivisions. Similarly, pathological stages pIIIA and pIIIB were grouped as pIII, and stages pN1, pN2, and pN3 as pN+.

The performance of the additional tests performed was described using sensitivity (S), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV), and accuracy. Fisher's exact test was used to analyze differences among different diagnostic imaging modalities or tumor stages.

To study the association between tumor length described in the EG and pT stage, the analysis of variance (ANOVA) was used after checking the comparability, normal distribution, and homogeneity of the samples. Additionally, attempts were made to predict pT stage based on tumor length using the receiver operating characteristic (ROC) curves and subsequent contingency tables.

P values < 0.05 were considered statistically significant. Data were collected using the Scientific Package of the Social Sciences 21.0 (SPSS, Chicago, IL, United States) and analyzed using SPSS and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 63 patients were included in the study whose characteristics are shown on table 1. Clinical staging was correct in 16 cases (25.4%). Over- and under-staging occurred in 21 (33.2%) and 26 (41.3%) patients, respectively. Given the low accuracy of clinical staging, the diagnostic performance of the different additional tests for T and N stages was analyzed.

Tumor staging

Ultrasound

The US was performed in 43 patients. The contingency table and the corresponding S, Spe, PPV, NPV, and overall diagnostic accuracy are shown on table 2. Tumor staging (uT) was correct in 20 patients (overall accuracy, 46.6%). In 23 patients (53.4%), the uT stage was incorrect, in 30.2% over-staged and in 23.2% under-staged.

To study S and Spe, uT0, uT1a, and uT4 stages were excluded due to the low number of patients. Looking at the table, we should mention that the S for the uT1b stage was low (33%), lower compared to other stages (66.7% and 64.3%, with p = 0.08 and p = 0.10, respectively). Additionally, Spe was also low (55.9%) for uT2 stage compared to other stages (96.2% and 82.8%), which was statistically significant (p < 0.001 and p = 0.03, respectively).

Since patients with cT1 stage tumors may be eligible for endoscopic treatment, the ability of US to distinguish

Table 1. Characteristics of the patients (n = 63)

Mean age, years (SD)	61.27 (9.39)
Men (%)	54 (85.7)
BMI, kg/m^2 (SD)	26.22 (3.64)
Mean time since diagnosis until surgery, days (SD)*	51.7 (33.09)
Type of cancer	
Squamous (%)	25 (39.7)
Adenocarcinoma (%)	38 (60.3)
Tumor location	
Upper thoracic third (%)	5 (7.9)
Middle thoracic third (%)	7 (11.1)
Lower thoracic third (%)/ gastroesophageal junction (%)	51 (81.0)
Imaging modalities	
TAP CT (%)	63 (100)
Upper digestive endoscopy with biopsy (%)	63 (100)
PET (%)	17 (27)
EG (%)	32 (50.8)
US (%)	43 (68.3)
Type of surgical procedure	
Ivor-Lewis (%)	24 (38.1)
McKeown (%)	25 (38.7)
Orringer (%)	14 (22.2)
Resection margins	
R0 (%)	56 (88.9)
R1 (%)	7 (11.1)
Diseased proximal longitudinal margin	3
Diseased circumferential margin	4
Approach	
Open (%)	8 (12.7)
Minimally invasive (%)	39 (61.9)
Hybrid (%)	16 (25.4)
Laparotomy + thoracoscopy (%)	4 (6.3)
Laparoscopy + thoracotomy (%)	12 (19.0)
Lymphadenectomy	
2-field standard (%)	49 (77.8)
Suboptimal lymphadenectomy (%)	23 (36.5)
No lymphadenectomy (%)	14 (22.2)
Number of nodes resected (SD)	15.11 (6.88)
Clinical stage	
I	13 (20.6)
II	36 (57.1)
II	14 (22.2)
Pathological stage	
0	4 (6.3)
I	24 (38.1)
II	9 (14.3)
II	15 (23.8)
IV	11 (17.5)

SD: standard deviation; EG: esophagogram; US: ultrasound; BMI: body mass index; PET: positron emission tomography; TAP CT: thoraco-abdominopelvic computed tomography.
*Considering the diagnostic moment as the day the upper digestive endoscopy was performed.

between T1 and T2 stages was analyzed. The PPV of those categorized as uT1 was 83.35%, compared to 28.6% for those categorized as uT2, with a 42.9% over-staging in the latter.

Computed tomography

All patients underwent CT scans. The cT staging was correct in 22 patients (overall accuracy, 34.9%), over-staged in 22.2% and under-staged in 42.9%. Table 3 shows that the S of the CT scan was higher in the advanced stage cT3 (68.4%) compared to cT1 and cT2 stages (11.1% and 36.4%, respectively) being the difference with respect to cT1 statistically significant ($p < 0.001$ and $p = 0.13$, respectively).

Esophagogram length

A total of 32 patients underwent EGs. The data showed a normal distribution ($p = 0.054$), and there was homogeneity in variances ($p = 0.53$). The tumor length (cm) on the EG was greater as the pT stage grew: for pT1, tumor length was 2.5 ± 1.68 cm; for pT2, 4.33 ± 1.21 cm; and for pT3, 4.47 ± 1.35 cm being the differences statistically significant if pT1 was compared to pT3 ($p = 0.006$), and almost statistically significance if pT2 was compared to pT1 ($p = 0.054$).

The diagnostic accuracy of the EG was analyzed using the ROC curve. Therefore, considering the results discussed and that pT1 could be eligible for less invasive treatments, 2 groups were created: those with pT1 stage and those with pT2 or higher stage. The area under the ROC curve was 0.804 (95% confidence interval, 0.633-0.975; $p < 0.004$). The value with the highest discriminative power was 3.5 cm (80% S and 74% Spe). Table 4 shows that using this value, tumors with lengths < 3.5 cm could be predicted—with an accuracy of 78.1%—to be stage T1, while those with greater lengths would be stage T2 or higher.

Nodal staging

The results are shown on table 5.

Computed tomography

The cN staging was correct in 42 cases (66.7% accuracy). A total of 19 patients (30.2%) were considered cN0 but turned out to be pN+, while in 2 cases (3.2%), nodal involvement was suspected, but they were ultimately pN0.

Ultrasound

US was performed on 42 patients. The uN staging was correct in 22 cases (52.4% accuracy). In 18 cases

Table 2. Comparison between the tumor clinical stage by ultrasound (uT) and the pathological one (pT)

pT0	pT							S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pT1a	pT1b	pT2	pT3	pT4a	Total						
uT												
uT0	0	0	1	0	0	0	1	-	97.7	100	0	97.7
uT1a	0	0	1	0	0	0	1	0	97.6	97.6	0	95.3
uT1b	0	0	5	1	0	0	6	33.3	96.2	67.6	83.3	69.8
uT2	0	1	8	6	5	1	21	66.7	55.9	86.4	28.6	58.1
uT3	0	0	2	2	9	1	14	64.3	82.8	82.8	64.3	76.7
uT4	0	0	0	0	0	0	0	0	100	95.2	-	93.0
Total	0	1	17	9	14	2	43					46.5%

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

Table 3. Comparison between the tumor clinical stage by computed tomography (cT) and the pathological one (pT)

	pT					Total	S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pT0/Tis	pT1	pT2	pT3	pT4						
cT											
cT0	2	13	5	0	0	20	66.7	70	97.7	10	68
cT1	0	3	0	1	0	4	11.1	97.2	59.3	75	60.3
cT2	0	7	4	5	1	17	36.4	75	84.8	23.5	68.3
cT3	1	4	2	13	2	22	68.4	79.6	85.4	59.1	76.2
cT4	0	0	0	0	0	0	0	100	95.2	-	95.2
Total	3	27	11	19	3	63					34.9%

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

Table 4. Correlation between tumor length and the pathological stage (pT)

	pT			S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pT1	≥ pT2	Total					
Length (cm)								
< 3.5	9	4	13	80.0%	75.0%	69.2	84.2%	78.1
≥ 3.5	3	16	19					
Total	12	20	32					

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

Table 5. Comparison between the clinical node stage (cN, uN) and the pathological one (pN)

	pN			S (%)	Spe (%)	NPV (%)	PPV (%)	Accuracy (%)
	pN–	pN+	Total					
CT								
cN0	34	19	53	29.6	94.4	64.1	80.0	66.7
cN+	2	8	10					
Total	36	27	63					
US								
uN0	20	18	38	10.0	90.9	52.6	50.0	52.4
uN +	2	2	4					
Total	22	20	42					
PET								
cN0	9	3	12	50.0	81.8	75.0	60.0	70.6
cN+	2	3	5					
Total	11	6	17					

Spe: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

(42.9%), no nodal disease was suspected, but they turned out to be pN+, while only in 2 cases (4.8%), nodal involvement was suspected without confirmation in the surgical specimen analysis.

Positron emission tomography

Among the 17 patients who underwent PET, nodal staging was correctly predicted in 12 cases (70.6% accuracy). Three cases, however, (17.6%) with nodal involvement were misdiagnosed by the PET, while 2 cases (11.8%) with suspected nodal involvement turned out to be pN0.

The specificity of the 3 imaging modalities was comparable (94.4%, 90.9%, and 81.8%, respectively), while the S (50.0%) and NPV (75.0%) of PET were higher. In the CT scan, and especially in the US, the large number of false negatives resulted in low S (29.6% and 10.0%, respectively) and low NPV (64.1% and 50.0%, respectively).

Discussion

Despite the availability of multiple diagnostic imaging modalities, and consistent with what has been reported in former studies[9], in our study, clinical staging was correct in only a quarter of the patients, with therapeutic and prognostic implications associated.

Regarding clinical tumor stage (cT), the accuracy of CT and US was 34.9% and 46.6%, respectively, being over-staging more common in the US (30.2% vs 22.2% for the CT) and under-staging more common in the CT (42.9% vs 23.2% for the US).

Former studies have reported CT accuracies of 68.7% to 76.3% for cT staging[16], which is higher than what we obtained. The CT scan cannot distinguish among T1, T2, and T3 stages[6]. However, it is very useful to assess infiltration of adjacent structures, with sensitivity and specificity rates of 85% to 100%, resulting in higher accuracy for T4 stage[17,18]. However, our study excluded cT4 tumors because they were not eligible for primary surgery, which may have negatively impacted the overall accuracy of this imaging modality.

A meta-analysis that studied the ability of US to establish cT reported S rates of 81% to 90% and Spe rates close to 99%[19]. Our data are worse compared to those reported in the medical literature available, being the accuracy rate of the US between 64% to 92%[7,8,20].

The pT stage was more advanced as tumor length grew in the EG, suggesting it could be an additional predictive tool. Although literature on this subject is limited, existing studies support its use because it improves the diagnostic accuracy of other imaging modalities[21].

Regarding nodal staging (cN), PET showed higher diagnostic accuracy (70.6%) compared to CT (66.7%) and US (52.4%). However, all 3 imaging modalities commonly produced tumor under-staging (PET, 17.6%; CT, 30.2%; US, 42.9%), with no statistically significant differences being reported among the three. These results are consistent with former studies published in the medical literature currently available[7,8].

The findings of this study, in conjunction with the existing literature, suggest that the clinical staging of esophageal cancer remains challenging despite the availability of various diagnostic imaging modalities. Consistent with former studies, the US appears superior for cT staging, especially regarding T1-T3 stages[6,19,22-24]. No significant differences in the accuracy of the 3 imaging modalities have been reported regarding nodal staging.

The absence of a clearly superior imaging modality is due to the limitations of each individual modality. Compared to the CT scan, the US provides better visualization of esophageal wall layers and higher sensitivity for nodal staging when combined with FNA of suspicious nodes. However, it does not provide information on distant spread, is invasive, operator-dependent, not feasible in stenosing tumors, and not all adenopathies are accessible through puncture[19,20,22,25]. On the other hand, the CT scan provides information on disease spread but is limited when it comes to detecting small tumor deposits that do not alter nodal morphology and distinguishing enlarged nodes for other reasons, such as smoking or inflammatory-infectious conditions[26]. Similarly, the PET cannot identify subcentimeter nodes and may not accurately evaluate proximal nodes due to significant tumor isotope uptake[27]. However, it has a high S for distant nodal metastases, which is its main advantage[6]. Lastly, the EG, although limited compared to other imaging modalities, provides useful additional information and is a non-invasive, low-radiation, and cost-effective option.

This study has limitations, including its retrospective nature, small sample size, the absence of advanced-stage (T4) patients, and very few patients in very early stages (T1). Additionally, multiple imaging modalities are operator-dependent and not all of them were used in all the patients studied. The extended study period

may have influenced the diagnostic yield of the imaging modalities and the evolution of surgical procedures.

Conclusions

Despite the various diagnostic imaging modalities used, their accuracy in localized esophageal cancer is limited, with the therapeutic and prognostic implications that this entails. The absence of an imaging modality standing out from the rest significantly reinforces the need for using them complementarily.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Kidney paired donation: benefit of this program on the transplant rate and graft survival

Donación renal pareada: beneficio de este programa en la tasa de trasplantes y sobrevida del injerto

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Abstract

Objective: *To demonstrate the experience since the transplant program under paired kidney exchange donation implementation; program that increases the donation rate by 25-30% in hospitals with no inferior graft survival compared to directed living donor kidney transplantation.* **Method:** *Observational, analytical, longitudinal and prospective study from December 2018 to July 2021. All G5 KDIGO chronic kidney patients who were HLA or ABO incompatible with their original donors in the pretransplant protocol and who were transplanted under the paired kidney exchange donation program, were included.* **Results:** *22 kidney transplants were performed under this program. Survival of the graft and the patient 1 year after transplantation was 100%. The post-transplant glomerular filtration rate was 72.5 ± 17 ml/min/1.73 m² body surface. 36.3% of hypersensitized patients were successfully transplanted. The in-hospital donation rate increased by 33.33%.* **Conclusions:** *Transplantation under the kidney paired donation program constitutes a real modality of successful transplantation when there is incompatibility with the original donor. The greater use and socialization of this program can increase the country kidney transplantation rate, reducing the waiting list. Our hospital represents the largest experience published in Mexico with this transplant program.*

Keywords: *Kidney paired donation. Kidney transplant. Exchange. Compatibility. HLA.*

Resumen

Objetivo: *Demostrar la experiencia adquirida desde la implementación del programa de donación renal pareada, el cual aumenta un 25-30% la tasa de donación en los centros hospitalarios sin inferioridad en la sobrevida del injerto comparado con el trasplante renal de donante vivo dirigido.* **Método:** *Estudio observacional, analítico, longitudinal y prospectivo de diciembre de 2018 a julio de 2021. Se incluyeron todos los enfermos renales crónicos G5 KDIGO que en el protocolo pretrasplante resultaron HLA o ABO incompatibles con sus donantes originales y que fueron trasplantados bajo el programa de donación renal pareada.* **Resultados:** *Se realizaron 22 trasplantes renales bajo este programa. La sobrevida del injerto y del paciente a 1 año postrasplante fue del 100%. La tasa de filtración glomerular postrasplante fue de 72.5 ± 17 ml/min/1.73 m² de superficie corporal. Fueron trasplantados exitosamente el 36.3% de pacientes hipersensibilizados. La tasa de donación intrahospitalaria aumentó un 33.33%.* **Conclusiones:** *El trasplante bajo programa de donación renal pareada constituye una modalidad real de trasplante exitoso cuando existe incompatibilidad con el donante original. La mayor utilización y la socialización de este programa pueden aumentar la tasa de trasplante renal nacional, disminuyendo la lista de espera. Nuestro hospital representa la mayor experiencia publicada en México con este programa de trasplante.*

Palabras clave: *Donación renal pareada. Trasplante renal. Cambio. Compatibilidad. HLA.*

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Date of reception: 07-12-2021
Date of acceptance: 25-05-2022
DOI: 10.24875/CIRUE.M23000427

Cir Cir (Eng). 2023;91(1):48-55
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Compared to dialysis, renal transplantation is the most cost-effective renal replacement therapy modality capable of providing better survival and quality of life to patients, both adults and pediatric[1]. According to data from the National Transplant Center (CENATRA), in 2019 and 2020, a total of 2986 and 914 renal patients were transplanted in Mexico, respectively. By the end of June 2021, 16,801 renal patients were waiting for their transplant. Our hospital transplanted 38, 14, and 14 renal recipients back in 2019, 2020, and the first half of 2021, respectively. Upon completing the transplant protocol, 30% to 40% of all couples will have ABO or HLA incompatibility[2]. In 1986, Rapaport proposed that patients who cannot receive a kidney from their donor should be given the opportunity to exchange donors in such a way that each recipient receives a compatible kidney and donors can fulfill their wish for donation[3].

The first actual exchange procedure took place in South Korea in 1991, followed by Europe in 1999, and the United States in 2000. The slow acceptance was mainly due to ethical and legal constraints[3]. In Mexico, the first cohort of renal transplant patients with donor exchange was published in 1998[4], and subsequently, further reports would be published in 2017. Some transplant centers have performed this modality anecdotally. Our hospital formally initiated this program at the end of 2018. Currently, paired donation is an alternative authorized by CENATRA.

Renal donor exchange is generally encompassed under the paired kidney exchange donation program, a program that has evolved over time. Initially, only the simplest modality was performed: pairwise exchange (simple swaps between 2 couples), later introducing exchanges among 3 couples and the concepts of renal donation chain, paired donation in domino, introduction of altruistic donors into the chains, non-simultaneous extended chains of altruistic donors[5], use of bridge donors, initiation of chains with deceased donors, exchange of lists in chains[6], (Figs. 1-3), and desensitization within the program. These variations arose to make sure donors could not withdraw after their paired recipient had received the kidney transplant[7].

In addition to facilitating exchanges between incompatible pairs, paired kidney exchange donation programs now welcome compatible pairs, allowing recipients to receive kidneys from younger donors, with better anthropometric matching with their donor

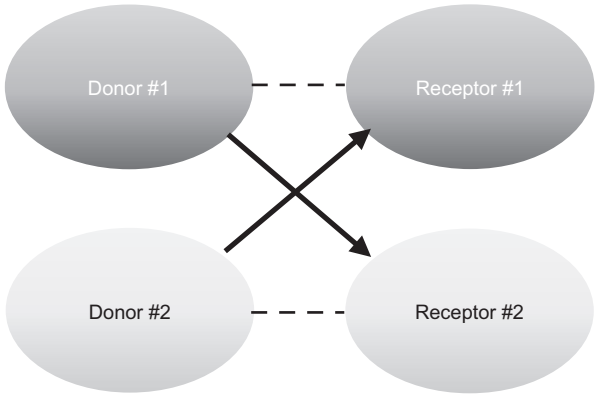

Figure 1. *Closed-loop chain of 2 couples (adapted from Bahena CL, 2018[6]).*

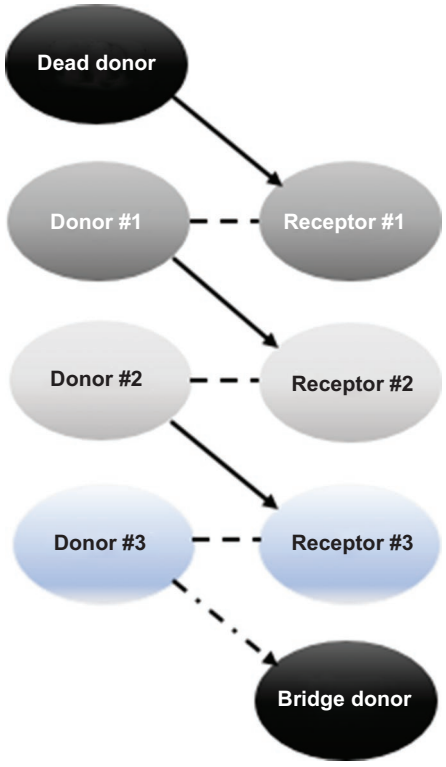

Figure 2. *Deceased donor initiating the transplant chain with use of a bridge donor (adapted from Bahena CL, 2018[6]).*

or better HLA compatibility. Adding compatible pairs to paired kidney exchange donation programs also increases the number of matches for incompatible pairs or hypersensitized patients, thereby improving the overall matching capabilites of the program[8,9].

To overcome the multiple challenges of selection within paired kidney exchange donation programs, manual mathematical calculations or highly efficient computer algorithms are used to select transplant

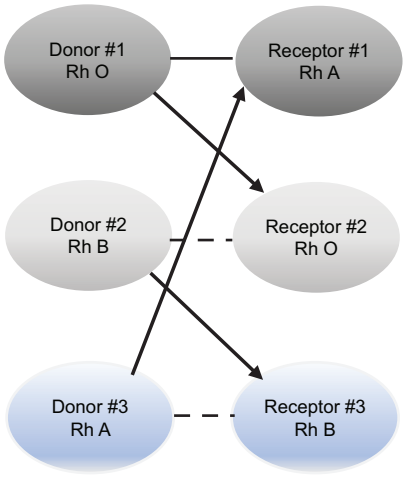

Figure 3. *Introduction of an unbalanced compatible altruistic pair (adapted from Bahena CL, 2018[6]).*

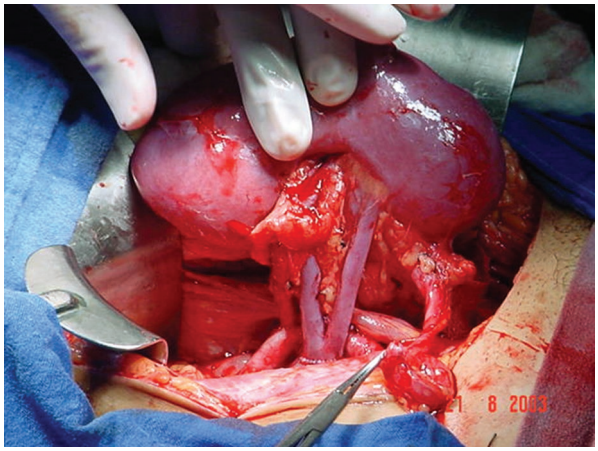

Figure 4. *Paired kidney transplant program. Implantation of the graft with end-to-side vascular anastomosis from renal vein to external iliac vein and from renal artery to external iliac artery.*

exchanges with *n* being the total number of incompatible donor-recipient pairs, the total number of combinations equals $(n^2 - n)/2$[10].

Mathematical algorithms based on the blood type of donors and recipients, sensitization status, and the size of the pool of incompatible pairs can determine the highest probabilities of successful matching within the program, optimizing the successful pairing of donors and recipients[11] based on the principles of fairness, utility, and justice[12].

Regardless of the immunological complexity and search for a compatible donor in the donor pool of a chain, there are also logistical challenges. Firstly, the creation of chains takes time and is often done electively in such a way that donor and recipient operations can be performed sequentially and within a reasonably short period of time. On the other hand, transplants from deceased donors are semi-urgent, and chains starting with deceased donors need to be mobilized urgently and non-electively[13].

Method

This study aims to demonstrate the experience gained since the implementation of the renal transplantation program under paired kidney donation, a modality that can increase the donation rate by 25% to 30% in the hospital without inferiority regarding graft survival compared to directed living donor renal transplantation.

This study was an observational, analytical, longitudinal, and prospective study of patients transplanted under the paired kidney exchange donation program at our hospital from December 2018 through July 2021. All the couples that accessed the program completed the pre-transplant protocol and were evaluated and authorized by the internal transplant committee. The donation risk was estimated for each donor, and the probability of matching-compatibility was estimated for each recipient and crossing[14]. The Alvin Roth algorithm was used to perform the pairings in the transplant chains. Each recipient's notarial contract deed was requested, and simultaneous or sequential nephrectomies of the donors were performed in adjacent operating rooms. Nephrectomies were performed using a conventional technique through open or laparoscopic nephrectomy, and the kidneys were perfused ex vivo with a preservation solution prior to implantation that was performed in the right iliac fossa and contralateral to the kidney obtained, with end-to-side vascular anastomosis from renal vein to external iliac vein and from renal artery to external iliac artery (Fig. 4) using 6-0 Prolene vascular sutures. Neoureterocystoanastomosis was performed using the Leich-Gregor technique with 6-0 PDS sutures and a ferule mounted over a 6-Fr double-J ureteral catheter.

The induction of immunosuppression was performed based on the baseline immunological risk, using basiliximab or thymoglobulin. Maintenance was completed with mycophenolic acid, tacrolimus, and prednisone. No renal patient was desensitized before or after transplantation. The baseline demographic, clinical, and biochemical characteristics of this group of patients were determined, along with post-transplant assessments in compliance with the hospital internal protocol. Renal allograft biopsy was performed between months 3 and 9,

and these were evaluated using Banff criteria (2017). Glomerular filtration rate (GFR) and graft survival 1 year after transplantation were determined, along with the GFR of each donor in the post-transplant period.

Statistical analysis

The variables analyzed were age, sex, etiology of chronic kidney disease, blood type and Rh, panel of reactive antibodies, type of induction to immunosuppression, type and level of maintenance immunosuppression, body mass index, hemoglobin and serum creatinine levels, GFR in mL/min/1.73 m^2 of body surface area, complications, and graft status at the time. Histological variables from renal allograft biopsy were obtained according to Banff classification (2017)[15]. The Student t test was used to compare the means of the GFR and the graft survival of patients transplanted under the paired kidney exchange donation program and in a cohort of patients with directed related/unrelated living donors in our hospital. Mean values with standard deviation and the percentages of the variables were calculated using SPSS 25.

Results

A total of 22 patients were transplanted using the following modalities: 1 chain of 5 couples, 1 chain of 4 couples, 3 chains of 3 couples, and 2 crossings of 2 couples. Among these, 4 renal recipients were transplanted through chains that started with a deceased donor. In the 5-couple chain (the last one performed), an important milestone was achieved in Mexico with the first inter-center transplantation (donor exchange between 2 hospitals).

A total of 63.6% of the patients included in the study were women (Table 1). Preemptive transplantation was performed in 9.1% of the patients. Both the PRA (panel of reactive antibodies) level and type of induction immunosuppression used are shown on table 2. The most common etiology of chronic kidney disease was not established in 31.8% of cases, followed by systemic arterial hypertension in 27.3% of cases. In 18.1% of cases there was list exchange (the chain started with a deceased donor). The mean post-transplant proteinuria levels were 150.38 mg/day. A total of 90.1% of the patients were on the reference immunosuppression scheme (FK: tacrolimus/MMF: mycophenolate mofetil/PDN: prednisone), and 9.1% on a minimized scheme. All grafts remain functional, including hypersensitized recipients, with a median post-transplant follow-up of 18.0 months. The mean GFR was 72.5 ± 17 mL/min/1.73 m^2, and the mean waiting time since accessing the cross-matching program until transplantation, 4.8 months.

Table 1. Clinical and biochemical characteristics of recipients and donors under the paired kidney exchange donation program

Variable	Mean (± SD)
Receptor	
Age (years)	35.27 (± 12.45)
Sex	
Men	8 (36.4%)
Women	14 (63.6%)
Body mass index (kg/m^2)	24.77 (± 3.30)
Panel of reactive antibodies	
Class I	25.18%
Class II	28.68%
Donor	
Age (years)	42.22 (± 10.52)
Post-donation creatinine levels (mg/dL)	1.18 (± 0.29)
Post-donation GFR ratio (mL/min/1.73 m^2)*	75.04 (± 15.98)

GFR: glomerular filtration rate; SD: standard deviation.
*Estimated using the CKD-EPI formula.

The study included a total of 2 sensitized patients (9.1%) with PRA levels ≥ 25% and 6 highly sensitized patients (27.27%) with PRA levels ≥ 80%.

Two surgical complications and 1 medical complication were reported, all of which resolved promptly, with fully functional grafts (Table 3).

In our hospital, during the study period, a total of 66 patients underwent transplantation, 40 of whom were from directed living related/unrelated donors, 4 from deceased donors, and 22 from the paired kidney exchange donation program, which represents a 33.33% increase in the rate of transplantation with the use of this novel program (Fig. 5)[16].

Discussion

According to CENATRA data from 2017 through 2020 in Mexico, the mean waiting time to receive a kidney from a deceased and a living donor was 30.2[17] and, 3.38 months, respectively[18]. In our cohort of patients transplanted under the paired kidney exchange donation program, the mean waiting time was 4.9 months, shorter than the waiting time for a deceased donor kidney.

Table 2. Demographic characteristics of patients transplanted under the paired kidney exchange donation program

Receptor	Sex	Age (years)	Etiology CKD	Type of dialysis	BT and Rh D/R	PRA class I/II	DSA	CMT	HLAmm	CMV	Induction
1	M	11	Valvas	HD	O+/O+	98/100%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (4 mg/kg/d)
2	W	60	SAH	PD	O+/O+	7/9%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
3	M	29	ND	HD	O+/O+	5/8%	No	Negative FC	2A/1B/1DR	D-/R+	Basiliximab
4	W	46	ND	PD	O+/O+	68/44%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (1 mg/kg/d)
5	W	44	ND	*Preemptive*	O+/O+	6/0%	No	Negative FC	1A/1B/2DR	D+/R+	Basiliximab
6	M	28	ND	HD	O+/O+	10/5%	No	Negative FC	1A/1B/2DR	D+/R+	Basiliximab
7	W	37	IgA	HD	O+/O+	6/2%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
8	M	28	ND	HD	A+/A+	8/14%	No	Negative FC	2A/1B/1DR	D+/R+	ATG (3.5 mg/kg/d)
9	W	24	ND	*Preemptive*	O+/O+	8/5%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (4 mg/kg/d)
10	W	41	SAH	HD	O+/O+	45/84%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (4.5 mg/kg/d)
11	M	31	SAH	HD	O+/O+	7/10%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
12	W	49	SAH	HD	O+/O+	4/24%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
13	W	39	SAH	HD	A+/A+	30/16%	No	Negative FC	1A/1B/0DR	D+/R+	ATG (3 mg/kg/d)
14	W	46	SAH	HD	O+/O+	100/99%	No	Negative FC	1A/0B/0DR	D+/R+	ATG (5.5 mg/kg/d)
15	M	42	MN	HD	O+/O+	68/82%	No	Negative FC	1A/2B/1DR	D+/R+	ATG (4 mg/kg/d)
16	M	32	CGN	PD	O+/O+	5/8%	No	Negative FC	2A/2B/1DR	D+/R+	Basiliximab
17	W	40	CGN	HD	O+/O+	52/88%	No	Negative FC	2A/B/1DR	D+/R+	ATG (4.5 mg/kg/d)
18	W	46	DM2	PD	O+/O+	2/7%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
19	W	30	SLE	PD	O+/O+	9/11%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
20	W	15	ND	HD	A+/A+	7/5%	No	Negative FC	0A/1B/0DR	D+/R+	Basiliximab
21	M	13	AHUS	HD	A+/A+	4/7%	No	Negative FC	2A/2B/1DR	D+/R+	Basiliximab
22	M	45	ADPKD	HD	O+/O+	5/3%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab

ADPKD: autosomal dominant polycystic kidney disease; AHUS: atypical hemolytic uremic syndrome; ATG: anti-thymocyte globulin; BT: blood type; CGN: chronic glomerulonephritis; CKD: chronic kidney disease; CMT: crossmatch testing; CMV: cytomegalovirus; D: donor; DM2: type 2 diabetes mellitus; DSA: donor specific antibodies; FC: flow cytometry; HD: hemodialysis; HLAmm: human leukocyte antigent mismatch; IgA: IgA-induced nephropathy; M: man; MN: membranous nephropathy; ND: not determined; PD: peritoneal dialysis; PRA: panel of reactive antibodies; R: receptor; SAH: systemic arterial hypertension; SLE: systemic lupus erythematosus; W: woman.

Although our experience with the paired kidney exchange donation program is limited to only 22 renal transplant patients, according to Massie et al.[19], our hospital qualifies as a center with very high utilization of the paired kidney exchange donation program.

In the Canadian registry, the mean number of days elapsed since a candidate participates in a compatibility cycle under the paired kidney exchange donation program until transplantation was actually performed was 182 days (range, 47-1741; mean ± SD, 275 ± 17)[20], while, at the Mayo Clinic (United States), the median waiting time since program enrollment until transplantation was 330 days (range, 178-539)[21]. Our hospital has an average of 147 days from admission to transplantation

Table 3. Biochemical and histological evolution of patients after kidney transplant under paired kidney exchange donation

Receptor	BMI	Hb	Proteinuria (mg/day)	Cr (mg/dL)	GFR (mL/min)	FK (ng/mL)	IS	Histological criteria Banff (2017)	Complications	Graft status
1	21.3	12.9	122	1.12	75	5.3	FK/MMF/PDN	g1, cg0, ci0, ta0, i1, t0, ptc0, ah1, v0	None	Functional
2	23.3	16.6	100	1.40	40	3.9	FK/mTORi/PDN	g1, cg0, ci2, ct2, i1, t0, ptc1, ah1, v0	VK	Functional
3	27.4	19.8	199	1.2	93	6.4	FK/MMF/PDN	g0, cg0, ci0, ta0, i0, t0, ptc0, ah0, v0	None	Functional
4	19.4	17.8	177	1.1	59	2.7	FK/mTORi/PDN	g2, cg0, if1, ta1, i1, t0, ptc3, ah1, v0	None	Functional
5	24.7	13.6	150	1.0	61	5.6	FK/MMF/PDN	g1, cg0, if1, ta1, i0, t0, ptc0, ah0, v0	None	Functional
6	23.5	16.6	167	1.3	77	5.3	FK/MMF/PDN	g1, cg0, if1, ta1, i1, t0, ptc1, ah2, v0	None	Functional
7	25.8	14.7	248	1.1	60	4.5	FK/MMF/PDN	g1, cg0, if1, ta1, i0, t0, ptc0, ah1, v0	None	Functional
8	24.2	20.6	139	1.5	60	6.3	FK/MMF/PDN	g2, cg0, if1, ta1, i1, t0, ptc3, ah0, v0	None	Functional
9	29.6	16.6	136	0.9	91	8.2	FK/MMF/PDN	g0, cg0, if1, ta1, i0, t0, ptc0, ah0, v0	None	Functional
10	23.6	19.3	229	0.8	73	7.2	FK/MMF/PDN	g1, cg0, ci0, ta0, i0, t0, ptc0, ah0, v0	None	Functional
11	27	15	102	1.2	84	8	FK/MMF/PDN	g1, cg0, ci2, ct2, i1, t0, ptc1, ah0, v0	None	Functional
12	25.2	13.4	262	0.8	89	5.6	FK/MMF/PDN		None	Functional
13	25.4	10	116	1.3	50	4.1	FK/MMF/PDN		Ureteral ischemia	Functional
14	27.1	13.9	232	0.9	73	8.1	FK/MMF/PDN		None	Functional
15	26.4	15.4	186	1.7	54	12.6	FK/MMF/PDN	g1, cg0, if1, ta1, i0, t0, ptc1, ah0, v0	None	Functional
16	24.4	16	192	1.33	73	4.8	FK/MMF/PDN	g0, cg0, if1, ta1, i0, t0, ptc0, ah1, v0	None	Functional
17	32.4	15.6	77	1.28	56	5.3	FK/MMF/PDN	g2, cg0, ci0, ta0, i0, t0, ptc3, ah0, v0	None	Functional
18	20.4	12.3	134	0.7	102	9	FK/MMF/PDN		None	Functional
19	20.1	12.3	165	1	64	7.7	FK/MMF/PDN		None	Functional
20	23.3	11	120	1	65	5.3	FK/MMF/PDN		None	Functional
21	21	12.8	126	0.7	101	5.1	FK/MMF/PDN		None	Functional
22	29.5	13.2	200	1.2	95	9.5	FK/MMF/PDN		Lymphocele	Functional

Ah: arteriolar hyalinosis; BMI: body mass index; cg: chronic glomerulitis; Cr: creatinine; FK: tacrolimus; g: glomerulitis; GFR: glomerular filtration rate; Hb: hemoglobin; I: interstitial inflammation; if: interstitial fibrosis; IS: immunosuppression; MMF: micophelonate mofetil; mTORi: mTOR inhibitor; PDN: prednisone; ptc: peritubular capilaritis; t: tubulitis; ta: tubular atrophy; v: intimal arteritis; VK: poliomavirus.

under this program, which is lower than the period reported in the medical literature.

We have already performed renal transplants with chains of 4 and 5 couples, although a Dutch study recommends that the maximum length of an optimal chain for all practical purposes is 3 couples, especially for newly initiated exchange programs, because several simultaneous surgeries can limit the technical

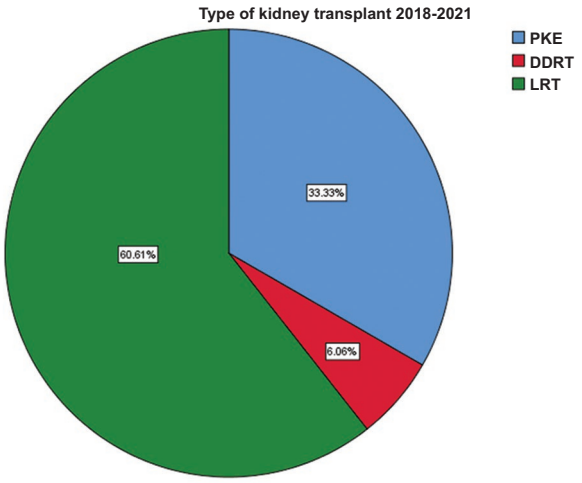

Figure 5. *Types of renal transplants performed at our hospital from December 2018 through July 2021. PKE: kidney paired exchange donation; DDRT: deceased donor renal transplant; LRT: directed living related/unrelated donor renal transplant (adapted from Bahena et al., 2022[16]).*

capabilities and resource of multiple centers, as significant coordination is required[11].

When the GFR of patients transplanted under the donor exchange program was compared, we saw that such GFR was 72.5 mL/min/1.73 m^2, higher than the GFR found in a cohort of 44 patients transplanted at our hospital throughout the same study period but from directed related/non-related living donors (66.56 mL/min/1.73 m^2; p = 0.123).

When we analyzed the GFR and graft survival free from rejection of our pediatric recipients under the donor exchange program, we saw that both values are similar to those reported by Sypek et al.[22] in the Australian registry of the pediatric paired renal exchange program.

The rate of graft survival in our center at follow-up was 100% in patients transplanted under the paired renal donation program, compared to 97.7% in directed living donors (p = 0.489). These data are similar to those reported by Kute et al.[23] who demonstrated that graft survival is similar when using related donation compared to donation under the paired program. Additionally, in the Canadian registry of paired kidney donation of 135 renal recipients followed for 1 year, the patients' and the allograft survival rates were 99% and 96%, respectively. In the same Canadian cohort, biopsy confirmed an acute rejection rate of 8%[20], compared to 9.1% in our patients from the paired program (all of these were subclinical rejections).

The 1-year adjusted graft survival after the transplant was 97.3%, 98.1%, and 97.7% for sensitized recipients with PRA levels of 0-79%, > 80%, and > 99.9% groups, respectively[24]. The overall graft survival rate in our cohort was 100% at 1-year follow-up.

The donors' dropout rate in our cohort was 0% because only in 13.6% of cases bridge donors were used, and they were advised in advance on the maximum waiting time of 3 weeks to donate their organs, as recommended by Kher and Kumar[25].

Conclusions

Renal transplantation under the paired kidney exchange donation program is an additional option to increase the rate of renal transplantation. However, it must be kept under strict in-hospital medical-ethical protocols and national legal regulations and consistent with the Declaration of Istanbul[26]. Transplantation groups should be encouraged to promote this modality to integrate regional or national donor exchange programs to reduce the national waiting list for renal patients and, consequently, increase the rate of renal transplants in Mexico.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Safety and quality of life of living kidney donors. Comparison between two techniques

Seguridad y calidad de vida de los donadores renales. Comparación entre dos técnicas

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Resumen

Background: *Currently there are no studies that determine the safety and quality of life of kidney donors in Mexico.* **Objective:** *To determine the safety of being a kidney donor and the quality of life, comparing the open approach with hand-assisted laparoscopic technique.* **Method:** *Observational, cross-sectional, analytical study of the kidney donors in our hospital from January 2015 to December 2018, in two groups: open technique and hand-assisted laparoscopic. To determine safety, the Clavien-Dindo scale and transoperative bleeding were used, and the SF-36 health-related quality of life questionnaire was applied.* **Results:** *There are no reports of peri-operative complications in any type of approach. All the patients obtained a grade I in the Clavien-Dindo scale. When the difference in the score of the SF-36 health-related quality of life questionnaire in kidney donor patients with hand-assisted laparoscopic surgical approach versus open approach was compared, a difference between both means of 14.05 was obtained, with p < 0.0001 in favor of the hand-assisted approach.* **Conclusions:** *Being a kidney donor is safe and the approach that we recommend is hand-assisted laparoscopic nephrectomy.*

Keywords: *Kidney transplant. Kidney donor. Quality of life. Safety. Nephrectomy.*

Abstract

Antecedentes: *Actualmente en México no hay estudios que determinen la seguridad y la calidad de vida de los donadores renales.* **Objetivo:** *Determinar la seguridad de ser donador renal y la calidad de vida, comparando el abordaje abierto frente al laparoscópico mano-asistido.* **Método:** *Estudio observacional, transversal, analítico, de todos los donadores renales de nuestro hospital de enero de 2015 a diciembre de 2018, con seguimiento mínimo de 2 años. Se dividieron en dos grupos: operados con técnica abierta o laparoscópica mano-asistida. Para determinar la seguridad se utilizaron la escala de Clavien-Dindo y el sangrado transquirúrgico, y se les aplicó el cuestionario SF-36 de calidad de vida relacionada con la salud.* **Resultados:** *No se reportan complicaciones transquirúrgicas en ningún tipo de abordaje. Todos los pacientes obtuvieron grado I en escala de Clavien-Dindo. En el puntaje del cuestionario SF-36 en pacientes donadores renales con abordaje quirúrgico laparoscópico mano-asistido versus abordaje abierto se obtuvo una diferencia entre ambas medias de 14.05, con p < 0.0001 a favor del abordaje mano-asistido.* **Conclusiones:** *Ser donador renal es seguro y el abordaje que recomendamos ofrecer es el laparoscópico mano-asistido.*

Palabras clave: *Trasplante renal. Donador renal. Calidad de vida. Seguridad. Nefrectomía.*

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Date of reception: 09-09-2021
Date of acceptance: 25-05-2022
DOI: 10.24875/CIRUE.M23000428

Cir Cir (Eng). 2023;91(1):56-61
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Chronic kidney disease (CKD) has become a public health issue in the Mexican population. Nearly 8% of Mexicans have CKD, and the incidence rate of end-stage kidney disease has increased dramatically along with risk factors such as type 2 diabetes mellitus, hypertension, obesity, and dyslipidemia[1]. Back in 2019, CKD was the 10th leading cause of death in Mexico, with 14,630 deaths reported[2].

Renal transplantation (RT) is the preferred replacement therapy for patients with end-stage CKD to increase survival and quality of life[3].

Although, historically, RT has grown significantly in Mexico[3], the waiting list for organ recipients is 5 times larger than the number of patients who actually end up receiving a transplant[4]. Unlike other countries like the United States or Spain, most kidneys in Mexico come from living donors[5]. It has been documented that recipients of a kidney graft from a living donor have better survival rates than those who receive a graft from a deceased one. This different survival is similar for grafts from related and unrelated living donors, which is one of the main reasons why the number of transplants from unrelated living donors has been increasing non-stop worldwide[6].

Living kidney donation for transplantation purposes is unique among surgical procedures in that a perfectly healthy person undergoes surgery not for his/her own benefit but for the benefit of someone else. The risks associated with unilateral nephrectomy for the donor include perioperative or short-term morbidity and mortality along with the long-term risk of living with only one kidney[6].

Very few studies have been conducted on the quality of life of kidney donors. Currently, in our setting, there are no studies determining the safety and quality of life of renal donors, and although it is a common practice, it is essential to determine these factors to make sure that performing live donor RT results in two healthy patients with a good quality of life, which is the primary goal of transplant surgery[7]. The study was conducted to determine the safety profile of being a kidney donor and how it affects quality of life, comparing the open and hand-assisted laparoscopic approaches, which happen to be the only two types of surgeries performed in our center since it is a public hospital with limited resources available.

Method

This was an observational, cross-sectional, and analytical study that examined all patients from the transplant unit of our hospital treated with nephrectomy for kidney donation from January 2015 through December 2018.

The patients were divided into 2 groups based on the approach used: open surgery or hand-assisted laparoscopic surgery. The main variables analyzed were the type of donor (related or unrelated), the surgical approach (open or hand-assisted laparoscopic), procedural time, anatomical variants, blood loss, transfusion requirements, intraoperative and postoperative complications according to the Clavien-Dindo classification, pre- and post-nephrectomy working activity, glomerular filtration rate before and after nephrectomy, and quality of life assessed using the 36-item short form health-related quality of life questionnaire via telephone calls.

The inclusion criteria were all adult living kidney donors during the aforementioned period, with a minimum follow-up of 2 years. The exclusion criteria included patients with incomplete health records, those who did not respond to the telephone call, those who did not give their prior written informed consent to be included in the study or those who died due to causes unrelated to kidney donation.

For normality testing, the Kolmogorov-Smirnov test was used. Based on their distribution, quantitative variables were expressed as measures of central tendency and dispersion, and the qualitative ones as absolute frequencies and percentages. Hypothesis testing was performed to assess quality of life using the SF-36 questionnaire as the main variable. The chi-square test or the Fisher's exact test was used to study qualitative or categorical variables, and the Student t test or the Mann-Whitney U test to analyze the quantitative ones, as appropriate. Statistical analysis was performed using GraphPad® version 6.01 and the Excel® spreadsheet program. P values < 0.05 were considered statistically significant.

Results

A total of 109 renal donor patients who met the previously mentioned inclusion criteria were included in the study. Among them, 91 (83.4%) underwent hand-assisted laparoscopic nephrectomy, none of them requiring conversion to open surgery. The remaining 18 patients (16.6%) underwent open nephrectomy.

Table 1. Demographic characteristics of both groups

Variables	Hand-assisted laparoscopic approach: 91 (83.4%)	Open surgery: 18 (16.6%)	p
Sex (feminine)	56 (62%)	9 (50%)	-
Age (years)	36.4 (SD, ± 10.3)	38.1 (SD, ± 11.7)	0.69
Relationship (related)	72 (79.1%)	16 (88.9%)	0.51
Weight (kg)	63.1 (SD, ± 10.6)	66.3 (SD, ± 11.8)	0.27
Height (m)	1.66 (SD, ± 0.07)	1.68 (SD, ± 0.07)	0.30
Working life pre-donation (yes)	73 (80%)	12 (66.6%)	0.22
Glomerular filtration rate pre-donation (mL/min)	115.7 (SD, ± 9.8)	117.2 (SD, ± 10.7)	0.50

SD, standard deviation.
No statistically significant differences were found in the demographic variables between the two groups.

The decision to perform either one was determined by the resources available and the patient's decision at the time of RT.

The mean ages of patients undergoing hand-assisted laparoscopic nephrectomy and open surgery was 36.4 and 38.1 years, respectively. Regarding the donors' demographic variables (sex, relationship with the recipient, weight, height, preoperative working activity, and glomerular filtration rate), no statistically significant differences were seen between the two groups (Table 1).

None of the donors had chronic-degenerative diseases (diabetes, hypertension, chronic kidney disease [CKD] or heart diseases) prior to nephrectomy, and at the time of the study, none of them had developed any of these either.

Regarding the intra- and postoperative outcomes of the different groups studied, no statistically significant differences were seen in the kidney provided, the anatomical variants reported, procedural time or the length of stay. However, a statistically significant difference was found regarding bleeding, higher in the open approach group, although no patient required blood transfusions during or after nephrectomy (Table 2). All patients experienced grade I complications according to the Clavien-Dindo scale. At the time of the study, no donor deaths have been reported.

The mean glomerular filtration rate reported before nephrectomy was 115.7 mL/min in patients treated with hand-assisted laparoscopic approach and 117.2 mL/min in those treated with open surgery, with no statistically significant differences between the two being reported. The mean glomerular filtration rate of donors before and after hand-assisted laparoscopic nephrectomy was –7.5 (standard deviation [SD], ± 1.4; 95% confidence interval [CI], –10.3 to –4.6; $p < 0.0001$) post-nephrectomy (latest value ever reported in the health records at the time of the study). The difference in the mean glomerular filtration rate of donors before and after open nephrectomy was –9 mL/min ($p = 0.01$) after surgery.

A total of 78% of the patients said they had a job prior to nephrectomy. However, at the time the study, only 65.1% were employed. Among them, a difference was seen in the number of donors with working activity before and after the hand-assisted laparoscopic surgery (relative risk [RR], 1.2; 95%CI, 1.01 to 1.45; $p = 0.04$). However, none of them reported it was directly related to their condition as renal donors. The different working activity before and after surgery in donors with open nephrectomy was of only 1 patient, which was not statistically significant.

When the differences in the scores obtained in the SF-36 health-related quality of life questionnaire of renal donor patients were compared between hand-assisted laparoscopic surgery and open surgery, the mean scores were 95.83 (SD, ± 0.53) and 81.79 (SD, ± 3.15), respectively. The difference between the two means was 14.05 (SD, ± 1.8; 95%CI, 17.68 to 10.41; $p < 0.0001$), which was statistically significant.

When we analyzed the groups and split the scale by functions, we found that all of them, except for social functioning decreased significantly in patients who underwent open surgery, especially regarding bodily pain, with a mean score of 73.88, and the emotional role, with a mean score of 38.88 (Fig. 1).

Discussion

RT is a procedure that has become widely popular in our region. Several studies have been published on the benefits patients with end-stage renal

Table 2. Intra- and postoperative outcomes of both groups

Variable	Hand-assisted laparoscopic approach	Open surgery	p
Kidney (n)	Left: 84 (92.3%) Right: 7 (7.7%)	Left: 17 (94.5%) Right: 1 (5.5%)	1.00
Anatomical variants (yes)	15 (16.4%)	3 (16.6%)	1.00
Procedural time (min)	99.4 (SD, ± 8.7)	100.3 (SD, ± 8.1)	0.58
Bleeding (mL)	20 (IQR, 20-30)	40 (IQR, 20-55)	0.002
Length of stay (days)	2.4 (SD, ± 0.5)	2.6 (SD, ± 0.5)	0.11

IQR: interquartile range; SD: standard deviation.
Greater bleeding was seen with the open approach compared to the hand-assisted laparoscopic approach, with a statistically significant difference without impacting procedural time or the length of stay.

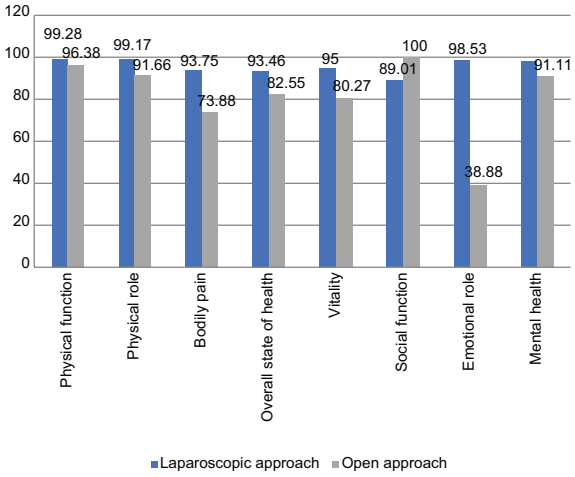

Figure 1. *SF-36 questionnaire scores according to its dimensions. The SF-36 health questionnaire evaluates 8 areas on a scale from 0 (worst health status) to 100 (best health status) using algorithms and indications provided in the questionnaire's interpretation manual. Higher scores indicate better quality of life. The results obtained with the hand-assisted laparoscopic approach were the best ones in all areas except for social functioning. The area most affected by open surgery was the emotional role.*

disease (ESRD) obtain from RT. In many countries across the world, deceased donor transplantation is preferred to avoid risking the life of a living donor. In our country, the demand of kidneys for this kind of patients exceeds the supply of deceased donors, making the living donor the best option to this date. Jalisco, Mexico is the state with the highest number of patients with chronic kidney disease[8,9], and our center is the largest public hospital in Western Mexico providing specialized care to patients without any kind of medical or social coverage, and during the study period, the second largest public hospital in Western Mexico in the number of RTs performed[5].

Due to the need and benefit for renal recipients to have a living donor, we must ensure that the lives of these donors are not put at risk.

In terms of surgical safety, we followed the recommendations from the Vancouver and Amsterdam forums regarding the care of renal donors[10,11]. We measured intraoperative bleeding, intra- and postoperative complications using the Clavien-Dindo scale[12], and mortality as the main variables to determine safety.

It is well-known that obesity increases the risk of complications in renal donors[13]. However, overall, our donors, are not obese, and based on our observations of our population, the body mass index is not a factor to determine the type of surgical approach that should be used.

Most studies comparing open and laparoscopic nephrectomy agree that laparoscopic nephrectomy takes longer (150 min compared to the 145 min of open nephrectomy)[14]. Studies comparing the hand-assisted and the pure laparoscopic techniques agree that the former is faster. However, there is no statistically significant difference between the two. The Mayo Clinic group (Rochester, MN, United States) reports a mean time of 121 ± 29 min for the hand-assisted laparoscopic nephrectomy[15]. Our procedural time is shorter than that reported in the medical literature. Procedural time may be an indirect determinant of difficulty in surgery, reflecting intraoperative complications and bleeding. In our study, no intraoperative complications were reported in either approach during this period. The reported bleeding was minimal, below what is found in the literature, although it was higher in the open approach, as expected. Our procedural time is shorter than what has been reported in the literature. Procedural time can be an indirect determinant providing insight on how

difficult surgery will be regarding complications and intraoperative bleeding. Nonetheless, no intraoperative complications were reported for either one of the two approaches during this period. The bleeding reported was minimal, and below what is commonly found in the medical literature, However, as expected, it was higher in the open approach.

The rate of postoperative complications in the medical literature ranges from 2% to 14%, while mortality ranges from 0.03% to 0.4%[16]. In our study, no postoperative complications were reported according to the Clavien-Dindo scale, since all our patients were categorized as grade I. At this point, no mortality has ever been reported. We should mention that one of the study limitations is that this is a retrospective, short-term study, and the appropriate time to measure long-term outcomes has not been established yet.

One of the greatest fears associated with living kidney donors is the risk of developing CKD. Although the glomerular filtration rate may drop by up to 50% immediately after nephrectomy, the risk of developing CKD has not been found to increase compared to the overall population[17]. Our patients' outcomes are consistent with those reported in the medical literature available.

Nowadays, it is necessary to address quality of life after a medical procedure. Although a consensus has not been reached on the best way to measure health-related quality of life, the SF-36 scale is one of the most widely used ones worldwide[18].

In living donor RT, favorable results must be guaranteed for both donor and recipient. Most studies conclude that renal donors have an excellent quality of life after donation[19].

In our study, although we expected patients treated with open nephrectomy to have a lower quality of life compared to those treated with hand-assisted laparoscopic nephrectomy, the difference was significant. The quality of life of patients treated with hand-assisted laparoscopic nephrectomy was better. Bodily pain and emotional role were impacted significantly in patients with open nephrectomy, whereas donors treated with hand-assisted laparoscopic nephrectomy did not experience this decline.

Several studies have been conducted on the renal donors' emotional role. Back in 2006, Clemens et al.[19] reported depression rates from 5% to 23% in kidney donors. In a retrospective study conducted on U.S. donors, Lentine et al.[20] found cumulative depression rates of 4.2% and 11.5% 1 year and 5 years after donation, respectively. The donor's risk factors associated with depression include being an unrelated donor, the death of the recipient, and renal graft failure. While donors undergo psychological and psychiatric evaluations as part of the pre-transplant protocol, post-donation follow-up is necessary to prevent adverse outcomes[20]. We believe that esthetics always comes second when it comes to surgical approaches. However, cosmetics is important for the patients on the psychological level, especially if surgery is unnecessary for their health, as is the case with kidney donation.

Conclusions

Based on the aforementioned results, we determined that there is no difference regarding safety when comparing donor nephrectomy with open surgery and hand-assisted laparoscopy. However, there is a significant difference regarding quality of life, with hand-assisted laparoscopic nephrectomy showing better results. Therefore, we believe that the latter should be the first-line therapy here.

In Mexico, no studies have ever been conducted to determine the quality of life of the overall population using this scale, so we could not compare our results with the quality of life of the overall population. Despite this limitation, we firmly believe that based on these results, living donor RT can still to be offered as a safe method for both donor and recipient. We consider the hand-assisted laparoscopic approach to be the best option, given our results. However, if the necessary resources are not available, open nephrectomy with donation purposes is a viable alternative.

As far as we know, this is the first study of its kind ever conducted in Mexico, making it worthwhile to continue with a long-term, prospective study to determine the quality of life of renal donors.

Funding

None whatsoever.

Conflicts of interest

none reported.

Ethical disclosures

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

Patients' data protection. 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

Exposure to ionizing radiation in orthopedic surgery residents in a referral hospital

Exposición a radiación ionizante en médicos residentes de ortopedia en un hospital de referencia

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Abstract

Objective: *To describe and analyze the exposure to ionizing radiation of orthopedic residents.* **Method:** *A prospective study was carried out to evaluate the degree of exposure to ionizing radiation with a bandage dosimeter placed under the lead apron for medical residents for 10 months. An online survey measured the degree of knowledge about radiation safety.* **Results:** *54 resident physicians participated. 55.6% report having knowledge of the existence of radiological protection equipment and 40.7% report that they had previous training in its use. 77.8% use the leaded apron and 31.5% use thyroid protection. 81.5% were positioned less than 1 meter from the source of the X-ray production of the arc in C. The total mean radiation exposure was 2.9 ± 2.17 mSv (95% confidence interval: 1.25-14.28; p = 0.424).* **Conclusions:** *Orthopedic medical residents present radiation doses below the International Commission on Radiological Protection recommended limit. However, there is a lack of knowledge of radiation protection and as well as a lack of interest and ignorance of the adverse effects of radiation.*

Keywords: *Ionizing radiation. Orthopaedics. Radiation safety. Protection. Medical training. Residents.*

Resumen

Objetivo: *Describir y analizar la exposición a radiación ionizante de los residentes de ortopedia.* **Método:** *Se realizó un estudio prospectivo para evaluar el grado de exposición a radiación ionizante con un dosímetro de placa colocado debajo del mandil plomado a médicos residentes, por 10 meses. Mediante una encuesta en línea se midió el grado de conocimientos sobre seguridad radiológica.* **Resultados:** *Participaron 54 médicos residentes. El 55.6% refiere tener conocimiento de la existencia de equipo de protección radiológica y el 40.7% refiere que tuvo entrenamiento previo en su uso. El 77.8% utiliza el mandil plomado y el 31.5% la protección tiroidea. El 81.5% se posicionó a menos de 1 metro de la fuente de producción de rayos X del arco en C. La exposición a la radiación media total fue de 2.9 ± 2.17 mSv (intervalo de confianza del 95%: 1.25-14.28; p = 0.424).* **Conclusiones:** *Los médicos residentes de ortopedia presentan dosis de radiación menores que el límite recomendado por la International Commission on Radiological Protection. Sin embargo, existe una falta de conocimientos sobre protección radiológica, así como falta de interés e ignorancia de los efectos adversos de la radiación.*

Palabras clave: *Radiación ionizante. Ortopedia. Seguridad radiológica. Protección. Residencia médica. Residentes.*

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Date of reception: 10-08-2021
Date of acceptance: 07-09-2021
DOI: 10.24875/CIRUE.M23000429

Cir Cir (Eng). 2023;91(1):62-70
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

The discovery of x-rays and their application in medicine revolutionized the management and diagnosis of diseases and conditions. The setback, though, is that ionizing radiation produces chemical changes in cells damaging the DNA and increasing the risk of certain conditions, such as cancer[1-5]. The annual dose threshold of ionizing radiation according to the International Commission on Radiological Protection (ICRP) established back in 1956, is 50 mSv for workers. However, it was reduced down to 20 mSv per year by 1990[1,4].

For over 50 years, orthopedic surgery has used fluoroscopy and x-rays as aids in numerous surgical procedures[4,5], becoming the standard of use in orthopedic surgery. Currently, he highest level of exposure is seen in vertebroplasty and kyphoplasty[5,6], followed by hip fracture reduction with dynamic screw[7,8], and centromedullary nailing of long bones[6,7]. As a result, orthopedic surgeons have been occupationally exposed to ionizing radiation fordecades, sometimes receiving significant amounts that exceed the annual doses recommended[9]. However, since the introduction of radiation protection equipment (RPE)[2,3,10-14] and updates and improvements in fluoroscopy machines, radiation doses have dropped significantly for both surgeons and patients[15]. New imaging technologies, such as computer-assisted navigation, have also contributed to reducing exposure[6].

Factors that may favor radiation exposure to radiation for orthopedic surgeons include fluoroscopy time and distance from the radiation source. Some of the radiological protection measures recommended include keeping some kind of distance between the surgeon's hands and the radiation source[11,16,17] and the use of RPE, such as lead aprons and collars[3,7,18,19].

Lead aprons are the most widely used RPE of all, with many surgeons using them routinely[14,20]. Another commonly used RPE is the lead collar, but resistance to its use varies between 4% and 14%[7,14]. As a matter of fact, less than 50% of orthopedic surgeons use it, despite reporting its availability[20]. The surgeon's hands are the part of the body most easily exposed to radiation, and lead gloves can effectively reduce the doses of radiation[3,9,15-18,21-23]. However, they are not as effective when placed directly against the beam, giving a false sense of security in some cases[24]. Studies have shown that the doses of radiation to the hands range somewhere between 0.1 mSv and 1 mSv per procedure[16,17,19,22], while doses to the chest and thyroid range from 0.154 mSv to 0.526 mSv. However, when using lead aprons and collars, the mSv values were below the dosimeter detection threshold (< 0.010 mSv) [3,15,19,22]. The use of lead glasses reduces the likelihood of cataracts in the lens[3], allowing for more fluoroscopic views before reaching the annual dose threshold of 20 mSv of radiation[9,13,15].

During their training and skill development period, orthopedic residents have a higher exposure to ionizing radiation especially when they're performing surgical procedures. This is due to their proximity to the x-ray source[20,25,26] while performing most surgeries using fluoroscopy, an inadequate use of RPE[14,20], and not having enough information on the risks associated with exposure to radiation[2]. The exposure level of orthopedic surgery residents in our setting has not been studied, but given their higher surgical activity compared to other countries, it is essential to study their exposure and compare it with the allowed threshold for health care personnel. Therefore, the objective of this study was to describe and analyze the exposure to ionizing radiation in orthopedic surgery residents in our setting.

Method

This was a prospective, longitudinal, and observational study conducted among medical graduates in the process of obtaining their medical specialization in orthopedics from January through November 2020. The study received approval from the health research and ethics committees with registration no. R-2020-2105-038. The study included all years of orthopedic residency, comprising all medical orthopedic residents.

Each medical resident was given a plate dosimeter (InLight, Landauer, Sweden) to carry across their entire working day, especially during surgeries and visits to tomography rooms, to measure radiation exposure. The dosimeter was placed below the lead apron on the surgical gown, at pocket level, as this is the area with the least radiation exposure underneath the lead apron, according to the medical literature available[3,15,16,26,27] (Fig 1). The dosimeter was changed every month for a period of 10 months. The radiation absorbed was measured by the radiology service provider in the hospital each month. The dosimeter has a half-life of 90 years and a 99.1% sensitivity rate.

To assess the behavior and knowledge on radiological safety and fluoroscopy use, each medical resident was sent an email with a link to a previously created survey on Google Forms (see Annex 1).

Figure 1. *Dosimeter location.*

Regarding the statistical analysis, the association of variables was conducted using the Student t test. P values ≤ 0.05 were considered statistically significant.

Results

The overall sample size included 54 participants, 81% of whom (n = 43) were men and 19% (n = 11), women. The mean age of the participants was 29.09 years, with a range of 25 to 41 years and a standard deviation of 2.631.

This was the distribution by year of residency: residency year #1 (R1), 16.7% (n = 18), residency year #2 (R2), 20.4% (n = 11), residency year #3 (R3), 29.6% (n = 16), and residency year #4 (R4), 16.6% (n = 9) (Fig. 2).

In terms of comorbidity assessment, 33.3% of participants had overweight/obesity. One participant had thyroiditis, another had asthma, and a third one, depression, all of whom were under treatment. Regarding the history of cancer, 2 participants reported having had gastric cancer, and 1, low-grade intraepithelial lesion in the cervix.

Regarding the frequency of radiation exposure, 27.8% reported being exposed to radiation 2 to 5 times/week; 33.3%, 6 to 10 times/week; and 38.9% > 10 times/week.

Regarding training on radiological protection, 59.3% reported having received previous training, while only 22.2% reported having received proper training on radiological safety. As a result, 87% of all medical residents did not feel safe while being exposed to radiation during fluoroscopy procedures, as opposed to 7% who said they actually felt safe (Table 1).

The study also measured the level of knowledge and compliance to radiological protection measures in the operating room. Results showed that 61.1% had the knowledge and applied the measures, 24.1% had the knowledge but did not apply them, and 14.8% did not have the knowledge or applied the measures. Additionally, only 16.7% of participants reported being aware of radiation hazard signs in the operating rooms where fluoroscopy is more widely used (Table 1).

In terms of awareness on the availability of RPE for medical residents at the hospital, 55.6% reported being aware of their existence, 38.9% not knowing anything about RPE, and 5.6% not being quite sure about the existence of RPE (Table 1).

Regarding the use of RPE, among the medical residents who actually use it, 77.8% used lead aprons; 31.5% used thyroid protection; and 5.6%, radiation protection glasses (Table 2). Only 13% of the participants were aware that they needed to check the integrity of their RPE before using it and actually did so, 53.7% knew about the need to verify the integrity of RPE but did not comply, and 33.3% were not sure whether such verification was necessary (Table 2).

To measure exposure to ionizing radiation, 87% of participants used dosimeters, while 13% did not. Most medical residents wore dosimeters during surgeries (83.3%) and while patients underwent CT scans (90.7%) (Table 2). Regarding CT scans, 77.6% of the medical residents used RPE during their stays in the CT room (Table 1).

Regarding the storage of the dosimeters, only 38.9% of the medical residents left them in their hospital lockers, despite each resident signing an agreement taking responsibility for the dosimeter. According to the rules effective at the center, dosimeters should be kept in the residents' personal lockers within the hospital premises, as dosimeters are not allowed to be taken outside the unit (Table 3).

Regarding knowledge of routine dosimeter measurements, 25.9% said they were aware of them,

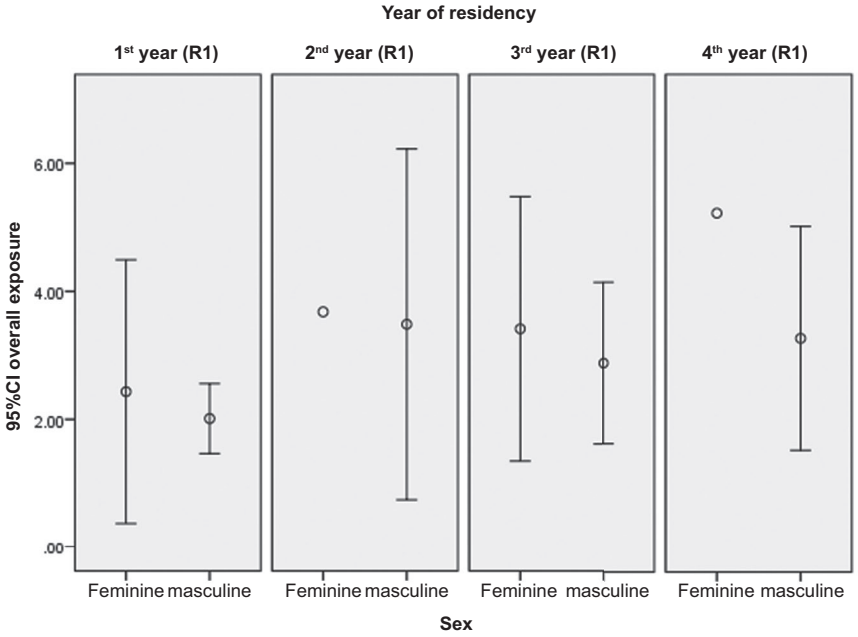

Figure 2. *Overall measurement of ionizing radiation exposure based on sex and year of specialty in orthopedic surgery residents.*

Table 1. Training and knowledge on radiological protection and safety in resident physicians (n = 54)

Topic	% (n)
Radiological protection training	
Yes	59.3 (32)
No	40.7 (22)
Radiological safety training	
Yes	22.2 (12)
No	77.8 (42)
Feeling of safety during exposure to radiation in fluoroscopies or x-ray studies	
Yes	13.8 (7)
No	87 (47)
Knowledge on radiological protection measures at the OR	
Yes, the resident knows the measures and implements them	61.1 (33)
Yes, the resident knows the measures but does not implement them	24.1 (13)
No, the resident does not know the measures or implement them	14.8 (8)
Knowledge on the existence of radiological hazard signs in surgical rooms with fluoroscopy	
Yes	16.7 (9)
No	83.4 (45)
Knowledge on the existence of RPE available for resident physicians in the hospital	
Yes	55.6 (30)
No	38.9 (21)
Not sure whether there are RPE or not	5.6 (3)

RPE: radiological protection equipment.

61.1% knew something about them but did not take appropriate measurements, and 13% did not know anything or took any measurements (Table 3).

When activities in the operating room related to exposure to ionizing radiation while performing postoperative radiographic controls were analyzed, we found that the medical resident was responsible for holding the portable x-ray machine 81.5% of the times. Regarding the personnel handling the fluoroscope during surgeries, 82.9% of the times, we found it was another medical

Table 2. Use of radiological protection equipment in resident physicians (n = 54)

Equipment	% (n)
Lead apron usage	
Yes	77.8 (42)
No	22.2 (12)
Thyroid shield usage	
Yes	31.5 (17)
No	68.5 (37)
Radiological eyewear usage	
Yes	5.6 (3)
No	94.4 (51)
Verification of EPR integrity prior to use	
Yes	13 (7)
No	53.7 (29)
Don't know	33.3 (18)
RPE usage while accessing the CT room with the patient	
Yes	75.9 (41)
No	24.1 (13)

CT: computed tomography; RPE: radiological protection equipment.

Table 3. Use and storage of dosimeters by resident physicians (n = 54)

	% (n)
General dosimeter usage	
Yes	87 (47)
No	13 (7)
Dosimeter carried during surgeries	
Yes	83.3 (45)
No	16.7 (9)
Dosimeter carried while accessing the CT room with the patient	
Yes	90.7 (49)
No	9.3 (5)
Dosimeter storage	
In the hospital locker room	38.9 (21)
Carries it in a backpack	3.7 (2)
At home	57.4 (31)
Routine dosimeter measurements	
Knowledgeable and takes these measurements	25.9 (14)
Knowledgeable but doesn't take these measurements	61.1 (33)
Not knowledgeable and doesn't take these measurements	13 (7)

CT: computed tomography.

resident outside the surgical team, while 17.2% of the times, it was actually a member of the surgical team (Table 4).

Regarding the distance from the fluoroscopy machine during surgeries where the fluoroscope is actually located, 81.5% of the residents placed themselves 1 or 2 steps away from the machine (< 1 meter), 16.7% less than 3 meters away, and 1.9% said that they did not pay any attention to the distance from the fluoroscopy machine. Additionally, during surgeries, 59.3% of the residents reported that the x-ray tube of the C-arm fluoroscopy machine was located above the operating table, while only 25.9% said it was placed underneath the table. Additionally, 14.8% of the residents surveyed did not consider the location of the x-ray tube an important issue.

Table 4. OR activities related to exposure to ionizing radiation in resident physicians (n = 54)

Activity	% (n)
Holding the x-ray machine during postoperative radiographic controls	
Yes	81.5 (44)
No	18.5 (10)
Handling the fluoroscope during surgeries	
Resident physician from the surgical team	18.5 (10)
A different resident physician unrelated to the surgical team	81.5 (44)

When the medical residents acted as the first or second assistant during surgeries, 48.1% placed themselves close to the x-ray tube, 33.3% next to the x-ray tube, while 18.5% did not care where they placed themselves. Most residents (98.1%) believed fluoroscopy shots are actually taken recurrently during surgery.

Regarding the assessment of dosimeter measurements taken on a monthly basis and based on sex (Table 5), the means were determined using the Student t test, with a 95% confidence interval (95%CI) while assuming equal variances. The mean total exposure to ionizing radiation in women was 3.260 ± 1.688 mSv compared to 2.807 ± 2.304 mSv in men, with an overall mean exposure of 2.9 ± 2.17 mSv (CI95%, 1.25-14.28; p = 0.424) (Table 5 and Fig. 2).

Regarding the assessment of monthly dosimeter measurements based on the year of residency, means were determined using the Student t test, with a 95% confidence interval (CI), assuming equal variances among subgroups (R1 and R2, R3, and R4). The overall exposure to ionizing radiation per year was: 2.105 ± 1.006 mSv for R1; 3.503 ± 2.635 mSv for R2; 3.079 ± 1.798 mSv for R3; and 3.480 ± 2.063 mSv for R4 (Table 6 and Fig. 2).

Discussion

The field of orthopedic surgery increasingly relies on fluoroscopy and x-ray imaging during surgical

Table 5. Measurement of exposure to ionizing radiation per month and sex based on resident physicians

Month	Exposure (mSv) Mean ± SD	Range*	p
January	Women: 0.445 ± 0.731 Men: 0.338 ± 0.642	−0.328-0.541	0.626
February	Women: 0.363 ± 0.455 Men: 0.564 ± 1.917	−1.328-0.925	0.721
March	Women: 0.215 ± 0.224 Men: 0.1898 ± 0.214	−0.117-0.167	0.722
April	Women: 0.245 ± 0.108 Men: 0.262 ± 0.254	−0.169-0.134	0.819
May	Women: 0.286 ± 0.444 Men: 0.243 ± 0.432	−0.243-0.328	0.764
June	Women: 0.233 ± 0.226 Men: 0.243 ± 0.216	−0.157-0.129	0.846
July	Women: 0.365 ± 0.383 Men: 0.276 ± 0.403	−0.173-0.351	0.499
August	Women: 0.219 ± 0.068 Men: 0.213 ± 0.372	−0.076-0.0.892	0.874
September	Women: 0.369 ± 0.525 Men: 0.242 ± 0.189	−0.663-0.319	0.193
October	Women: 0.520 ± 0.731 Men: 0.233 ± 0.163	−0.047-0.528	0.020
Overall Exposure	Women: 3.260 ± 1.688 Men: 2.807 ± 2.304	−0.984-1.890	0.529
	Overall: 2.9 ± 2.17	1.25-14.28	0.424

SD: standard deviation. *Calculated with a 95% confidence interval.

procedures as aids for treatment and quality control. Orthopedic surgeons are continuously exposed to ionizing radiation and its potential biological effects on the body, with a high probability of developing radiation-induced cancers due to chronic exposure to low doses over time, leading to an increased risk of cancer after 10-15 years[1,3]. Therefore, to mitigate radiation exposure and reduce stochastic effects, the measures recommended by the ICRP are maintaining a security distance from the radiation source and using RPE such as lead aprons, thyroid collars, lead gloves, and protective eyewear.

The study states that 77.8% of all medical residents wear lead aprons, compared to only 31.5% who wear thyroid collars. Lead aprons are the most commonly used RPE, followed by thyroid collars, with a lower percentage of usage and some resistance among the surgical staff to wearing them, despite their availability[2,6,14,20,27]. The hospital provides RPE to all medical residents, including lead aprons, thyroid collars, and lead eyewear. Also, the

Table 6. Measurement of exposure to ionizing radiation per month and by specialization level in resident physicians

Month	Exposure (mSv) Mean ± SD	Range*	p
January		−0.459-0.213	0.000
R1	-		
R2	0.336 ± 0.257		
R3	0.633 ± 0.877	−0.767-0.757	0.990
R4	0.638 ± 0.908		
February		−3.261-0.183	0.005
R1	-		
R2	0.564 ± 1.917	−0.637-0.304	
R3	0.384 ± 0.353		0.471
R4	0.551 ± 0.789		
March		−0.304-0.203	0.00
R1	-		
R2	0.189 ± 0.214		
R3	0.287 ± 0.223	−0.265-0.134	0.506
R4	0.352 ± 0.248		
April		−0.163-0.314	0.520
R1	0.299 ± 0.379		
R2	0.224 ± 0.068		0.710
R3	0.239 ± 0.098	−0.102-0.071	
R4	0.254 ± 0.104		
May		−0.231-0.585	0.380
R1	0.326 ± 0.654		
R2	0.148 ± 0.035		
R3	0.169 ± 0.078	−0.471-0.047	0.104
R4	0.381 ± 0.498		
June		−0.013-0.273	0.073
R1	0.276 ± 0.228		
R2	0.146 ± 0.033		
R3	0.206 ± 0.109	−0.448-0.128	0.241
R4	0.366 ± 0.372		
July		−0.138-0.656	0.192
R1	0.450 ± 0.637		
R2	0.191 ± 0.048		0.498
R3	0.250 ± 0.221	−0.105-0.209	
R4	0.198 ± 0.060		
August		−0.058-0.577	0.104
R1	0.184 ± 0.046		
R2	0.205 ± 0.051		
R3	0.256 ± 0.240	−0.108-0.195	0.561
R4	0.212 ± 0.641		
September		−0.188-0.360	0.525
R1	0.313 ± 0.434		
R2	0.227 ± 0.091		
R3	0.243 ± 0.641	−0.181-0.229	0.809
R4	0.284 ± 0.234		
October		−0.121-0.168	0.741
R1	0.257 ± 0.205		
R2	0.234 ± 0.143		
R3	0.393 ± 0.641	−0.353-0.569	0.633
R4	0.284 ± 0.234		
Total Exposure		−3.245-0.449	0.132
R1	2.105 ± 1.006		
R2	3.503 ± 2.635		
R3 R4	3.079 ± 1.798	−0.203-1.232	0.616

R1, first-year resident, R2: second-year resident; R3, third-year resident; R4, fourth-year resident; SD, standard deviation.
*Calculated with a 95% confidence interval.

hospital Education and Research Directorate has issued a mandate to deny access to the operating room if RPE are not worn during surgeries involving fluoroscopy. Some resistance to the use of RPE has been reported, particularly thyroid collars, despite the fact that 55.6% of the residents are aware of the availability of RPE for medical residents.

Regarding the distance kept by the surgeon from the x-ray source, the greater the distance, the lower the risk of being exposed to ionizing radiation. According to the survey, 81.5% of the residents placed themselves at a distance of < 1 meter from the x-ray source. The medical literature available tells us that the chances of experiencing stochastic effects due to occupational exposure to ionizing radiation are limited when the OR personnel keeps more than just 1 meter as a security a distance from the x-ray source and wears lead aprons[3,9,26,28].

We should mention that having the x-ray source of the fluoroscope located underneath the operating table means that the dose of radiation is lower in the surgeon's chest, pelvis, and fingers[3], provided the surgeon wears a lead apron to protect his/her chest and gonadal region. In contrast to the study conducted in our hospital, we found that in 59.3% of all surgeries performed using fluoroscopy, the x-ray tube is often placed above the operating table, compared to 25.9% of the cases where it is placed underneath the table.

However, the study demonstrated that the 11-month cumulative overall exposure dose for orthopedic surgery residents at the hospital had a mean of 2.9 ± 2.17 mSv, which is below the threshold recommended by the ICRP of 20 mSv[5,23] despite the fact that 13% of all medical residents did not wear the dosimeter at some point during their routine clinical practice (during rotations and on-call duties) or used the RPE appropriately, and 81.5% placed themselves less than 1 meter away from the x-ray source. A study conducted among consolidated physicians and orthopedic surgery residents showed that the dose received was lower than the dose recommended[25]. A different study conducted in Turkey[26] compared radiation exposure in orthopedic surgeries and found that the overall annual exposure to ionizing radiation was lower than the threshold set by the International Commission on Radiological Protection (ICRP). Nonetheless, occupational radiation exposure was higher in assistant physicians than surgeons. The authors of this study attributed the higher exposure observed to the fact that the x-ray source is often located closer to the side of the assistant surgeon (< 1 meter away) despite the use of lead aprons and thyroid shields.

We should mention that this is the first study ever conducted in Mexico and Latin America with orthopedic surgery residents, a group with higher exposure rates to ionizing radiation. Like Matityahu et al.[6] say, younger surgeons have a higher risk of exposure because they use fluoroscopy more often during surgery compared to more experienced surgeons. Medical residents from most Mexican hospitals, especially those in their third and fourth year of residency (R3 and R4), display a greater surgical activity. They participate in more surgical procedures during their on-call duties and make greater use of the fluoroscope in orthopedic surgeries. Due to their inexperience and lack of skills, they may be more exposed to x-ray than consolidated physicians, which leads to more exposure to ionizing radiation. A strength of this study is the significant sample size, which is the first of its kind in the region.

The study also found that women were more exposed to radiation than men. The analysis hypothesizes that this could be due to an inadequate use of the dosimeter, not following the instructions on how to wear it underneath the lead apron or exposure to ionizing radiation through other means or failure to wear the RPE during fluoroscopy-guided surgeries. This finding was made during the monthly follow-up conducted by the company responsible for measuring exposure to radiation. To address this issue, the female medical residents who showed greater exposure were called on the proper use of the dosimeter and the importance of wearing RPE properly.

The study has some limitations, such as the measurement of exposure for first-year residents (R1) being conducted only for 8 months instead of the entire year, because since the medical specialization course starts in March, after October 2020, the dosimeter was not available to take 1-year measurements. Additionally, there is a lack of awareness among medical residents on the risks involved in prolonged exposure to ionizing radiation and its stochastic effects on the body. To address this issue, starting March 2021, all medical residents are reinforced on radiological protection measures and given an organizational chart on the proper use of RPE and verification of its integrity (Figs. 3 and 4) to build up awareness on its proper use.

Figure 3. *Dosimeter location underneath the lead apron.*

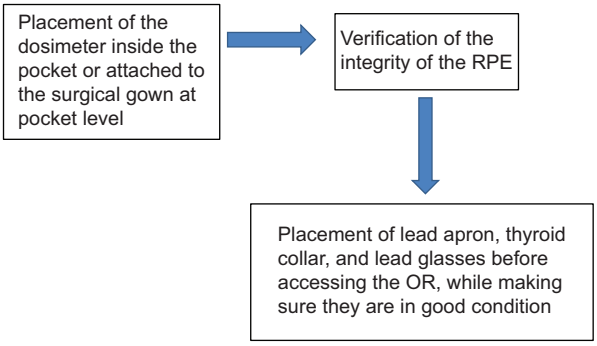

Figure 4. *Flowchart for the verification of radiation protection equipment (RPE) prior to accessing an orthopedic surgery unit where fluoroscope is often used.*

Conclusions

The study demonstrated that orthopedic surgery residents receive doses of radiation below the threshold recommended by the ICRP. However, it also revealed a lack of knowledge among residents regarding radiological protection and the adverse events associated with radiation, despite having received prior training on the use of RPE and radiological safety issues.

To address this issue, greater awareness and consciousness is needed among medical residents on the proper use of complete RPE during orthopedic surgeries involving fluoroscopy. Additionally, continuous medical education programs on radiological protection measures should be added to the medical specialization course to better provide the health care personnel with knowledge on radiological safety.

Acknowledgements

The authors wish to thank the staff from the radiology and imaging modality unit of Unidad Médica de Alta Especialidad Hospital de Traumatología y Ortopedia Manuel Ávila Camacho in Puebla, Mexico for their unconditional support.

Funding

None whatsoever.

Conflicts of interest

none reported.

Ethical disclosures

Protection of human subjects and animals in research. 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).

Patients' data protection. 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.

Supplementary data

Supplementary data for this study is available at the following DOI: 10.24875/CIRUE.M23000429. This material is provided by the corresponding author and published online for the reader's own benefit. The content of the supplementary data is the authors' sole responsibility.

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ORIGINAL ARTICLE

Effect of skeletal muscle area and prognostic nutritional index in periampullary tumors

Efecto del área del músculo esquelético y del índice nutricional pronóstico en los tumores periampulares

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Abstract

Introduction: *The skeletal muscle area (SMA) and prognostic nutritional index (PNI) are both considered as predictive parameters for mortality and morbidity for various type of cancer. In this study, we aimed to identify the effects of pre-operative SMA and PNI values on post-operative mortality and morbidity in patients with periampullary region tumors (PRT).* **Methods:** *Patients between 2010 and 2020 were retrospectively analyzed and divided into two groups according to SMA and PNI cutoff values. Univariate and multivariate analysis was performed to find potential risk factors.* **Results:** *The mean age was 65.94 ± 11.242 and 54 (60.6%) of the patients were male. Hypertension was found a reducing factor for morbidity in both univariate and multivariate analysis (p = 0.039; p = 0.045). Chronic obstructive pulmonary disease and low PNI were found as factors affecting mortality in univariate analysis (p = 0.046; p = 0.014). However, only low PNI was found as an enhancing factor for mortality in multivariate analysis.* **Conclusion:** *Although SMA is not a risk factor for post-operative morbidity and mortality, PNI can be considered as a risk factor for mortality in patients with PRT.*

Keywords: *Periampullary region tumor. Prognostic nutritional index. Skeletal muscle area.*

Resumen

Introducción: *El área del músculo esquelético (SMA) y el índice nutricional pronóstico (PNI) se consideran parámetros predictivos de mortalidad y morbilidad para varios tipos de cáncer. En este estudio, nuestro objetivo fue identificar los efectos de los valores preoperatorios de SMA y PNI sobre la mortalidad postoperatoria. y morbilidad en pacientes con tumores de la región periampular (PRT).* **Métodos:** *Los pacientes entre 2010-2020 fueron analizados retrospectivamente y divididos en dos grupos según los valores de corte de SMA y PNI. Se realizaron análisis univariados y multivariados para encontrar posibles factores de riesgo.* **Resultados:** *La edad media fue de 65.94 ± 11.242 y 54 (60.6%) de los pacientes eran varones. Se encontró que la hipertensión es un factor reductor de la morbilidad tanto en el análisis univariado como en el multivariado (p = 0.039; p = 0.045). La EPOC y el PNI bajo se encontraron como factores que influyen en la mortalidad en el análisis univariante (p = 0.046; p = 0.014). Sin embargo, solo el PNI bajo se encontró como un factor potenciador de la mortalidad en el análisis multivariado.* **Conclusión:** *Aunque la SMA no se consideró un factor de riesgo de morbilidad y mortalidad posoperatorias; La PNI puede considerarse un factor de riesgo de mortalidad en pacientes con PRT.*

Palabras clave: *Tumor de la región periampular. Índice nutricional pronóstico. Área del músculo esquelético.*

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Date of reception: 02-07-2021
Date of acceptance: 07-01-2022
DOI: 10.24875/CIRUE.M22000559

Cir Cir (Eng). 2023;91(1):71-76
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Periampullary region tumors (PRT) include the tumors arising from pancreatic head, ampulla of Vater, duodenum, and distal common bile duct[1]. Among these tumors, pancreatic head adenocarcinomas present the worst prognosis with a 5-year overall survival of 20%[2,3]. Pancreaticoduodenectomy (PD) is considered as the curative resection method for the PRT. However, mortality rates of PD are reported < 5% in many published series, morbidity rates are still remains high from 40% to 50%[4].

Sarcopenia is defined as loss of skeletal muscle mass, strength and function. It is related to prolonged hospitalization, mortality, adverse metabolic affects, and poor quality of life[5]. There are many different types of methods used for evaluating the quantity and quality of muscle mass such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, lumbar muscle cross-sectional area by computed tomography (CT), or magnetic resonance imaging. The skeletal muscle area (SMA) is one of the parameters that shows sarcopenia. SMA is measured on the inferior end plate of the L3 vertebra and reflects the sum of the surface areas of all the muscles (i.e., psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, and internal and external obliques) in this axial image[6,7]. Prognostic nutritional index (PNI) is calculated with the formula 10 × serum albumin level (g/dL) + 0.005 × total peripheral lymphocyte count (per mm^3) from serum albumin level and total lymphocyte count[8]. PNI shows the nutritional status of the patients and it is known as a predictive value of morbidity and mortality in pancreatic cancer[9]. In this study, we aimed to identify the effects of preoperative SMA and PNI values on post-operative mortality and morbidity in patients with PRT.

Materials and methods

Patients that underwent PD for periampullary region malignant tumors between January 2010 and January 2020 were retrospectively analyzed. Patients' age, gender, comorbidities, localizations of the tumor, histological types of tumor, tumor stages, American Society of Anesthesiology (ASA) scores, total lymphocyte counts, pre-operative levels of albumin, pre-operative PNI, preoperative SMA, post-operative mortality and morbidity, post-operative hospital stay, and post-operative Clavien Dindo complication scores were defined as parameters. PNI was calculated with the formula of Onodera according to the laboratory parameters that checked 1 week before the operation. SMA values of patients were measured by retrospective examination of CT scans that taken in the supine position for the tumor staging before the surgery. Patients were divided into two groups for SMA and PNI according to their cutoff values that found in receiver operating characteristic (ROC) curve analysis. Differences between these groups for post-operative hospital stay, mortality, and morbidity were statistically analyzed. Data were statistically analyzed using IBM SPSS Statistics 25.0 package program. As the descriptive statistics, the number of units (n), percent (%), mean ± standard deviation ($x' \pm ss$), and Median (Q1-Q3) values was given. Pearson Chi-square and Fisher's exact test were used to evaluate categorical variables. The normal distribution of data's continuous variables were evaluated by Shapiro–Wilk, normality test, and Q-Q graphs. In the comparison of the continuous variables of the two groups, the Independent Sample T test was used for variables with normal distribution, and Mann–Whitney U test for variables that did not fit the normal distribution. Univariate analysis was performed to find potential risk factors and then multivariate analysis was added to identify independent factors. $p < 0.05$ value was considered statistically significant.

Results

A total of 89 patients were detected. The mean age was 65.94 ± 11.242 and 54 (60.6 %) of the patients were male. Eleven (12.4%) patients were diagnosed as distal common bile duct tumor, 42 (47.2%) patients were diagnosed as pancreatic head tumor, and 36 (40.4%) patients were diagnosed as ampulla tumor. Patients' tumor localizations, histological types of tumor, and stages are summarized in table 1 in detail. The mortality and morbidity rate were 19% and 30%, respectively. The most common complication after PD was surgical site infection with 13 patients and the second one was pneumonia with 10 patients. Other complications are summarized in table 2 with details. Patients were divided into two groups according to their cutoff PNI and SMA values that calculated with the ROC analysis. Mean for the PNI in patients who have morbidity and mortality was found 42.52 ± 8.034 and 38.40 ± 7.881, respectively. Cutoff value for PNI was found 43 and patients were divided into two groups as patients with PNI ≤ 43 and PNI > 43. Morbidity, mortality, hospital stay, and Clavien Dindo complication scores were compared between these

Table 1. Localizations, histological types, and stages of the periampullary region tumors

Histological type and stage	Localization of the tumor, n (%)		
	Distal Choledoc (n = 11) (12.4%)	Pancreatic head (n = 42) (47.2%)	Ampulla of Vater (n = 36) (40.4%)
Histological type of tumor			
Adenocarcinoma	7 (63.6%)	33 (78.6%)	34 (94.4%)
Cholangiocarcinoma	4 (36.4%)	-	-
Intraductal papillary mucinous neoplasia	-	6 (14.35%)	-
Neuroendocrine tumor	-	2 (4.8%)	-
Lymphoma	-	1 (2.4%)	-
Squamous cell cancer	-	-	1 (2.8%)
Gastrointestinal Stromal tumor	-		1 (2.8%)
Tumor stages			
Stage 1	2 (18.2%)	5 (11.9%)	12 (33.3%)
Stage 2	6 (54.5%)	18 (42.9%)	3 (8.3%)
Stage 3	3 (27.3%)	10 (23.8%)	19 (52.8%)

Table 2. Post-operative complications in patients underwent PD

Complication	Number of patients (n)
Surgical site infection	13
Pneumonia	10
Acute renal failure	4
Brid ileus	3
Intra-abdominal abscess	2
Eviscereation	2
Gastrointestinal bleeding	1
Grade D esophagitis	1
Hepatic abscess	1
Cholangitis	1
Central venous catheter infection	1

PD: pancreaticoduodenectomy.

groups. In patients with low PNI group, mortality and Clavien Dindo complication score were significantly higher (p = 0.010, p = 0.011) (OR for mortality 0.220, 95% CI 0.065-0.740) (Table 3). SMA values were calculated separately for male and female patients. Mean SMA values for male and female in patients with mortality and morbidity were found as 112 ± 26.453, 109.83 ± 26.713, and 94.20 ± 14.412, 87.55 ± 15.572, respectively. According to SMA ROC analysis, cutoff values for female and male were 87 and 113, respectively. Patients were divided into two groups and they were compared for morbidity, mortality, hospital stay, and Clavien Dindo complication scores. In both groups, SMA was not associated with morbidity, mortality, hospital stay, and Clavien Dindo complication score (Table 3). We also categorized patients according to presence of mortality and morbidity. Then, we compared these groups for age, gender, ASA score, lyphocyte count, serum level of albumin, and comorbidities. Hypertension and diabetes mellitus were significantly lower in patients with morbidity (p = 0.035 and p = 0.045). Serum level of albumin was lower in patients with mortality (p = 0.011). Furthermore, chronic obstructive pulmonary disease (COPD) was higher in patients with mortality (p = 0.040) (Table 4). Distribution of comorbidity numbers according to Clavien Dindo complication score was also analyzed and we could not find an association between these parameters (Fig. 1). We did univariate and multivariate analysis for factors affecting morbidity and mortality. Hypertension was found a reducing factor for morbidity in both univariate and multivariate analysis (p = 0.039 and p = 0.045) (odds ratio [95% CI]: 0.350 [0.129-0.946] and 0.303 [0.095-0.973]). COPD and low PNI were found as enhancing factors for mortality in univariate analysis (p = 0.046 and p = 0.014) (odds ratio [95% CI]: 3.177 [1.019-9.907] and 4.550 [1.351-15.329]). However, only low PNI was found as enhancing factor for mortality in multivariate analysis (p = 0.024) (odds ratio [95% CI]: 4.836 [1.233-18.967]) (Table 5).

Discussion

Our study showed that low PNI is an independent prognostic factor for post-operative mortality in patients underwent PD for PRT. On the other hand SMA was not effective on post-operative mortality and

Table 3. Factors associated with low and high PNI and SMA values

Postoperative features	All patients (n = 89)	Low PNI (PNI ≤ 43) (n = 43)	High PNI (PNI > 43) (n = 46)	p value	Low SMA (n = 43)	High SMA (n = 46)	p value
Postoperative length of hospital stay; median (Q1-Q3)	13 (10-20)	13 (9-21)	13 (11-18.5)	0.360*	13 (10-20)	13.5 (10-20.25)	0.490*
Morbidity, n (%)				0.367**			0.630**
Yes	27 (30.3)	15 (34.9)	12 (26.1)		12 (27.9)	15 (32.6)	
No	62 (69.7)	28 (65.1)	34 (73.9)		31 (72.1)	31 (67.4)	
Clavien-Dindo classification, n (%)				0.011**			0.902**
0	45 (50.6)	15 (34.9)	30 (65.2)		23 (53.5)	22 (47.8)	
1	11 (12.4)	8 (18.6)	3 (6.5)		4 (9.3)	7 (15.2)	
2	7 (7.9)	4 (9.3)	3 (6.5)		4 (9.3)	3 (6.5)	
3	9 (10.1)	3 (7.0)	6 (13.0)		4 (9.3)	5 (10.9)	
5	17 (19.1)	13 (30.2)	4 (8.7)		8 (18.6)	9 (19.6)	
Mortality, n (%)				0.010**			0.908**
Yes	17 (19.1)	13 (30.2)	4 (8.7)		8 (18.6)	9 (19.6)	
No	72 (80.9)	30 (69.8)	42 (91.3)		35 (81.4)	37 (80.4)	

Low SMA: SMA≤87 for female or SMA≤113 for male; High SMA: > 87 for female or SMA>113 for male. *Mann-Whitney U test was used for P values. **Pearson Chi-square test was used for P values.
PNI: prognostic nutritional index; SMA: skeletal muscle area.

Table 4. Factors associated with presence of mortality and morbidity

Demographic characteristics of patients	Patients with morbidity (n = 27)	Patients without morbidity	p value	Patients with mortality (n = 17)	Patients without mortality	p value
Age; mean ± standard deviation	66.93 ± 10.63	65.52 ± 11.55	0.589*	68.94 ± 9.73	65.24 ± 11.52	0.224*
Sex			0.771**			0.705**
Male	17 (63%)	37 (59.7%)		11 (64.7%)	43 (59.7%)	
Female	10 (37%)	25 (40.3%)		6 (35.3%)	29 (40.3%)	
ASA score			0.527**			0.098**
ASA I	0	0		0	0	
ASA II	17 (63%)	32 (51.6%)		10 (58.8%)	39 (54.2%)	
ASA III	10 (37%)	29 (46.8%)		6 (35.3%)	33 (45.8%)	
ASA IV	0	1 (1.6%)		1 (5.9%)	0	
Pre-operative total peripheral lymphocyte count (per mm^3);			0.989***			0.113***
Median (Q1-Q3)	1800 (1300-2400)	1800 (1200-2400)		1300 (1100-2200)	1900 (1300-2400)	
Pre-operative level of albumin (g/dl);			0.543*			0.011*
Mean ± standard deviation	3.34 ± 0.67	3.44 ± 0.72		3.02 ± 0.78	3.5 ± 0.65	
Comorbidities****						
Hypertension (HT)	7 (25.9%)	31 (50%)	0.035	6 (35.3%)	32 (44.4%)	0.493
Diabetes Mellitus (DM)	5 (18.5%)	25 (40.3%)	0.045	3 (17.6%)	27 (37.5%)	0.119
Coronary Artery Disease	1 (3.7%)	5 (8.1%)	0.663	2 (11.8%)	4 (5.6%)	0.322
Atrial fibrillation	1 (3.7%)	2 (3.2%)	0.909	2 (11.8%)	1 (1.4%)	0.092
Chronic obstructive pulmonary disease	4 (14.8%)	16 (25.8)	0.253	7 (41.2%)	13 (18.1%)	0.040

*Independent sample T test was used for p values. **Pearson Chi-square test was used for p values. ***Mann–Whitney U test was used for p values. ****Fisher's exact test was used for p values.
ASA: American Society of Anesthesiology.

morbidity in these patients. PD is still a complicated surgery with 5% of mortality and 50% of morbidity rate. Factors affecting the post-operative mortality and morbidity are still maintain importance. Importance of nutritional status in these patients before the operation is well known. Cancer cachexia is a multifactorial syndrome characterized by a sustained loss of skeletal muscle mass and cannot be completely reversed

Table 5. Univariate and multivariate analysis for the factors affecting morbidity and mortality

Variables	Morbidity				Mortality			
	Univariate analyses	p value	Multivariate analyses	p value	Univariate analyses	p value	Multivariate analyses	p value
	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
Age (year)	1.011 (0.971-1.054)	0.585	1.035 (0.980-1.093)	0.219	1.032 (0.981-1.085)	0.223	1.003 (0.943-1.067)	0.930
Male Gender	1.149 (0.453-2.915)	0.771	1.160 (0.381-3.532)	0.793	1.236 (0.411-3.717)	0.705	0.935 (0.263-3.323)	0.917
Hypertension	0.350 (0.129-0.946)	0.039	0.303 (0.095-0.973)	0.045	0.682 (0.227-2.044)	0.494	0.895 (0.242-3.310)	0.868
Diabetes mellitus	0.336 (0.112-1.006)	0.051	0.396 (0.122-1.287)	0.124	0.357 (0.094-1.357)	0.131	0.339 (0.077-1.485)	0.151
Chronic obstructive pulmonary disease	0.500 (0.150-1.668)	0.259	0.284 (0.074-1.092)	0.067	3.177 (1.019-9.907)	0.046	2.892 (0.821-10.185)	0.098
Low SMA	0.800 (0.323-1.983)	0.630	0.633 (0.224-1.785)	0.387	0.940 (0.326-2.708)	0.908	0.810 (0.246-2.668)	0.729
Low PNI	1.518 (0.612-3.767)	0.368	1.327 (0.438-4.023)	0.617	4.550 (1.351-15.329)	0.014	4.836 (1.233-18.967)	0.024

Low SMA: SMA ≤ 87 for female or SMA ≤ 113 for male; High SMA: > 87 for female or SMA > 113 for male.
CI: confidence interval; PNI: prognostic nutritional index; SMA: skeletal muscle area.

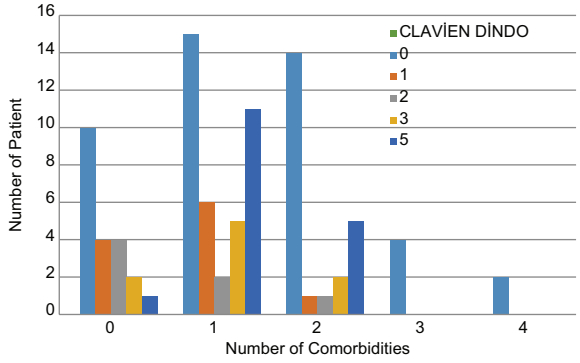

Figure 1. *Distribution of comorbidity numbers according to Clavien Dindo complication score.*

with conventional nutritional support and cause progressive functional impairment[10]. Studies showed that complex tumor–host interactions, inflammatory cytokines, hormones, and neuropeptides cause the development of cancer cachexia in patients with pancreatic cancer[11]. In the literature, SMA value is used for many malignancies as a predictive value for mortality and morbidity[12-14]. Furthermore, it is measured in healthy populations in many studies[5,15,16]. In the study of Kim et al.[5], the cutoff values for male and female were found as 119.3 cm^2 and 74.2 cm^2. On the other hand in the study of A. Van der Werf et al.[16], they found the cutoff values in healthy Caucasian population as 134 cm^2 and 89.2 cm^2. In our study, we found the cutoff values in patients with PRT as 113 cm^2 in male and 82 cm^2 in female which were both lower than healthy population and the median that found in the study of Linder et al.[17]. That shows that patients with PRT are inclined sarcopenia than the healthy population. Whereas we could not find any association between the SMA value and increased morbidity and mortality rate. In many studies, SMA is used for predicting the sarcopenia and patients' survival in patients that followed in oncology departments[14,15,17]. Unfortunately, we could not compare the patients' follow-up SMA values due to having missing data. On the other hand, SMA values in our patients were lower than the healthy population and the patients that underwent PD in the literature. The mortality and morbidity rate in our study was 19% and 30%, respectively. We think that these mortality and morbidity rates in our study are due to being a less experienced hepatopancreatic biliary center with a low annual patient volume and patients with high ASA scores.

PNI was reported as a predictive value for nutritional risk in many studies[8,9,18,19]. In the study of Hoon Lee et al.[9], they found the PNI as a predictive parameter for

patients' survival with the 49.5 cutoff in all stages of pancreas cancer. Whereas in another study of Dogan et al., they found that PNI was not a predictive parameter for survival in patients with metastatic pancreatic cancer[20]. In our study, we found an association between Low PNI and Clavien Dindo complication score and mortality. Furthermore, we found PNI as a risk factor for post-operative mortality in multivariate analysis.

We also analyzed association between patients' age, sex, ASA score, and comorbidities with the mortality and morbidity. In addition, to the literature, hypertension and diabetes mellitus were significantly lower in patients with morbidity. Furthermore, serum level of albumin was significantly lower, and COPD was significantly higher in patients with mortality.

Limitations

The primary limitation of the study is to be a retrospective study. Second, we being a less experienced hepatopancreaticobiliary center with a low annual patient volume caused an incompatible morbidity and mortality rates according to the literature. Third, due to missing data of the patients, we could not analyze the skeletal muscle index which is more predictive parameter for these patients. That may have caused to find the SMA as non-effective parameter for morbidity and mortality.

Conclusion

Although patients have lower SMA values, SMA is not a risk factor for mortality and morbidity in patient that underwent PD for PRT. However, low PNI can be considered as a risk factor for post-operative mortality in these patients.

Funding

No funding was received by any author from any person and/or institution.

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

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ORIGINAL ARTICLE

Medium platelet volume and lymphocyte-platelet index as prognosis factors in papillary thyroid cancer

Volumen plaquetario medio e índice de plaquetas-linfocitos como factores de pronóstico en cáncer papilar de tiroides

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Abstract

Background: *Papillary thyroid cancer is the most common endocrine neoplasia. There are prognostic factors that establish risk of recurrence and mortality; however, patients considered low risk may have a less favorable evolution and hence the importance of finding new markers.* **Objective:** *To assess whether the mean platelet volume (MPV) and the platelet-lymphocyte index (PLI) show a relationship with the clinical staging in papillary thyroid cancer.* **Method:** *Retrospective, observational and analytical study. Preoperative MPV and PLI were recorded, its relationship with TNM and MACIS systems was sought, as well as locally advanced invasion and tumor focality.* **Results:** *107 cases treated from November 2017 to February 2020. No statistically significant difference was observed in these two preoperative parameters with advanced and initial stages, risk groups or tumor focality. The statistical analysis used was one-way ANOVA with SPSS 25, a 95% confidence interval and $p < 0.05$.* **Conclusions:** *Despite the logical reasoning of tumor pathophysiology, our study did not find a relationship between papillary thyroid carcinoma with MPV and PLI, and should be complemented with more extensive studies.*

Keywords: *Papillary thyroid cancer. Lymphocyte platelet index. Mean platelet volume.*

Resumen

Antecedentes: *El cáncer papilar de tiroides es la neoplasia endocrina más frecuente. Existen factores pronósticos que establecen el riesgo de recurrencia y mortalidad; sin embargo, los pacientes considerados de bajo riesgo pueden llegar a presentar una evolución menos favorable, y de ahí la importancia de encontrar nuevos marcadores.* **Objetivo:** *Evaluar si el volumen plaquetario medio (MPV) y el índice plaquetas-linfocitos (PLR) presentan una relación con la etapificación clínica en el cáncer papilar de tiroides.* **Método:** *Estudio retrospectivo, observacional y analítico. Se registraron el MPV y el PLR preoperatorios, y se buscó su relación con los sistemas TNM y MACIS, así como con la invasión localmente avanzada y la focalidad del tumor.* **Resultados:** *Se trataron 107 casos de noviembre de 2017 a febrero de 2020. No se observó diferencia estadísticamente significativa en estos dos parámetros preoperatorios o en estadios avanzados e iniciales, grupos de riesgo ni focalidad del tumor. El análisis estadístico utilizado fue ANOVA de una vía, con SPSS 25, con intervalo de confianza del 95% y $p < 0.05$.* **Conclusiones:** *Pese al razonamiento lógico de la fisiopatología tumoral, en nuestro estudio no se encontró relación entre el carcinoma papilar de tiroides, el MPV y el PLR, y debiera complementarse con estudios más extensos.*

Palabras clave: *Cáncer papilar de tiroides. Índice plaquetas-linfocitos. Volumen plaquetario medio.*

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Date of reception: 19-05-2021
Date of acceptance: 04-05-2022
DOI: 10.24875/CIRUE.M23000430

Cir Cir (Eng). 2023;91(1):77-83
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

The functional relationship between inflammation and cancer has always existed. The fact that tumors often grow in sites of chronic inflammation led Rudolf Virchow, in 1863, to suggest that there is a link between the immune system and cancer[1,2]. At first, it may seem contradictory that the immune system and platelet function can promote the development of tumor cells in sites of chronic inflammation and, on the other hand, contribute to its elimination[3].

The main cellular mediators of the anti-tumor immune response are the activated CD8+ T cells and CD4+ Th1 lymphocytes. The former are responsible for eliminating tumor cells through the production of apoptosis-inducing molecules or cytotoxic granules (eg, granzymes, perforin, and granulysin), while the latter promote the production of anti-tumor cytokines, such as interferon-gamma[4]. On the other hand, the mechanisms that drive tumorigenesis through inflammation are as diverse as DNA damage due to inflammatory mediators (oxygen free radicals and extracellular matrix metalloproteinases), as well as cytokines such as interleukins 1B and 8, which promote neoplastic risk. Similarly, once a tumor has popped up, growing malignant cells promote neoangiogenesis, the acquisition of new mutations, extracellular matrix disruption, tumor cell migration, and ultimately metastasis. This is how cancer can regulate the production of circulating platelets[5,6].

Platelet biology is essential for hemostasis, vascular integrity, angiogenesis, inflammation, innate immunity, wound healing, and cancer biology. Also, platelets are the first cells to be activated during the process of hemostasis[7,8]. The growth of tumor masses depends on the creation of new blood vessels, a process that is known as tumor angiogenesis[9,10]. Angiogenesis occurs during tumor growth, requires increased oxygen supply, and is due to the activation of Ras and Raf oncogenes[11,12], which stimulate the release of pro-angiogenic factors such as vascular endothelial growth factor, platelet-derived endothelial growth factor, and angiopoietins 1 and 2[13-15]. As a matter of fact, former studies have demonstrated the presence of a specific receptor, called the alpha receptor for the platelet-derived growth factor, which, if expressed by papillary thyroid cancer cells, confers greater aggressiveness associated with lymph node metastases compared to patients who do not express it constitutively[16].

Platelet coatings also protect circulating tumor cells from high-flow shear forces in the vascular wall, and evade the immune system and tumor necrosis factor-alpha-mediated cytotoxicity[17-19]. A plethora of preoperative hematological parameters, such as platelet count, platelet size evaluated by the mean platelet volume, the neutrophil-lymphocyte ratio, and the platelet-lymphocyte ratio have been associated with the clinical, pathological, and survival characteristics of many different cancers. However, the role of these indices in papillary thyroid cancer is still to be elucidated[20-23].

Papillary thyroid cancer is the most common endocrine neoplasm and often responds well to treatment[24,25]. Surgical resection and adjuvant therapy for this type of malignant neoplasm have been defined based on well-known prognostic factors that determine the risk of recurrence and long-term mortality, such as advanced age, sex, tumor size, invasion of the thyroid capsule and extrathyroidal tissues, lymphovascular invasion or incomplete tumor removal. Some of these factors are more relevant than others[26,27]. This is why some patients have less favorable outcomes, with long-term recurrences despite of being initially considered as low-risk patients[28]. Therefore, the early identification of patients who may have unfavorable outcomes despite being from low clinical risk groups is of paramount importance.

We have been able to see that tumors of the same histological lineage behave different biologically, perhaps due to the presence of genes that better evade the immune response or because they have more effective metastasis mechanisms, which are not clearly understood at the moment[29]. Nevertheless, these factors ultimately make these tumors more aggressive. However, in the case of papillary thyroid carcinoma, this cannot yet be detected in early treatment periods.

The mean platelet volume (MPV) and platelet distribution width are early indices of platelet activation[30,31]. Their value, along with the platelet-lymphocyte ratio (PLR), has been relevant when it comes to comparing malignant thyroid disease to benign conditions[32]. Therefore, if the MPV and PLR were related to these mechanisms that confer greater tumor aggressiveness, they would create the possibility of being able to plan the proper therapeutic approach for patients classified as low risk, thus avoiding incomplete treatments. Therefore, these platelet and lymphocyte characteristics could represent an additional, accessible, and easily applicable tool.

The objective of this study was to evaluate whether the MPV and the PLR change in patients with papillary thyroid cancer according to their initial risk group assessment or staging.

Method

This was a retrospective, observational, analytical, and cross-sectional study of 107 patients with papillary thyroid cancer treated at the Thyroid Clinic of the General Surgery Department at the Hospital General de Mexico Dr. Eduardo Liceaga, Mexico City, Mexico from November 1, 2017 through February 28, 2020.

The study analyzed 3 variables: preoperative mean platelet volume (MPV), preoperative absolute lymphocyte count, and preoperative absolute platelet count. These measurements were systematically reported in a complete blood count and obtained using the MAPPS method by impedance and optical vision using ethylenediaminetetraacetic acid as anticoagulant agent.

The PLR was estimated dividing the absolute platelet count by the absolute lymphocyte count.

To confirm the patients' risk group classification, surgical reports and histopathological study results were retrieved from the hospital electronic database to gather intraoperative findings. All patients were classified according to the TNM (Tumor, Node, Metastasis) staging system of the American Joint Committee on Cancer (stages I, II, III, and IV) and based on severity according to the MACIS (Metastases, Age, Completeness of resection, Invasion, Size) system (very low risk < 6; low risk, 6-6.99; intermediate risk, 7-7.99; and high risk > 8).

Inter-group comparisons were made based on the MACIS and TNM classifications, and the statistical analysis used a 4 × 1 one-way ANOVA test that was complemented with Tukey's post hoc test if there were any inter-group differences and effect size. The latter was considered low if $f \leq 0.24$, medium if f = 0.25-0.39, and large if $f \geq 0.40$. Focality and age interactions with MPV and PLR were analyzed using factorial ANOVA. P values < 0.05 were considered statistically significant. Scatter plots of variables were created showing means and confidence intervals, and effect sizes were considered low if η^2 = 0.01-0.05, medium if η^2 = 0.06-0.13, and large if $\eta^2 \geq 0.14$. Statistical calculations were performed using SPSS 25.0 statistical software package for Windows.

Results

Out of the 107 patients included, 90 were women (84.11%) and 17 were men (15.88%). The overall mean age was 48.45 years, being women's mean age, 48.27 years (24 to 85 years) and men's mean age 50.05 years (26 to 76 years).

The overall mean MPV was 8.76 fl (8.57 to 8.96 fl), while the mean PLR was 138.77 (126.8 to 150.74).

Based on the MACIS score, the patients were divided into 4 groups:

- Group #1: 64 patients (10 men, 54 women) with MPV of 8.64 and mean PLR of 145.
- Group #2: 20 patients (3 men, 17 women) with MPV of 8.72 and mean PLR of 137.55.
- Group #3: 13 patients (4 men, 9 women) with MPV of 9.16 and mean PLR of 131.63.
- Group #4: 10 patients (all women) with MPV of 9.13 and mean PLR of 110.35.

A comparison of the 4 groups was performed using 2 variables, MPV and PLR through the 4 × 1 one-way ANOVA test way used as parametric statistical analysis. No statistically significant differences were reported between the cancer severity groups and MPV based on the MACIS score, with a low effect size ($F_{(3,103)}$ = 1456; p = 0.231, f = 0.203). No statistically significant differences were seen either when these groups and PLR were compared, also with a low effect size ($F_{(3,103)}$ = 0.963; p = 0.413; f = 0.164) (Table 1).

Similarly, based on the TNM staging system, patients were divided into four groups: 80 patients as stage I, 14 patients over the age of 55 as stage II, 5 patients as stage III, and 8 patients as stage IV. The ANOVA test did not show any statistically significant differences between the cancer severity groups and MPV based on TNM staging ($F_{(3,103)}$ = 0.119, p = 0.949; f = 0.006). Similarly, no statistically significant differences were reported between the cancer severity groups and the PLR ($F_{(3,103)}$ = 1.940; p = 0.128; f = 0.103). Both analyses presented a low effect size (Table 2).

As a third aspect, a factorial ANOVA analysis was performed to examine the interaction between focality, age (taking age younger or older than 55 years as the reference based on TNM staging in its eighth edition), and MPV. The results obtained were F = 0.891, p = 0.348, and η^2 = 0.009, indicative that the interaction was not statistically significant. Similarly, the effect of these two variables on the PLR was also examined, yielding the following values: F = 1.816, p = 0.181, and η^2 = 0.017, which was not statistically significant either. Additionally, the interaction between the MACIS score and age with MPV was assessed too, yielding the following values: F = 0.82, p = 0.48, and η^2 = 0.024, along with the interaction between these variables and the PLR, resulting in F values of 1.13, p = 0.34, and η^2 = 0.033. All of these interactions showed no statistically significant associations and had low effect sizes.

Table 1. Comparison between mean platelet volume and platelet-to-lymphocyte ratio by groups based on the MACIS score

Risk Group	MPV (mean ± SD)	PLR (mean ± SD)
Very low risk (< 6)	8.64 (0.84)	145.04 (68.93)
Low risk (6-6.99)	8.72 (1.08)	137.55 (56.08)
Intermediate risk (7-7.99)	9.16 (1.03)	131.63 (55.89)
High risk (> 8)	9.13 (1.56)	110.36 (25.23)
p	0.23	0.41
f	0.20	0.16

MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.

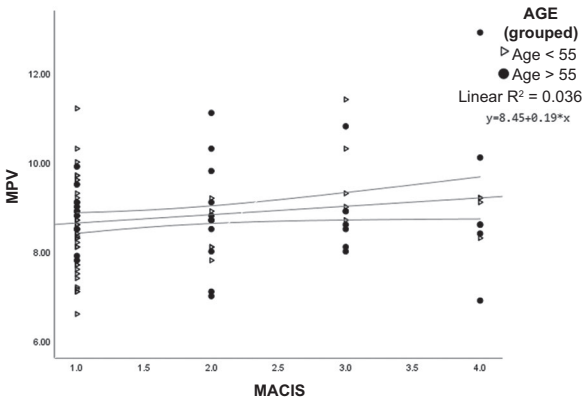

Figure 1. *MACIS-MPV scatter plot.*

Table 2. Group comparison based on the TNM classification

Stage	n (total = 107)	MPV (fl)	PLR (thousands/μL)
Stage I, mean (SD)	n = 80	8.73 (0.876)	143.50 (62.62)
Stage II, mean (SD)	n = 14	8.87 (1.48)	146.52 (70.67)
Stage III, mean (SD)	n = 5	8.90 (1.12)	89.00 (29.43)
Stage IV, mean (SD)	n = 8	8.82 (1.25)	108.97 (43.59)

MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.
p = 0.94 for MPV, and p = 0.12 for PLR groups.

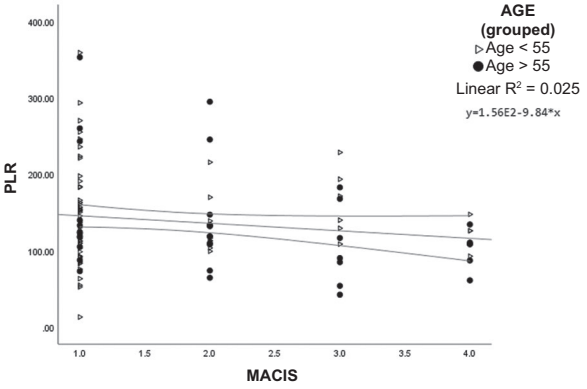

Figure 2. *MACIS-PLR scatter plot.*

Scatter plots were used to analyze the relationship between the MACIS score and MPV and PLR, considering two age groups with a cut-off value of 55 years. The graphs displayed the mean values and confidence intervals. Figure 1 shows that for lower MACIS score categories, MPV values tend to be more closely clustered and homogeneous compared to higher MACIS score categories, showing wider dispersions. Additionally, a positive trend was seen with a regression model y = 8.45 + 0.19*x, with an r² value of 0.036 for MPV, indicating that as the MACIS score increases, the MPV value also tends to go up. Regarding the PLR, the trend was negative with a regression model y = 1.56e2-9.84*x, and an r² value of 0.025. It is obvious that the distribution of PLR values become less scattered as the MACIS score increases, meaning that higher MACIS scores are associated with lower PLR values (Figs. 1 and 2).

Similarly, scatter plots were used to explore the relationship between TNM staging and MPV, as well as between TNM staging and PLR, with consideration of two age groups using 55 years as the cut-off value. The graphs showed the mean values and confidence intervals. Figure 3 shows that the lower the TNM stage, the more closely grouped together the MPV values are compared to higher TNM staging categories, exhibiting more scattered values. A positive trend was also seen with a regression model $y = 8.0.7+0.05*x$, $r^2 = 0.002$ for MPV. Regarding the PLR, the trend is negative with a regression model $y = 1.58e2-13.08*x$, $r^2 = 0.035$, in such a way that the higher the TNM staging, the lower the PLR (Fig. 4).

One notable observation is that in all the graphs, patients under the age of 55 tend to be in lower MACIS score categories, both for MPV and PLR, as well as for TNM.

According to what figures 1 to 4 show regarding the levels of MACIS and TNM in their last categories, linearity seems to be lost. Therefore, it was decided to transform these variables into dummy variables, resulting into 2 different categories: low and high risk. Subsequently, a comparison of the variables MPV and PLR was made with these new levels whose results are shown on table 3.

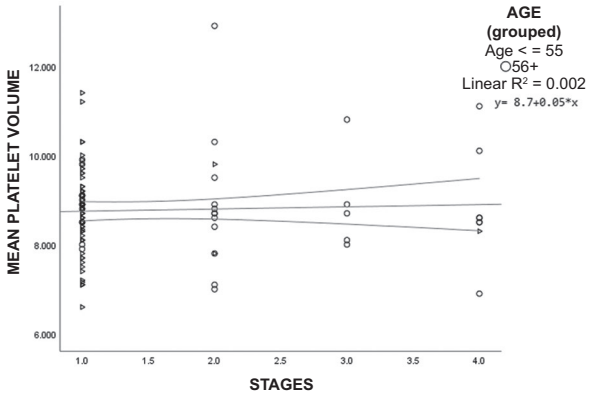

Figure 3. *TNM-MPV scatter plot.*

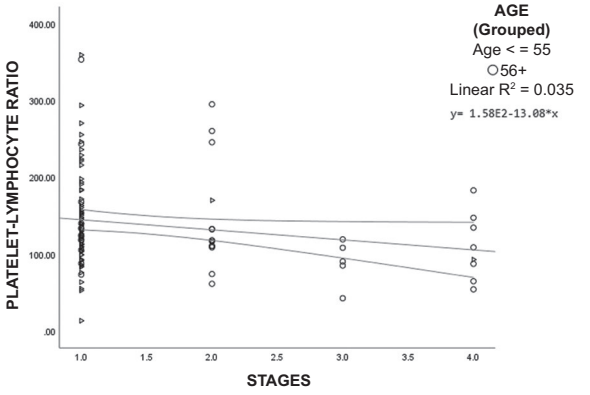

Figure 4. *TNM-PLR scatter plot.*

Table 3. Dummy variables for MACIS and TNM classifications

Category	MPV (fl) (mean ± SD)	PLR (mean ± SD)
MACIS		
Low risk	0.86 (0.89)	143.26 (65.85)
High risk	9.14 (1.25)	122.38 (45.61)
p	0.040	0.157
d	0.49	0.33
TNM		
Stages I & II, mean (SD)	8.72 (0.87)	143.83 (62.3)
Stages III & IV, mean (SD)	8.90 (1.32)	123.00 (61.51)
p	0.419	0.140
d	0.18	0.33

MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.

As we can see, statistically significant differences were found for the MACIS variable. Those in the high category had higher MPV values compared to those in the lower category. However, the effect size in these results was low. On the other hand, no differences were seen regarding the TNM variable.

Discussion

The current approach for patients with papillary thyroid microcarcinoma classified as low risk involves "active surveillance"[33,34]. However, as it occurs with almost everything in medicine, this strategy is not perfect, and over time, some patients may still require conventional treatment. Up until now, the reason why some low-risk patients eventually experience disease persistence or recurrence is not yet clearly understood, not even after identifying the genetic factors associated with aggressiveness[35,36]. Therefore, we should have accessible diagnostic tools to help us make the proper therapeutic decisions[37,38].

MPV has been investigated in multiple types of cancer, and it has been demonstrated that MPV values are significantly higher in patients with endometrial, ovarian, colorectal, and gastric cancers compared to healthy controls. However, the findings related to thyroid cancer are inconclusive. Baldane et al.[39] reported on significantly higher MPV values in thyroid cancer patients compared to benign goiters and healthy subjects, with a significant decrease after tumor resection.39 However, a different study conducted by Dincel and Bayraktar[40] failed to find such difference. Both studies included very few patients and did not discard the impact of comorbidities and use of drugs. A different study found that blood cell indices, specifically the PLR and MPV, can provide information on multifocal tumors, extrathyroidal spread, and presence of a T3 tumor, thus serving as a means to exclude these characteristics[41]. In our study, we sought to investigate the interaction between age and tumor focality, but no such association was found. Similarly, no relationship was ever found between the PLR and MPV in the detection of more advanced stages based on the MACIS and TNM classifications. In both analyses, both the P values and the effect size did not show any differences or interactions, as the effect size was consistently low. We should remember that low effect sizes indicate, in this case, that the levels of MACIS and TNM cannot account for the differences or interactions described in the dependent variables of PLR and MPV.

Another study conducted by Yu et al.[42] found no significant correlations between the MPV and platelet distribution width with TNM classification, lymph node metastases or distant metastases in patients with papillary and medullary thyroid cancer. However, it was

useful in follicular thyroid cancer stages T3 and T4, with lower MPV values being reported in the presence of lymph node metastases. This effect was not seen in patients in stages T1 and T2, suggesting that platelets may exert different effects based on the different subtypes of thyroid cancer. This leads us to believe that our study focused specifically on papillary thyroid cancer, without including patients with follicular, medullary or anaplastic thyroid cancer. We chose to study this population group because papillary thyroid cancer is the most predominant type worldwide and is the most prevalent one among Mexicans. However, we should determine whether these platelet markers are useful in other subtypes of thyroid cancer, something we did not analyze in our study. Still, its clinical utility should not be overlooked.

Our study is no stranger to limitations given its observational and cross-sectional nature, which affects our ability to draw conclusions of causality. It was also impossible to exclude unmeasured confounders, such as comorbidities that could be altering platelet index counts (diabetes, hypertension, obesity, history of heart diseases or smoking), and the use of certain drugs. Despite these limitations, our study had strengths, including a sample size that was not as small as in other studies and the fact that it was conducted at a single center, thus ensuring more uniform data curation, especially obtaining preoperative platelet index measurements, and avoiding biases that could arise from data obtained from external laboratories or hospitals. The findings of this study might serve as a starting point for further research, considering the heterogeneity of results on this topic and the fact that the mechanisms through which papillary thyroid cancer evades or elicits the immune response and its degree of invasion and recurrence are still to be elucidated.

An incidental finding of the study was that, when the issue of linearity in MACIS and TNM scores was addressed by downgrading from 4 (very low, low, intermediate, and high risk) to just 2 categories (low and high risk), statistically significant differences were found in MPV for MACIS, although the effect size was low. However, in the case of TNM, where 4 categories were downgraded into 2 based on the absence or presence of lymphovascular invasion, no statistically significant differences were seen.

Conclusions

In our study, the PLR and the MPV did not show any possible relationships to distinguish between early and advanced stages of papillary thyroid cancer. Additionally, no association was found between locally advanced invasion or multifocality, which is indicative that these platelet markers cannot predict a more aggressive behavior of cancer initially classified as early stage despite de reasoning behind tumor pathophysiology We should understand that this study represents only the first step in the ongoing search for new markers that can help us make better decisions to treat patients with papillary thyroid cancer. By identifying such markers preoperatively, we could gain a deeper understanding of the tumor's biological behavior.

Acknowledgements

The authors express their gratitude to their teachers and colleagues from the General Surgery Department, as well as all the medical residents and staff who make the Hospital General de México a great health center.

Funding

None whatsoever.

Conflicts of interest

none reported.

Ethical disclosures

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

Patients' data protection. 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

Naso-sinus findings by computed tomography in pediatric chronic dacryocystitis

Hallazgos nasosinusales por tomografía computada en dacriocistitis crónica pediátrica

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Abstract

Objective: *To evaluate the preoperative tomographic characteristics of the nose and paranasal sinuses of children with chronic dacryocystitis.* **Method:** *Prospective, observational, cross-sectional, and descriptive study. CT scans of the paranasal sinuses of patients candidates for endoscopic dacryocystorhinostomy were evaluated for two years. Demographic characteristics, radiological findings, inflammatory processes and anatomical variants were identified using the Lund-Mackay classification. Statistic analysis. Stata 10.0, descriptive analysis, Student's t: mean difference and χ2. Logistic studies to estimate the probability between variables.* **Results:** *27 men and 11 women (n = 38) were included. Of these, 22 had unilateral and 16 bilateral nasolacrimal duct involvement. Lund-Mackay score range: 2-20. Eleven patients had associated pathology. The most affected were anterior and maxillary ethmoidal sinus (69%), osteomeatal complex (68%), posterior ethmoidal (51%). Patients with severe rhinosinusitis are 12 times more likely to develop dacryocystitis than patients with < 12 points. Men presented greater severity, affectation, and clinical repercussion.* **Conclusions:** *There is radiological rhinosinusal involvement in dacryocystitis, which must be evaluated and treated preoperatively to avoid postoperative complications or reinfections.*

Keywords: *Dacryocystitis. Sinusitis. Computed tomography. Paranasal sinuses. Nasolacrimal duct. Dacryostenosis.*

Resumen

Objetivo: *Evaluar las características tomográficas preoperatorias de la nariz y los senos paranasales de niños con dacriocistitis crónica.* **Método:** *Estudio prospectivo, observacional, transversal y descriptivo. Se evaluaron tomografías de senos paranasales de pacientes candidatos a dacriocistorrinostomía endoscópica, durante 2 años. Se identificaron características demográficas, hallazgos radiológicos, procesos inflamatorios y variantes anatómicas, utilizando la clasificación Lund-Mackay. Análisis estadístico con Stata 10.0, análisis descriptivo con t de Student: diferencia medias y χ2. Estudios logísticos para estimar la probabilidad entre variables.* **Resultados:** *Se incluyeron 27 hombres y 11 mujeres (n = 38). De ellos, 22 tenían afección del conducto nasolagrimal unilateral y 16 bilateral. Rango de puntuación de Lund-Mackay: 2-20. Once pacientes tuvieron patología asociada. Seno etmoidal anterior y maxilar más afectados (69%), complejo osteomeatal (68%), etmoidal posterior (51%). La probabilidad de que los pacientes con rinosinusitis grave puedan presentar dacriocistitis es 12 veces mayor que en los pacientes con < 12 puntos. Los hombres presentaron mayor gravedad, afectación y repercusión clínica.* **Conclusiones:** *Existe afección rinosinusal radiológica en la dacriocistitis, que debe ser evaluada y tratada en el preoperatorio para evitar complicaciones o reinfecciones posquirúrgicas.*

Palabras clave: *Dacriocistitis. Sinusitis. Tomografía computada. Senos paranasales. Conducto nasolagrimal. Dacrioestenosis.*

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Date of reception: 09-12-2020
Date of acceptance: 11-03-2021
DOI: 10.24875/CIRUE.M23000431

Cir Cir (Eng). 2023;91(1):84-90
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

In cases of chronic dacryocystitis, which involve inflammation of the sac and nasolacrimal duct for over 6 months, surgical treatment is required for some patients. The surgical technique often used is either open or endoscopic, but before deciding what the proper therapeutic approach is and regardless of its etiology, it is of paramount importance to assess the anatomical and pathological conditions of the lacrimal apparatus and paranasal sinuses—closely related structures—using computed tomography (CT) of the nose and paranasal sinuses. Multiple imaging modalities, such as dacryocystography, 3D images[1], CT dacryocystography, and magnetic resonance imaging[2,3], can be used to study both the sac and the lacrimal passage. Nonetheless, high-resolution CT plays a crucial role in the evaluation of patients, providing a map of the region of interest eligible for endoscopic surgery. The technological advancements made that have improved the quality of the CT scan have allowed us to conduct comprehensive assessments and make effective decisions, thus avoiding unnecessary treatments and reducing the extent of the lesion. Over the past decade, there has been a growing interest in endoscopic facial surgery with a focus on minimally invasive approaches, leading to a lower morbidity rate.

The management of the lacrimal system has proven to be effective and safe. However, it requires a thorough evaluation of the nasosinusal condition, including CT imaging. Correlating preoperative images and clinical findings allows the surgeon to consider suitable surgical options, leading to fewer complications and optimal resolution of the clinical condition[4].

To identify and understand the facial areas requiring special care, proper understanding of the anatomy and its variants through imaging is essential. These variants can be stratified based on the Lund-Mackay classification[5].

In the surgical planning of patients with dacryocystitis or dacryostenosis, studies often focus on evaluating the lacrimal sac and surrounding structures. However, while treating multiple pediatric patients, it has been confirmed that some were not only carriers of dacryocystitis but also had concomitant rhinosinusitis, raising the question of whether the lacrimal obstructive process may have contributed to exacerbating a surrounding infection, thus requiring control to avoid complications or recurrences. Therefore, we decided to conduct the present study to identify the characteristics of the sac and the incidence rate of sinusitis as a comorbidity among the pediatric population.

The Lund-Mackay system is the most widely used method to stage rhinosinusitis in clinical trials[5]. This method was developed as an evaluation tool to facilitate therapeutic decision-making in the mid-1980s[6]. The system uses CT images to study paranasal sinuses. Each group of sinuses is classified as 0 (complete absence of opacity), 1 (partial opacity), and 2 (total opacity). The sum of these scores results in a value ranging from 0 to 24.

Various anatomical variants can be identified, such as the absence of frontal sinus, the presence of concha bullosa, the paradoxical curvature of the middle turbinate, the existence of Haller cells, the inverted uncinate process, and the pneumatized agger nasi.

The history of previous surgery is rated as either 0 or 1, and current symptoms are assessed on a scale from 0 to 10. However, it is not taken into consideration in the overall score of the classification of tomographic findings.

In addition to the imaging findings, surgical observations, such as the presence of polyps, purulent secretions, mucosal edema, scarring, and synechiae, are graded on a scale from 0 to 2 each[7].

Method

This was a prospective, observational, descriptive, and cross-sectional study. Patient recruitment and treatment were conducted over a 2-year period. The following inclusion criteria were considered: a) pediatric patients (under 16 years) of both sexes; b) with a clinical diagnosis of unilateral or bilateral chronic dacryostenosis; c) scheduled for endoscopic dacryocystorhinostomy surgery; d) evaluated preoperatively with high-resolution helical CT scans in axial and coronal views of the nose and paranasal sinuses, specifically requested for the surgical procedure; e) beneficiaries of the center; f) no prior surgical treatment in the region of interest or ocular area, no congenital or traumatic alterations affecting the anatomy or nasal or sinus anatomy or known carriers of rhinosinusitis with previous rhinosinusal treatments; and g) with consent from the patient's family or tutor to participate in the study after written prior informed consent. Patients with incomplete studies, lost studies, or technical problems resulting in poor image quality were excluded.

After the project was authorized by the research and ethics committee, and after clinical evaluation and CT

assessment, the study proceeded to look for and identify anatomical and pathological findings on both the nose and paranasal sinus CT scans performed with a Siemens Somatom AR system and a Magic View SIEMENS image viewing station. The CT scan was interpreted by an expert radiologist and an otolaryngologist. The study included the characteristics, development, and pneumatization of ethmoid, sphenoid, maxillary, and frontal sinuses based on age, inflammatory processes, patency of the ostium, anatomical changes, and nasolacrimal duct conditions, among others. The findings were classified using the Lund-Mackay scale.

Results

A total of 38 patients who were scheduled for dacryocystorhinostomy. CT scans of the nose and paranasal sinuses were performed. The patients' mean age of 5.7 years (standard deviation, ± 2.8 years) and age range from 2 to 12 years. Patients were boys (27 [71%]), and girls (11 [29%]) (Table 1).

The site of chronic dacryocystitis due to congenital stenosis was determined as bilateral in 15 cases (40%), right-sided in 13 (34%), and left-sided in 10 (26%). In males, the incidence rate of bilateral dacryocystitis was slightly higher (10 cases). However, the statistical analysis did not show any significant differences in the presence of dacryocystitis between the two sexes (p = 0.99) or predominance of one side over the other (p = 0.38).

In the clinical assessment, most patients did not show any comorbidities. In 27 children (72%), eye conditions were the only disease found, and given the patient's age, in 5 children (13%), adenoid hypertrophy was associated with rhinosinusal signs given the age of the patient. Additionally, 3 children (8%) showed a deviated septum, 2 (5%) turbinal hypertrophy, and 1 (3%) allergic rhinitis, that were identified as contributing factors to the disease. There was a statistically significant difference between those with an associated condition and those without one (p = 0.03).

Clinical findings

Regarding the clinical findings, although they were not the objective of the study, intercurrent tearing, yellowish and thick discharges, and conjunctival injection were identified in 100% of the patients during acute episodes, which improved with medical therapy with antibiotics, ocular hygiene, and massage. In some cases, given the presence of intercurrent abscesses

Table 1. Overall characteristics of the population (n = 38)

Age (years)	No. of patients	Percentage
2	1	3%
3	8	24%
4	10	26%
5	2	5%
6	4	11%
7	2	5%
8	4	11%
9	2	5%
10	2	5%
11	1	3%
12	2	5%

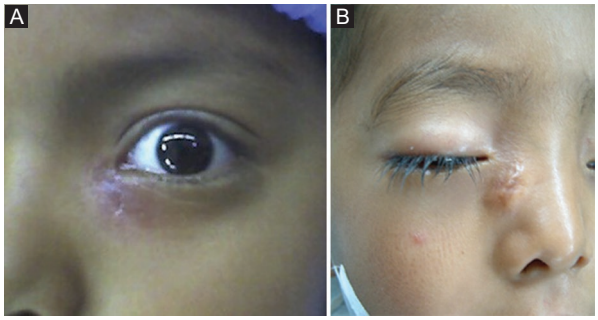

Figure 1. *Scar changes* **A:** *in the inner corner of the eye.* **B:** *in the lacrimal sac.*

in the lacrimal sac, classical inflammatory changes were seen during the acute phase: warmth, redness, and hyperemia, which resolved with scarring in the area (Fig. 1). Rhinoscopy revealed the presence of thick yellowish rhinorrhea of different amounts in 30 patients (79%) in the nasal passages and, in some cases, through the middle meatus, along with nasal congestion and hyperemia. All patients received antibiotic treatment and nasal washes for control prior to surgery. Figure 2 shows the intraoperative appearance of the lacrimal sac opening with a very thick and hard to eliminate mucopurulent secretion.

Radiological assessment

According to the Lund-Mackay classification, the maximum score to assess the extent and severity of

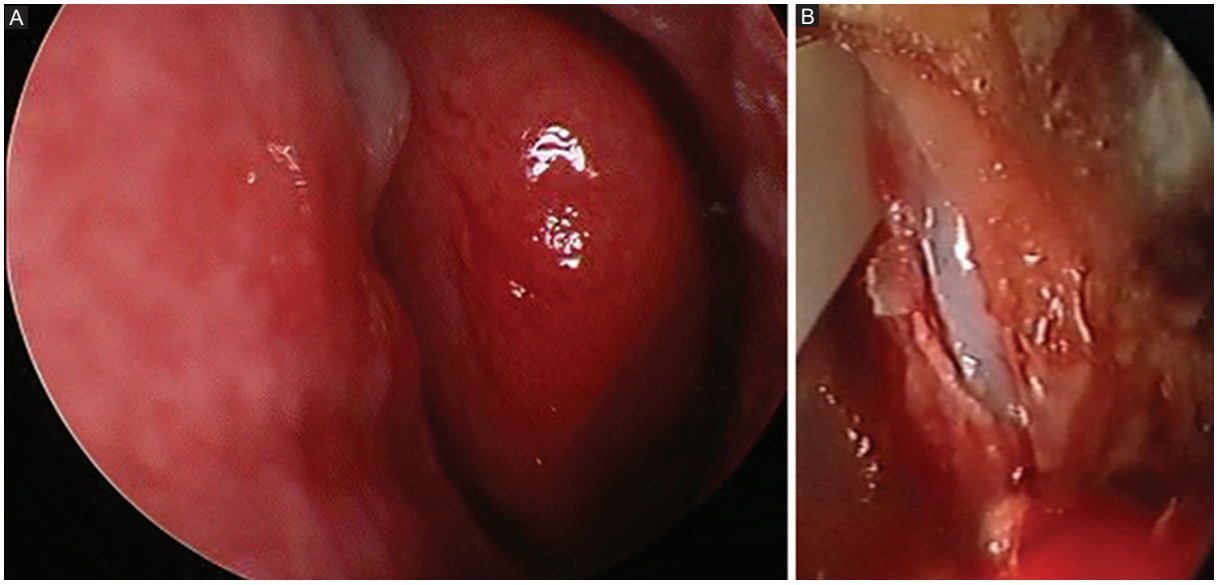

Figure 2. A: *endonasal endoscopic view showing mucosal congestion and hyperemia.* **B:** *after opening the lacrimal sac, abundant mucopurulent secretion can be seen.*

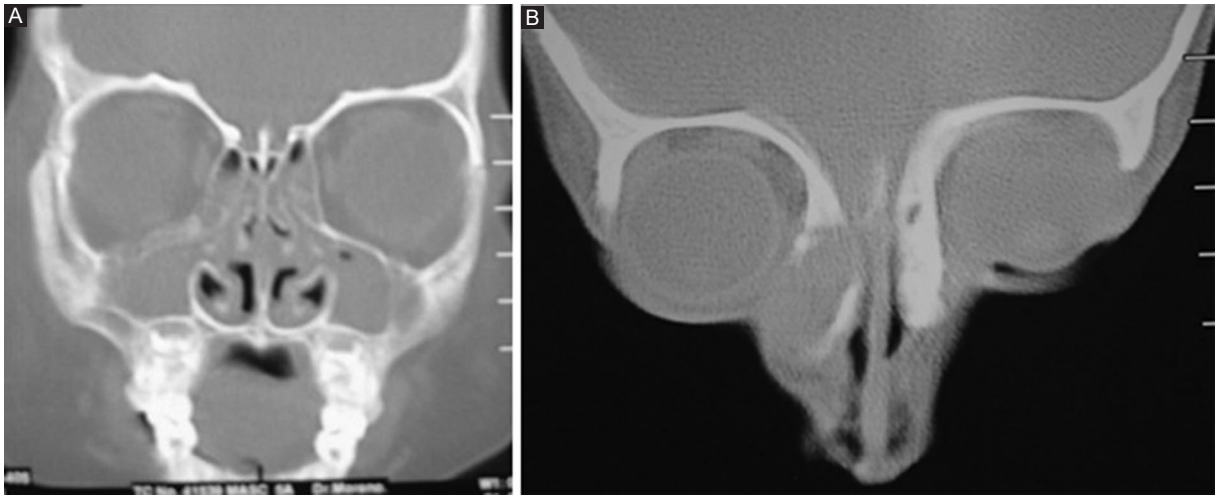

Figure 3. A: *coronal computed tomography scan showing total opacity of the bilateral ethmoidal and maxillary paranasal sinuses.* **B:** *dilated lacrimal sac filled with soft tissue density.*

the inflammatory process detected in the CT scans of paranasal sinuses was between 0 and 12 in 29 patients (76%), while the remaining 9 patients (24%) scored over 13 points. The score range went from 2 to 20 points (Table 2). The right side was more frequently and severely damaged. Most children with right-sided dacryocystitis (54%) scored 5 in the Lund-Mackay scale, 3 children scored > 8 points, and 3 < 4 points.

Among the patients with right-sided radiological changes on the CT scan, 11 did not show homolateral ocular involvement; instead, another sinus was affected with an inflammatory process, obtaining scores of 7 and 11 points on the scale used. In contrast, when it comes to left-sided chronic dacryocystitis, 10 children did show homolateral pathology as seen on the images, with variable scores from 2 to 9 points.

The highest number of patients and scores was found in those with bilateral involvement (15 patients) (Fig. 3). In these patients, the changes seen on the CT scan were greater, with scores ranging from 5 to 10, especially on the left side, which was not always the most

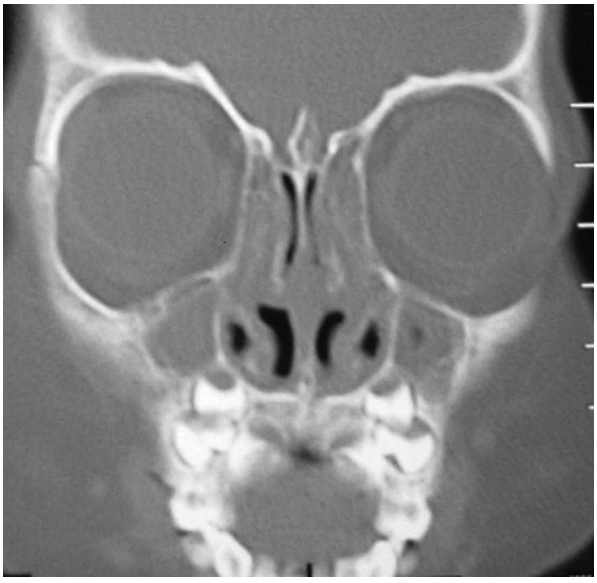

Figure 4. *Coronal computed tomography scan showing total opacity of paranasal sinuses in a child with chronic dacryocystitis.*

Table 2. Scores obtained on the computed tomography scan based on the Lund-Mackay scale

Lund-Mackay Score	Bilateral	Frequency	Cumulative percentage
2	1	2.63%	2.63%
4	2	2.67%	7.89%
5	13	34.21%	42.11%
8	4	10.53%	52.63%
10	5	13.16%	65.79%
12	4	10.53%	76.32%
13	1	2.63%	78.95%
14	1	2.63%	81.58%
15	1	2.63%	84.21%
16	3	7.89%	92.11%
18	1	2.63%	94.74%
20	2	5.26%	100%
Total	38	100%	100%

clinically diseased one. However, we saw that younger patients had a higher degree of involvement (Fig. 3).

Considering the predominance of chronic rhinosinusal data in the side damaged, we found that in right-sided dacryocystitis, 13 patients showed bilateral sinusitis with scores of 5 points (7 patients [54%]), 12 points (3 patients [23%]), 8 points (2 patients [15%]), and 4 points (1 patient [8%]).

When dacryocystitis was left-sided, cases of bilateral sinusitis showed scores of 5 points (4 patients [40%]), 8 points [2 patients (20%)], 12 points (1 patient [10%]), 15 points (1 patient [10%]), 4 points (1 patient [10%]), and 2 points (1 patient [10%]).

Finally, in the presence of bilateral dacryocystitis and sinusitis, 5 patients (33%) scored 10 points, 3 patients (20%), 16 points; 2 patients (13%), 20 points; 2 patients (13%), 5 points; 1 patient (7%), 14 points; and 1 patient (7%), 13 points.

Pathology in the osteomeatal complex was identified in 28 patients (74%); of these, 24 patients (63%) on the left side and 28 (74%) on the right side. The most frequently damaged paranasal sinuses were the maxillary and the anterior and posterior ethmoid sinuses.

The maxillary sinus was damaged in 25 patients, with peripheral mucosal thickening in 18 patients and complete opacification in 10. The anterior and posterior ethmoid sinuses were damaged in 28 patients, with partial and complete opacification in 13 and 15 patients, respectively. The frontal sinus was damaged in 5 patients, with complete opacification in 4, of the homolateral side of the lacrimal issue. Only 3 patients showed pathology in the sphenoid sinus: mucosal thickening (2) and complete opacification (1) (Fig. 4).

The analysis of results showed that whenever the osteomeatal complex was obstructed, the ethmoid cells were also partially or completely opacified ($p = 0.00$), unlike the association between the levels of obstruction in the frontal ($p = 0.271$) or sphenoid sinuses ($p = 0.45$). Also, an association was found between the obstruction of the osteomeatal complex and the partial or total opacification of the maxillary sinus ($p = 0.00$).

Statistically significant differences ($p = 0.00$) were found in the mean opacity of the anterior ethmoid among individuals with grade 1 compared to grade 2 involvement (22 vs 16). This means that the degree of opacity of the anterior ethmoid was statistically higher in individuals with higher scores on the Lund-Mackay scale.

Similarly, statistically significant differences were found ($p = 0.0001$) in the mean opacity of the maxillary sinus between the group of individuals with grade 1 and grade 2 involvement (22 vs 16). This means that the degree of opacity of the anterior ethmoid sinus was statistically higher in individuals with higher degrees of involvement according to the Lund-Mackay scale.

No statistically significant differences were found in the mean level of opacity between the frontal and the sphenoid sinuses among individuals with different degrees of involvement according to the Lund-Mackay scale.

The mean opacity of all paranasal sinuses was statistically higher (p = 0.00) in individuals with a high compared to a low degree of involvement of left paranasal sinuses according to the Lund-Mackay scale.

The logistic analysis showed that sex contributes marginally (p = 0.094) to the degree of involvement in patients, being the severity of involvement lower in girls (odds ratio [OR]: 0.28) compared to boys. However, sex *per se* does not contribute to the development of dacryocystitis.

This is consistent with the medical literature available, which suggests that girls have fewer chances (OR, 0.81)8,9 than boys to show high values of bilateral rhinosinusitis according to the Lund-Mackay scale (p = 0.016). Results suggest that girls have fewer chances (OR, 0.2) of scoring > 12 points on the Lund-Mackay scale (p = 0.054). Individuals scoring > 12 points on this scale have 12 times more chances of experiencing dacryocystitis (OR, 13.05; p = 0.014).

Discussion

Chronic rhinosinusitis and dacryocystitis are two conditions that often appear together as changes on the CT images specifically obtained to study dacryocystitis.

When dacryocystitis requires endoscopic surgery, the evaluation of the CT images of paranasal sinuses and the nasolacrimal duct is performed comprehensively, because the surgical technique of endoscopic dacryocystectomy directly involves the anterior ethmoid cells, which are part of the group of paranasal sinuses (in addition to frontal and maxillary sinuses) that drain into the middle meatus and create structures and spaces of the osteomeatal complex to avoid complications. Therefore, the interrelation of these structures in an inflammatory process should be seen as part of a whole in the target surgical area.

No studies have been identified in the medical literature available that relate the presence of rhinosinusitis with dacryocystitis, sex or age. No studies have been found either discussing the relationship between anatomical variants and dacryocystitis. In patients with dacryocystitis, the condition of paranasal sinuses is not often assessed in a standard way, which could exacerbate the clinical picture or limit the response to treatment.

The results obtained in the group we studied drew our attention to the higher frequency of dacryocystitis and rhinosinusitis in boys and the higher prevalence of both conditions in the 3 to 6 years age group.

Some studies suggest that women have a higher risk of chronic rhinosinusitis (CRS), with sex differences in the degree of opacification of paranasal sinuses[8,9]. Masculine sex has also been associated with higher scores, with 2.7 times more chances of experiencing diffuse sinus involvement compared to females[10], as it was the cases of the present study, which requires further specific research.

We did not find a relationship between the existence of anatomical variant and the presence of dacryocystitis. The severity of rhinosinusitis in patients with dacryocystitis was not a parameter of evaluation. However, a relationship was found between dacryocystitis and the severity of paranasal sinuses disease in the patients studied, which opens further lines of research on the convenience of combined treatments between otorhinolaryngology and ophthalmology to prevent infections during surgery, and even elucidate to what extent the coexistence of both conditions could be a determining factor in the persistence of dacryocystitis or if it could reduce the need for surgery.

Finally, the tomographic evaluation of patients with dacryocystitis eligible for surgery using the technique of endoscopic dacryorhinocystostomy is crucial to know the state of paranasal sinuses, assess the conditions of the lacrimal pathway more accurately, and avoid complications when performing the procedure[11,12].

Conclusions

in our study, the highest incidence rate of dacryocystitis was found in the 3 to 6 years age group. Whenever the osteomeatal complex was obstructed, the paranasal sinuses draining into this substructure were partially or completely damaged, which is explained by the common drainage of this complex. The frontal and sphenoid sinuses are rarely damaged due to their anatomophysiology.

Patients with chronic dacryocystitis may present with 12-fold higher chances of severe rhinosinusitis than patients scoring < 12 points in the Lund-Mackay scale.

The associated nasal comorbidity has no relation to the presence of dacryocystitis, most likely because neither adenoid hypertrophy nor septal deformity directly obstruct the nasolacrimal duct drainage.

There is no known cause that may explain why males are more affected by rhinosinusitis, which is probably a random finding.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. 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).

Patients' data protection. 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

Cavernous sinus: anatomy, histology and terminology

Seno cavernoso: anatomía, histología y terminología

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Abstract

Background: *Although the cavernous sinus (CS) has been studied since 1695, its anatomy and name are still under discussion.* **Method:** *Anatomy and histology of 40 CS from human cadavers were studied, included both from a newborn specimen.* **Results:** *Two walls limit the CS, an inferior medial one composed only of the dura's outer layer and a superior lateral one consisting of both dura's layers. Sinusoidal veins pass through the lateral wall of the CS as a transition between venous tributaries and the CS. An endothelial layer covers the inner surface of the CS and the outer surface of the internal carotid artery. The space within the CS shows trabeculae, which are rarer in adults compared to the newborn. The loss of trabeculae in the CS may be a natural process along with life.* **Conclusions:** *In conclusion, the CS is a real sinus, and the term "cavernous sinus" is appropriately applied.*

Keywords: *Cavernous sinus. Internal carotid artery. Venous sinus. Lateral sellar compartment. Parasellar venous pathway.*

Resumen

Antecedentes: *Si bien el seno cavernoso (SC) ha sido estudiado desde 1695, su anatomía y nombre aún están bajo discusión.* **Métodos:** *Se estudiaron la anatomía y la histología de 40 SC de cadáveres humanos, incluyendo los dos de un recién nacido.* **Resultados:** *El SC está limitado por dos paredes, una inferomedial compuesta solo por la capa más externa de la duramadre y otra superolateral compuesta por ambas capas de la duramadre. Hay venas sinusoidales que atraviesan la pared lateral del SC formando una transición entre venas tributarias y el SC. Una capa endotelial recubre la superficie interna del SC y la superficie externa de la arteria carótida interna. El espacio dentro del SC presenta trabéculas, las cuales son escasas en el adulto en comparación con el recién nacido. La pérdida de trabéculas en el SC puede ser un proceso natural a lo largo de la vida.* **Conclusiones:** *En conclusión, el SC es un verdadero seno, por lo que el término «seno cavernoso» se aplica de forma correcta.*

Palabras clave: *Seno cavernoso. Arteria carótida interna. Seno venoso. Compartimento lateral selar. Vía venosa paraselar.*

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Date of reception: 28-02-2021
Date of acceptance: 25-05-2021
DOI: 10.24875/CIRUE.M23000432

Cir Cir (Eng). 2023;91(1):91-96
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

The dura mater is the outermost meningeal layer made up of 2 layers according to some authors. The outermost layer includes the periosteum or, as some authors call it, the endosteum. The inner layer includes the true dura mater, the dural or meningeal layer[1-5]. However, other authors propose that only the outer layer should be considered the dura mater[6,7]. Venous sinuses are spaces that contain and drain venous blood from the brain and pericranial structures. The two layers of the dura mater outline the venous sinuses, according to Carpenter[1]. According to Barr[6], the 2 layers outline true dura mater and the periosteum. In any case, a venous sinus can be intra- or extradural, considering that "sinus" means "cavity."

The term "cavernous sinus" (CS) was first coined by Winslow bak in 1732[8,9], and has been studied since 1695. However, there is still no consensus on its anatomy, histology, and terminology. The CS is a paired space, lateral to the sella turcica, located on the intracranial surface of the sphenoid and temporal bones. The internal carotid artery (ICA) runs through it, while the oculomotor and trochlear cranial nerves are found inside its lateral wall, as well as the ophthalmic and maxillary branches of the trigeminal nerve. The abducens cranial and sympathetic nerves run medial to the lateral wall inside the CS[2-5,9-14].

There is controversy on the location of the CS with respect to the dura mater; an extradural space for some authors[6,10,11,15-21], an intradural space for others[3,9,22-27].

Several reports on the interior anatomy of the CS describe it as a trabeculated space filled with blood[8,9,14,24], while others describe it as a space where a venous plexus surrounding the ICA is located[2,10,15,28-30]. It is precisely because of this duality of concepts, that the term "cavernous sinus" has become a topic of discussion. Some authors maintain the concept of CS[2-4,9,13,14,22,23,31,32], while others prefer to call it lateral sellar compartment or parasellar venous pathway[10]. However, many of these observations were done in dissections under stereoscopic microscopy, and only a few were histological observations. Therefore, we decided to study the anatomy of the CS using both stereoscopic microscopy and histological sections.

Method

This was a cross-sectional, observational, and descriptive study of 40 cavernous sinuses from 19 adult human cadavers and 1 newborn whose cause of death was not cerebral. From the adult cadavers, blocks from the parasellar and sellar regions were obtained that were fixed in a 10% formaldehyde solution after being injected with liquid acetate colored with red paint through the common carotid arteries and internal jugular veins. The two cavernous sinuses of each specimen were dissected under microscopic vision, and then, paraffin sections stained with hematoxylin-eosin were obtained from each CS. The newborn's cavernous sinuses were fixed with a 1.5% glutaraldehyde solution to obtain semi-thin araldite sections stained with toluidine blue after being washed with a sodium cacodylate buffer solution (pH 7.2) through the common carotid arteries.

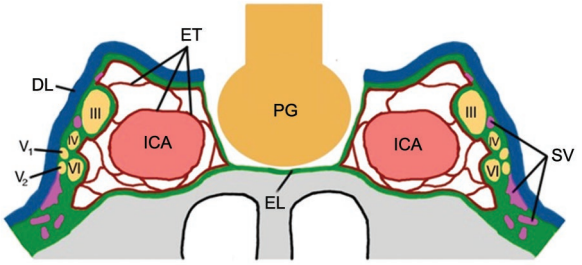

Figure 1. *Internal anatomy of the cavernous sinus (coronal section). DL: dural layer; EL: endosteal layer; ET: endothelium; ICA: internal carotid artery; III, oculomotor nerve; IV, trochlear nerve; PG: pituitary gland; SV: sinusoidal veins; V_1: ophthalmic branch of the trigeminal nerve; V_2: maxillary branch of the trigeminal nerve; VI: abducens nerve.*

Results

We found that the CS superolateral wall is a thick wall made by both layers of the dura mater (Figs. 1 and 2). We saw venous channels in the lateral wall ending inside the CS, through which the afferent veins drain; these venous channels separate the two layers of the lateral wall. These channels are similar to those in the superior longitudinal sinus, those that Testut and Latarjet[24] referred to as sinusoidal veins (Figs. 3 and 4)[24].

The inferomedial wall is thinner than the lateral one and is only made up of the outer layer of the dura mater that represents the periosteum or endosteum of the base of the skull. This layer surrounds the structures inside the CS lateral wall (oculomotor and trochlear cranial nerves, ophthalmic branches, and maxillary branches of the trigeminal nerves). We also found that the endosteum surrounds the abducens

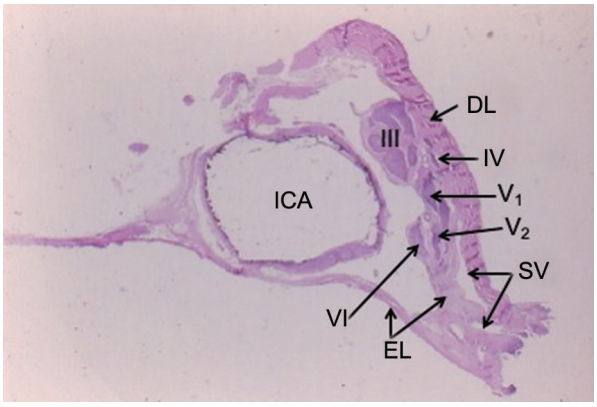

Figure 2. *Microscopic image of the cavernous sinus. Coronal section of a paraffin block stained with hematoxylin-eosin. DL: dural layer; EL: endosteal layer; ICA: internal carotid artery; III, oculomotor nerve; IV: trochlear nerve; SV: sinusoidal veins; V_1: ophthalmic branch of the trigeminal nerve; V_2: maxillary branch of the trigeminal nerve; VI: abducens nerve.*

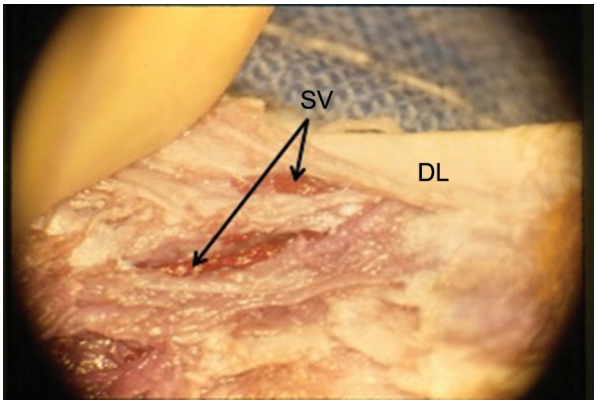

Figure 3. *Dissection of the cavernous sinus lateral wall, longitudinally traversed by the sinusoidal veins. DL: dural layer; SV: sinusoidal veins.*

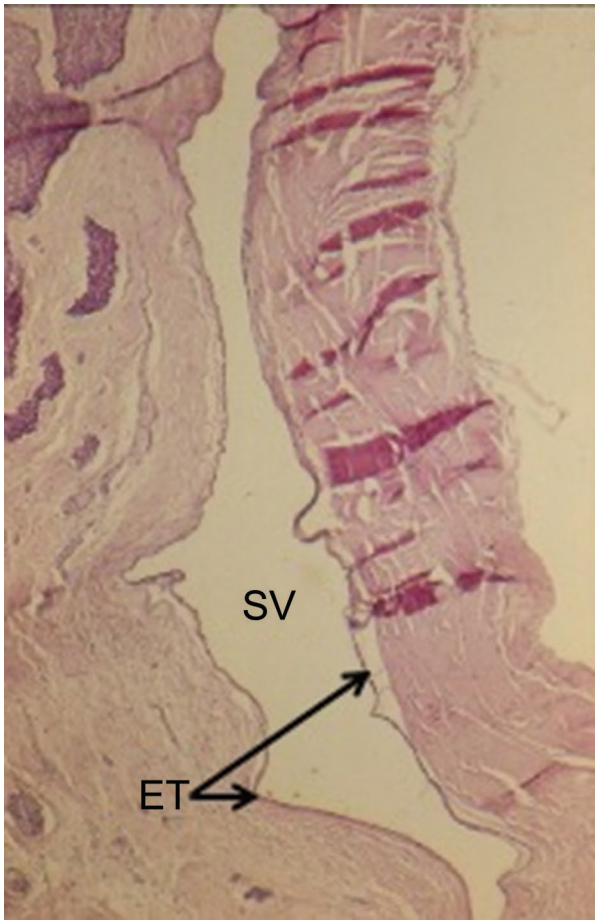

Figure 4. *Microscopic image of the cavernous sinus (close-up of figure 2). Coronal section of a paraffin block stained with hematoxylin-eosin. ET:, endothelium; SV: sinusoidal veins.*

cranial and sympathetic nerves that run medial to the CS lateral wall (Fig. 5).

The cavernous portion of the ICA runs inside the CS. There are multiple irregular trabeculae between the walls of the CS and the ICA. A layer of modified endothelium covers the inner surface of the CS and reflects to cover the tunica adventitia of the ICA. This arrangement resembles the visceral peritoneum (Fig. 6).

The newborn's CSs showed more trabeculae than the adults' CSs.

Discussion

Our results are consistent with those proposed by Carpenter[1], Loveren et al.[2], Campero et al.[3], and Boardman et al.[14], that the dura mater is made up of two layers. It is well known that some venous sinuses are limited by the two layers of the dura mater, as it is the case of the superior longitudinal sinus, or solely by the dural layer (the case of the inferior longitudinal sinus).

We found that the CS is a unique structure divided by trabeculae, not a venous plexus with multiple veins. This is consistent with the descriptions given by authors such as Harris and Rhoton[9], among others[8,14,24], but in contrast with what other authors have described[2,10,15,28-30]. Given this finding, we consider the use of the term "cavernous sinus" is the proper term to use (Fig. 7). However, Hashimoto et al.[4] argue that both concepts are not mutually exclusive and that based on the different variations in the development of the CS, it can be arranged as a sinusoidal venous space with trabeculae or as a venous plexus with multiple veins.

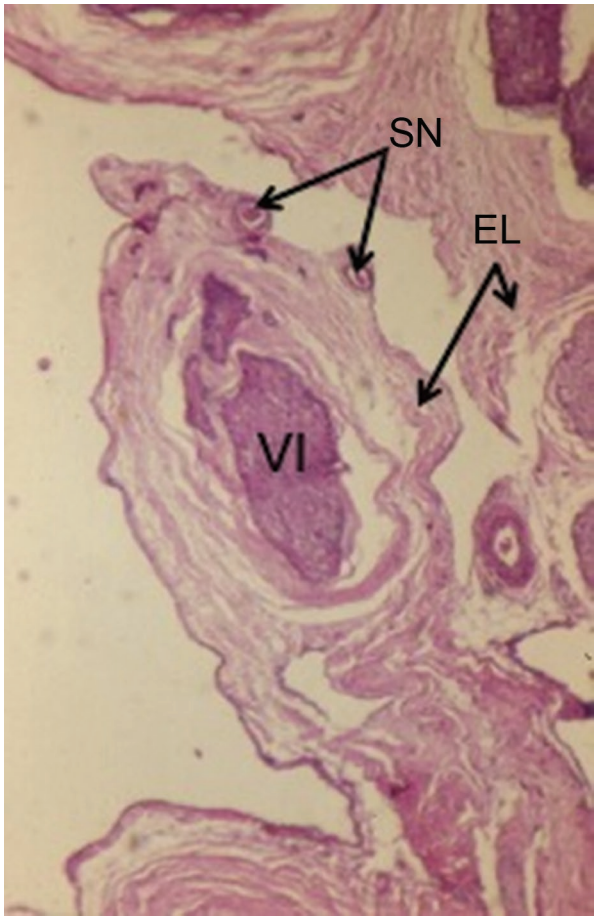

Figure 5. *Microscopic image of the cavernous sinus (close-up to the abducens nerve). Coronal section of a paraffin block stained with hematoxylin-eosin. EL, endosteal layer; SN, sympathetic nerves; VI, abducens nerve.*

We agree with the authors who propose that the CS is limited by two walls, an inferomedial and a superolateral one. The inner and outer layers of the dura mater create the lateral wall, which also makes up the roof of the CS[3,14].

Although it has been described that the abducens cranial and sympathetic nerves run medial to the lateral wall. Inside the CS, these observations have mostly been made through microscopic dissections[3] or imaging rather than histological studies[16]. In the present study, it has been demonstrated that these nerves are surrounded by lateral wall endosteum (Figs. 2 and 5). These observations are consistent with what Hashimoto et al.[4] have reported during the embryonic development of the CS.

Our observations prove that the inferomedial wall is thinner and made up of only the outer layer of the dura mater, which reinforces the notion proposed by Campero et al.[3], who also suggested that this wall creates, simultaneously, the hypophyseal fossa lateral wall.

The CS lateral wall is a structure that, according to some authors, is of dual embryonic origin: on the one hand, the inner wall, actually limiting the CS, originates from extracranial structures and drains venous blood through the superior ophthalmic vein, the only afferent before birth. On the other hand, based on this theory, the outer layer of the CS lateral wall would have a different embryonic origin from a primitive tentorial sinus that originally, before the 8th week of gestation, drains blood from the superficial middle cerebral vein (SMCV). According to this theory, the formation of the CS lateral wall involves the fusion of both systems, the CS itself and the primitive tentorial sinus[31,34,35]. These two structures would fuse and, depending on the degree of fusion, would give rise to 3 types of SMCV drainage into the CS: 1) persistence of the primitive tentorial sinus in adults, known as the paracavernous sinus, which receives the SMCV; 2) the formation of a venous sinus inside the CS lateral wall, the laterocavernous sinus, which also receives blood from the SMCV and may or may not have secondary connections to the CS, and 3) direct drainage of the SMCV into the CS[31,35,36]. According to Gailloud et al.[31], the first pattern is the most common of them all, while the third one is the least common, although the most reported of all. In this regard, our findings of venous structures within the lateral wall suggest the presence of sinusoidal veins draining directly into the CS and receiving blood from the CS afferent veins. We consider that, since the observations made by Gailloud et al.[31] were angiographic, the pattern found in our study can be easily mistaken with the second and third patterns described by Gailloud et al.[31] and other authors[36].

The findings that the endothelium that covers the CS inner surface reflects to cover the outer layer of the tunica adventitia of the ICA are not described in the literature we have looked into[1-36].

The presence of fewer trabeculae in the newborn's CSs compared to adults's CSs suggests the possible disappearance of trabeculae throughout life. These findings are consistent with what Hashimoto et al.[4] have reported, who found less venous spaces during fetal development.

Conclusions

The CS is a true venous sinus made up by two walls, an inferomedial one consisting only of the

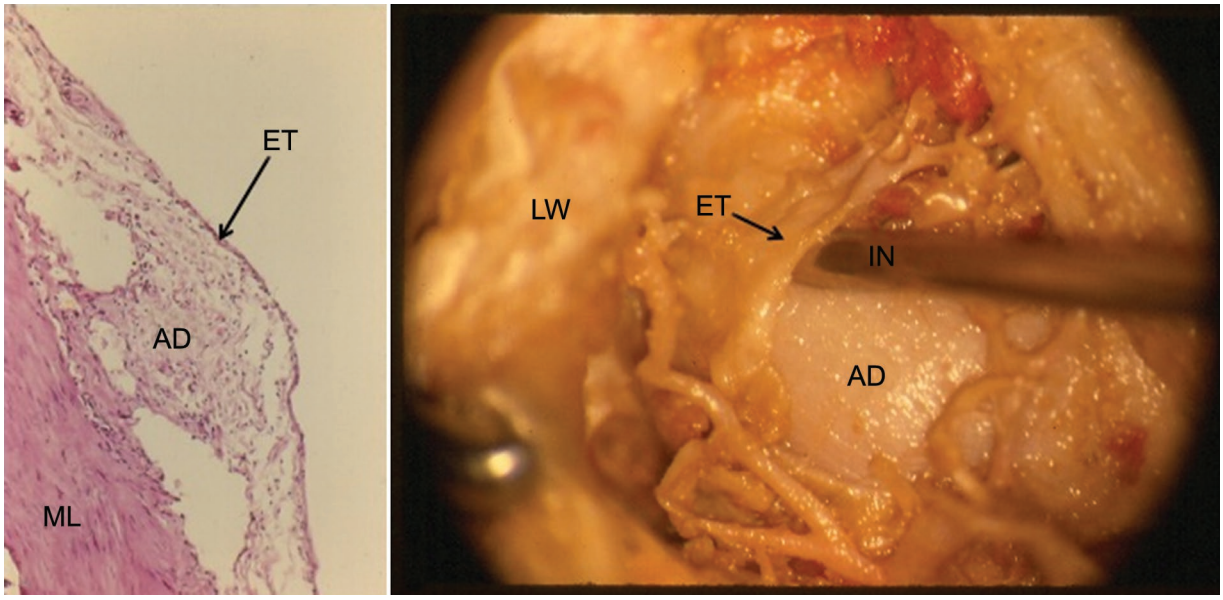

Figure 6. *External surface of the internal carotid artery (ICA) covered by a thin layer of modified endothelium.* **A:** *microscopic image of the cavernous sinus (CS) (close-up to the ICA).* **B:** *dissection of the CS lateral wall (the ICA tunica adventitia is separated from the endothelium using an insulin needle). AD: adventitia of the ICA; ET: endothelium; IN: insulin needle; LW: cavernous sinus lateral wall; ML: muscular layer of the ICA.*

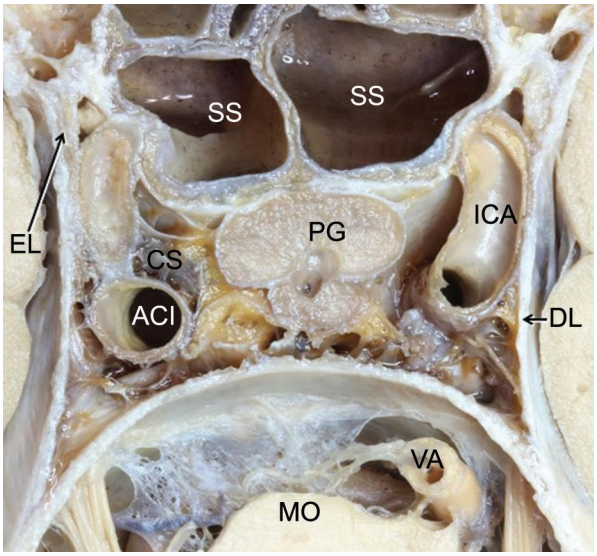

Figure 7. *Cross-section of a block of the sellar and parasellar regions. CS: cavity of the cavernous sinus showing the internal trabeculae; DL: dural layer; EL: endosteal layer; ICA: internal carotid artery; MO: medulla oblongata; PG: pituitary gland; SS: sphenoidal sinuses; VA: vertebral artery.*

outer layer of the dura mater, and a superolateral one including both layers of the dura mater. Inside the CS lateral wall, there are sinusoidal veins showing the transition between the CS afferent veins and the CS itself. Both the inner surface of the CS walls and the outer surface of the ICA are covered by an endothelial layer. It is possible that, in time, the loss of trabeculae inside the CS is just a natural process.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. 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).

Patients' data protection. 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

Prevalence of impaired fasting glucose and dyslipidemia among Mexican HIV antiretroviral-naïve patients

Prevalencia de glucosa alterada en ayuno y dislipidemia entre pacientes mexicanos con VIH naïve a tratamiento antirretroviral

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Abstract

Background: *Metabolic complications have become more relevant in the care of patients with HIV. However, little is known about the incidence and risk factors for these disorders among HIV-infected antiretroviral treatment naïve (ARTn) patients.* **Objective:** *To recognize the prevalence of Impaired Fasting Glucose (IFG) and dyslipidemia among HIV-infected ARTn Mexican individuals and identify associated risk factors.* **Method:** *A retrospective study was conducted in HIV-1-infected ART-N patients, referred for attention to a general hospital in Mexico City, between 2009 and 2019. We collected information for anthropometric, clinical, biochemical and HIV status variables.* **Results:** *We included 221 patients, 97% were males, mean age 30 years (interquartile range [IQR]: 25-38); median CD4 count was 250 cells/mm3 (IQR: 120.25-391) and median log10 HIV viral load was 4.69 HIV-1 RNA copies/ml (IQR: 3.64-5.25). Prevalence of IFG was 22.6% and was associated with overweight-obesity (odds ratio [OR]: 2.75; 95% confidence interval [95%CI]: 1.36-5.55; p-value < 0.05). Hypoalphalipoproteinemia was the most frequent dyslipidemia: 69.46%. An association between count CD4 < 250 and lower HDL cholesterol levels was found (OR, 3.23; 95CI%: 1.61-6.5; p- value < 0.05).* **Conclusions:** *IFG and dyslipidemia are highly prevalent among HIV-infected ART-naïve Mexican patients, therefore, screening for glucose and lipids abnormalities always should be considered among ARTn patients.*

Keywords: *Dyslipidemia. Pre-diabetes. Prevalence. HIV infection. Antiretroviral naïve.*

Resumen

Antecedentes: *Las alteraciones metabólicas se han vuelto más relevantes en el cuidado de los pacientes con infección por el virus de la inmunodeficiencia humana (VIH). Existe poca información sobre estas alteraciones en pacientes naïve a tratamiento antirretroviral (nART).* **Objetivo:** *Identificar la prevalencia de glucosa alterada en ayuno y dislipidemia entre individuos mexicanos con VIH nART e identificar los factores asociados.* **Método:** *Estudio retrospectivo en pacientes con VIH nART valorados en un hospital general de la Ciudad de México de 2009 a 2019. Se recabaron datos antropométricos, clínicos, bioquímicos y relacionados con el estado del VIH.* **Resultados:** *Se incluyeron 221 pacientes, el 97% hombres, con mediana de edad 30 años (rango intercuartil [RIC]: 25-38), cuenta de linfocitos CD4 250 células/mm3 (RIC: 120.25-391) y carga viral log10 4.69 copias/ml (RIC: 3.64-5.25) de VIH-1 ARN. La prevalencia de glucosa alterada en ayuno fue del 22.6% y presentó asociación con sobrepeso-obesidad (razón de momios [RM]: 2.75; intervalo de confianza del*

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Date of reception: 16-07-2021
Date of acceptance: 29-10-2021
DOI: 10.24875/CIRUE.M23000433

Cir Cir (Eng). 2023;91(1):97-103
Contents available at PubMed
www.cirugiaycirujanos.com

95% [IC95%]: 1.36-5.55; p < 0.05). La dislipidemia más frecuente fue la hipoalfalipoproteinemia (69.46%), asociada con CD4 < 250 (RM: 3.23; IC95%: 1.61-6.5; p < 0.05). **Conclusiones:** *Las alteraciones en el metabolismo de los lípidos y de la glucosa son frecuentes entre individuos mexicanos con VIH nART; por lo tanto, es importante una adecuada evaluación antes de iniciar el tratamiento.*

Palabras clave: *Dislipidemia. Prediabetes. Prevalencia. Infección por VIH. Naïve tratamiento antirretroviral.*

Introduction

Over the past two decades, lower morbidity and mortality rates have been documented in patients infected with the human immunodeficiency virus (HIV) due to the effectiveness of antiretroviral therapy (ART)[1-3], leading to a significantly higher life expectancy. Consequently, patients with HIV are more commonly affected by chronic diseases[4]. In fact, currently, over half of the deaths reported in these patients do not account for infection-related complications[5,6]. Therefore, the evaluation of chronic diseases, such as type 2 diabetes mellitus (T2DM) and dyslipidemias, has become more relevant in the management of these patients[7-10]. However, most epidemiological data on HIV-related metabolic disorders come from studies conducted among patients treated with ART[11,12]. Nonetheless, these changes have also been described in treatment-naïve HIV patients (nART)[13,14]. On the other hand, impaired fasting glucose (IFG) is considered an intermediate condition in the transition from normal glucose to T2DM[15]. Few studies have discussed the prevalence of IFG and dyslipidemia in nART HIV patients. Also, it has been proposed that the prevalence of metabolic abnormalities in these patients may vary depending on the population studied[16].

The objective of this study was to assess the prevalence of IFG and dyslipidemia in nART HIV patients and their association with age, body mass index (BMI), smoking status, CD4 lymphocyte count (CD4c), viral load (VL), and disease duration in a population of patients treated in a general hospital of Mexico City, Mexico.

Method

This was a retrospective study conducted in adult nART patients infected with HIV treated in a general hospital of Mexico City, Mexico from July 1, 2009 through August 31, 2019. The study was approved by the hospital research and ethics committees. Patients who had been hospitalized or had an active HIV-related infection 3 months prior to their initial assessment at the hospital were excluded.

Population

The following data were collected: age, sex, previous diagnoses, anthropometric parameters (weight and height), lab test results (fasting glucose, total cholesterol [TC], high-density lipoproteins [HDL-C], low-density lipoproteins [LDL-C], and triglycerides [TG]), as well as parameters associated with the HIV infection status (approximate disease duration in months, CD4c, and HIV-1 RNA VL). The BMI was calculated by dividing the weight in kilograms squared by the height in centimeters and then stratified into 4 different categories according to the World Health Organization classification: underweight (BMI $\leq$ 18.4 kg/m^2), normal weight (BMI = 18.5-24.9 kg/m^2), overweight (BMI = 25-30 kg/m^2), and obesity (BMI $\geq$ 30 kg/m^2). The diagnosis of IFG was achieved following the criteria established by the American Diabetes Association: fasting glucose levels between 100 mg/dL and 125 mg/dL. This was the definition of dyslipidemia used: hypercholesterolemia if TC > 200 mg/dL, hypertriglyceridemia if TG > 150 mg/dL, and hypoalphalipoproteinemia if HDL-C < 50 mg/dL in women and < 40 mg/dL in men. Patients were divided based on disease duration (> or < 6 months).

Statistical analysis

Data were analyzed using the statistical software package SPSS (IBM Corp, Armonk, NY, United States), version 24. The distribution of quantitative data was determined using the Kolmogorov-Smirnov test. Variables with parametric distribution were expressed as mean ± standard deviation, and those with non-parametric distribution as median and interquartile range. Categorical variables were expressed as percentages. Continuous variables with non-parametric distribution were transformed using the natural logarithm function. The continuous variables comparison regarding BMI categories, disease duration, presence of IFG, and presence of dyslipidemia was performed using the Student t test and the ANOVA test. The association

Table 1. Characteristics of the population

Variable	All patients (n = 221)	Subgroup with lipid values (n = 167)
Men (%)	97.28	98.2
Age	30 (25-38)	30 (25-35)
Weight (kg)	65.96 (± 11.7)	66.9 (± 11-31)
Height (cm)	170.08 (± 7.79)	170.82 (± 7.57)
Body mass index	22.73 (± 3.21)	22.82 (± 3.09)
Disease duration (months)	2.43 (1.08-9.52)	3.07 (1.17-10.83)
Viral load log10 (copies/mL)	4.69 (3.64-5.25)	4.62 (3.37-5.11)
CD4 Lymphocyte Count (cells/mL)	250 (120.25-391)	286 (169-434.5)

Data are expressed as mean ± standard deviation, median and interquartile range or frequency.

between the characteristics of participants with IFG and dyslipidemia was determined using the chi-square test or Fisher's exact test. Bonferroni correction was used for the BMI-stratified analysis. The odds ratio (OR) and 95% confidence interval (CI) were estimated to evaluate the strength of the association. P values < 0.05 were considered statistically significant ($p < 0.0083$ for Bonferroni correction). To identify variables independently associated with IFG, a binary logistic regression analysis with the "backward stepwise" method, by blocks, was used, with IFG as the dependent variable, eliminating variables that did not contribute to the model. The variables included in the model were age, BMI, disease duration, VL, and the CD4c.

Results

A total of 221 patients were included in the study. Since the patients' lipid values were not available entirely, the analysis of dyslipidemia was conducted in a subgroup of 167 patients. The population characteristics are shown on table 1. The prevalence of IFG was 22.6% (95%CI, 17.07-28.18). No association among the VL, the CD4c, smoking, and age with IFG was reported (Table 2). A total of 153 participants (69.2%) had normal weight; 21 (9.5%), low weight; 42 (19%), overweight; and 5 (2.3%), obesity. Due to the low prevalence of obesity, these participants were included in the same overweight group (overweight-obesity group). The CD4c was significantly higher in the overweight-obesity group, while the low-weight group had a significantly higher VL (Table 3). After Bonferroni correction, a significantly higher prevalence of IFG was seen in the overweight-obesity group (OR, 2.75; 95%CI, 1.36-5.55). Table 4 shows the overall and age-stratified prevalences of both IFG and dyslipidemia. Among the studied population, 76.05% of participants (95%CI, 6.51-82.59) presented with some form of dyslipidemia. The most common impairment was hypoalphalipoproteinemia (69.46% [95%CI, 62.4-76.52]) with hypertriglyceridemia as the second most common impairment (32.9% [95%CI, 25.73-40.14]). A total of 11.8% of the patients had elevated LDL-C levels (95%CI, 6.51-16.24) while 7.2% (95%CI, 3.23-11.11) had hypercholesterolemia (Table 4). Patients with low weight had significantly lower TG and TC levels (Table 5). A relationship was found between a low CD4c (cut-off value, 250 cells/mm^3) and hypoalphalipoproteinemia (OR, 3.23; 95%CI, 1.61-6.5). Patients with disease durations > 6 months had significantly lower HDL-C and triglyceride levels, and lower CD4c (Table 6). In the multivariate analysis, the variable independently associated with IFG was the BMI category of overweight-obesity (OR, 2.75; 95%CI, 1.36-5.55; $p = 0.007$).

Discussion

There is limited information on metabolic changes in Mexican nART HIV patients. In our study, the low prevalence of obesity found was similar to the one reported by Faurholt-Jepsen et al.[17] in nART patients. However, the prevalence of IFG in our population was higher, while Srivanich et al.[18] reported a 27.5% prevalence in a heterogeneous population of patients with and without ART.

Data on the prevalence of prediabetes in Mexico are also limited. Guerrero-Romero et al.[19] reported a rate of 24.6% in the adult population, while in subgroups

Table 2. Characteristics of the population based on glucose status

Variable	Normal glucose (n = 171)	IFG (n = 50)	p
Men (%)	97.1	98	0.892
Age (years)	30 (25-37)	31.5 (27.7-40)	0.188
Smoking (%)	49.8	50.2	0.391
Weight (kg)	65.5 (± 11.56)	67.52 (± 12.14)	0.155
Height (cm)	170.5 (± 7.99)	168.5 (± 6.88)	0.103
Body Mass Index	22.44 (± 3.0)	23.74 (± 3.7)	0.011
Viral load log10 (copies/mL)	4.73 (3.96-5.25)	4.32 (3.10-5.11)	0.177
CD4 lymphocyte count (cells/mL)	239 (109-394)	304 (209.5-389.5)	0.268

IFG: impaired fasting glucose.
Data are expressed as mean ± standard deviation, median and interquartile range or frequency.

Table 3. Characteristics of the population based on different body mass index categories

	Low weight (n = 21)	Normal weight (n = 153)	Overweight-Obesity (n = 47)	p
Age (years)	27 (24-36.5)	30 (25-37.5)	31 (28-40)	0.319
Smoking (%)	42.9%	49%	57.4%	0.582
Viral Load log10 (copies/mL)	4.87 (3.62-5.25)	4.86 (3.88-5.83)	4.28 (3.31-4.77)	0.045
CD4 lymphocyte count (cells/mL)	76 (31.5-245.5)	229 (121-370)	334 (248-576)	< 0.0001
IFG, n (%)	4 (19)	28 (18.3)	18 (38.3)	0.015

BMI: body mass index; IFG: impaired fasting glucose.
Data are expressed as mean ± standard deviation, median and interquartile range or frequency.

Table 4. Overall prevalence of metabolic changes, stratified by age

	IFG, n (%)	Elevated TC[a] (%)	Elevated TG[b], n (%)	Low HDL-C[c], n (%)	Elevated LDL-C[d], n (%)
All Patients	50 (22.6%)	12 (7.2%)	55 (32.9%)	116 (69.46%)	19 (11.38%)
18-30 years	23 (19.9%)	4 (4.4%)	24 (26.4%)	55 (60.4%)	7 (7.7%)
30-40 years	16 (24%)	6 (10.9%)	22 (40%)	46 (83.6%)	10 (18.2%)
≥ 40	11 (29.8%)	11 (9.5%)	9 (42.9%)	15 (71.4%)	2 (9.5%)

HDL-C: high-density lipoprotein cholesterol; IFG: impaired fasting glucose; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.
Data is presented as frequencies.
[a]TC > 200 mg/dL.
[b]TG > 150 mg/dL.
[c]HDL-C < 40 mg/dL in men and < 50 mg/dL in women.
[d]LDL-C > 100 mg/dL.

with normal weight and aged 30 to 40 years, the rates were 16.7% and 22.1%, respectively. On the other hand, Ureña-Bogarín et al.[20] reported a rate of 14.6% in adults aged 18 to 30 years. Therefore, the prevalence of IFG in our population is higher than that reported in the overall population with similar characteristics.

On the other hand, the prevalence of dyslipidemia is higher than that reported by Ekrikpo et al.[14] and more similar to the one described by Muyanja et al.[11] in patients with ART. Consistent with our results, hypoalphalipoproteinemia has been reported as the most common type of dyslipidemia among individuals with HIV[21,22], and in our patients, it was associated

Table 5. Plasma lipid values and frequency of dyslipidemia based on body mass index

	BMI categories			
	Low Weight (n = 14)	**Normal weight (n = 118)**	**Overweight-Obesity (n = 35)**	**p**
TC (mg/dL)	123.35 (± 18.3)	142.7 (± 38.1)	156.48 (± 33.5)	0.006
HDL-C (mg/dL)	34.78 (± 7.87)	34.42 (± 12.19)	38 (± 8.3)	0.195
LDL-C (mg/dL)	68.35 (± 16.7)	71.3 (± 29.53)	80.88 (± 25.9)	0.101
TG (mg/dL)	93 (80.75-117.25)	128 (86-166)	137 (106-190)	0.035
TC > 200 mg/dL, n (%)	0	9 (7.6)	3 (8.5)	0.544
TG > 150 mg/dL, n (%)	1 (7.14)	38 (32.2)	16 (45.7)	0.284
HDL-C < 40 mg/dL in men or < 50 mg/dl in women, n (%)	9 (64.2)	85 (72)	22 (62.8)	0.531
LDL-C > 100 mg/dL, n (%)	0	14 (11.8)	5 (14.2)	0.237

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; IFG: impaired fasting glucose; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.
Data are expressed as mean ± standard deviation, median and interquartile range or frequency.

Table 6. Characteristics of the population based on disease duration

Variable	**Patients > 6 months**	**Patients < 6 months**	**p**
Age (years)	31 (26.75-40)	28 (23.75-31)	< 0.0001
Weight (kg)	65.01 (± 11.91)	68.26 (± 10.85)	0.054
BMI	23.29 (± 3.22)	22.49 (± 3.20)	0.086
Glucose (mg/dL)	91.66 (± 10.5)	92.81 (± 10.19)	0.447
TC (mg/dL)	143.98 (± 31.27)	144.26 (± 39.72)	0.783
TG (mg/dL)	101.5 (86-153.75)	136.5 (95.75-187)	0.031
HDL-C (mg/dL)	33.69 (± 10.24)	37.95 (±12.45)	0.038
LDL-C (mg/dL)	68.28 (± 28.24)	75.80 (± 27.96)	0.242
Viral load log10	4.73 (3.51-5.26)	4.49 (3.75-5.08)	0.808
CD4 lymphocyte count	229 (87-359)	314.5 (184.25-476.25)	0.004

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; IFG: impaired fasting glucose; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.
Data are expressed as mean ± standard deviation, median and interquartile range or frequency.

with low CD4c and disease durations > 6 months. Additionally, the prevalence in our population is higher than that reported by the National Health Survey 2012 (55.2%) in the overall Mexican population.[23] As in former studies,13 our patients with low weight had higher VL and lower TC and TG levels.

The development of metabolic changes in HIV-infected patients has been associated with a series of factors: inflammation, immune system activation, traditional risk factors, and the action of the virus. Some studies suggest that HIV infection affects the physiology of adipose tissue even before starting ART[24,25] through mechanisms of inflammation and accelerated fibrosis associated with the immune response[26].

These changes are associated with the so-called lipodystrophy syndrome (loss of subcutaneous fat in face and extremities, and gain of central and visceral fat)[27]. Although this syndrome has been described mainly in patients on ART[28], it has also been identified in nART patients[29] and is associated with an increase in the secretion of inflammatory mediators, such as tumor necrosis factor-alpha and leptin, potential mediators of insulin resistance[30,31]. It has been reported that in HIV-infected men, fat redistribution contributes

to hyperinsulinemia[32], while in women, increased abdominal fat is associated with insulin resistance[33]. Abdominal fat has also been associated with elevated TG and low HDL-C levels in both men and women with HIV[34,35]. Additionally, it has been speculated that nART patients have different degrees of inflammation and associated metabolic changes[36,37]. According to this concept, our study demonstrated that there was an association between decreased CD4c and hypoalphalipoproteinemia, as well as an association between disease duration > 6 months and high viral replication, low weight, and decreased levels of TC and TG.

In the population studied, an independent association was found between IFG and BMI, a traditional risk factor for glucose metabolic changes. On the other hand, the high prevalence of IFG in young individuals with normal weight from our population suggests that HIV-infected people may have a tendency to develop prediabetes and dyslipidemia at younger ages compared to uninfected individuals, as suggested in former studies[38]. However, we did not find an association between CD4c, VL, and IFG.

Prospective studies are needed to identify the impact of treatment and other factors in the progression to diabetes and cardiovascular diseases in Mexican subjects infected with HIV. Nonetheless, based on our findings, a careful evaluation of metabolic changes in HIV patients prior to the start of ART is advised to guide the type of initial drug that should be used, considering that new ART regimens are associated with significant weight gain[39].

The study has some limitations: predominantly, our population consists of men meaning that our conclusions cannot be extrapolated to women. Additionally, because of the study retrospective design, we could not include other variables associated with adiposity and the HIV infection status, such as waist circumference, body fat percentage, CD8c or the CD4/CD8 ratio.

Conclusions

In our study, we found a higher prevalence of IFG and dyslipidemia in Mexican nART HIV patients compared to the overall population. Overweight or obesity (according to the BMI) was independently associated with IFG. Additionally, low CD4c and disease duration > 6 months were associated with the presence of hypoalphalipoproteinemia. Therefore, we should assess the metabolic status of patients before putting them on ART while considering traditional risk factors such as BMI and the HIV infection status.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Ultrasound biomicroscopy and stability of intraocular lens in patients with myopia after phacoemulsification cataract surgery

Ultrabiomicroscopía ultrasónica y estabilidad de la lente intraocular en pacientes con miopía axial sometidos a cirugía de facoemulsificación

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Abstract

Purpose: *To evaluate the stability and the refractive error of the different intraocular lens (IOL) after cataract surgery.* **Method:** *Retrospective, observational and single-center study. Patients diagnosed with cataract and myopia who underwent a phacoemulsification surgery with intraocular lens placement without complications were included. All patients underwent a complete ophthalmological examination, ultrasound biomicroscopy was performed at 2 weeks, 1 and 3 months after surgery. Descriptive statistics were performed using measures of central tendency and comparative analyzes. A value of p < 0.05 was considered significant.* **Results:** *Thirty-one subjects with a diagnosis of axial myopia and senile cataract were included, 20 women (64.5%) and 11 men (35.5%), with a mean age was 62.8 ± 13.14 years. The IOL displacement were not different for the upper, lower, temporal and nasal quadrants; however, we observed a tendency to inclination to the temporal sector (p = 0.054) between the first and third postoperative month. Therefore, the were no significant differences in spherical equivalent between groups postoperatively.* **Conclusions:** *The inclination of the IOL did not change over time after surgery, the changes were similar with the different three types of IOL.*

Keywords: *Phacoemulsification. Intraocular lens. Myopia. Ultrasound biomicroscopy.*

Resumen

Objetivo: *Evaluar la estabilidad y el desplazamiento de diferentes lentes intraoculares (LIO) a los 3 meses y los cambios refractivos asociados después de la facoemulsificación.* **Método:** *Estudio retrospectivo, observacional y unicéntrico. Se revisaron expedientes de pacientes sometidos a cirugía de facoemulsificación con colocación de LIO. Se realizó un examen oftalmológico completo, ultrabiomicroscopía a las 2 semanas, 1 y 3 meses después de la cirugía. Se realizó estadística descriptiva y análisis comparativos. Se tomó como diferencia significativa un valor de p < 0.05.* **Resultados:** *Se incluyeron 31 ojos con diagnóstico de miopía y catarata senil, 20 mujeres (64.5%) y 11 hombres (35.5%), con una edad media de 62.8 ± 13.14 años. En cuanto al desplazamiento de la LIO, no se observaron diferencias significativas para los cuadrantes superior, inferior, temporal y nasal. Se observa una tendencia hacia temporal (p = 0.054) entre el primer y el tercer mes posoperatorios. El equivalente esférico tampoco mostró diferencias.* **Conclusiones:** *El desplazamiento de la LIO no cambió con el tiempo después de la facoemulsificación. Los cambios fueron similares con los tres diferentes tipos de LIO y al compararlos proporcionan estabilidad refractiva en pacientes miopes.*

Palabras clave: *Facoemulsificación. Lente intraocular. Miopía. Ultrabiomicroscopía.*

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Date of reception: 19-09-2021
Date of acceptanca: 27-01-2022
DOI: 10.24875/CIRUE.M23000434

Cir Cir (Eng). 2023;91(1):104-109
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Age-related cataract and myopia are among the main causes of visual disability in both developed and developing countries. With the currently increasing life expectancy worldwide, the impact of age-related cataracts is expected to rise. Pan et al.[1] observed that myopia was associated with a higher prevalence of nuclear and posterior subcapsular cataracts.

Despite achievements in standardizing surgical techniques, developing better intraocular lenses (IOL) power calculation formulas, and more precise biometry techniques, refractive surprises are still a significant problem[2]. After uncomplicated cataract surgery, any changes to the IOL optics can lead to unexpected visual outcomes, such as residual astigmatism or higher-order aberrations, being IOL tilt and decentration among the main contributing factors[3].

Ultrabiomicroscopy (UBM) provides accurate and reliable in vivo imaging of the anterior segment and IOL, making it a useful method to confirm that the IOL is inside the capsular bag and measure the depth of the pseudophakic anterior chamber[4], defined as the distance from the central corneal endothelium to the IOL anterior surface, which serves as an indicator of the IOL axial position. Errors predicting the IOL axial position impact postoperative refractive errors significantly. IOL tilt can cause both spherical and cylindrical errors. Thus, the IOL forward movement from its effective position results in myopia, while backward movement leads to hypermetropia[5]. Capsular bag fibrosis, zonular status, and the IOL characteristics (material, haptic design, and diameter) have been reported to play a significant role in the IOL axial position and the final pseudophakic anterior chamber depth[5]. Although refractive results are not the sole measure of success, predictable refractive results and prompt stabilization serve to improve the patients' function and satisfaction[6].

The objective of this study was to assess the stability and displacement of different IOLs over time as well as their refractive impact on myopic patients after cataract surgery.

Method

This was a retrospective, observational, and single-center study that reviewed a total of 38 health records, 31 of which met the inclusion criteria: patients who underwent uncomplicated phacoemulsification surgery with IOL placement, treated in the anterior segment unit of our hospital from March through November 2019, after providing their written informed consent. The study was approved by our center Research Ethics Committee. The study design was conducted in observance of the principles of the Declaration of Helsinki (1975) and its revised version from 2013. Data were anonymized regarding collection and analysis to preserve data privacy.

All patients underwent a comprehensive eye examination, including medical history, visual acuity, refraction, keratometry, slit-lamp biomicroscopy, applanation tonometry, and indirect ophthalmoscopy. The surgical technique involved phacoemulsification and aspiration through a clear corneal incision, followed by IOL implantation in the capsular bag. The IOL selection was randomized, and 3 types of IOLs were assigned due to their wide dioptric range: enVista MX60E (Bausch & Lomb, Rochester, New York, United States), ASPHINA CT 509M (Carl Zeiss Meditec, Jena, Germany), and AcrySof MA60MA (Alcon Laboratories, Inc., Fort Worth, TX, United States). Exclusion criteria included any history of ocular trauma, vitreoretinal surgery, and ocular inflammatory diseases. Patients with surgical complications requiring changes to the surgical technique described were also cleared from the study.

The UBM was performed using a Vumax HD SonoMed Escalón device after 2 weeks, and 1 and 3 months after surgery using a 35 MHz transducer that produces images with 50 μm resolution and 4 mm tissue penetration in ocular tissues. The eye examinations were performed under constant room illumination, while the patient was lying on his/her back in the supine position. Accommodation remained constant by asking the patient to focus on a small point of light held 1 m away from the other eye and look at the ceiling, where there is a mirror that duplicates the distance between the patient's eye and the mirror, resulting in a total distance of 4 m, thus allowing for accommodation relaxation. The UBM was performed by the same specialist in eye ultrasounds. Calibrators included in the machine software were used, and the following variables were measured: anterior chamber depth from the center of the cornea at endothelial level to the echoes of the IOL anterior surface, iris, and distance of IOL contact. The optics was considered tilted with differences > 0.1 mm in the distance between the 2 edges of the optics and the plane of the iris in any UBM section.

Descriptive statistics, including measures of central tendency, were used. Before conducting comparative

analyses, the Kolmogorov-Smirnov test was used to assess data distribution, and the proper parametric and non-parametric tests were performed sometime later. P values < 0.05 were considered statistically significant. GraphPad Prism V5.0 software (San Diego, CA, United States) was used for analysis.

Results

This study included 38 eyes, 7 of which were excluded because they were lost to follow-up. The final study sample included 31 eyes (17 right and 14 left eyes) with a diagnosis of axial myopia and senile cataract. Among these patients, 20 were women (64.5%) and 11 were men (35.5%), with a mean age of 62.8 ± 13.14 years (ranging from 30 to 90 years). The baseline preoperative characteristics are shown on table 1.

Patients were randomized to 3 different groups based on the type of IOL implanted: 9 received enVista MX60E; 10, ASPHINA CT 509M; and 12, AcrySof MA60MA.

The mean age of the enVista group was 68 years; 77.8%, women. The maximum dioptric power used was +18.5 D, and the minimum, +3 D. The range of axial length was 28.4 ± 1.57 mm. The mean age of the ASPHINA group participants was 59 years; 40%, men, the maximum dioptric power used, +12.5 D, the minimum, 0 D, and the range of axial length, 28.9 ± 2.36 mm. Finally, the mean age of the MA60MA group was 67 years; 58.3%, women, the maximum dioptric power used, +16.0 D, the minimum, −5 D, and the range of axial length, 29.9 ± 3.31 mm.

The preoperative anterior chamber depth measured by partial coherence interferometry (Lenstar) increased significantly from a preoperative mean value of 3.603 ± 0.579 mm up to 5.310 ± 0.465 mm at 1 month, and up to 5.309 ± 0.482 mm 3 months after cataract surgery (p < 0.0001).

IOL displacement

Across time, the enVista (Fig. 1), ASPHINA (Fig. 2), and MA60MA (Fig. 3) groups were not statistically different regarding each variable studied. The following p values were obtained in the groups studied: superior p = 0.091; inferior p = 0.104; nasal p = 0.329; and temporal p = 0.054. Similarly, individual comparisons were made for each period (Table 2) The contact distance between the iris and the IOL, measured by UBM, was similar in all postoperative periods without any significant inter-group differences being reported, which is indicative of stability in the capsular bag regardless of the characteristics of the MA60MA, ASPHINA, and enVista IOLs (Fig. 4).

Table 1. Baseline preoperative characteristics of the patients

Characteristics		p
Age, years (men/women)	44-90/30-84	0.068*
Sex (men/women) ± SD	35.5/64.5% ± 0.48	0.012*
Axial length, mm (RE/LE)	28.9 ± 2.7/29.5 ± 2.5	0.533**
Anterior chamber depth ± SD	3.6 ±	0.58

LE: left eye; RE: right eye; SD: standard deviation.
*Mann-Whitney test.
**Student t test.

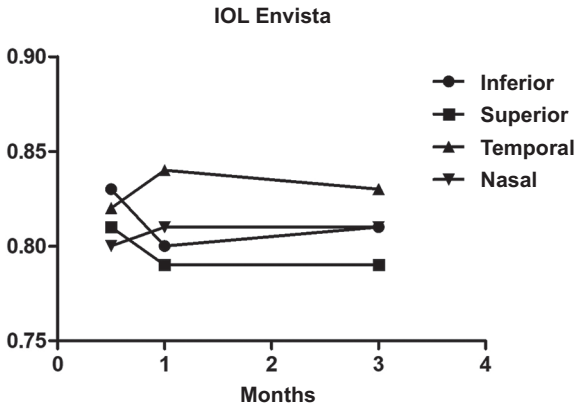

Figure 1. *Behavior of the enVista intraocular lens by sectors over time.*

Spherical equivalent

Postoperative refractive stability occurs between weeks 2 and 6. Any axial displacement in the optical position of the IOL would be seen as a change in the anterior chamber depth, as well as a change in the refractive status. However, in our study, no significant differences were found, which could be attributed to the fact that the variation seen in the anterior chamber depth 3 months after surgery is < 1 mm and, therefore, uncapable of creating a clinically significant change in the spherical equivalent (Table 3).

Discussion

The mechanical stability of IOLs is an important factor that should be taken into consideration because it

Table 2. Displacement of intraocular lenses by sectors

	Week 2 Mean (SD)	Month 1 Mean (SD)	Month 2 Mean (SD)	p
Inferior deviation				
enVista	0.8311 (0.082)	0.799 (0.124)	0.806 (0.1079)	0.796*
ASPHINA	0.81 (0.082)	0.915 (0.189)	0.912 (0.201)	0.374*
ASPHINA	0.918 (0.176)	0.930 (0.186)	0.892 (0.251)	0.895*
Superior deviation				
enVista	0.81 (0.082)	0.788 (0.124)	0.793 (0.115)	0.904*
ASPHINA	0.786 (0.152)	0.878 (0.191)	0.872 (0.196)	0.454*
ASPHINA	0.883 (0.183)	0.898 (0.184)	0.864 (0.243)	0.924*
Temporal deviation				
enVista	0.823 (0.083)	0.838 (0.123)	0.828 (0.107)	0.957*
ASPHINA	0.827 (0.161)	0.908 (0.214)	0.930 (0.195)	0.457*
ASPHINA	0.925 (0.194)	0.927 (0.189)	0.905 (0.240)	0.961*
Nasal deviation				
enVista	0.796 (0.080)	0.808 (0.116)	0.813 (0.106)	0.93*
ASPHINA	0.793 (0.155)	0.891 (0.218)	0.906 (0.195)	0.371*
ASPHINA	0.898 (0.195)	0.886 (0.174)	0.882 (0.233)	0.978*

SD: standard deviation.
*One-way ANOVA.

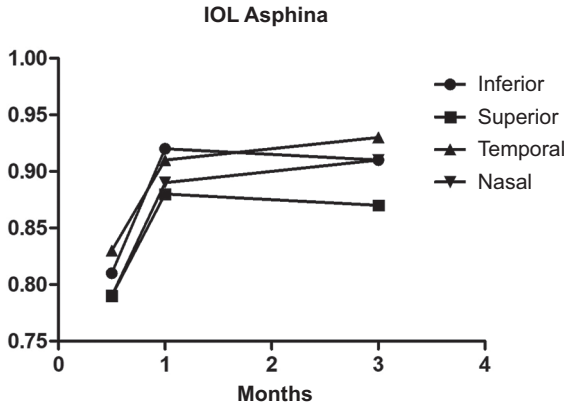

Figure 2. *Behavior of the ASPHINA intraocular lens by sectors over time.*

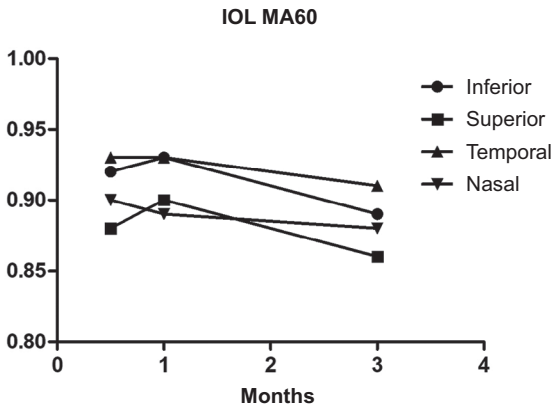

Figure 3. *Behavior of the MA60MA intraocular lens by sectors over time.*

impacts the refractive outcomes of cataract surgery, and, consequently, axial displacement can result in residual refractive errors. Postoperative refractive stability occurs between weeks 2 and 6. It has been reported that for every 1 mm change in the anterior chamber depth, there is a variation of 0.32 D in the spherical equivalent in the postoperative period.6 Standardizing procedures regarding UBM, and controlling accommodation and room illumination, are also essential to avoid any physiological changes in the parameters studied. The reproducibility of measurements taken by UBM has already been studied by other authors[7].

The anterior chamber depth increased significantly after surgery (approximately 1.706 mm; $p < 0.0001$) due to a backward movement of the iris diaphragm away from the inner surface of the cornea. It has been documented that IOL axial displacement is one of the main parameters associated with postoperative refractive changes[8]. Findl et al.[9] described that the IOL axial position changes within the first 3 months after surgery, which is why this period was chosen as the cut-off timeframe of our study.

It has been reported that the design of the IOL plays a significant role to determine the postoperative anterior chamber depth. Hayashi et al.[10] proved that, after cataract surgery, IOLs with rigid haptics often have better fixation in the capsule compared to IOLs with flexible haptics. However, the postoperative anterior

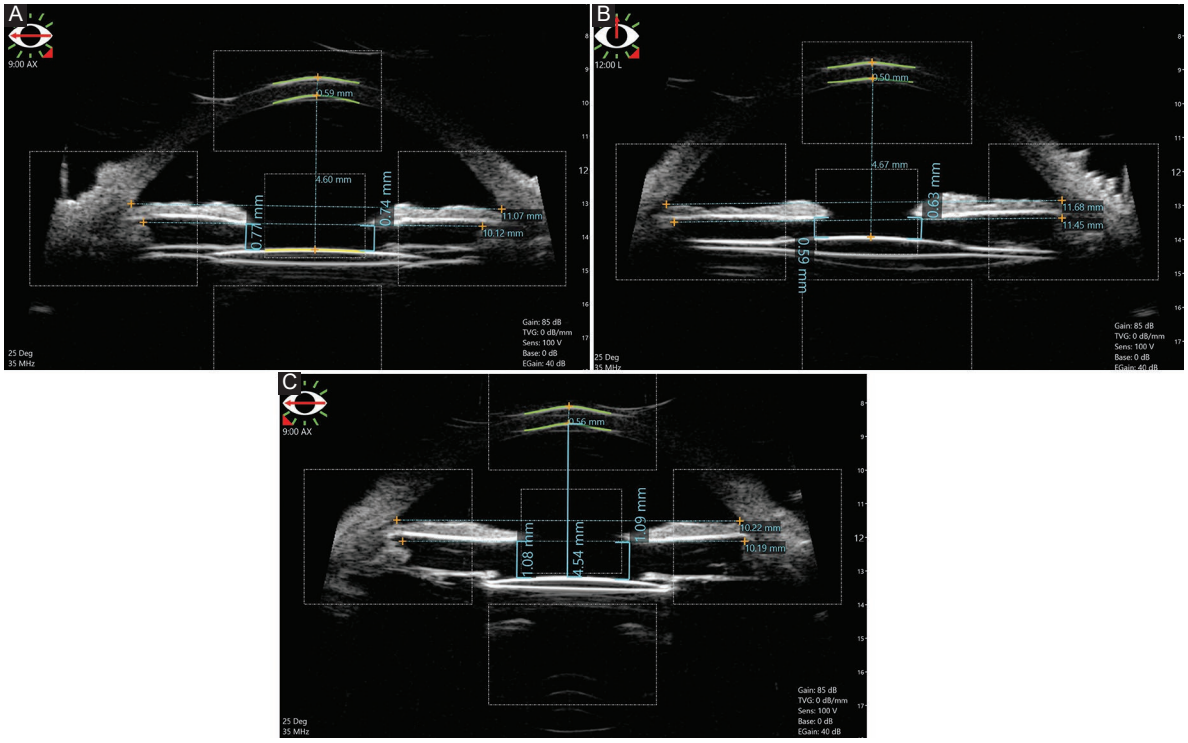

Figure 4. *Measurements taken through ultrasound biomicroscopy.* **A:** *MA60MA.* **B:** *ASPHINA.* **C:** *enVista.*

Table 3. Spherical equivalent

	1 month	3 months	p
enVista	–0.33 ± 1.01	–0.57 ± 0.88	0.152*
ASPHINA	–1.48 ± 1.24	–1.30 ± 1.02	0.202*
MA60MA	–1.33 ± 1.13	–1.47 ± 1.17	0.709*

*Student t test.

chamber depth did not change in eyes with 1-piece IOLs compared to 3-piece IOLs, showing a shallow anterior chamber in the early postoperative period. These results suggest that the axial movement of the 1-piece IOL in the capsular bag is less pronounced than that of the 3-piece IOL. Consequently, they saw that the spherical equivalent in eyes with 1-piece IOLs did not change after surgery, while eyes with 3-piece IOLs showed myopic shifts of nearly 0.4 D. Therefore, they concluded that the postoperative refractive status was more stable with the 1-piece acrylic IOL than with the 3-piece one.

Contrary to these findings, our study demonstrated that the spherical equivalent and the stability of the IOL remained unchanged over time after phacoemulsification being the tilt similar with the 3 different types of IOLs studied, with no significant differences being reported in the spherical equivalent (p = 0.38). New IOLs tend to have better tolerance to tilt and decentration, resulting in minimal impact on the postoperative visual acuity.

Conclusions

We can conclude that the 3 types of IOLs that exist provide refractive stability to myopic patients. The location and size of the corneal incision reduce postoperative corneal aberrations significantly. However, there are several limitations in our study, the main ones being its retrospective nature and the relatively small sample size, although it is comparable to other studies of IOLs with UBM.

Acknowledgemets

The authors would like to express their gratitude to Fundación Hospital Nuestra Señora de la Luz I.A.P. Hospital Foundation for their valuable support.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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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CLINICAL CASE

Delayed tracheal perforation after thyroid surgery in patient with neck radiotherapy

Perforación traqueal diferida tras cirugía tiroidea en un paciente con radioterapia cervical

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Abstract

Tracheal perforation is a rare complication of thyroid surgery. A 36-year-old man with previous neck radiotherapy due to a nasopharyngeal cancer. After right hemithyoidectomy and isthmusectomy, the patient presented a tracheal perforation. The diagnosis was confirmed with computed tomography and bronchoscopy. A conservative management was performed with drainage and antibiotic therapy, and the evolution was satisfactory. If recognized at the time of the surgery, perforations should be closed primarily. Delayed perforations will be treated with an emergency surgery or conservatively depending on the clinical situation of the patient.

Keywords: *Tracheal perforation. Radiotherapy. Hemithyroidectomy.*

Resumen

La perforación traqueal es una rara complicación de la cirugía tiroidea. Varón de 36 años con antecedente de radioterapia cervical por una neoplasia de cavum sometido a hemitiroidectomía derecha e istmectomía que durante el posoperatorio presentó una perforación traqueal confirmada por tomografía computarizada y broncoscopia. Se realizó manejo conservador con drenaje y antibioticoterapia, evolucionando de forma favorable. Las perforaciones identificadas durante la cirugía deben ser reparadas intraoperatoriamente, mientras que las diferidas se tratarán de forma quirúrgica urgente o de manera conservadora en función de la situación clínica del paciente.

Palabras clave: *Perforación traqueal. Radioterapia. Hemitiroidectomía.*

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Date of reception: 30-07-2021
Date of acceptance: 17-09-2021
DOI: 10.24875/CIRUE.M23000435

Cir Cir (Eng). 2023;91(1):110-113
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Thyroid surgery is a safe procedure with a low rate of complications, including paralysis of the vocal cords due to injury to the recurrent laryngeal nerve, hypoparathyroidism, hypocalcemia, asphyctic hematoma, and surgical wound infection[1]. However, tracheal injury of intraoperative or delayed perforation origin due to necrosis is extremely rare[2].

Case report

This is the case of a 36-year-old man with a past medical history of stage III undifferentiated nasopharyngeal carcinoma (T1 N2 M0) 2 years ago, treated with chemotherapy (bleomycin, epirubicin, and cisplatin) and radiation therapy on the nasopharynx and cervical area, resulting in a complete response. At follow-up, a computed tomography (CT) scan revealed a 12 mm nodule in the thyroid isthmus that had increased its size compared to a previous study (7 mm). The fine-needle aspiration biopsy of the lesion turned out suspicious for follicular neoplasm (Bethesda IV).

The patient underwent uneventful surgery (right hemithyroidectomy and isthmectomy) with intermittent neuromonitoring of the right recurrent laryngeal nerve. The patient's recovery was favorable, and he was discharged from the hospital 24 hours after surgery. The definitive histological study of the specimen revealed the presence of thyroid multinodular hyperplasia, with the largest 10 mm nodule exhibiting solid, pseudoencapsulated characteristics, and no malignancy criteria being located in the isthmus.

Seven days after surgery, the patient presented to the ER following a 3-day history of odynophagia (painful swallowing) associated with fever. He remained hemodynamically stable, with a low-grade fever (37.7 °C). The examination revealed an increased cervical perimeter with crepitus at surgical wound site level, without flogotic signs. Lab test results showed elevated C-reactive protein levels (6.54 mg/dL) and a white blood cell count of 14,500/mm^3 with neutrophilia (85%).

The CT revealed the presence of an air collection at the site of the hemithyroidectomy and 3 focal defects in the trachea, on its right lateral side and right paramedial region of 3 mm, 4 mm, and 7 mm, respectively (Fig. 1). No findings were made of pneumomediastinum or pneumothorax. A bronchoscopy confirmed the presence of these openings at anterolateral right side level of the upper trachea, 2 cm above the vocal cords and 11 cm away from the main carina.

The surgical wound was reopened, and air was released that resulted in a reduced cervical perimeter. Two Penrose drains were placed inside the collection. The patient received conservative treatment with antibiotic therapy (piperacillin-tazobactam, 4/0.5 g every 8 hours), methylprednisolone (40 mg every 24 hours), and daily wound dressings. To avoid any episodes of bronchial aspiration with coughing, a nasogastric tube was inserted, through which enteral nutrition was administered.

The patient's recovery was favorable, and he was discharged from the hospital with the fistula closed 2 weeks after admission. The follow-up bronchoscopy performed 2 months after surgery confirmed the complete closure of the tracheal wall fistula, without any residual stenosis.

Discussion

Latrogenic tracheal rupture has been described as a complication of external radiation therapy, airway manipulation, or cervical and mediastinal surgery.3 However, tracheal perforation after thyroid surgery is a rare complication, especially in cases of hemithyroidectomy. As a matter of fact only the case of a patient treated with right hemithyroidectomy and isthmectomy due to a right thyroid nodule that presented with tracheal perforation 4 weeks after surgery has been reported[4].

Gosnell et al.[5] conducted a retrospective analysis of the incidence rate of tracheal perforation over 45 years in 2 Australian hospitals. A total of 7 perforations were described among the 11,917 thyroidectomies performed, all of which were identified and repaired intraoperatively, resulting in an incidence rate of 0.06%.

Risk factors for tracheal perforation include female sex, toxic goiter, prolonged intubation with high-pressure endotracheal balloon cuff, use of diathermy (in cases of bleeding), and persistent postoperative cough.[2]

Tracheal injuries during thyroid surgery can be identified intraoperatively. In such cases, primary closure of the defect is advised. Perforations that go unnoticed or develop postoperatively due to tracheal perforation may show as a surgical wound infection, subcutaneous emphysema, and dyspnea with respiratory involvement. The patient's medical history may reveal a significant coughing episode before symptom onset.

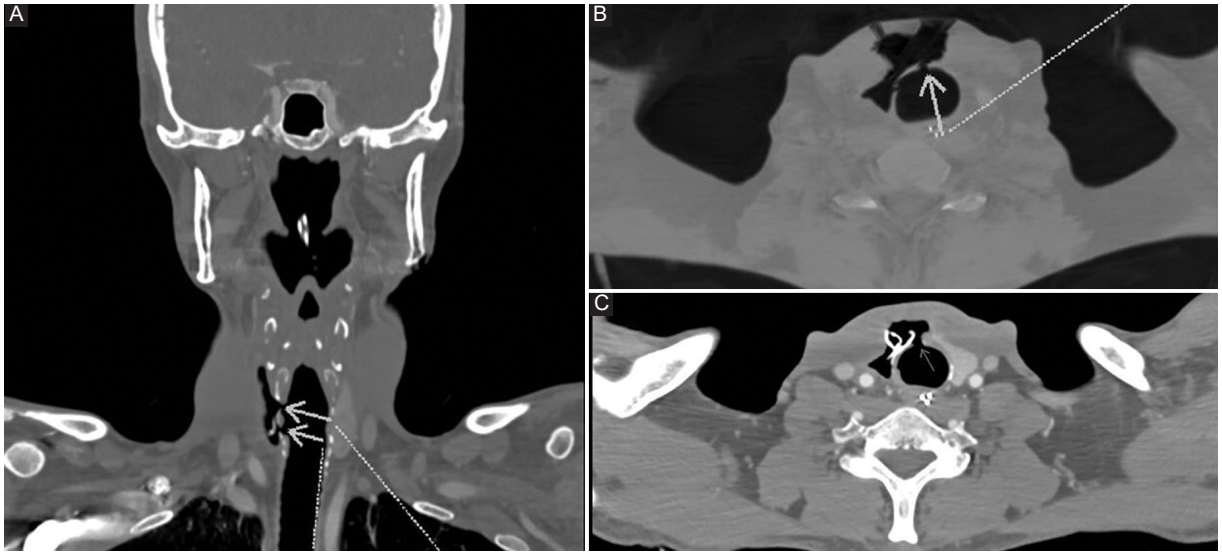

Figure 1. A: *coronal section of computed tomography (CT) scan showing 2 defects in the tracheal wall communicating with an air collection.* **B:** *axial section of CT scan also showing 2 defects in the tracheal wall.* **C:** *axial section of CT scan showing a defect in the tracheal wall communicating with a collection after placing a Penrose drain inside.*

Retrosternal pain suggests pneumomediastinum or pneumothorax. In some cases, hemoptysis, cervical or facial edema, and stridor may also be observed[2].

Delayed perforation is often due to tracheal wall necrosis following the use of diathermy to achieve hemostasis during surgery capable of damaging adjacent structures through lateral heat dispersion[6]. In this patient, we believe that the lesion occurred due to the combined effect of diathermy usage and the impact of radiation therapy on the tracheal wall.

The most common location for tracheal perforation is the posterolateral region of the trachea, in the Berry ligament area. However, perforations at anterior and lateral levels have also been reported as it was our case[2].

The diagnosis is clinical and based on the presence of cervical crepitus upon palpation due to subcutaneous emphysema. Bronchoscopy can identify the perforation in most cases, although its normal appearance does not rule out the diagnosis.[3] The thoracic x-ray can assess the presence of pneumothorax or pneumomediastinum, and the CT can be useful to identify both the location and size of the perforation[6], as in our case where 3 defects were seen in the right anterolateral area.

The management will depend on when the lesion is identified and the patient's condition. As mentioned before, perforations identified intraoperatively should be closed primarily with resorbable sutures[2].

Patients with delayed presentation due to tracheal necrosis following thermal injury without respiratory distress or signs of infection, can be treated conservatively with antibiotic therapy and wound care[3], as was done in this case that met both requirements. Other patients need urgent procedures, prioritizing airway control. Emergency tracheostomy material should be available if necessary. However, a rapid sequence of anesthetic induction along with orotracheal intubation and placement of a pneumo-tamponade balloon distal to the lesion is often enough to achieve good airway control. Positive pressure in the airway should be avoided because it can worsen subcutaneous emphysema and cause respiratory distress, pneumothorax, and pneumomediastinum[2].

The procedure will involve closing the defect with resorbable sutures on viable tissue, with or without the use of a muscle flap. The use of a collagen adhesive matrix coated with human fibrinogen and thrombin has also been described[7].

In conclusion, delayed tracheal perforation after hemithyroidectomy is an exceptionally rare complication often due to thermal injury. The treatment will vary depending on the patient's clinical status, with conservative management being possible in cases without respiratory distress or signs of infection.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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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CLINICAL CASE

Botulinum toxin A (IncobotulinumtoxinA) and pneumoperitoneum image-guided for hernia repair with loss of dominance

Toxina botulínica A (IncobotulinumtoxinA) y neumoperitoneo guiados por imagen para la reparación de hernia con pérdida de dominio

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Abstract

Post-incisional ventral hernia is estimated at 5-30%, when the content of the abdominal cavity migrates to the hernial sac (HSV), with a HSV/abdominal cavity volume ratio > 25%, conditioning systemic changes defined as "loss of domain". A 27-year-old male presented with ventral hernia with loss of domain that required pre-operative preparation techniques, using application of botulinum toxin A (IncobotulinumtoxinA) and pneumoperitoneum, both guided by image. A ventral plasty was performed with adequate return of the viscera to the abdominal cavity. The combination of both techniques seems to be a safe procedure to carry out a tension-free repair.

Keywords: *Ventral Hernia. Pneumoperitoneum. Botulinum toxin A. IncobotulinumtoxinA.*

Resumen

La hernia ventral postincisional se estima en 5 al 30%, cuando el contenido de la cavidad abdominal migra al saco herniario, con una relación VSH/VCA > 25% condicionando cambios sistémicos se define como "pérdida de dominio". Masculino de 27 años con hernia ventral con pérdida de dominio que ameritó técnicas de preparación preoperatoria, utilizando toxina botulínica A (IncobotulinumtoxinA) y neumoperitoneo, ambos guíados por imagen. Se realizó una plastia ventral con adecuado regreso de las vísceras a la cavidad abdominal. La combinación de ambas técnicas es un procedimiento seguro para realizar una reparación libre de tensión.

Palabras clave: *Hernia Ventral. Neumoperitoneo. Toxina botulínica A. IncobotulinumtoxinA.*

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Date of reception: 26-07-2021
Date of acceptance: 24-08-2021
DOI: 10.24875/CIRUE.M21000560

Cir Cir (Eng). 2023;91(1):114-118
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Post-incisional ventral hernias are abdominal wall defects secondary to a previous surgical event. The risk of presenting this complication is 5-30%[1] after a midline exploratory laparotomy. It is an entity that increases morbidity and has a direct impact on the quality of life of patients. The ventral hernia that initially formed tends to increase in dimensions due to a mechanical effect, generating retraction of the muscles of the wall in a lateral direction, which conditions atrophy and fibrosis[2]. When presenting these anatomical changes, a series of events occur that can modify the respiratory physiology. As the viscera migrate to the hernial sac (HSV), there is a decrease in intra-abdominal pressure, affecting the stability, balance, and movement of the diaphragm, as well as a decrease in venous return in the porta and cava. The mesentery, omentum, and intestine become swollen and thickened by chronic inflammation caused by mechanical irritation with the hernial ring, with the consequent formation of flanges or adhesions. The skin and subcutaneous cellular tissue atrophy by mechanical compression of the HSV[3]. The dimensions of the defect and the systemic effects classify it as a hernia with loss of dominance, of which there is no standardized definition[2]. Tanaka et al., through tomography, he described the volume of the HSV and volume of the abdominal cavity (VAC) to generate a HSV/VAC ratio, if it is > 25% then it can be defined as loss of domain[4]. There is the possibility of performing pre-operative procedures such as the application of tissue expanders, bolutinum toxin Type A (BTA), and progressive pneumoperitoneum (PN).

Clinical case

This is a 27-year-old male patient, which presents Grade 3 obesity according to the body mass index (43.4 kg/m^2), without chronic degenerative diseases. He suffered from complicated appendicitis in 2019, which required emergency exploratory laparotomy. A post-incisional ventral hernia involving the midline was detected (Fig. 1). The patient was classified as a ventral hernia with loss of domain of 19 months of evolution. We use application of BTA in the muscles of the lateral wall of the abdomen and NP. Before applying both techniques, the patient was given an informed consent form, explaining the risks and benefits of both procedures. It began with a tomographic

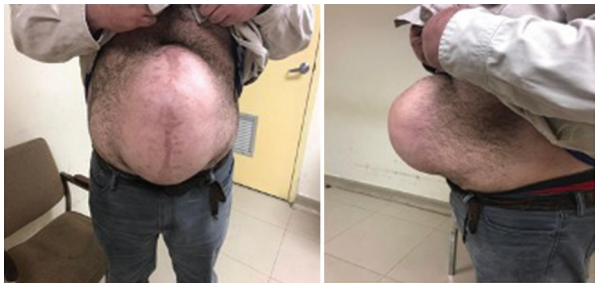

Figure 1. *Patient preview application of the bolutinum toxin type A and NP.*

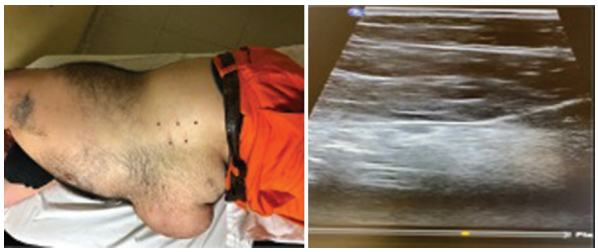

Figure 2. *Application of bolutinum toxin type Ain the muscular layers by ultrasound.*

control in which a defect of the abdominal wall of 18.46 cm in its transverse diameter and a diameter of 28.43 mm and 28.52 mm of the muscle groups of the lateral wall (right and left, respectively), with a Tanaka index of 58%. The first step was the application of BTA Xeomeen® (Merz Pharmaceuticals GmbH, Frankfurt, Germany). The procedure was scheduled in the ultrasound room, 1 month before the planned date for surgery. The presentation of the vial of BTA (Xeomeen®) is 100 units. Three vials were used, each diluted in 5 mL of 0.9% sodium chloride solution. Our goal was to use 300 units in total, of which 150 U on each side of the abdomen and 30 U per application site. The patient was placed in a lateral decubitus position, after mapping the 5 points established in the literature. Under the asepsis and antisepsis protocol, local anesthesia with 2% lidocaine was infiltrated at the puncture sites. By means of ultrasound, the muscular bellies were located; The 22 Gauge Quincke needle was introduced, depositing 0.5 mL in each muscle layer, starting in the transverse muscle, followed by the minor oblique and finally the greater oblique; depositing 1.5 mL in total, which is equivalent to 30 U of BTA (Fig. 2). The application is made on both sides of the abdominal wall. At the end of the procedure, the patient was kept under observation for 1 h without complications. The patient was summoned

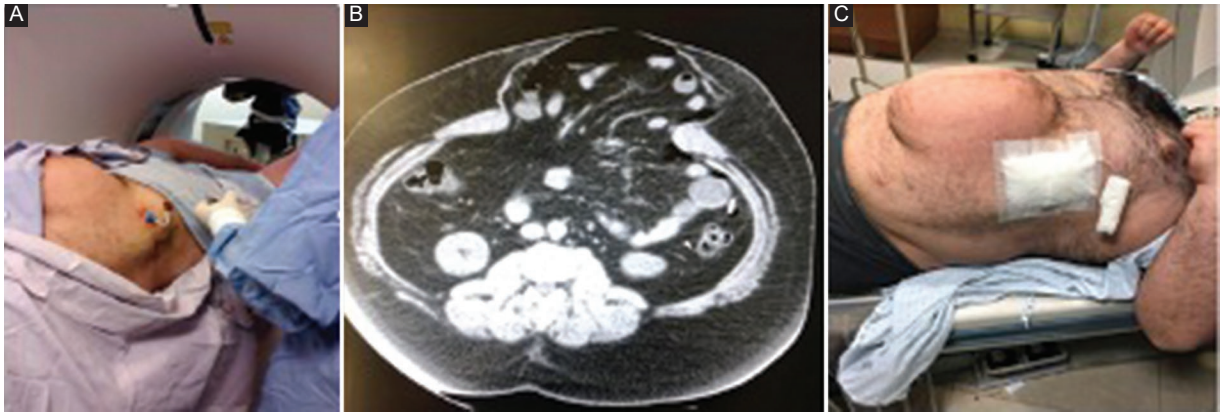

Figure 3. *Tomography-guided PN placement.* **A:** *insufflation of ambient air through the catheter.* **B:** *axial tomography with the presence of the catheter and PN.* **C:** *the catheter is covered and the PN is maintained.*

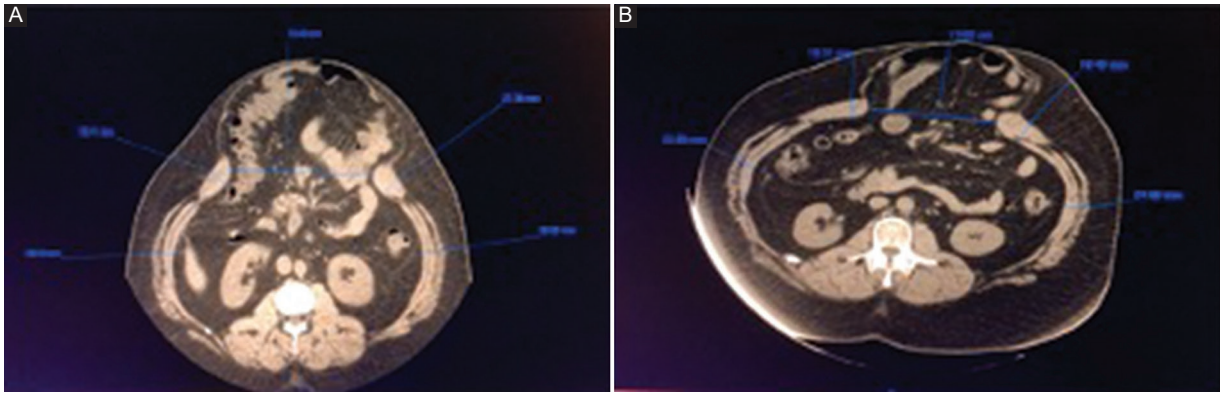

Figure 4. *Tomography in axial section.* **A:** *prior to the application of bolutinum toxin type A (BTA).* **B:** *4 weeks after the application of BTA. The reduction in the diameter of the defect and hernial sac can be seen.*

4 weeks later, who only mentioned perceiving the sensation of "flaccidity" in the abdomen.

The PN guided by tomography was performed in week 4. Local anesthesia was infiltrated with 2% lidocaine and the Veress needle was inserted at the Palmer point corroborating its entry into the abdominal cavity by means of tomography. Subsequently, the metal guide was inserted and the Veress needle was withdrawn; the site is enlarged with a scalpel and the dilator is placed, which is then removed, and the central venous catheter is inserted through the guide (a double lumen catheter of 7Fr and 20 cm in diameter was used). With a 60 cc syringe, 100 cc of ambient air was introduced, corroborated by image and at the moment of insufflation with the movement of the HSV; therefore, the administration of 2000 cc of ambient air is concluded. Finally, the catheter is fixed to the skin and covered with sterile gauze. The patient is kept under surveillance for 2 h without complications. Was monitored as an outpatient with analgesics and antibiotics. The patient was summoned 9 days later to the outpatient clinic to maintain the PN, performing the insufflations and applying approximately 500-1000 cc once a day, to observe distension of the abdominal cavity and a feeling of fullness (Fig. 3). A total of 7500 cc was insufflated for 9 days. The patient presented left subscapular pain that subsided with the administration of paracetamol and emphysema in the lateral wall of the abdomen that resolved spontaneously.

The baseline tomography was compared with the control at week 4 after the application of BTA, where a reduction of 4.81 cm was evidenced in the defect, as well as 5.55 mm in the right and 3.86 mm in the left in the diameter of the lateral muscle groups (Fig. 4). The patient was hospitalized 24 h before the date of surgery. The ventral plasty was performed with Rives technique 5 weeks after the application of BTA and 9 days of PN (Fig. 5). The catheter was removed

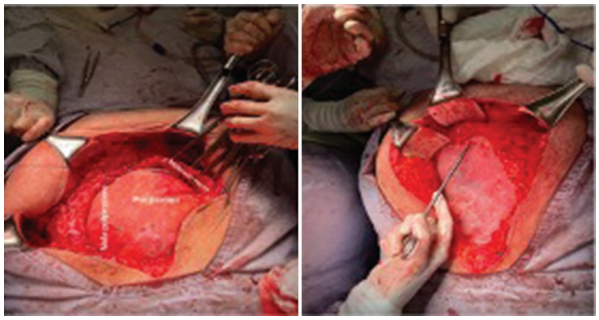

Figure 5. *Hernia repair with rives technique and onlay mesh placement.*

Figure 6. *Follow-up at 6 months, with adequate evolution, without evidence of hernia.*

in the operating room. With a surgical time of 180 min, the surgery was completed with the patient hemodynamically stable. The patient undergoes the mediate postoperative period in adequate general conditions; Intra-abdominal pressure was monitored, ruling out intra-abdominal hypertension. It was started orally at 24 h, did not present complications, and was discharged at 96 h. In outpatient follow-up, drains were removed at 2 weeks when the output was < 30 cc/24 h and the skin staples at 3-week postoperatively. In 6 months of follow-up (Fig. 6), the patients were without complications, clinical evidence of recurrence, with a full reintegration to work life.

Discussion

Botulinum toxin Type A is one of the eight toxin serotypes (A-H) produced by bacteria of the genus clostridium (botulinum, argentinensis, barati, and butyrricum)[5]. Known for its multiple medical applications in urological conditions, achalasia, hyperhidrosis, migraines, cerebral palsy, cosmetics, strabismus, depression, and among others[6,7]. It acts at the nerve endings, inhibiting the release of acetylcholine in the neuromuscular plate[8], causing a chemical denervation that will weaken muscle contraction, generating reversible muscle atrophy. Its use has currently been implemented in the preparation of patients with incisional hernias of the abdominal wall, first reported in 2009 by Ibarra-Hurtado et al.[9] There is no equivalence or standard dose between the different commercial presentations for use on the abdominal wall. Studies have been carried out on the pharmaceutical and biological properties of the different BTA presentations, finding a 1:1 relationship between Xeomeen® and Botox® (Allergan, Irvine, CA), and these in turn 1: 2.5-3 with Dysport® (Ipsen Ltd, Slough, Berkshire, UK)[10]. Its application in the muscles of the lateral wall of the abdomen will condition a flaccid paralysis that will allow its lengthening temporarily[11], with a maximum effect reported between week 4 and 6 after its application, which is reversible and can last from 6 to 9 months. Achieving a decrease in the transverse diameter of the HSV, thinning the diameter of the lateral muscles and the dimensions of the abdominal cavity, favoring a tension-free repair[9,12]. Contraindications for its use are hypersensitivity to the toxin or its components, infection of the site, and myasthenia gravis[7]. The application is carried out by electromyography and guided by ultrasound to deposit the BTA with precision in each muscle layer[13]. Using anatomical references, Ibarra-Hurtado et al.[9] described 5 points of application on each side of the abdomen and later other authors have proposed 3 points of application[12,13]. The dose varies in different reviews, documenting from low doses of 100 U[14]-500 U[9] in total. The toxic dose was studied by intraperitoneal injection in mice (MLD50) and in Rhesus monkeys, calculating that the toxicity in intramuscular application is 2730 U of Botox® and the lethal dose is 5,000 U of Botox®[7,15]. Its use is considered safe, since the dose used is well below the toxic dose; in the same way, due to its localized effect at the application site, reporting up to 25% of mild, temporary, and non-systemic adverse effects related to the mechanism of action[6], no mortality has been reported due to its application to the abdominal wall. Incobotulinumtoxin A itself does not have complex proteins; therefore, it has low immunogenic potential. Some studies describe that it does not produce antibodies[10], reducing the probability of tachyphylaxis.

PN as a preparation for ventral hernias was first described in 1946 by Goni-Moreno[16]. Its objective is to increase intra-abdominal pressure to improve ventilatory function, correcting the position of the diaphragm, returning the organs to the cavity, improving portal circulation, and reducing intestinal and mesentery edema.

The presence of air in the cavity generates pneumatic lysis of adhesions, it also has an impact on the immune system, improving healing. The puncture site described varies according to the patient, identifying a point far from the scars on the skin from the previous surgeries. The amount of ambient air to be insufflated will depend on the size of the hernia and the patient's tolerance to PN; which regularly does not exceed 12-15 mmHg. Initially, 1000-4000 cc of ambient air are introduced, and later maintenance with daily insufflation of 1000-2000 cc[17]. An objective measurement can be carried out with the insufflator of the laparoscopy tower or a sphingomanometer. The PN maintenance time varies according to the authors, from 7 to 15 days until the day of surgery. Up to 12% complications are reported due to its application, mainly pain radiating to the scapular region, subcutaneous emphysema, and infection of the puncture site, without associated direct mortality. There are case series in which both techniques were used[18,19]. During the review of the literature for the preparation of this article, we did not find another publication in which incobotulinumtoxin A has been used for application to the abdominal wall.

Conclusion

Both techniques have shown a benefit to achieve a tension-free closure of the abdominal wall, which is one of the objectives when performing hernia repair. These advantages are also reflected in the post-operative period avoiding the presence of abdominal compartment syndrome, although the number of cases should be increased. Despite not being standardized the dose of BTA and the amount or time of PN. Both techniques are easy to reproduce and safe, increasing their level of safety when performed guided by image. It will be necessary to carry out more studies to be able to specify it.

Funding

The authors declare that no funding was received for this case.

Conflicts of interest

The authors declare that there are 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. 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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REVIEW ARTICLE

Medical-nutrition therapy in polytraumatized patients: a race against time

Terapia médico-nutricional en pacientes politraumatizados: una carrera contra el tiempo

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Abstract

A polytraumatized patient is defined as one who has multiple lesions involving different organs and systems, which are usually serious and lead to life-threatening respiratory or circulatory dysfunction. Traumatic stress in the polytraumatized patient results in many metabolic changes that are evident from the first days, but usually persist for weeks, requiring adequate nutritional support as they influence outcomes. Nutritional treatment should be a priority in the comprehensive treatment of polytraumatized patients since it attenuates the metabolic response to trauma and prevents the deterioration of body reserves. It should be noted that some patients present previous nutritional risk. Nutritional intervention should be considered at the same level as any other therapy that supports organic functions, especially in patients in the intensive care unit. Nutritional intervention in polytraumatized patients is a pillar of treatment that has multiple benefits and can improve prognosis. All efforts must be aimed at the early detection of malnourished patients at nutritional risk and providing timely therapies that improve clinical outcomes.

Keywords: *Polytraumatized patient. Nutritional risk. Enteral nutrition. Parenteral nutrition. Metabolic changes.*

Resumen

El paciente politraumatizado se define como aquel que tiene múltiples lesiones que involucran diferentes órganos y sistemas, suelen ser graves y conllevan una disfunción respiratoria o circulatoria que pone en riesgo la vida. El estrés traumático en el paciente politraumatizado da lugar a muchos cambios metabólicos que son evidentes desde los primeros días, pero suelen persistir durante semanas y exigen un adecuado soporte nutricional, ya que influyen en los desenlaces. El tratamiento nutricional debe ser una prioridad en el tratamiento integral de los pacientes politraumatizados, porque atenúa la respuesta

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Date of reception: 31-03-2022
Date of acceptance: 08-07-2022
DOI: 10.24875/CIRUE.M23000436

Cir Cir (Eng). 2023;91(1):119-126
Contents available at PubMed
www.cirugiaycirujanos.com

metabólica al trauma y evita el deterioro de las reservas corporales (cabe mencionar que algunos pacientes presentan riesgo nutricional previo). La intervención nutricional debe considerarse al mismo nivel que cualquier otra terapia que apoye las funciones orgánicas, sobre todo en pacientes en la unidad de terapia intensiva. La intervención nutricional en pacientes politraumatizados es un pilar en el tratamiento que tiene múltiples beneficios y puede mejorar el pronóstico. Todo esfuerzo debe ir encaminado a la detección temprana de pacientes desnutridos o en riesgo nutricional, y proporcionar de manera oportuna terapias que mejores los desenlaces clínicos.

Palabras clave: *Paciente politraumatizado. Riesgo nutricional. Nutrición enteral. Nutrición parenteral. Cambios metabólicos.*

Introduction

A polytraumatized patient is that who has multiple injuries involving different organs and systems, often severe and leading to life-threatening respiratory or circulatory dysfunction. The injuries often include spinal, cranioencephalic, thoracic, pelvic, abdominal, and limb traumas. A total of 80% of all deaths occur within 60 min after the injury, which is why health care professionals must undertake a series of coordinated measures for damage control, as well as to provide prompt care due to the high morbidity and mortality rates involved[1,2].

Traumatic stress in polytraumatized patients results in many metabolic changes that are evident from the early days but tend to go on for weeks, requiring proper nutritional support because they can impact the patient's outcomes. Patients who do not receive nutritional therapy within the first few first days after the injuries develop energy and nutrient deficiencies that contribute to an increased risk of complications such as infections and multiorgan failure[3,4].

Nutritional therapy should be a priority as part of the comprehensive management of polytraumatized patients, because it attenuates the metabolic response to trauma and stops the deterioration of reserves from the body (we should mention that some patients have prior nutritional risk). Nutritional intervention should be considered on the same level as any other therapy supporting organ functions at the intensive care unit (ICU) setting[5-7]. The objective of this review is to guide the process of nutritional support in polytraumatized patients to improve their prognosis and reduce the morbidity and mortality rates associated with this condition.

Epidemiology

Polytrauma is a non-natural cause of death worldwide, being one of the major causes for disability. In Mexico, it is considered a problem of public health because accidents rank seventh in the overall mortality rate and are among the leading 9 causes of death across all age groups. Polytrauma ranks first in children aged 1 to 14 years and second in individuals aged 15 to 34 years. In 2018, a total of 34,589 accident-related deaths were reported, being the rate higher in men (75.8%)[8]. Back in 2017, the Global Burden of Disease report indicated that the disability-adjusted life years were 4042.79 per 10,000 inhabitants (16.04% overall) while the years lived with a disability were 422.45 per 10,000 inhabitants (4.42% overall)[9].

Metabolic response to trauma

Traumatic stress triggers a series of stimuli that predisposes a response from the body in the process of restoring homeostasis or counteracting the threat. Trauma triggers metabolic, endocrine, hemodynamic, and immune responses that can go on for weeks and induce inflammatory and hormonal reactions that alter metabolic processes and, consequently, nutritional requirements[10]. The metabolic response to trauma has been defined in 3 phases whose characteristics are shown on table 1. It is mediated by catabolic hormones such as glucagon, catecholamines, corticosteroids, and insulin resistance, all of which increase after trauma and lead to increased mobilization of energy substrates[11]. Amino acids (especially glutamine, alanine, and arginine) play a key role not only in the synthesis of acute-phase proteins but also in wound healing and in the successful recovery from injuries[12].

Nutritional state assessment

Patients with polytrauma should be nutritionally assessed upon admission to the ICU to identify those at nutritional risk who would benefit from nutritional support. Overall, these patients are not malnourished before sustaining the injuries, but all critically ill patients who stay in the ICU for over than 48 hours

Table 1. Phases of the metabolic response to trauma[7,11,12,29]

Phase	Ebb phase	Flow phase	Anabolic phase
Other names	Shock phase, reflux, decay, or hypodynamic	Flow phase, hyperdynamic or catabolic	Repair or convalescence phase
Duration	Minutes to hours after the injury	Days to weeks after the injury, depending on severity	Weeks to months after the injury
Description	Immediate consequence of the injury resulting from fluid loss and characterized by efforts to protect homeostasis	Compensatory response to trauma and hypercatabolism	Occurs with prolonged maintenance of compensatory systems, depending on the severity of the injury
Characteristics	↓ Decreased cardiac output ↓ Decreased blood pressure ↓ Less circulating volume ↓ Lower body temperature ↓ Decreased urine nitrogen excretion ↓ Decreased insulin secretion ↓ Decreased basal metabolic rate ↓ Decreased glucose tolerance ↓ Increased hepatic gluconeogenesis ↑ Increased insulin resistance ↑ Increased hyperglycemia ↑ Increased sympathetic activity ↑ Increased catecholamines and cortisol ↑ Increased hepatic acute phase response ↑ Increased immune activation	↑ Increased metabolic stress ↑ Increased cardiac output ↑ Increased baseline metabolic rate ↑ Increased oxygen consumption ↑ Increased temperature ↑ Increased respiratory rate ↑ Increased proteolysis and lipolysis ↑ Increased insulin concentration ↑ Increased production and consumption of energy ↑ Increased negative nitrogen balance ↑ Increased hepatic gluconeogenesis ↑ Increased insulin resistance ↑ Increased hyperglycemia ↑ Increased catecholamines ↑ Increased systemic swelling (proinflammatory cytokines, activation of the complement system and immunosuppression)	↓ Decreased energy output ↑ Increased anabolism ↑ Increased gradual restoration of protein and lipid reservoirs ↑ Increased would scarring, capillary growth, functional recovery and tissue remodeling Normalization of nitrogenated balance after stopping metabolic response to trauma

are at nutritional risk due to the hypermetabolic response to the injury and subsequent complications. A detailed medical history, including weight loss, physical examination, and body composition evaluation, should be collected[4,5].

Multiple tools can be used to assess nutritional status, such as the Subjective Global Assessment (SGA), the Malnutrition Universal Screening Tool (MUST), the Nutritional Risk Screening 2002 (NRS 2002), and the Nutrition Risk in the Critically Ill Score (NUTRIC). The latter two are the most widely used ones in these patients[5]. The NRS includes body mass index (BMI), weight loss, intake, and disease severity. Scores ≥ 3 are indicative of nutritional risk, while scores ≥ 5 are indicative of very high nutritional risk[13]. The NUTRIC scale identifies patients who would benefit from early enteral nutrition (EN) prescription. It considers age, severity as seen on the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment Score (SOFA) scores, comorbidity, length of stay prior to ICU admission, and optionally, inflammation indicated by interleukin 6 (IL-6) levels. Scores range from 0 to 10, and high scores (≥ 6 with IL-6 or ≥ 5 without IL-6) are associated with a high nutritional risk[13]. Regarding the diagnosis of malnutrition, the criteria of the Global Leadership Initiative on Malnutrition (GLIM) should be used[14].

While at the ICU, patients usually lose between 5% and 10% of their muscle mass per week, with losses reported of up to 1 kg/day due to increased proteolysis from the catabolic effects of stress, imbalance between intake and requirements, inactivity, bed rest, and immobility. Muscle mass can be measured using electrical bioimpedance, dual-energy x-ray absorptiometry or computed tomography. Supplementary measurements include calf and arm circumferences and dynamometry. Loss of muscle mass is associated with increased mortality and longer hospital stays, and it interferes with the patient's quality of life and functional capacity[15,16]. The phase angle, obtained through electrical bioimpedance, has been proposed as an objective and non-invasive indicator of functional and nutritional health. Low values are indicative of cell membrane breakdown and, therefore, impaired energy storage and metabolic functions[17,18].

Serial measurements of acute-phase protein concentrations (C-reactive protein, fibrinogen, alpha-1-glycoprotein, etc.) along with constituent proteins (prealbumin, albumin, retinol-binding protein, transferrin) can improve the values of nitrogen balance as a

nutritional monitoring tool. Glucose should be closely monitored and maintained within a range of 140 mg/dL to 180 mg/dL. Electrolytes (potassium, magnesium, and phosphorus) should be measured at least once a week. In the presence of the refeeding syndrome, daily monitoring is advised[5,6,16].

Energy and protein requirements

Caloric and nutritional requirements, and the route of administration should be constantly monitored because they change depending on the patient's condition. The objective of meeting the requirements should be achieved progressively and preferably not before 48 hours to avoid overfeeding. Indirect calorimetry is the reference method to determine nutritional requirements. However, if unavailable, the carbon dioxide production from the ventilator with the Weir formula, and oxygen consumption from the pulmonary artery catheter with the Fick method can be used. Another practical method commonly used is to estimate calories per kilogram of weight per day (Table 2). Although predictive equations of energy expenditure can be used, they are ill-advised because they often under- or overestimate nutritional requirements by up to 60%.[19] The calories from propofol and dextrose infusions should be included in the calculation since they are often sources of hidden and potentially excessive calories[4-7,20].

Polytraumatized should receive hyperproteic nutrition to support wound healing, increase the immune response, the accelerated protein synthesis, and hypercatabolism. The protein requirements recommended are 1.2-2.0 g/kg per day[20]. In patients with an open abdomen, an additional 15-30 g of protein per liter of lost exudate is advised[16]. In obese patients[16], 2.0 g/kg of ideal body weight per day is advised for patients with BMIs of 30-40 kg/m^2 or 2.5 g/kg of ideal body weight per day for those with BMIs ≥ 40 kg/m^2. The non-protein calories/grams of nitrogen ratio should be 80:1 to 120:1[4].

Vitamins and trace elements must be a comprehensive part of enteral and parenteral nutritional support. Many micronutrients are severely depleted during the inflammatory response. Immediate supplementation—especially of water-soluble vitamins—reduces the risk of developing multiorgan failure. Selenium, zinc, and copper are essential for the anabolic phase after trauma. the administration of manganese should be cut down to 30-60 μg/day. In critically ill patients with vitamin D deficiency (< 12.5 ng/mL), a high single dose is advised[21].

Table 2. Caloric requirements in polytraumatized patients[4-7,15,20]

Polytrauma with moderate-severe injuries (non-obese patients with ISS 25-30)	– 20-25 kcal/kg/day during acute and early phases – 25-30 kcal/kg/day (120% to 140% HB REE)
Polytrauma in obese patients	– 65% to 70% of the energy expenditure measured by indirect calorimetry – BMI = 30 to 50 kg/m^2: 11-14 kcal/kg of actual body weight per day – BMI ≥ 50 kg/m2: 22-25 kcal/kg of ideal body weight per day
Severe cranioencephalic injuries (GCS < 8)	– Non-pharmacologically paralyzed patients: ~30 kcal/kg per day (140% HB REE) – Pharmacologically paralyzed patients: ~25 kcal/kg per day (100% HB REE)
Patients with spinal cord injuries	– Tetraplegics: 20-22 kcal/kg/day (55% to 90% Harris HB REE) – Paraplegics: 22-24 kcal/kg/day (80% to 90% HB REE)
Patients with burns	Multiple formulas can be used depending on the body surface area damaged; the Curreri formula is one of the commonly used ones but tends to make 25% to 50% overestimations or else the HB formula multiplied by a stress and activity factor.

BMI: body mass index; GCS: Glasgow Coma Scale; HB: Harris Benedict formula; ISS: Injury Severity Score; REE: resting energy expenditure.

Enteral nutrition

The provision of exogenous substrates when demand is increased due to the hypercatabolic state improves the clinical outcomes. Most patients with severe injuries who are expected to survive 24 to 48 hours will probably have long stays at the ICU and remain at risk of infection, acute respiratory distress syndrome, multiple organ dysfunction, and even death. Nutritional support should be considered in all patients with intolerance to oral intake 72 hours after the event or with multiple interruptions due to medical procedures[21]. The main goal of nutritional treatment is to maintain immune defenses by supporting hypercatabolism and preserving muscle mass[6].

Early EN should be the first-line therapy for nutritional support in polytraumatized patients. It is a safe route of administration that can be used in most of these patients once the fluid resuscitation phase has been completed and hemodynamic stability has been achieved[22]. The European Society for Clinical Nutrition and Metabolism (ESPEN) defines early EN as feeding within the first 24 to 48 hours after ICU admission;5 during this time, there is a therapeutic

window where nutritional support can positively impact the outcomes and improve GI tolerance[23].

Early EN is recommended because it spares the anatomical and functional integrity of intestinal mucosa and gut-associated lymphoid tissue (GALT), maintains the immune response, reduces oxidative stress, the risk of infections, the length of stay, mortality, the development of multiple organ failure, the rate of intra-abdominal abscesses, and episodes of ventilator-associated pneumonia eventually improving the clinical outcomes. For EN to provide these benefits, at least, 50% to 65% of the total energy expenditure (TEE) should be administered[23-25].

EN is contraindicated in patients who have not been fully resuscitated, remain hemodynamic unstable, have uncontrolled shock, hypoxemia, hypercapnia or uncontrolled acidosis, require high doses of inotropic and vasopressor support, have GI bleeding, gastric residual volume ≥ 500 mL/6 h, intestinal discontinuity, mesenteric ischemia, ileus, polytrauma with significant retroperitoneal hematoma and peritonitis, intestinal obstruction, abdominal compartment syndrome, and high-output fistulas. Under these conditions, starting parenteral nutrition (PN) is advised[19,23].

EN should be initiated at gastric level, often through a nasogastric or orogastric tube (indicated in patients with severe injuries in the facial, maxillary, and basal frontal areas). Gastric tolerance should be monitored on a daily basis. Gastric intolerance is characterized by abdominal distension, vomiting, risk of bronchoaspiration, high gastric residual volume, or failure to achieve, at least 50%, of the target values within 48 hours. However, if tolerance is not achieved with the use of prokinetics (metoclopramide or erythromycin), with the transition to strategies such as continuous infusion, or when gastric feeding is contraindicated, the tube should be placed at jejunal level. In patients with traumatic brain injury, septic complications, burns or certain drug-related adverse events, the presence of gastroparesis should be assessed because, in these cases, gastric feeding is contraindicated[26].

In patients requiring prolonged nutritional support, the placement of enteral devices (gastrostomy) should be considered, such as in patients with severe brain injuries. They are, however, contraindicated in patients with an open abdomen if the intestine is fragile, swollen or edematous. Jejunostomy is ill-advised as the first method for EN. It is indicated in patients with pancreaticoduodenal, esophageal, gastric, or duodenal injuries in which EN will be required for an extended period, with gastric access being contraindicated here[26].

Careful gradual reintroduction of nutrition reduces the risk of the refeeding syndrome in patients with severe malnutrition or low intake prior to admission. Once the patient has been stabilized, hypocaloric EN (< 70% of TEE) can be started with continuous infusion or bolus feeding and a low infusion rate (10 mL/h to 40 mL/h) with trophic effects on the intestinal mucosa[5]. The feeding rate can be increased by 10 mL/h to 25 mL/h every 8 to 12 hours to reach the target in the absence of intolerance[27]. Progression to achieve the goal set can be slower in patients with abdominal trauma index scores ≥ 40.6 Patients at high nutritional risk or with severe malnutrition should reach their caloric goals within the first 24 to 48 hours, always observing the risk of the refeeding syndrome. Efforts should be made to provide > 70% (estimated energy) or > 80% (measured energy) of the energy and protein goals within 72 hours to achieve the clinical benefits of EN within the first week of hospitalization (Fig. 1)[16].

Standard polymeric formulas of 1.0 kcal/mL to start EN are advised, preferably high in proteins. However, in patients requiring volume restriction, formulas with a caloric density of 1.5-2.0 kcal/mL are advised. Additionally, the use of specialized formulas low in carbohydrates for patients with diabetes improves the glycemic profile. Carbohydrate requirements should be individualized based on the patient's blood glucose levels and glucose intolerance[16,20].

The use of immunomodulatory formulas with arginine, nucleotides, and omega-3 is also indicated in patients with trauma, acute respiratory distress syndrome or moderate, non-severe sepsis (APACHE II < 15). The administration of these formulas to critically injured polytraumatized patients for 7 to 10 days has been reported to reduce infection rates, complications, antibiotic use, the risk of multiple organ failure, and the length of stay, and increase survival[16,22].

Despite being the most abundant amino acid in the body, glutamine is depleted during trauma-related stress. It is the primary energy source for rapidly dividing cells such as enterocytes, lymphocytes, macrophages, bone marrow cells, endothelial cells, and proliferating cells in wounds and swollen regions. Glutamine should be added to standard formulas in all patients sustaining traumas and burns. Doses of 0.2 to 0.3 g/kg/day within the first 5 days of EN can be used. This course can be extended for up to 10 to 15 days. For patients with > 20% total body surface area burned, 0.3 to 0.5 g/kg/day is advised for 10-15 days at the beginning of EN[28].

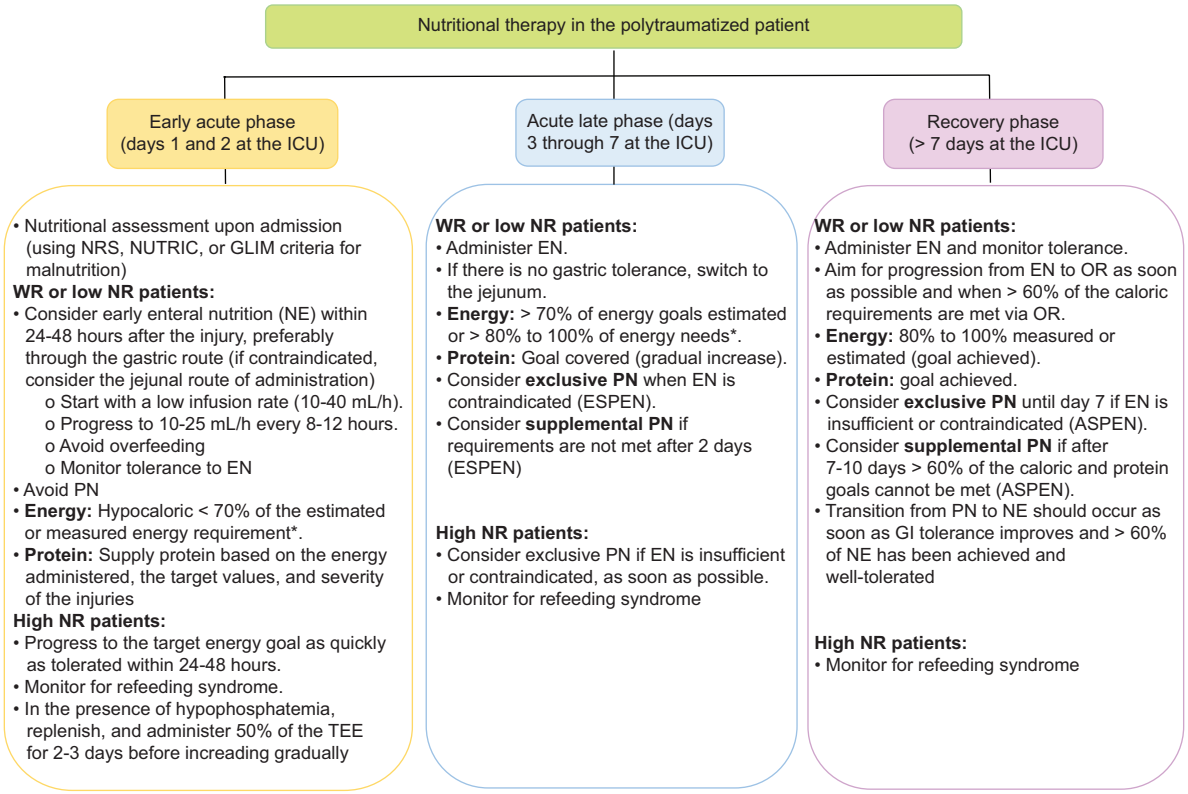

Figure 1. *Nutritional treatment synthesis in polytraumatized patients. ASPEN: American Society for Parenteral and Enteral Nutrition; EN: enteral nutrition; ESPEN: European Society for Clinical Nutrition and Metabolism; GLIM: Global Leadership Initiative on Malnutrition; ICU: intensive care unit; NR: nutritional risk; NRS: Nutritional Risk Screening 2002; NUTRIC: Nutrition Risk in the Critically Ill Score; OR: oral route; PN: parenteral nutrition; WR: without risk.*
**Energy estimated using formulas or measured using indirect calorimetry.*

Parenteral nutrition

Although EN has fewer complications, PN is an essential and vital treatment to provide nutritional substrates to patients without functional GI tracts.28 In some cases, EN may not be feasible, either because it is not fully tolerated within the first week at the ICU, due to contraindications (such as intestinal failure or high-output enterocutaneous fistulas) or because it cannot provide the proper nutrients according to the body's demand. In such situations, the use of PN is advised. However, PN should not be started until all the strategies mentioned before have been tried to maximize tolerance to EN[19,20]. In cases treated with PN, transition to EN should be made after GI tolerance has improved, when EN can account for > 60% of the TEE and is well-tolerated.

In polytraumatized patients with or without low nutritional risk, exclusive PN should be avoided until day 7 in cases when proper intake cannot be maintained or EN is not feasible according to the guidelines of the American Society for Parenteral and Enteral Nutrition (ASPEN).16 On the other hand, ESPEN guidelines propose that PN should be administered within the first 3-7 days to patients in whom EN is contraindicated or not tolerated[5]. Contraindications for PN include the possibility of enteral feeding, severe hemodynamic instability, and metabolic changes[19].

Exclusive, low-dose PN can be administered as soon as possible after the ICU admission if there is high nutritional risk or severe malnutrition, and when EN is not feasible, always considering that the risk of refeeding syndrome can outweigh the expected benefits. Hypocaloric nutrition and proper doses of proteins can be gradually administered based on the patient's clinical status during the first week at the ICU. Overall, PN is administered through a central venous catheter that supports high-osmolarity emulsions that cover the total nutritional requirements, unlike peripheral PN[15,16,19].

PN can be administered independently or together with EN to improve energy and nutrient delivery.

Therefore, in low or high nutritional risk patients, the use of supplemental PN is advised after 7-10 days if > 60% of energy and protein requirements cannot be met via enteral route, as per the ASPEN guidelines[16]. The ESPEN guidelines propose that all patients receiving less than the target intake after 2 days should be considered for supplemental PN[5]. Initiating supplemental PN before this time does not improve the outcomes and may be detrimental to the patient increasing the risk of infections. It is recommended to use both routes concomitantly, whenever feasible, to reduce the risk of hyperglycemia, hepatocellular damage, immunosuppression, and GALT dysfunction[24,25].

Complications associated with PN include access, mechanical issues, infections, and metabolic concerns[15]. Concerns during glucose administration and hyperglycemia are particularly relevant for patients receiving PN. Monitoring blood glucose levels and paying careful attention to infusion rates is of paramount importance, because it is a common thing to mistakenly administer excessive glucose and calories intravenously for a short period of time, which triggering complications[20].

IV lipid emulsions with long-chain, medium-chain triglycerides or a combination of the two can be safely administered at a rate of 0.7 g/kg up to 1.5 g/kg for 12-24 hours[5,6]. Soy-based lipid emulsions should be restricted or limited to 100 g/week (divided into two doses) in critically ill patients if there are concerns of potential essential fatty acid deficiency. Olive oil-derived emulsions are a neutral source of essential fatty acids and contain a low amount of omega-6. Fish oil-based emulsions have effects on the cellular membranes and anti-inflammatory processes and are associated with fewer infections, shorter courses of mechanical ventilation, and fewer days at the hospital[16]. Some studies have reported that the complete limitation or minimal administration of lipids in polytraumatized patients during the acute phase of the injury can minimize susceptibility to infections and reduce the length of stay[28,29].

Within PN, carbohydrate administration should not exceed 5 mg/kg/min and be adapted to each patient's tolerance. The minimum requirements are 2 g/kg/day, and 150 g/day is advised to maintain the preference of certain organs for glucose, such as brain, erythrocytes, immune cells, and kidneys. Excess glucose intake is associated with overfeeding, hyperglycemia, increased carbon dioxide production, lipogenesis, and insulin requirements.5,6 The amino acid solution should contain 0.2-0.4 g/kg/day of L-glutamine or 0.3-0.6 g/kg/day of alanyl-glutamine dipeptide[5,29].

Conclusions

Nutritional intervention in polytraumatized patients is an essential pillar to improve prognosis and obtain multiple benefits. Many of these patients cannot be fed orally due to the severity of their injuries, making nutritional support essential for their recovery. It is important to conduct nutritional assessments upon admission to determine what the appropriate approach should be. Early EN is the preferred approach in patients with a functional GI tract. However, if enteral access is not possible or nutritional requirements cannot be fully met, PN should be used. In malnourished patients, early and progressive PN is recommended as soon as possible to avoid periods of fasting. PN should also be used in cases where EN is contraindicated. It is crucial to avoid overfeeding and the refeeding syndrome when administering EN and PN. Therefore, nutritional goals should be achieved gradually and adjusted daily based on the patient's tolerance and biochemical parameters. Overall, continuous monitoring of the patient's enteral tolerance and biochemical parameters along with daily follow-ups are important to make sure that nutritional goals are met and contribute to a more successful recovery.

Acknowledgements

The authors wish to thank the Department of Internal Medicine of Hospital Civil de Guadalajara Fray Antonio Alcalde, Jalisco, Mexico.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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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REVIEW ARTICLE

Extrapulmonary tuberculosis: a public health problem

Tuberculosis extrapulmonar: un problema de salud pública

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Abstract

Extrapulmonary tuberculosis is defined as that case of tuberculosis clinically diagnosed and confirmed by bacteriological studies that affects tissues and organs outside the lung parenchyma. Mexico is in third place among Latin American countries in terms of the incidence of pulmonary and extrapulmonary tuberculosis. Culture methods are still the gold standard for the diagnosis of extrapulmonary tuberculosis since they identify the species and susceptibility to drugs.

Keywords: *Extrapulmonary tuberculosis. Tuberculosis diagnosis. Mycobacterium tuberculosis.*

Resumen

La tuberculosis extrapulmonar es aquella tuberculosis diagnosticada clínicamente y confirmada por estudios bacteriológicos que afecta a tejidos y órganos fuera del parénquima pulmonar. México es el tercer lugar en América Latina en incidencia de tuberculosis pulmonar y extrapulmonar. Los métodos de cultivo siguen siendo el método de referencia para el diagnóstico de tuberculosis extrapulmonar, ya que identifican la especie y la sensibilidad a los fármacos.

Palabras clave: *Tuberculosis extrapulmonar. Diagnóstico de tuberculosis. Mycobacterium tuberculosis.*

Introduction

Definition

The World Health Organization (WHO) defines extrapulmonary tuberculosis (EPTB) as clinically diagnosed tuberculosis (TB) confirmed by bacteriological studies affecting tissues and organs outside the lung parenchyma[1].

Epidemiology

Tuberculosis (TB) ranks among the ten leading causes of death across the world, with nearly 4500 deaths and 30,000 new cases reported daily. In Latin America, Mexico ranks third in the incidence rate of pulmonary TB and EPTB with 23,000 cases in 2017 (being 80% and 20% of these cases of pulmonary and extrapulmonary location, respectively). The states with the highest incidence rates were

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Date of reception: 01-09-2021
Date of acceptance: 09-12-2021
DOI: 10.24875/CIRUE.M23000437

Cir Cir (Eng). 2023;91(1):127-134
Contents available at PubMed
www.cirugiaycirujanos.com

Baja California, Sonora, Tamaulipas, Guerrero, and Sinaloa[2]. The age group most affected is between 15 and 45 years, with higher mortality rates seen among older adults, particularly in the presence of risk factors[3]. Regarding the anatomical regions of the human body affected by TB, the lung is the most common one, accounting for 80.7% of the cases, followed by EPTB (17.7%), and meningeal TB (1.6%). These infections are more predominant in men[4,5]. A study conducted in 2017 reported that 34 out of 528 patients with suspected serositis due to TB had meningeal TB; 14, pleural TB; 8 had peritoneal TB; and 2, pericardial TB, which is indicative of a growing trend of spread and dissemination to these locations[6].

We should mention infections due to *Mycobacterium bovis*, which accounts for 10% of all cases of EPTB. These infections are relevant due to their clinical repercussions and treatment plan[7].

Risk factors

In a study conducted at Hospital General of Mexico Dr. Eduardo Liceaga, Mexico City, Mexico, a total of 420 cases of TB were identified, 56% being pulmonary TB and 44%, EPTB. Among these cases, 60% were men and 40%, women. Regarding the EPTB cases, 63% were co-infections with the human immunodeficiency virus (HIV) or AIDS; 30% were associated with alcoholism; 30% were smokers; and 17% were associated with diabetes mellitus. We should mention that according to the WHO, individuals infected with HIV have a 30-fold higher risk of developing TB, and a higher prevalence to acquire the *Mycobacterium bovis* complex[8]. This co-infection accelerates the multiplication of HIV and leads to a rapid progression into AIDS.

Pathophysiology

The bacterium *Mycobacterium tuberculosis* is mainly transmitted through the air via Flügge droplets containing the bacillus that can be inhaled by close contacts. Disease develops in 4 stages: bacillus phagocytosis, intracellular multiplication, latent phase, and active lung infection. These stages can progress into different clinical situations: disease healing, disease development, latent infection, and reactivation or reinfection[9]. *M. tuberculosis* bacilli present in the lungs or lymph nodes can undergo reactivation and enter the systemic circulation, leading to extrapulmonary spread to multiple locations, such as the pleura, pericardium, or peritoneum[5]. In susceptible hosts, protective responses, like granuloma formation fail to restrict disease activity, thus promoting dissemination. Additionally, there is a deficit of interleukin-4 secretion that induces Toll-like receptors 2 and macrophage activation, which determines whether the *M. tuberculosis* infection will becomes latent or progressive[10]. The genes responsible for mycobacterial pathogenicity have been grouped based on their function, including envelope genes and cellular metabolic enzymes[11]. The former synthesize proteins exposed to the bacterium's growth environment. Currently, nearly 200 genes are known, being ESAT-6 and CFP-10 the most important of all. These proteins reduce the host's innate immune response in the early stages of infection by inactivating macrophages. The cellular metabolic enzymes including icl, lipF, fadD33, phospholipases C, and panC/panD are involved in the bacterium's lipid and fatty acid metabolism for growth purposes[11].

The involvement of neutrophils in immunopathology is controversial to this date. It has been reported that the sera of patients with active pulmonary tuberculosis induce a series of changes in the nuclear morphology of neutrophils from healthy donors. The dominant global changes seen were apoptosis (preceded by pyknosis and karyorrhexis) and netosis (with extrusion of DNA mixed with elastase, myeloperoxidase: MPO, and histone: HIS) in some cases. All sera from patients with active pulmonary tuberculosis induced some type of change. Changes that were also common in a significant number of household contacts. Sera from healthy individuals without any contact among themselves did not produce changes or only minor changes (mainly pyknosis or nuclear inflammation, but not apoptosis or netosis). These changes were attributed to the normal short lifespan of neutrophils in vitro[12].

Ocular tuberculosis

Its incidence rate ranges from 1.4% to 18% of EPTB. It can be acquired through direct local spread, and affect the eyes and surrounding orbital tissues. Clinical signs may include exophthalmos, unilateral involvement, diplopia due to cranial nerve impairment, dacryoadenitis, abscesses, chronic blepharitis, conjunctivitis, tuberculomas, ulcers, nodular scleritis, and corneal erosions, among others[13].

Cutaneous tuberculosis

Its incidence rate ranges from 1% to 1.5%. It can be acquired through direct inoculation and is characterized by clinical signs such as inflammatory papules, verrucous plaques, suppurative nodules, chronic ulcers, and other atypical lesions, predominantly in areas such as face, neck, and torso. There are 2 different types of cutaneous TB: endogenous, which has 3 subtypes (orificial, scrofuloderma or lupus vulgaris), and exogenous, subclassified into tuberculous chancre and verrucous cutaneous tuberculosis[14,15].

Intestinal tuberculosis

Abdominal TB is rare. It can occur concomitantly with diseases such as hepatic cirrhosis, carcinomatosis, sarcoma, and patients on peritoneal dialysis. It occurs due to the reactivation of latent TB disseminated through the intake of contaminated food or sputum from pulmonary TB. Symptoms are nonspecific, including chronic abdominal pain, fever, weight loss, decreased appetite, night sweats, general deterioration, malnutrition, diarrhea, and occasionally intestinal malabsorption. Ascites, fibrous bands, and adhesions between intestinal loops are often present. Additionally, complications such as intestinal obstruction, abscesses, and hemoperitoneum can occur[16].

Meningeal tuberculosis

With an incidence rate ranging from 1% to 2%, it is considered the most serious dissemination, leading to significant neurological complications, sequelae, and even death. Signs are nonspecific, due to basal meningeal fibrosis and vascular swelling: overall discomfort, fatigue, anorexia, vomiting, headache, mood swings, paralysis of cranial nerves II, III, IV, VI, and VIII, strokes, seizures, and hydrocephalus due to tuberculous exudate accumulation at the cranial base. In the end stages, it causes spasticity and coma[17,18]. Meningeal signs may be absent[19].

Miliary tuberculosis

It is due to the lymphohematogenous dissemination of bacilli, which can occur during primary infection with mycobacteria or during the reactivation of a latent infection. It has multiple ways of presentation, but the involvement of multiple systems is a common characteristic, being the lungs the organs primary damaged, followed by the liver, the spleen, and the central nervous system. It often develops in a nonspecific clinical picture, with fever and predominantly nighttime sweating, anorexia, weight loss, and cough[20].

Tuberculous pleural effusion

It is mainly due to the rupture of subpleural caseous focus, leading to access to pleural space, with the generation of an inflammatory reaction and increased capillary patency, and the influx of proteins, which stimulates pleural fluid formation even further. It can resolve spontaneously or progress into pleural effusion with loculations and empyema[21].

Genitourinary tuberculosis

It is the second most common extrapulmonary localization (5% to 30% of the cases). It affects the epididymis or the prostate, commonly in men aged 30 to 50 years[22]. In the initial stages, it can be asymptomatic, and when it spreads into the ureter and the bladder, it causes symptoms of a urinary syndrome with sterile pyuria and microhematuria in 90% of the cases[23]. Granuloma formation leads to fibrosis and ureteral stenosis, resulting in obstructive uropathy with the development of hydronephrosis[23].

Cervical tuberculous lymphadenitis

It is the most common extrapulmonary localization in adults and children[24]. Its diagnosis is difficult to achieve due to various etiological factors causing lymph node enlargement[25]. It often presents unilaterally, single or multiple, and is mainly located in axillary, thoracic, and abdominal lymph nodes. It can present with necrosis, fluctuate, produce ulcers, fistulas in 10% of cases, and discharge caseous material to the outside (scrofula)[26,27].

A study conducted at the Hospital General de Mexico Eduardo Liceaga, Mexico City, Mexico on 87 patients with cervical lymph node tuberculosis found that 67 patients (77%) presented with unilateral lymphadenopathy (51 in the right lymphatic chain and 16 in the left one), while the remaining 20 patients showed bilateral lymphadenopathy[24,28].

Non-tuberculous mycobacteria commonly involved are *Mycobacterium avium, Mycobacterium gordonae,* and *Mycobacterium xenopi*. In studies of patients with

cervical lymphadenopathy, non-tuberculous mycobacteria have been reported in only 6.6% of the cases, identifying *Mycobacterium intracellulare, M. gordonae,* and *Mycobacterium fortuitum. Mycobacterium kumamotonense* is a slow-growing mycobacterium of the *Mycobacterium terrae* complex. The occurrence of non-tuberculous mycobacteria in HIV-positive individuals[27] occurs after CD4 count drops < 200 cells/mm^3.

Osteoarticular tuberculosis

It represents 9% to 20% of EPTB cases. Among them, tuberculous arthritis, tuberculous osteomyelitis, and tuberculous spondylodiscitis or Pott's disease can be found (that amounts to 50% of the cases)[28]. The latter is characterized by an infection of intervertebral discs and the adjacent vertebral bodies. It often starts on the anterior side of vertebral bodies and spreads towards the discs. In advanced cases, the infection progresses into the adjacent soft tissues causing paravertebral abscesses and damaging the posterior side of the vertebral body and spinal canal, potentially causing spinal cord compression[28]. Symptom onset includes mechanical pain (90% of the cases) and general symptoms[29].

Tuberculous arthritis has been reported in 30% of the cases of bone tuberculosis, erodes the bone of the joint and destroys the adjacent cartilage. Clinical signs include chronic monoarthritis of large joints such as the coxofemoral or sacroiliac one (12-15%), followed by the knee (10%), shoulder (7%), ankle (7%), elbow (2%), and wrist (2%). Slow increase in pain, decreased range of motion, and local inflammation are common symptoms, along with other general symptoms[30].

Tuberculous osteomyelitis is considered rare (2% to 3% of all cases of bone TB) and predominantly affects children. Clinical signs include pain, local swelling, fever, and nighttime sweats. In later stages, it may lead to fistula formation on the skin[31].

Peritoneal tuberculosis

It represents 25% to 50% of all cases of abdominal TB, and 0.1% to 0.7% of all cases of TB. It affects individuals between 35 and 45 years old. Three different types have been reported: 1) wet ascites with high ascitic fluid and protein content; 2) fibrocitic type, characterized by intertwined adhesions of the intestines along the omentum and mesentery; and 3) dry plastic type, with inflammatory reaction, diffuse fibrous adhesions, and nodules along the peritoneum. A total of 70% of all patients experience fever; 60%, weight loss, abdominal pain, and distension; and 15%, diarrhea, being ascites the most relevant finding[32]. Besides the well-known dissemination, there are two 2 different routes of infection: through the intake of infected milk or sputum, causing epithelioid tubercles in the intestinal submucosa with subsequent caseous necrosis and ulceration affecting deeper layers and infecting the peritoneum and lymphatic vessels or through direct spread from an adjacent focus, such as the fallopian tubes or an abscess in the psoas[32,33].

Serositis

Serous membranes are an increasingly common site of dissemination, such as the pleura, meninges, pericardium, and peritoneum, leading to an exudate and accumulation of a large amount of fluid. Although it represents < 1% of all extrapulmonary forms, its mortality rate remains high[34].

Diagnosis

Definitive diagnosis is achieved through positive *M. tuberculosis* culture. However, diagnosing EPTB is challenging since samples obtained from less accessible sites may have few bacilli, thus reducing sensitivity of the diagnostic test. The different diagnostic methods used to confirm the presence of tuberculosis can be divided into direct and indirect methods (Table 1).

Conventional smear microscopy has low sensitivity rates (0% to 40%) compared to cultures (30% to 80%).[35] The Xpert MTB/RIF test detects both pulmonary and extrapulmonary TB, as well as rifampicin resistance[36-38].

A study conducted in Hospital General de Mexico Dr. Eduardo Liceaga, Mexico City, Mexico on the cost-effectiveness of diagnostic methods concluded that various forms of EPTB show that "recent" diagnostic techniques such as polymerase chain reaction and adenosine deaminase offer significant advantages (Fig. 1)[39-42].

Treatment

The overall objective of TB treatment is to eradicate the infection, prevent progression into active disease, improve the patient's clinical status, manage resistance exacerbation, and prevent relapse (Table 2)[43,44].

Table I. Direct and indirect methods for the diagnosis of tuberculosis

Direct methods	Indirect methods
Ziehl-Neelsen staining	Histopathology; it is considered the method of choice to diagnose extrapulmonary tuberculosis
Microscopy	Excision biopsy with systematic histological analysis, Ziehl-Neelsen staining, M. tuberculosis culture, and fine needle aspiration cytology
Culture remains the reference method to diagnose both pulmonary and extrapulmonary tuberculosis, identify species, and drug sensitivity. Notable methods include: Lowenstein-Jensen culture médium BACTEC MGIT 960 system (mycobacteria growth indicator tube) Agar-based (Middlebrook 7H10/11) culture base	Serological tests based on antibodies; cutaneous tests (Mantoux), interferon-gamma release assays, and adenosine deaminase activity. The tuberculin skin test (Mantoux) only detects the presence or absence of infection, indicating exposure to M. tuberculosis or latent tuberculosis. The WHO accepts only two tuberculins as standards: PPD-S PPD and PPD RT 23.
Antigen detection assays	Other indirect methods include: – Volatile organic compounds – Betalactamase detection
Molecular detection: nucleic acid amplification tests such as polymerase chain reaction and automated molecular assay Xpert MTB/RIF. Sensitivity and specificity are 85% and 97%, respectively. These tests play a key role in the diagnosis of meningeal tuberculous. Currently, 3 methods are available, being the first 2 recommended by the WHO: – Cartridge-based nucleic acid amplification test (CB-NAAT) – Line probe assay (LPA) – Loop-mediated isothermal amplification (LAMP)	

Discussion

Back in 2018, approximately 1.5 million people died from TB, and around 10 million individuals were infected with tuberculous mycobacteria across the world. The global goal of the World Health Organization is to reduce the incidence rate of TB by 90% and mortality by 80% by 2030[45]. In Mexico, its incidence rate ranks third in Latin America[2].

In Poland, 5487 cases of TB were reported back in 2018, 95% of which were pulmonary TB and 5%, EPTB. Among all cases, 83 patients (1.5%) showed resistance to isoniazid alone, while 48 (0.9%) showed multidrug resistance to anti-tuberculosis drugs[45]. In Mexico, these figures amount to 80% for pulmonary TB and 20% for EPTB, respectively[2].

In Argentina, in 2019, 12,499 cases of TB were reported (a 6% higher incidence rate compared to 2018). New cases represented 93.3% of all diagnoses. Of the total number of cases, 78.6% were pulmonary TB; 11.1%, EPTB; and 10.3% lacked anatomical localization. A total of 325 cases (2.6%) of resistant TB were reported, 43.1% of which were multidrug-resistant and 2.1% extensively drug-resistant[46].

The TB disease requires extensive attention, especially in Latin American countries, without disregarding other continents, as drug-resistant strains are becoming more prevalent, requiring molecular biology diagnostic methods only available in tertiary-level hospitals, as the one discussed in this study.

On the other hand, non-tuberculous mycobacterial disease has been on the rise in China, where a study of 607 cases of non-tuberculous mycobacteria conducted during the 2013-2016 period found that the most prevalent species were *M. avium complex* (44.5%), *Mycobacterium abscessus* complex (40.5%), *Mycobacterium kansasii* (10%), and *M. fortuitum* (2.8%)[47]. In Mexico, from January 2013 through December 2014, a total of 120 patients were studied. A total of 30.8% of these patients were infected with a non-tuberculous mycobacterium. The most prevalent infections were due to *M. avium* (54.1%) and *M. intracellulare* (18.9%), while other non-tuberculous mycobacteria species accounted for 27% of the cases[44].

Table 2. Therapy for extrapulmonary tuberculosis

	6 m	Isoniazid	Including EPTB, except CNS, bone, and joints
	2 HRZE/4HR	Rifampicin	
		Pyrazinamide	
		Ethambutol	
Standard initial phase	Intensive	Isoniazid	300 mg
First-line drugs	60 doses (2 m)	Rifampicin	600 mg
For EPTB (CNS, bone, and joints)	Monday-Saturday	Pyrazinamide	1500-2000 mg
		Ethambutol	1200 mg
	Continuation Phase	Isoniazid	800 mg
	45 doses (10 m)	Rifampicin	600 mg
	3/7 days		
Retreatment	Relapse: 8 m	2HRZES/1HREZ/5H3R3E3	
	Failure	COEFAR (State Drug Resistance Committee)	
Standardized retreatment	24 m	G1: oral first-line drugs useful in TB-MDR → E, Z	
Second-line therapy		G2: injectables → S, KM, AM, CM	
		G3: fluoroquinolones → OFX, LFX, MFX	
		G4: oral second-line bacteriostatics → ETO, PTO, CS, TRD, PAS	
		G5: poor efficacy → CFX, AMX/CLV, CLR, LZD, TH, IPM/CLN, high-dose H	
Individualized retreatment	Administered for any disease location/GANAFAR (National Advisory Group on Drug Resistance)		
Second-line therapy			
EPTB	Intensive	Isoniazid	
	2 m	Rifampicin	
	Monday-Saturday	Pyrazinamide	
		Ethambutol	
	Continuation	Isoniazid	
	10 m	Rifampicin	
	3/7 d		
Meningitis and tuberculous pericarditis	6 to 8 weeks	Initial adjuvant therapy with corticosteroids (dexamethasone or prednisolone)	
Directly observed treatment	In the presence of non-compliance risk		
TB due to *Mycobacterium bovis*	Regimen extended due to up to 38% rates of pyrazinamide resistance having been reported		

AM: amikacin; AMX/CLV: amoxicillin/clavulanate; CFX: ciprofloxacin; CLR: clarithromycin; CM: capreomycin; CP: capreomycin; CS: cycloserine; E: ethambutol; ETO: ethionamide; H: isoniazid; IPM/CLN: imipenem/cilastatin; KM: kanamycin; LFX: levofloxacin; LZD: linezolid; MDR: multidrug-resistant; MFX: moxifloxacin; OFX: ofloxacin; PAS: para-aminosalicylic acid; PTO: prothionamide; R: rifampicin; S: streptomycin; CNS: central nervous system; TB: tuberculosis; EPTB: extrapulmonary tuberculosis; TH: thioacetazone; TRD: terizidone; Z: pyrazinamide

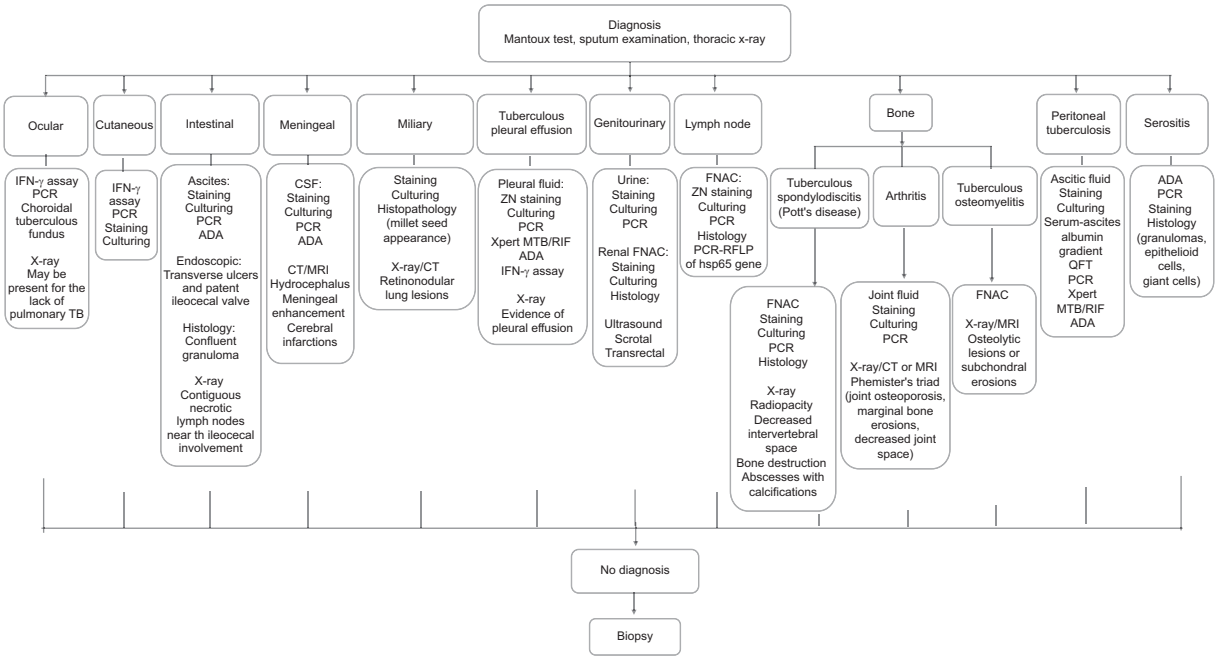

Figure 1. *Diagnostic methods to identify different types of extrapulmonary tuberculosis. ADA: adenosine deaminase; CSF: cerebrospinal fluid; CT: computed tomography; FNAC: fine needle aspiration cytology; INFγ: interferon-gamma; MRI: magnetic resonance imaging; QFT: QuantiFERON; RFLP: restriction fragment length polymorphism; Rx: x-ray; TB: tuberculosis; USG: ultrasonography; ZN: Ziehl-Neelsen staining.*

Conclusions

Although the WHO strategy has been established in recent years to reduce the mortality and incidence rates associated with TB, we'll only see this reduction when a more accurate number of diagnosed patients becomes available and when primary and secondary health care centers, upon suspicion of TB, promptly refer cases to tertiary-level hospitals. These forms of tuberculosis are challenging because it is difficult to achieve a definitive diagnosis, because both the clinical signs and the imaging modalities can be nonspecific.

Acknowledgements

The authors wish to extend their gratitude to the late mentor Raúl Cicero Sabido for his unwavering support in the research endeavors at the tuberculosis clinic of Hospital General of Mexico Dr. Eduardo Liceaga, Mexico City, Mexico.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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

Colonoscopy as a therapeutic option for acute after sigmoidectomy rectal bleeding

Colonoscopia como opción terapéutica ante rectorragia aguda tras sigmoidectomía

Araceli Moreno-Navas, Irene Gómez-Luque, César Díaz-López, and Javier Briceño-Delgado*
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To the Editor,

This is the case of a 58-year-old man with a past medical history of appendectomy diagnosed as part of a colorectal cancer screening program through colonoscopy with a nipple-like ulcerated lesion located 25 cm away from the anal margin. Biopsy results revealed the presence of adenocarcinoma, and staging studies showed no evidence of spread. The patient was scheduled for laparoscopic sigmoidectomy with end-to-end mechanical anastomosis using an ILS 29 circular stapler. The specimen resected was extracted through a Pfannenstiel incision, with Penrose drain placement in the pelvis. The surgery was uneventful.

In the immediate postoperative period, a few hours after surgery, the patient experienced 2 episodes of overt rectal bleeding without hemodynamic repercussions, but with a gradual drop of hemoglobin levels (14.3 g/dL, 13 g/dL, 12 g/dL). Due to persistent anemia, an emergency coronary computed tomography angiography was performed that revealed contrast extravasation in the arterial phase inside the rectum, specifically at the colorectal anastomosis site. Contrast extravasation increased in the venous phase, which was indicative of active bleeding. No fluid was seen in the pelvis.

An on-call gastroenterologist was consulted for early therapeutic colonoscopy in the endoscopy suite, along with an anesthesiologist and a surgeon. During the colonoscopy, the anastomosis was identified 18 cm away from the anal margin, with significant fresh bleeding. An active arterial jet of blood was seen at the staple line of the anastomosis at the 6 o'clock position (Fig. 1 A). After washing the anastomotic region, the blood clot was removed using a tripod snare, and 6 mL of epinephrine 1:10,000 were infused. Mechanical zip closure was performed using 5 hemoclips along the staple line (Fig. 1 B) that successfully stopped the bleeding leaving a stable suture line without active bleeding.

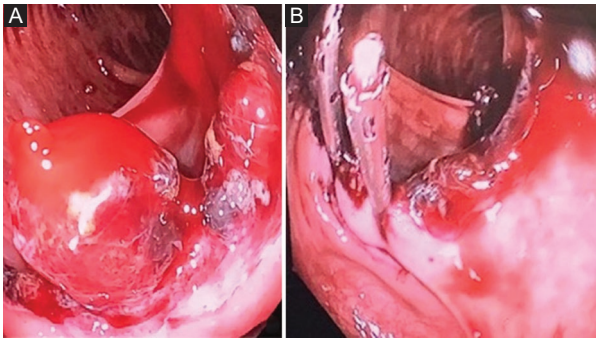

Figure 1. *A: colonoscopic image. At 6 h, bleeding in an active arterial jet is observed. B: endoscopic treatment. Mechanical zipper closure with five hemoclips on the staple line.*

The patient was, then, transferred to the recovery room where he remained hemodynamically stable at all times, without amines and with hemoglobin levels

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Date of reception: 07-02-2022
Date of acceptance: 18-02-2022
DOI: 10.24875/CIRUE.M23000438

Cir Cir (Eng). 2023;91(1):135-136
Contents available at PubMed
www.cirugiaycirujanos.com

of 10.4 g/dL. Since the postoperative period was uneventful, the patient was discharged 6 days after surgery.

Severe bleeding from a colorectal anastomosis is a rare complication. Its incidence rate is close to 1% according to the medical literature available[1]. The rate of therapeutic effectiveness of colonoscopy is almost 81% being good prognostic factors the use of hemoclips and bleeding within the first 5 days after surgery. No correlation has been reported between early colonoscopy and the development of anastomotic dehiscence[2].

This case highlights the importance of considering early therapeutic colonoscopy as an option in cases of acute postoperative rectal bleeding. This technique facilitates the direct visualization of the lesion and the performance of therapeutic interventions to manage bleeding lesions, and potentially avoid the need for surgical procedures[3].

Performing an early colonoscopy and the use of hemoclips is a safe and efficient approach to manage severe rectal bleeding as a complication of colorectal surgery[1,4].

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

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

Patients' data protection. 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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LETTER TO THE EDITOR

A commentary on "Surgical results of Hartmann procedure in emergency cases with the left-sided colorectal cancer"

Un comentario sobre "Resultados quirúrgicos del procedimiento de Hartmann en casos de emergencia con cáncer colorrectal del lado izquierdo"

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Dear Editor,

We have read with great interest the article published by Altin et al.[1] titled "Surgical results of Hartmann procedure (HP) in emergency cases with the left-sided colorectal cancer (CRC)", where the authors refer to predominantly left CRC and its complications such as obstruction and perforation, leading the patient to a surgical intervention as in the case of the HP with the need for a second operation to reverse the colostomy, leading to anastomotic dehiscence, which generates psychological and physical difficulties that deteriorate the quality of life of the patient[1]. We thank the authors for such valuable evidence. However, we would like to make a few comments.

According to Sciuto et al.[2], most patients have considered that the closure of the colostomy would improve their quality of life, a procedure that could not be performed because there are adhesions that have appeared when the colostomy is longer, thus generating high risk of injury to the intestine or other viscera due to a second intervention. Another factor that should be evaluated when defining HP is the colonic stenosis present in 5.8-20% in initially anastomosed patients, considered as a protective factor against stenosis, different from patients with colostomy, where it is considered a risk factor and greater difficulty for the patient to be taken to a subsequent reconstruction[3]. On the other hand, in HP, high conversion rates to open surgery have been observed, ranging from 24% to 50%, this is significantly unfavorable, since minimally invasive surgery has shown a reduction in the risks of infection, hematoma, evisceration, and eventration versus open surgery[2]. However, despite these new technologies mentioned, the risk of anastomotic dehiscence has not been eliminated. Finally, it should be noted that procedures such as laparoscopic ultra-low anterior resection of the rectum with coloanal anastomosis should not be ruled out or replaced by HP, as it is a safe technique with excellent results in terms of local recurrence and overall survival[4].

It is concluded that new scientific productions that compare the performance of tumor resection and anastomosis in the same surgical time and HP are essential to be able to define more clearly the specific indication of the type of patient.

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.

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Date of reception: 21-05-2021
Date of acceptance: 07-07-2021
DOI: 10.24875/CIRUE.M21000561

Cir Cir (Eng). 2023;91(1):137-138
Contents available at PubMed
www.cirugiaycirujanos.com

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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LETTER TO THE EDITOR

Brief commentary about the origin of the anterolateral thoracotomy for the surgical treatment of cardiac wounds

Breve comentario sobre el origen de la toracotomía anterolateral para el tratamiento quirúrgico de las heridas cardíacas

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To the Editor,

We have read with great interest the article written by Velázquez-Santiago et al.[1] on the surgical treatment of penetrating cardiac injuries, and we would like to share some thoughts on the naming of the incision used.

Apparently, in 1926, Claude Beck noted that Spangaro had used the left anterolateral thoracotomy for the first time as an emergency approach to treat cardiac wounds back in 1906. For almost a century, this incision has been named after Spangaro, thus attributing this Italian surgeon an authorship that may not be entitled to[2].

According to the small biography available, Saverio Spangaro (February 29, 1870 - December 12, 1946) was a talented, brilliant, meticulous, and daring surgeon. He ventured into gynecological and GI surgery and published on topics related to bacteriology, anatomopathology, and experimental pathology. However, interestingly enough, no experience has been attributed to him regarding general or thoracic surgery, despite supposedly making contributions in that field for which he is currently remembered. There is no scientific evidence either to suggest that he ever operated on a human heart. His 1907 article titled "Experimental research on the functional behavior of the wounded heart subject to surgical procedures" supposedly described the thoracotomy discussed above, focusing on "the cardiac condition of the thorax and of the dog in cardiac injuries and surgeries [where] opening the heart through the fifth intercostal space was the preferred access"[3].

On the other hand, in a compilation on sutured cardiac wounds up to 1909, reference is made to Spangaro's experimental work. However, he is not identified as the author of any of the operations studied[4]. But, experimental medical practice does not set any milestones in surgical history. Therefore, besides being unfair to credit Spangaro as the creator of the left anterolateral thoracotomy in the fifth intercostal space, this also indicates a sort of superficial historical research, as Daniel Hale Williams had already used that approach in his famous cardiac surgery performed in July 10, 1893[2,5].

Funding

None whatsoever.

Conflicts of interest

None reported.

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Date of reception: 24-06-2021
Date of acceptance: 07-07-2021
DOI: 10.24875/CIRUE.M23000439

Cir Cir (Eng). 2023;91(1):139-140
Contents available at PubMed
www.cirugiaycirujanos.com

Ethical disclosures

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

Patients' data protection. 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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