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ORIGINAL ARTICLE

Basic and combined peripheral biomarkers have no predictive and prognostic value in breast cancer patients undergoing pre-operative systemic therapy

Los biomarcadores periféricos básicos y combinados no tienen valor predictivo ni pronóstico en pacientes con cáncer de mama sometidas a terapia sistémica preoperatoria

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Abstract

Objective: *The main goal in breast cancer patients receiving neoadjuvant chemotherapy (NAC) is to achieve a pathologic complete response (pCR). Our study examines whether neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), NLR/PLR, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation-value (PIV) indices can be used to determine pCR and prognosis.* **Methods:** *The study included 228 patients who received NAC for breast cancer between 2010 and 2021.* **Results:** *Fifty-nine (25.9%) patients had pCR to NAC. In univariate analysis, a significant difference was found between clinical node status, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), breast cancer molecular subtypes, and pCR ($p < 0.05$). However, in multivariate analysis, only breast cancer molecular subtypes and HER2 status were significantly associated with pCR ($p < 0.05$).* **Conclusions:** *Our study did not find a significant relationship between NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices and pCR, disease-free survival, and overall survival in breast cancer patients who received NAC.*

Keywords: *Neoadjuvant chemotherapy. Breast cancer. Disease-free survival.*

Resumen

Objetivo: *El propósito principal en las pacientes con cáncer de mama que reciben quimioterapia neoadyuvante (NAC) es lograr una respuesta patológica completa (RPC). Nuestro estudio examina si el índice neutrófilos/linfocitos (INL), el índice plaquetas/linfocitos (IPL), el índice monocitos/linfocitos (IML), la ratio INL/IPL, el índice de inmunidad-inflamación sistémica (IIS), el índice de respuesta inflamatoria sistémica (IRIS) y el valor de pan-inmuno inflamación (VPI) pueden utilizarse para determinar la RPC y el pronóstico.* **Métodos:** *El estudio incluyó 228 pacientes que recibieron NAC por cáncer de mama entre 2010 y 2021.* **Resultados:** *Cincuenta y nueve (25.9%) pacientes tuvieron RPC a NAC. En el análisis univariante, se encontró una diferencia significativa entre el estado de los ganglios clínicos, el receptor de estrógenos, el receptor de progesterona, el receptor del factor de crecimiento epidérmico humano 2 (HER2), los subtipos moleculares de cáncer de mama y la RPC ($p < 0,05$). Sin embargo, en el análisis multivariante solo los subtipos moleculares de cáncer de mama y el estado de HER2*

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se asociaron significativamente con la RPC (p < 0.05). **Conclusiones:** *Nuestro estudio no encontró una relación significativa del INL, el IPL, el IML, la INL/IPL, el IIS, el IRIS y el VPI con la RPC, la supervivencia libre de enfermedad y la supervivencia global en pacientes con cáncer de mama que recibieron NAC.*

Palabras clave: *Quimioterapia neoadyuvante. Cáncer de mama. Supervivencia libre de enfermedad.*

Introduction

Breast cancer surpassed lung cancer as the most common cause of cancer globally in 2020. In addition, breast cancer still accounts for a significant proportion of cancer-related deaths among women[1]. Therefore, focusing on the treatment of patients with breast cancer is critical for public health.

In recent years, neoadjuvant chemotherapy (NAC) has been used with increasing frequency in breast cancer. However, there are uncertainties about which patients are sensitive to NAC and which patients are not sensitive to NAC and, therefore, delayed surgical treatment. Hence, it is essential to determine who will benefit from NAC to optimize the treatment of patients. Estrogen receptor (ER), progesterone receptor (PR), Ki67 level, and human epidermal growth factor receptor 2 (HER2) status are often used to predict response to NAC. However, they do not accurately predict pathologic complete response (pCR). Tumor-infiltrating lymphocytes (TILs), programmed death-ligand 1 expression, artificial intelligence-assisted magnetic resonance imaging, quantitative ultrasound, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography can also be used. However, these examinations are costly. In addition, access to these examinations is only sometimes possible, and further studies are needed for their use in routine practice[2]. Therefore, there is a need for parameters that are inexpensive, easily accessible, and not difficult to interpret[3]. For this purpose, the literature has turned toward inflammatory bioindices analyzed from peripheral blood. These indices are calculated by various ratios of white blood cell (W), neutrophil (N), monocyte (M), platelet (P), and lymphocyte (L) cells in peripheral blood. The literature has mainly focused on the association of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) with pCR and survival. However, studies have shown that NLR and PLR have conflicting results in predicting pCR, disease-free survival (DFS), and overall survival (OS)[4-8]. However, few studies have focused on more combined peripheral indices such as NLR/PLR, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation-value (PIV). These studies suggest that more complex calculations predict PCR and prognosis better than individual biomarkers[7]. However, there are few publications on combined indices and conflicting reports on these indices.

The main goal of breast cancer patients receiving NAC is to achieve a PCR. In the above-mentioned studies, the main issue investigated is whether peripheral biomarkers can predict pCR in breast cancer patients receiving NAC. However, giving NAC to breast cancer patients to achieve an axillary complete response based on these indices may lead to overtreatment of the axilla because axillary dissection (AD) is recommended even if the patient's axilla remains clinically positive after NAC or if micrometastases are detected on sentinel lymph node biopsy (SLNB) in patients whose axilla turns clinically negative. However, AD is not always recommended in patients who have not received NAC if the axilla is positive under certain conditions or if macrometastasis is detected on SLNB[9].

For the reasons mentioned above, we focused on the contradictions and problems in the clinical use of simply calculated indices such as NLR, PLR, monocyte lymphocyte ratio (MLR), and more combined indices such as NLR/PLR, SII, SIRI, and PIV. We aimed to examine the relationship of these indices with pCR, DFS, and OS in a group of breast cancer patients receiving NAC. Our study is also important as it is the first publication in the literature to evaluate these indices together in terms of both pCR and prognosis.

Methods

Patients

Patients who were admitted to SBU Izmir Tepecik Training and Research Hospital between 2010 and 2021 and received NAC for breast cancer were included in the study. After obtaining permission from the Local Ethics Committee, patient data were obtained retrospectively from the electronic record system and physical files of the medical oncology department.

All patients were diagnosed histopathologically and were presented to the multidisciplinary session after appropriate screening according to their stage. The standard treatment regimens for patients with NAC decisions are anthracycline and taxane-based. Patients with HER2-positive tumors received standard trastuzumab in addition to anthracycline and taxane.

Surgical procedures included breast conserving surgery, level 1, 2, and 3 oncoplastic surgery or mastectomy. The axilla was evaluated by imaging and physical examination after NAC. SLNB was performed in patients with clinically negative axilla after NAC. No additional procedure was performed in patients with negative SLNB, while AD was performed in patients with positive (macro- or micrometastases). Clinical and pathological tumors were defined according to the American Joint Committee Cancer Staging Manual 8th Edition.

Exclusion criteria were as follows: diagnosis of cancer in an organ other than breast cancer, active infection at the time of diagnosis, inflammatory or autoimmune disease, recent steroid therapy, inflammatory breast cancer, metastasis to distant organs at the time of diagnosis, no surgery after NAC, and no follow-up.

Pathological assessments

Residual cancer burden (RCB) was calculated by the computerized MD Anderson RCB Calculator[10]. Accordingly, RCB 0 = pCR. pCR was defined as the absence of a tumor in both breast and axillary lymph nodes (LNs) after NAC (ypT0/ypTis, ypN0). The non-pCR group included RCBs 1, 2, and 3 (minimal, moderate, and extensive residual disease, respectively).

Study patients were classified into four main molecular subtypes. HR-positivity (HR+) was defined as ER-positive and/or PR-positive, while HR-negativity (HR–) was defined as ER-negative and PR-negative. HER2-positivity (HER2+) was defined as a score of 3 + on immunohistochemical staining and/or positive *HER2* gene amplification by FISH. Triple-negative breast cancer was defined as HR–/HER2-, HER2-enriched breast cancer as HR–/HER2+, luminal A as HR+, HER2–, Ki67 ≤ 14 and luminal B as HR+, HER2–, Ki67 > 14 or HR+, and HER2+[11].

Blood sample analysis

NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV values were calculated from peripheral blood values obtained from patients diagnosed with breast cancer before NAC treatment. The indices were calculated as follows; NLR; N/L, PLR; P/L, MLR; M/L, SII; N*P/L, SIRI; N*M/L, PIV; and N*P*M/L.

Patient follow-up and prognostic assessment

The patients whose treatments were completed were followed up in outpatient departments. Patients were followed up by physical examination, blood tests, and imaging methods and additional procedures were performed when necessary.

Statistical analysis

Statistical analyses were performed using IBM® Statistical Package for the Social Sciences (SPSS)® 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) software. The conformity of the variables to normal distribution was analyzed using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were given as mean ± standard deviation for normally distributed variables, median and min-max for those not normally distributed. Descriptive statistics of categorical variables obtained from sociodemographic and clinical information were analyzed using frequency and percentage values. Pearson's or Fisher's Exact X^2 test was used to examine the characteristics of patients between pCR response states. With receiver operative characteristics (ROC) analysis, cutoff values were determined for NLR, MLR, PLR, PIV, SII, and SIRI parameters (follow-up parameters analyzed) according to pCR status. According to these cutoff values, dichotomous (Low/High) variables were created for each parameter. Univariate and multivariate logistic regression analyses were performed to evaluate the effects of the characteristic variables of the disease and the follow-up parameters on the pCR response. Cox regression survival analysis was performed on these follow-up parameters (NLR, PLR, NLR/PLR, MLR, SIRI, SII, and PIV) to examine whether they could be predictive markers on OS and DFS times and whether a model could be established. Kaplan–Meier survival analysis was performed to compare OS and DFS durations between dichotomous (Low/High) variables of NLR, PLR, NLR/PLR, MLR, SIRI, SII, and PIV parameters. P values below 0.05 were considered statistically significant.

Table 1. Clinicopathological characteristics of the patients

Characteristics	n	%
Age		
Median (range)	50 (24-78)	
Clinical T stage		
1	31	13.6
2	150	65.8
3	31	13.6
4	16	7.0
Clinical T stage groups		
T1-T2	181	79.4
T3-T4	47	20.6
Clinical node stage		
0	46	20.2
1	137	60.1
2	41	18.0
3	4	1.8
Clinical node status		
Negative	46	20.2
Positive	182	79.8
Stage		
1	3	1.3
2	147	64.5
3	78	34.2
Stage groups		
≤ 2	150	65.8
3	78	34.2
Grade		
Missing	3	1.3
Good	5	2.2
Moderate	126	55.3
Poor	94	41.2
Moleculer subtype		
Luminal A	24	10.5
Luminal B	123	53.9
ER and PR–. Her2+	34	14.9
Triple-negative	47	20.6
Histotype		
Invasive ductal carcinoma	206	90.4
Other histology types	22	9.6
Estrogen receptor status		
Negative	81	35.6
Positive	147	64.4
PR receptor status		
Negative	83	36.4
Positive	145	63.6
HER-2 status		
Negative	162	71.1
Positive	66	28.9
Ki-67 index, n (%)		
Median (range)	30 (0-90)	
Ki67 classification		
Ki67 < 14	34	14.9
Ki67 ≥ 14	194	85.1
Pathologic complete response		
Yes	59	25.9
No	169	74.1
Recurrence		
No	188	82.5
Yes	40	17.5
Recurrence location		
No	188	82.5
Liver	5	2.2
Bone	3	1.3
Lung	6	2.6
Brain	4	1.8
Multiple	16	7.0
Breast axilla	6	2.6
Mortality		
Ex	43	18.9
Live	185	81.1

HER2: human epidermal growth factor receptor 2.

Results

The study included 228 patients with breast cancer who received NAC. The median age of the patients was 50 years (range 24-78). Fifty-nine (25.9%) patients had pCR to NAC and 169 (74.1%) patients had non-pCR. Recurrence was detected in 40 (17.5%) patients. Forty-three (18.9%) of the patients died. Detailed clinicopathological characteristics of the patients are summarized in table 1.

The relationship between pathological complete response and indices was calculated according to ROC analysis. Cutoff values of NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices were calculated according to maximum specificity and sensitivity. According to this analysis, no significant difference was found between pCR and indices ($p > 0.05$) (Table 2).

The relationship between pCR and clinicopathological characteristics of the patients was examined by univariate and multivariate analyses. In univariate analysis, a significant difference was found between clinical node status, ER, PR, HER-2, breast cancer molecular subtypes, and pCR ($p < 0.05$). However, in multivariate analysis, only breast cancer molecular subtypes and HER-2 status were significantly associated with pCR ($p < 0.05$). Detailed data are given in table 3.

Cox regression analysis was applied to examine whether NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV

Table 2. ROC curve analyses for pathological complete response

Test result variable (s)	AUC	Standard error	p	95% CI for AUC		Sensitivity (%)	Specificity (%)	Cut-off value
				Lower bound	Upper bound			
MLR	0.581	0.044	0.067	0.494	0.668	55.2	56.4	0.262
NLR	0.566	0.045	0.138	0.477	0.654	55.2	55.8	2.24
PIV	0.557	0.045	0.198	0.468	0.646	55.2	56.4	335.7
PLR	0.500	0.047	0.998	0.407	0.593	50.0	57.0	141.2
SII	0.540	0.046	0.362	0.450	0.630	50.0	64.2	597.5
SIRI	0.584	0.044	0.057	0.498	0.669	53.4	57.6	1.18

The test result variable (s): NLR, MLR, PLR, SII, and SIRI have at least one tie between the positive actual state group and the negative actual state group. $p < 0.05$ considered significant. Youden's J statistic used for cutoff. AUC: area under curve; CI: confidence interval; ROC: receiver operating characteristic; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PIV: pan-immune-inflammation-value; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index, SIRI: systemic inflammation response index.

Table 3. Univariate and multivariate logistic regression analysis for the predictors of pathological complete response

Factors	Univariate analysis				Multivariate analysis			
	OR	95% C.I. for EXP (B)		p	OR	95% C.I. for EXP (B)		p
		Lower	Upper			Lower	Upper	
Age	1.0	1.0	1.1	0.142				
Clinical T stage (T1-2 vs. T3-4)	1.2	0.6	2.5	0.664				
Clinical node status (Positive vs. Negative)	2.8	1.4	5.6	0.003	2.1	0.8	4.5	0.057
Triple-negative versus luminal A	17.0	2.1	136.9	0.008	30.8	2.5	380.9	0.008
Triple-negative versus luminal B	3.8	1.8	8.1	< 0.0001	14.8	2.8	79.5	0.002
Triple-negative versus ER and PR–. HER2+	1.6	0.6	3.7	0.356	4.1	1.1	16.0	0.040
Stage (≤ 2 vs. 3)	1.2	0.7	2.2	0.563				
Histopathology (IDC vs. Other)	1.9	0.8	4.9	0.172				
ER (Positive vs. Negative)	4.1	2.2	7.6	< 0.0001	2.9	0.4	24.0	0.325
PR (Positive vs. Negative)	3.7	2.0	6.9	< 0.0001	1.4	0.2	7.6	0.737
HER-2 status (Negative vs. Positive)	3.8	2.0	7.2	< 0.0001	6.1	2.2	16.9	< 0.0001
Ki67 index (High vs. Low)	1.2	0.5	2.7	0.735				
MLR group (High vs. Low)	1.6	0.9	2.9	0.131				
NLR group (High vs. Low)	1.5	0.8	2.7	0.193				
PIV group (High vs. Low)	1.5	0.8	2.6	0.221				
PLR group (High vs. Low)	1.3	0.7	2.3	0.429				
SII group (High vs. Low)	1.8	1.0	3.3	0.055				
SIRI group (High vs. Low)	1.6	0.9	2.3	0.140				

Logistic regression analysis was used and $p < 0.05$ considered significant.
CI: confidence interval; OR: odds ratio; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PIV: pan-immune-inflammation-value; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index, SIRI: systemic inflammation response index.

Table 4. Univariate and multivariate Cox regression analysis for OS and DFS

Variables	Univariate analysis						Multivariate analysis					
	β	SE	p	OR	95.0% CI for OR		β	SE	p	OR	95.0% CI for OR	
					Lower	Upper					Lower	Upper
OS												
MLR	–0.18	0.14	0.177	0.83	0.64	1.09	–0.23	0.18	0.200	0.80	0.56	1.13
NLR	–0.09	0.13	0.518	0.92	0.71	1.19	–0.23	0.19	0.224	0.79	0.55	1.15
PIV	0.04	0.13	0.783	1.04	0.80	1.35	0.09	0.23	0.700	1.09	0.70	1.71
PLR	–0.10	0.13	0.468	0.91	0.70	1.18	–0.14	0.18	0.435	0.87	0.60	1.24
SII	0.12	0.14	0.401	1.12	0.86	1.47	0.35	0.21	0.095	1.42	0.94	2.16
SIRI	–0.05	0.13	0.725	0.95	0.73	1.24	0.05	0.24	0.828	1.05	0.66	1.68
DFS												
NLR	–0.187	0.135	0.168	0.830	0.636	1.082	–0.189	0.174	0.276	0.828	0.589	1.163
MLR	–0.051	0.134	0.705	0.951	0.732	1.235	–0.174	0.191	0.363	0.840	0.578	1.222
PLR	0.047	0.134	0.728	1.048	0.806	1.363	0.366	0.253	0.148	1.441	0.878	2.365
PIV	–0.077	0.134	0.567	0.926	0.712	1.205	–0.094	0.186	0.613	0.910	0.633	1.310
SII	0.148	0.138	0.282	1.159	0.885	1.519	0.343	0.210	0.102	1.409	0.934	2.126
SIRI	–0.119	0.134	0.375	0.888	0.682	1.155	–0.337	0.255	0.188	0.714	0.433	1.178

Cox Regression analysis was used and $p < 0.05$ considered significant. CI: confidence interval; SE: standard error; DFS: disease-free survival; OS: overall survival; MLR: monocyte/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PIV: pan-immune-inflammation-value; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; OR: odds radio.

indices could be used in univariate and multivariate calculations for OS and DFS follow-up. It was determined that each index could not be used in the follow-up of OS and DFS in the analyses performed alone or in combination ($p > 0.05$). Detailed data are given in table 4.

The low and high groups created in NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices separately in pCR and non-pCR groups were evaluated in terms of OS, and DFS evaluation. However, no significant discrimination was found in the mentioned indices ($p > 0.05$). Detailed representation is available in figuras 1 and 2.

Discussion

Our study evaluated NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices regarding pCR, DFS, and OS in breast cancer patients receiving NAC. In our study, these indices failed to predict pCR, DFS and OS. This finding is critical because our study underlines that the parameters mentioned above are still contradictory in deciding NAC in clinical use. As far as we can see, none of the publications on this subject have analyzed both pCR and prognosis together using the above-mentioned indices simultaneously.

As a result of tumor-induced changes in the immune system, inflammatory immune cells in the peripheral blood may be affected[12]. Lymphocytes in peripheral blood are related to adaptive immunity. In addition, lymphocytes may show anti-tumoral activity by inhibiting tumor growth and progression. Platelets play an essential role in the development and spread of cancer and in regulating inflammation. Neutrophils have a central role in the systemic inflammatory response and immunity. Neutrophils can also initiate metastasis in breast cancer by secreting immunosuppressive mediators and angiogenetic factors. Monocytes are also associated with tumor angiogenesis and metastasis[2,13]. Theoretically, it can be said that each of the mentioned indices or their combinations may be related to pCR, DFS, and OS in breast cancer patients. In the literature, an increasing number of publications have examined the relationship between these indices and breast cancer patients who will receive NAC. Among these indices, NLR and PLR indices have been analyzed most frequently for this purpose. However, studies have shown that NLR and PLR have conflicting results in predicting pCR, DFS and OS in breast cancer patients receiving NAC[4-8]. With the idea that more combined indices may be better predictors, Graziano et al.[6] compared NLR and PLR values with NLR/PLR combination. This study found that NLR and PLR alone could not predict pCR, whereas there was a significant relationship between NLR/PLR combination and pCR. In two other studies in the literature, it was shown that NLR and PLR values were better in indicating pCR when evaluated in combination rather than when used alone[3,14]. In these three studies, NLR/PLR combination was found to be significant in

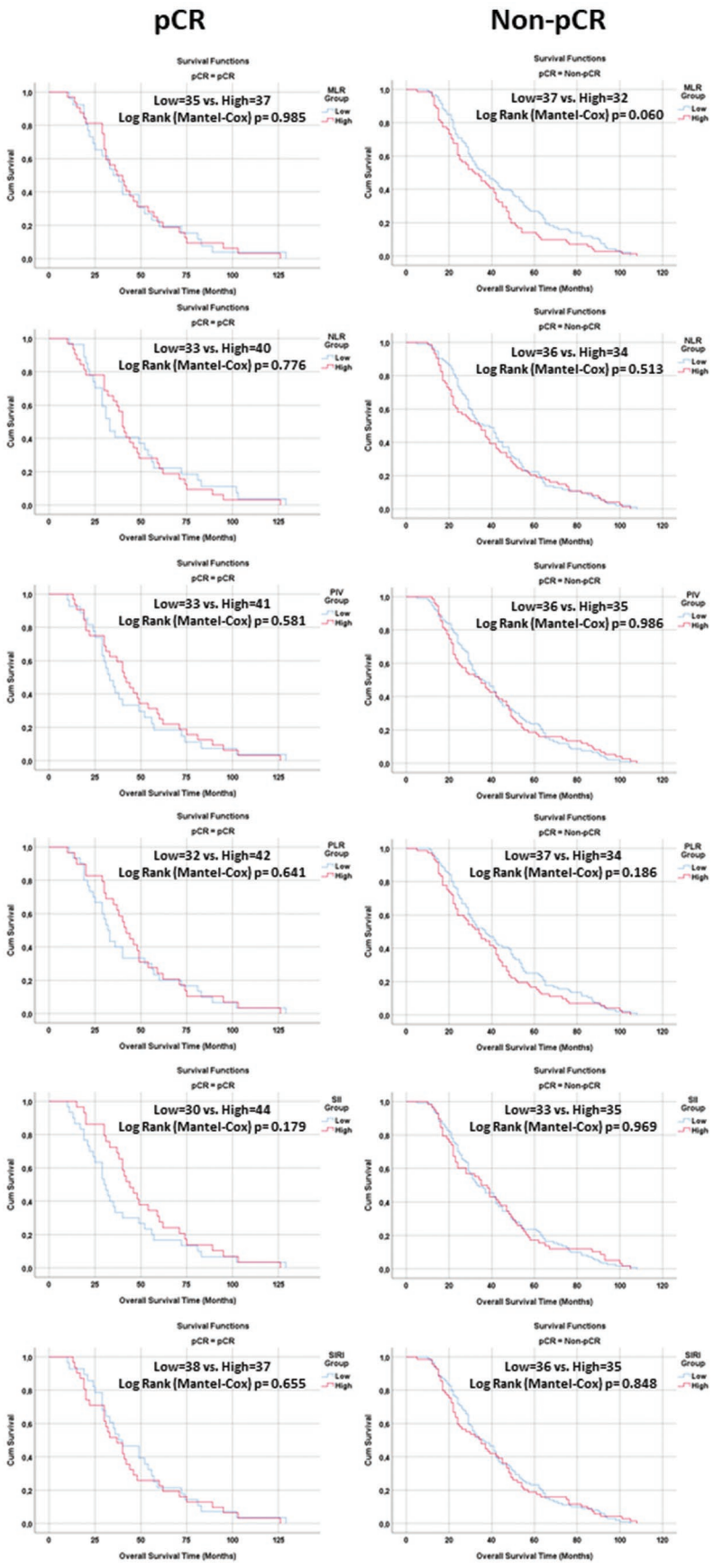

Figure 1. *Comparison of low and high overall survival times in rates and indices in pathologic complete response (pCR) and non-pCR groups.*

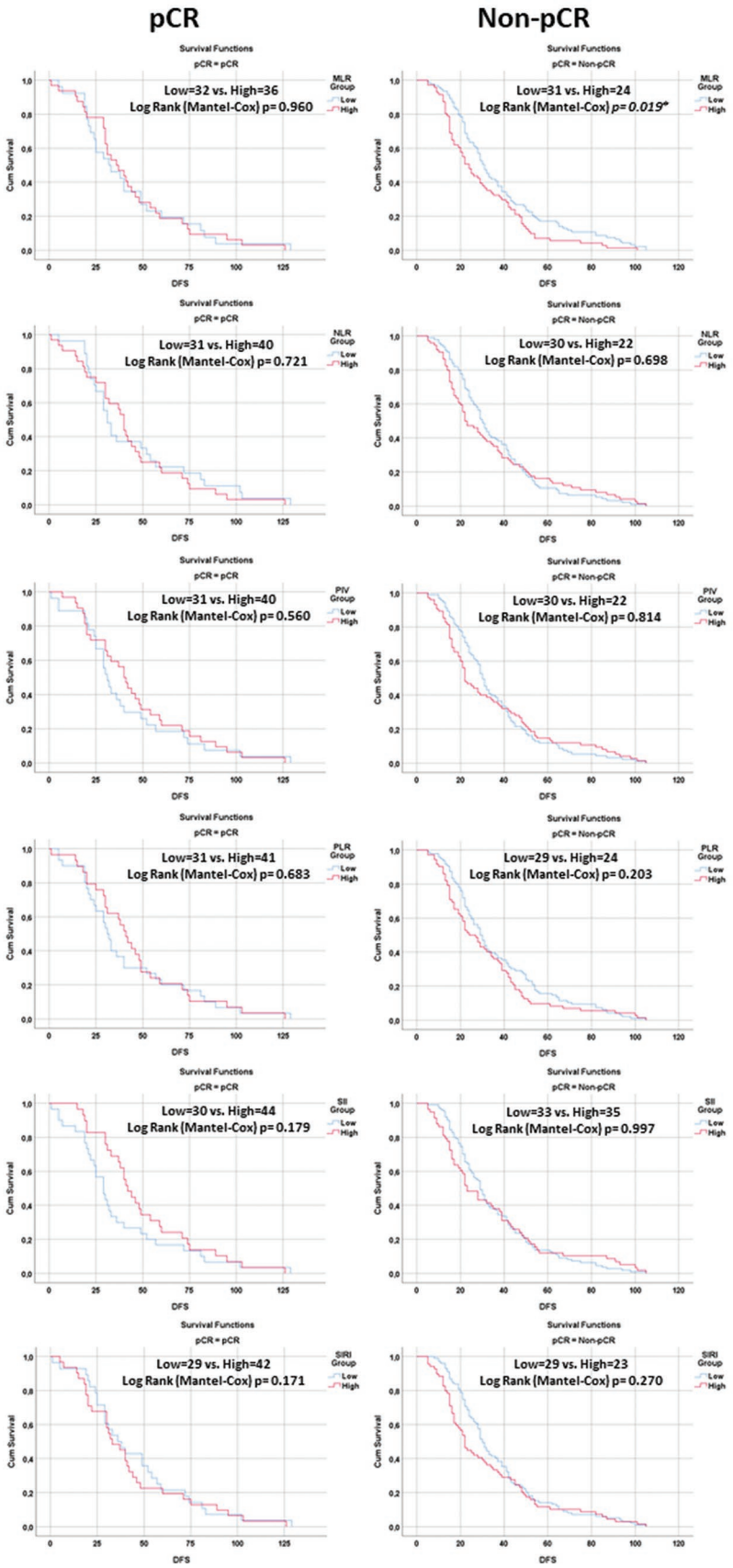

Figure 2. *Comparison of low and high disease-free survival times in rates and indices in pathologic complete response (pCR) and non-pCR groups.*

evaluating pCR in contrast to our study. Among these three studies, only Kim et al.[3] analyzed the relationship between prognosis and NLR/PLR combination and found a significant relationship in contrast to our study. However, there is a significant methodological difference between the study of Kim et al.[3] and our study regarding pCR evaluation, as we will mention later. In addition, there are not enough publications on NLR/PLR index in the literature yet. As far as we can see, our article is the first study in the English literature showing that the NLR/PLR combination fails to predict pCR and prognosis.

One of the other combined parameters is SIRI. In SIRI calculation, monocytes are included in the calculation in addition to NLR. First, Dong et al.[15] analyzed the relationship between SIRI, and pCR. According to this study, SIRI showed pCR to NAC better than other indices (lymphocyte monocyte ratio, absolute lymphocyte count, and NLR). However, this study did not analyze DFS and OS. In the study of Chen et al.[13], SIRI was significant in determining OS and DFS in breast cancer patients receiving NAC. However, no significant difference was found in terms of pCR, similar to our study.

In SII, another combined parameter, platelets, which have an essential role in the development and spread of breast cancer, are included in the calculation in addition to NLR. In the study of Yang et al.[16], a significant correlation was found between NLR, PLR, SII, and pCR. In contrast, in another study of Chen et al.[17], no significant correlation was found between SII and pCR as in our study. However, Chen et al.[17] found that patients with low SII values had longer DFS and OS rates.

Compared with individual blood cell parameters, combined indices may more comprehensively identify multiple components of antitumor immunity, each of which may reflect and regulate different aspects of antitumor immunity. For this purpose, in the study of Şahin et al.[7], the PIV index, which includes all the parameters mentioned above (neutrophils, platelets, monocytes, and lymphocytes), was used. Indeed, supporting the theoretical knowledge, NLR, PLR, MLR, and PIV successfully showed pCR in univariate analysis. In contrast, only PIV, a more complex marker, maintained its statistical value in multivariate analysis. Furthermore, PIV was found to have a prognostic effect on survival. This is important because it is the first study in the literature to examine the relationship between PIV value and response to NAC and survival in breast cancer. However, contrary to this study, we could not reach similar results in our study.

When considered together with our study, many factors can be counted to explain the contradictory results of those mentioned above simple and complex indices on pCR and prognosis in breast cancer patients receiving NAC. Many factors can easily affect inflammatory markers (lymphocytes, neutrophils, platelets, and monocytes). For example, many factors can easily affect inflammatory events, including connective tissue diseases, medications used, bacterial or viral diseases, nutritional status, severe stress, and severe exercise[3]. In addition, breast cancers have the least immunogenic type compared to other cancer types[2]. In addition, TILs are less common in HR+ positive breast cancers compared to HR– breast cancers[18]. In other words, anticancer immunity is not dominant in hormone receptor-positive breast cancers. Therefore, it is thought that absolute lymph count is not a good predictor in HR+ breast cancers compared to HR– breast cancers[19]. Lymphocyte count is included in the denominator of calculations in all indices we investigated and, therefore, affects all calculations. Finally, it is thought that lymphocytic infiltration in the tumor microenvironment is not sufficiently reflected in peripheral blood cells[20]. All the factors mentioned above give us a clue to explain the conflicting data on these indices.

One of the reasons for the conflicting reports on these indices is the methodological difference between studies. There are differences in the definition of pCR in the literature. Miller-Payne (MP) classification was used in some publications. In this classification, unlike the RCB classification, the axilla is not evaluated, and only the response in the breast is considered. In other words, a patient with a complete response to the tumor in the breast is considered to have a complete response even if tumors are detected in the LNs. In addition, in some of the studies using the MP classification, both MP 4 (> 90% response to NAC) and MP 5 (no tumor cells) were included in the group of patients who responded to NAC. However, it is known that the survival time of patients with pCR is higher than those with residual cancer[21]. For example, in the studies of Kim et al.[3] evaluating NLR/PLR combination and in two separate studies of Chen et al. evaluating SIRI[13] and SII[17], clinical response was evaluated as MP 4-5. In contrast to these studies, RCB was used in two other studies evaluating NLR/PLR combination[6,14], SIRI by Dong et al.[15], NLR, PLR, and SII by Yang et al.[16], and PIV index by Şahin et al.[7]. This

confusion in the evaluation of pathological response may have caused contradictions in the correct evaluation of the indices. However, to use a standard criterion in the literature and make comparisons, it would be more accurate to use RCB when investigating pCR as in our study[22].

Although there are publications examining the relationship of these indices with pCR and prognosis, there are very few comments on how their clinical use will be in routine practice. Therefore, we would like to discuss a topic that has not been emphasized in the literature. In the recently updated NCCN guidelines, patients with clinically node negative or clinically non-palpable lymph but with up to two positive LNs by imaging or biopsy may undergo SLNB if NAC was not performed. However, in breast cancer patients who receive NAC, AD is performed if there is a clinically positive LN after NAC or a positive sentinel LN (micro or macrometastasis)[9]. In this case, in patients with low axillary LN metastasis in whom NAC is not considered (especially in HR+, HER2– tumors), giving NAC by relying on the indices listed above may lead to some problems. The most important of these problems will arise if the patient's axilla does not respond fully to NAC. A patient with a low axillary tumor burden who would not usually be given NAC can typically be satisfied with SLNB. In contrast, AD will be necessary in the patient receiving NAC, even if micrometastases are found on SLNB. In this case, overtreatment will be applied to the patient's axilla. In addition, since the methods used to reduce false negativity during SLNB application in the patient receiving NAC are technically more complex, we argue that the decision of NAC in patients with breast cancer should not be based on the mentioned indices.

Our study has limitations: a small number of patients, single-center experience, and retrospective nature.

Conclusion

Our study did not find a significant relationship between NLR, PLR, MLR, NLR/PLR, SII, SIRI, and PIV indices and pCR, DFS, and OS in breast cancer patients who received NAC. In our opinion, the decision to apply NAC to the patient should still be made according to the molecular subtypes of the breast tumor. It should continue to be discussed in patient-based multidisciplinary sessions. In addition, although no correlation was found between the indices mentioned in our study and pCR, DFS, and OS, it would be helpful to continue studies on this subject considering the advantages of these indices, such as easy calculation and obtaining them from blood samples in routine practice.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Pelvic index/mesorectal length ratio: a new predictive factor for rectal cancer prognosis and low anterior resection syndrome

Relación índice pélvico/longitud mesorrectal: un nuevo factor predictivo para el pronóstico del cáncer de recto y el síndrome de resección anterior baja

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Abstract

Objective: *This study aimed to evaluate whether the pelvic index/mesorectal length (PI/ML) ratio is an effective factor in recurrence, anastomotic leakage, mesorectal excision status, and low anterior resection syndrome (LARS) development in rectal cancer patients undergoing total mesorectal excision.* **Methods:** *A total of 47 patients who underwent surgery for rectal cancer between January 2016 and December 2021 were included. Demographics, clinical data, and pre-operative PI measurements were recorded. Post-operative LARS was assessed using the LARS questionnaire in patients followed for at least 12 months.* **Results:** *A significant association was found between PI/ML ratio and tumor recurrence ($p < 0.0001$). Receiver operating characteristic analysis identified a cutoff value of PI/ML < 1.6 for predicting tumor recurrence, with 100% sensitivity and 84.6% specificity. After applying Bonferroni correction for multiple comparisons ($n = 4$, adjusted significance threshold $p < 0.0125$), this association remained statistically significant. The association between PI/ML ratio and anastomotic leakage (cutoff < 2.15; sensitivity 100%, specificity 53.7%) showed marginal significance ($p = 0.009$). No significant association was found between PI/ML ratio and LARS or mesorectal excision status after correction.* **Conclusions:** *PI/ML ratio appears to be a useful predictor for tumor recurrence and may help identify patients at risk for anastomotic leakage in rectal cancer surgery. However, this ratio was not significantly associated with the development of LARS. Further research with larger cohorts is needed to validate these findings and clarify the potential prognostic value of the ratio.*

Keywords: *Rectal cancer. Pelvic index. Low anterior resection syndrome. Total mesorectal excision.*

Resumen

Objetivo: *Evaluar si la relación índice pélvico/longitud mesorrectal (IP/LM) es un factor predictivo eficaz en la recurrencia, la fuga anastomótica, el estado de la escisión mesorrectal y el desarrollo de síndrome de resección anterior baja (SRAB) en pacientes con cáncer de recto sometidos a escisión mesorrectal total.* **Métodos:** *Se incluyeron 47 pacientes sometidos a cirugía por cáncer rectal entre enero de 2016 y diciembre de 2021. Se registraron características demográficas, datos clínicos y mediciones preoperatorias del índice pélvico. El SRAB posoperatorio se evaluó mediante un cuestionario en pacientes con un seguimiento mínimo de 12 meses.* **Resultados:** *Se encontró una asociación significativa entre la relación IP/LM y la recurrencia tumoral ($p < 0.0001$). El análisis de la curva ROC identificó un valor de corte de IP/LM < 1.6 para predecir la recurrencia*

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tumoral, con una sensibilidad del 100% y una especificidad del 84.6%. Tras aplicar la corrección de Bonferroni para comparaciones múltiples (n = 4, umbral de significación ajustado p < 0.0125), esta asociación siguió siendo estadísticamente significativa. La asociación entre la relación IP/LM y la fuga anastomótica (valor de corte < 2.15; sensibilidad 100%, especificidad 53.7%) mostró una significación marginal (p = 0.009). No se encontró ninguna asociación significativa entre la relación IP/LM y el SRAB, ni con el estado de la escisión mesorrectal tras la corrección. **Conclusiones:** *La relación IP/LM parece ser un predictor útil para la recurrencia tumoral y podría ayudar a identificar a los pacientes con riesgo de fuga anastomótica en la cirugía de cáncer de recto. Sin embargo, esta relación no se asoció significativamente con el desarrollo de SRAB. Se necesitan más estudios con cohortes más grandes para validar estos hallazgos y aclarar el potencial valor pronóstico de esta relación.*

Palabras clave: *Cáncer rectal. Índice pélvico. Síndrome de resección anterior baja (SRAB). Escisión mesorrectal total.*

Introduction

Colorectal cancer (CRC) remains a major health problem worldwide and is the third leading cause of cancer-related death. Recent data indicate that rectal cancer accounts for nearly 39% of all CRC cases and contributes substantially to morbidity and mortality[1-3]. A narrow pelvis and difficult pelvic anatomy are considered to be important risk factors for rectal cancer surgery[2]. Different angles and strictures in the pelvis can lead to the possibility of difficult and incomplete resection. Although the length of the mesorectum may appear relatively short or long on the pathology slides, depending on an individual's pelvic anatomy, pathological evaluation can provide significant insights[1,2].

Appropriate oncologic resection is critical in the surgical treatment of rectal cancer, with total mesorectal excision (TME) becoming the gold standard[2]. However, even with modern techniques, post-operative functional disorders such as low anterior resection syndrome (LARS) remain significant complications, occurring in up to 50-80% of patients[3,4]. LARS encompasses symptoms such as fecal urgency, incontinence, and frequent bowel movements, significantly impacting quality of life[4,5].

Recent meta-analyses and multicenter trials have identified important risk factors for LARS, including low tumor height, low anastomotic height, neoadjuvant therapy, anastomotic leakage, and protective stomas[4,5]. Furthermore, new surgical approaches such as transanal TME have shown promise in reducing conversion rates and potentially improving functional outcomes, although concerns about specific complications and local recurrence remain[6].

The basic pathophysiology of LARS involves a combination of colonic motility disorder, neo-rectal reservoir dysfunction, and impaired anal sphincter function. Dysfunction after rectal resection leads to LARS symptoms due to denervation, decreased functional capacity, and hypogastric plexus injury. Therefore, the pelvic angle and the size of the resected pathologic lesion are among the determining factors for the development of LARS[7,8].

In rectal cancer surgery, new markers are needed to predict the patient's prognosis, and studies on this topic are ongoing. In this context, pelvimetric measurements have increasingly been explored as potential predictors of surgical outcomes. Therefore, in our study, we calculated the pelvic index (PI) value based on the pre-operative tomography images of the patients. In addition, we recorded the mesorectal length (ML) and complete/incomplete mesorectal excision data from the pathological reports of rectal cancer. By calculating the "Pelvic Index/Mesorectal Length (PI/ML) Ratio" using pelvimetric measurements, we aimed to contribute to the literature by investigating the relationship between this ratio and factors that influence the prognosis of rectal cancer surgery and the development of LARS. We hypothesize that a lower PI/ML ratio is an independent predictor of an increased risk of anastomotic leakage, tumor recurrence, and the development of LARS in patients undergoing TME for rectal cancer.

Methods

Study design and participants

In this retrospective observational study, patients who underwent surgery for rectal cancer in the General Surgery Clinic of Istanbul Training and Research. Hospital between January 2016 and December 2021 were analyzed. Patients who could not undergo curative surgery, whose clinical data could not be reached in the post-operative period, or who could not participate in the LARS questionnaire (or who had not completed 1 year postoperatively) were excluded from the study.

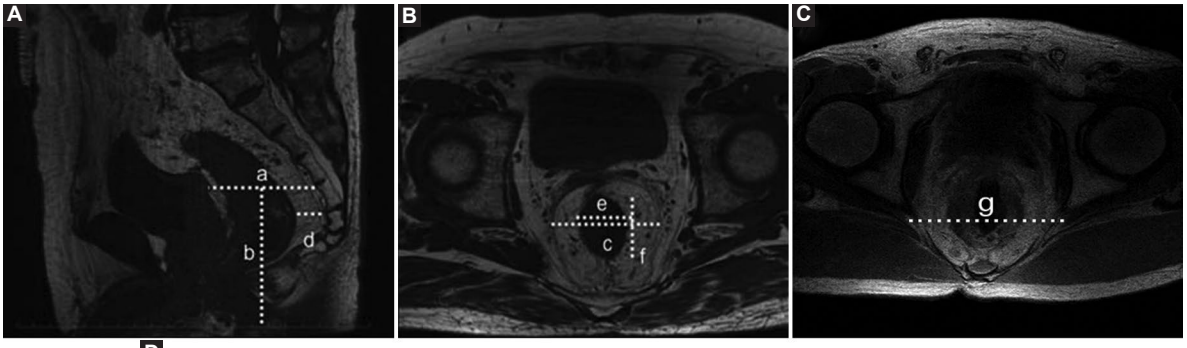

Figure 1. *Magnetic resonance imaging measurements and schematic diagram for calculation of the pelvic index (PI) in rectal cancer patients.* **A:** *sagittal plane image showing the pelvic inlet width (a) measured as the transverse diameter of the pelvic brim, the depth of cavity of the lesser pelvis (b) the length measured between the middle point of line "a," and the mesorectal thickness (d).* **B:** *axial plane image showing the mesorectal diameter (c) measured at the point of maximum width, transverse rectal diameter (e), and longitudinal rectal diameter (f).* **C:** *axial plane image illustrating the interspinous distance defined as the narrowest distance between the ischial spines (g).* **D:** *schematic diagram demonstrating the formula used for calculating the pelvic index using the distance between the spina ischialis, the diameter of the mesorectum in the axial plane, and the depth of the small pelvis.*

A priori power analysis was performed using G*Power (Heinrich Heine University Düsseldorf, Germany). For detecting differences between two independent means (two-tailed *t*-test), an effect size (Cohen's d) of 1.64 was assumed, with an alpha level of 0.05 and statistical power set at 95%. The effect size was estimated based on preliminary analyses of institutional data, which demonstrated substantial differences in pelvic measurements between patient groups. Similar large effect sizes have also been reported in previous studies investigating pelvic anatomy and surgical outcomes in rectal cancer. The analysis indicated that a total sample size of 22 patients (11/group) would be sufficient. As our study included 47 patients, the sample size was deemed adequately powered for the analyses conducted.

Data collection

Demographic and clinical data

Demographic data, operative data, pathology reports, and radiologic imaging were analyzed. Clinical files of the patients were scanned, and demographic data, as well as recurrence and anastomotic leakage status, were recorded.

Pre-operative imaging and PI measurement

All PI measurements were performed by a single experienced radiologist to ensure consistency (Fig. 1). Interobserver variability was not assessed in this study, which represents a limitation. In the pre-operative period, tomography images taken within 1 week before surgery were evaluated by a radiologist, and the PI was calculated using the following formula presented in figure 1[9].

Pathologic evaluation

We obtained the mesorectal length (ML) data from the pathologic slide reports.

LARS score

The LARS questionnaire was administered via telephone to patients with at least 12 months of post-operative follow-up. According to the results of the questionnaire, patients were classified as follows:

- No LARS: 0-20 points
- Minor LARS: 21-29 points
- Major LARS: 30-49 points
- We evaluated patients in two groups: those with LARS (minor + major) and patients without LARS[10].

Ethical approval

The study was initiated with the approval of decision number 391 from the Ethics Committee of Istanbul

Training and Research Hospital on December 23, 2022. This was a retrospective observational study and was not registered in a public trials registry, as registration is not required for retrospective studies under current regulations.

Results

The study was conducted with a total of 47 patients, 21 (44.7%) females and 26 (55.3%) males. The mean age was 62.1 ± 9.8 years (range: 37-86), and body mass index (BMI) was 26.6 ± 4.9 kg/m^2 (Table 1). The number of patients who received neoadjuvant chemoradiotherapy in our case series was 33 (70.2%), whereas the number of patients who did not receive neoadjuvant chemoradiotherapy was 14 (29.8%).

We observed an anastomotic leakage in 12.8% of patients (six cases) and detected recurrent tumoral lesions in 17% (eight cases). In the evaluation of mesorectal excision in pathologic slides, we found incomplete mesorectal excision in 36.2% (17 cases) and complete mesorectal excision in 63.8% (30 cases) (Table 1).

In terms of tumor localization, 29 (61.7%) patients had tumor localization in the proximal rectum, 13 (27.7%) in the middle rectum, and 5 (10.6%) in the distal rectum. In terms of surgical method, laparoscopic surgery was performed in 33 cases, and loop ileostomy was performed in 21 of them. Conventional surgery was performed in 13 cases, and loop ileostomy was performed in addition to resection in nine of them. When the stage distribution was analyzed in our study, the most common stage was E3b with 26 cases (54.6%), and at least 1 case (2.1%) was the E3c stage (Table 1).

Twenty patients (42.6%) showed LARS findings, and the mean LARS score was 17.1 ± 13.1. The mean interspinous distance was 11.3 ± 1.2 cm, the radiologic diameter of the mesorectum was 7.83 ± 1.05 cm, and the depth of the small pelvic cavity was 9.64 ± 1.2 cm. The mean PI value was calculated as 36.7 ± 12.5 cm. The average pathologic mesorectal length was 16.8 ± 4.2 cm, and the ratio of PI to mesorectal length was 2.4 ± 1.3 (Table 1).

The mean BMI of the female group was 28.5 ± 5.2 and 25.0 ± 4.0 in the male group (Table 2). The mean BMI of the female group was higher than that of the male group, and this difference was statistically significant and was found to have a large effect size (Cohen's d = 0.758, 95% confidence interval [CI] = –1.350-–0.158, p = 0.013).

The mean PI/ML was 2.6 ± 1.3 in the female group and 2.2 ± 1.3 in the male group. There was no statistically significant difference between the sexes in terms of PI/ML (p > 0.05) (Table 2).

To correct for multiple comparisons (n = 4), we applied a Bonferroni correction, setting the

Table 1. Demographic, clinical, pathological, and treatment characteristics of patients undergoing total mesorectal excision for rectal cancer

Parameters	Mean ± SD or n (%)
Age (years)	62.1 ± 9.8
Sex, n (%)	Male: 26 (55.3) Female: 21 (44.7)
BMI (kg/m^2)	26.6 ± 4.9
Tumor location, n (%)	Proximal: 29 (61.7) Middle rectum: 13 (27.7) Distal: 5 (10.6)
Pathological stage (pTNM), n (%)	Stage I: 6 (12.8) Stage II: 3 (6.4) Stage III: 36 (76.6) Stage IV: 2 (4.3)
Neoadjuvant radiotherapy, n (%)	33 (70.2)
Complete mesorectal excision, n (%)	30 (63.8)
Anastomotic leakage, n (%)	6 (12.8)
Tumor recurrence, n (%)	8 (17.0)
LARS n (%) Mean score	 20 (42.6) 17.1 ± 13.1
Interspinous distance (cm)	11.3 ± 1.2
Mesorectum radiologic diameter (cm)	7.83 ± 1.05
Depth of small pelvic cavity (cm)	9.64 ± 1.2
PI (cm)	36.7 ± 12.5
Pathologic mesorectal length (cm)	16.8 ± 4.2
PI/ML (cm)	2.4 ± 1.3

LARS: low anterior resection syndrome; PI/ML: pelvic index/mesorectal length; BMI: body/mass index, SD: standard deviation.

Table 2. Comparison of age, BMI, PI/ML ratio, and tumor localization between male and female patients

Parameters	Mean ± SD		Effect size (95% CI)	p
	Female	Male		
Age	61.4 ± 10.7	62.6 ± 9.1	0.12 (–0.46-0.70)	0.683
BMI	28.5 ± 5.2	25.0 ± 4.0	–0.76 (–1.35 –0.16)	0.013
PI/ML (cm)	2.6 ± 1.3	2.2 ± 1.3	–0.28 (–0.86-0.30)	0.339

PI/ML: pelvic index/mesorectal length; BMI: body/mass index, SD: standard deviation, 95% CI: confidence interval.

Table 3. ROC analysis results for predicting anastomotic leakage, tumor recurrence, complete mesorectal excision, and LARS based on the PI/ML ratio

Parameters	AUC ± SD	Cutoff	Sensitivity	Specificity	95% CI	p
Anastomotic leakage	0.833 ± 0.079	< 2.15	100	53.7	0.679-0.988	0.009
Recurrence	0.929 ± 0.037	< 1.6	100	84.6	0.858-1.000	0.00001
Complete mesorectal excision	0.520 ± 0.093	> 1.64	73.3	41.2	0.338-0.701	0.825
LARS	0.589 ± 0.088	< 1.90	55	66.6	0.436-0.730	0.315

PI/ML: pelvic index/mesorectal length; LARS: low anterior resection syndrome; AUC: area under the curve; SD: standard deviation; CI: confidence interval; ROC: receiver operating characteristic.

Table 4. Comparison of demographic and clinical characteristics between patients with and without LARS

Parameters	No. LARS (n = 27)	LARS present (n = 20)	Odd ratio/effect size (95% CI)	p
Gender, n (%)			0.40 (0.12-1.35)*	0.394
Male	13 (48.1)	13 (65.0)		
Female	14 (51.9)	7 (35.0)		
Age, X ± SD	61.67 ± 10.1	62.65 ± 9.5	0.01 (–0.57-0.60)**	0.957
BMI, X ± SD	24.77 ± 3.4	28.02 ± 5.3	0.46 (–0.13-1.05)**	0.035
Mesorectal excision, n (%)			0.20 (0.06-0.72)*	0.045
Complete	21 (77.8)	9 (45.0)		
Incomplete	6 (22.2)	11 (55.0)		
PI, X ± SD	38 ± 13	35 ± 12	–0.27 (–0.85-0.32)	0.241
Mesorectal length (ML), X ± SD	16.50 ± 3.79	18.41 ± 4.15	0.44 (–0.16-1.02)**	0.140
PI/ML, X ± SD	2.4 ± 1	1.8 ± 1	0.34 (0.02-0.25)**	0.040

*Odd ratio.
**Effect size (Cohen's d).
BMI: body mass index; X ± SD: mean ± standard deviation; PI/ML: pelvic index/mesorectal length ratio; LARS: low anterior resection syndrome.

significance threshold at $p < 0.0125$. Under this correction, the relationship between recurrence and PI/ML remained statistically significant ($p = 0.00001 < 0.0125$), and the association between anastomotic leakage and PI/ML was marginally retained ($p = 0.009 < 0.0125$). Associations with complete mesorectal excision and LARS did not reach the adjusted significance level (Table 3).

When the PI/ML cutoff value ≤ 2.1 for anastomotic leakage, sensitivity and specificity were 100% and 53.7%, respectively. There was a statistically significant correlation between PI/ML and anastomotic leakage ($p < 0.05$) (Fig. 2A). We found the sensitivity and specificity to be 100% and 84.6%, respectively, when the PI/ML cutoff value was ≤ 1.6 for recurrence. PIML was found to be significantly associated with the recurrence ($p < 0.05$) (Fig. 2B). Sensitivity and specificity were 73.3% and 41.2%, respectively, when the PI/ML cutoff value was > 1.64. PI/ML was not statistically significantly associated with complete mesorectal excision ($p > 0.05$) (Fig. 2C). Sensitivity and specificity were found to be 55% and 66.6%, respectively, when the cutoff value for PI/ML was < 1.90. We did not find a statistically significant correlation between PI/ML and LARS ($p > 0.05$) (Fig. 2D and Table 3).

Patients in our study were divided into two groups: no LARS (0-20) and LARS (21-42 minor + major). Demographic and clinical data are analyzed in table 4. Twenty-seven patients had no LARS, and 20 patients had LARS findings (minor + major). There was no statistical significance between these groups in terms of age and gender ($p > 0.05$). BMI was 28.02 ± 5.3 in the group with LARS findings and 24.77 ± 3.4 in the group without LARS, which has a moderate effect size ($p = 0.035$; Cohen's $d = 0.462$; 95% CI: –0.131-1.050).

While there was no statistical difference between the LARS groups in terms of T, N, and Stage, no statistical difference was observed in terms of tumor localization ($p > 0.05$). There was no statistical significance between

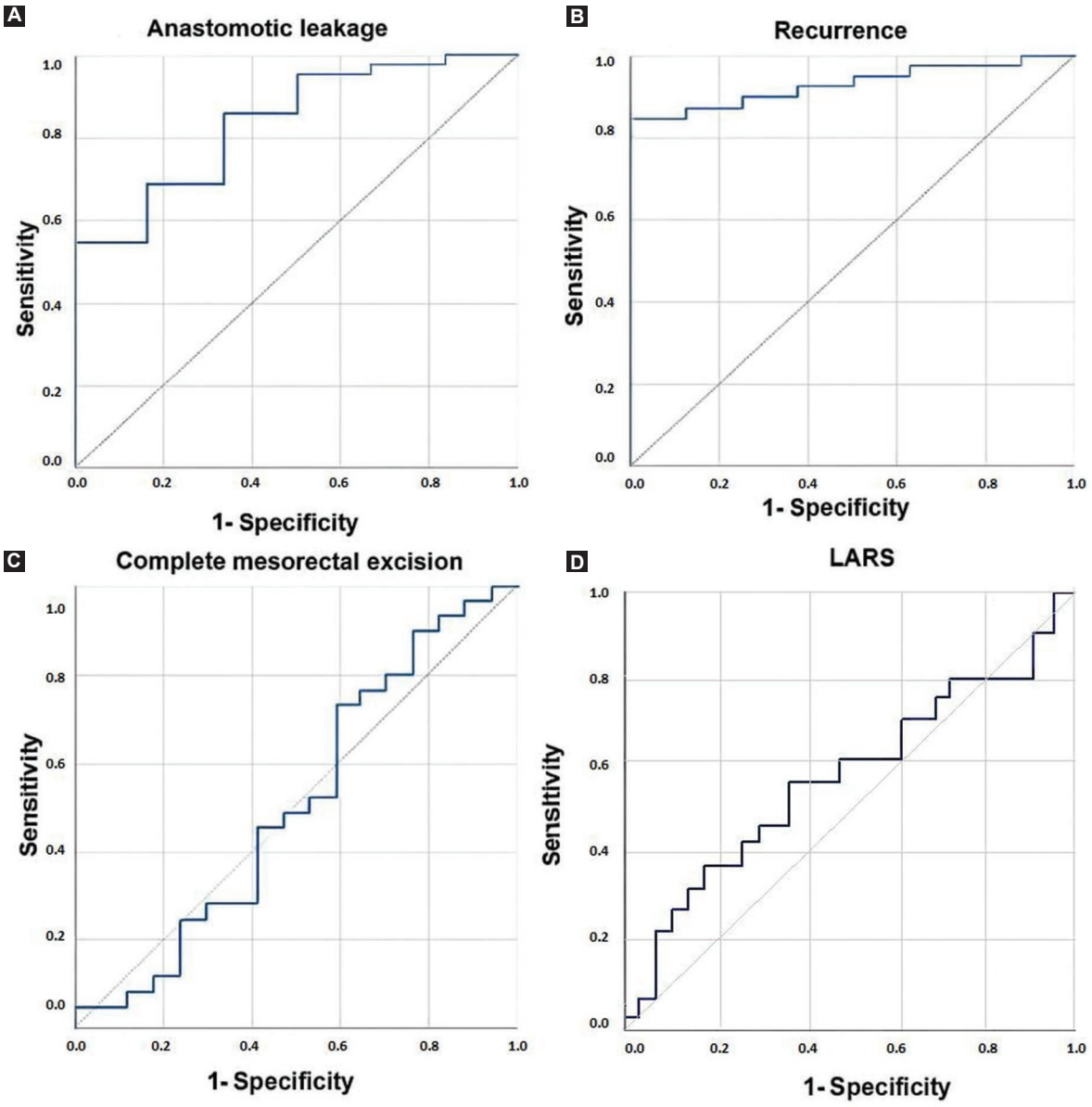

Figure 2. *Receiver operating characteristic analyses of anastomotic leakage* **(A)**, *recurrence* **(B)**, *complete mesorectal excision* **(C)**, *and low anterior resection syndrome* **(D)** *according to the pelvic index/mesorectal lenght ratio.*

the PI and ML between the groups according to the presence of LARS. The PI/ML ratio was found to be higher in individuals without LARS than in individuals with LARS. This difference had a small effect size (p = 0.040; Cohen's d = 0.336; 95% CI: 0.020-0.253) (Table 4).

Incomplete mesorectal excision was reported in 11 cases (55%) with LARS, whereas complete mesorectal excision was reported in 21 cases (77.8%) without LARS (Table 4). Cases with complete excision were 5.05 times less likely to develop LARS than individuals without complete excision (p = 0.045; OR = 0.198; 95% CI: 0.055-0.715).

In the correlation analysis between LARS score and demographic and clinical data, no statistical significance was observed in the correlation between age, BMI, PI, ML, and PI/ML (Table 5).

Discussion

In our study, we investigated whether the PI/ML ratio, derived from pre-operative pelvic measurements,

Table 5. Correlation analysis between LARS scores and continuous demographic and clinical variables

Parameters	r	p	95% CI	
			Lower	Upper
Age	–0.156	0.295	–0.431	0.146
BMI	0.198	0.182	–0.103	0.466
PI	–0.167	0.262	–0.441	0.135
ML	0.140	0.349	–0.162	0.418
PI/ML	–0.160	0.284	–0.434	0.142

LARS: low anterior resection syndrome; BMI: body mass index; CI: confidence intervals; PI/ML: pelvic index/mesorectal length ratio.

could predict surgical and oncological outcomes in rectal cancer patients undergoing TME, which is critical for patient prognosis. After correcting for multiple comparisons using the Bonferroni method, we found that the PI/ML ratio remained significantly associated with tumor recurrence and showed a marginally significant association with anastomotic leakage. However, the PI/ML ratio was not significantly associated with the development of LARS.

The relationship between pelvic anatomy and surgical outcomes has been discussed in the literature[11,12]. Several studies have shown that a narrow pelvis and difficult pelvic anatomy can lead to more challenging resections, higher rates of incomplete excision, and potentially higher recurrence rates[7,8,11,12]. High-resolution magnetic resonance imaging studies have recently provided more detailed insights, demonstrating that pelvic dimensions and mesorectal involvement are crucial factors for rectal cancer staging and surgical planning. Narrow pelvic dimensions may complicate surgical access and influence resection margins and oncological outcomes[7,8]. Our study's findings regarding PI/ML ratio align with these anatomical considerations, suggesting that the PI/ML ratio might serve as a quantitative reflection of pelvic complexity in rectal cancer surgery.

In our series, we found a significant correlation between PI/ML ratio and tumor recurrence. This supports the hypothesis that pelvic anatomy, as reflected in pelvimetric measurements, may influence oncological outcomes. For tumor recurrence, a PI/ML cutoff value of < 1.6 was identified, with high sensitivity and specificity. Our findings suggest that pre-operative pelvic measurements could assist in risk stratification for tumor recurrence in rectal cancer patients. This finding is consistent with recent imaging literature emphasizing how mesorectal involvement and pelvic constraints may influence local recurrence risk[11]. However, Huang et al. found no significant difference between radiologically measured pelvic parameters and recurrence and mortality[13].

A significant association was also observed between the PI/ML ratio and anastomotic leakage. In patients with a PI/ML ratio < 2.15, the sensitivity and specificity for predicting anastomotic leakage were 100% and 53.7%, respectively. While pelvic anatomy has long been recognized as an important factor in surgical difficulty[11,12], our study contributes quantitative data supporting its association with post-operative complications. Accordingly, the PI/ML ratio can be used in determining the surgical strategy and may be of clinical benefit in applications such as controlling anastomotic tension and monitoring anastomotic viability.

Our findings regarding LARS differ from earlier assumptions that pelvic anatomy directly predicts functional outcomes. Although we observed a trend toward lower PI/ML ratios in patients with LARS, this did not reach statistical significance. This is in line with a recent systematic review and meta-analysis, which reported a pooled incidence of major LARS of approximately 44%[8]. Sun et al. highlighted that the major risk factors for LARS include neoadjuvant radiotherapy, low tumor height, low anastomotic level, anastomotic leakage, and diverting stomas, rather than purely anatomical parameters such as pelvic dimensions. Thus, while pelvic anatomy may play a role in surgical difficulty, its direct correlation with post-operative functional disorders remains uncertain[8].

Recent evidence suggests that BMI may influence oncological outcomes in rectal cancer patients. Although BMI was not independently associated with the PI/ML ratio in our cohort, the post-operative LARS rate in patients with high BMI was statistically significant in our study. High BMI values cause an increase in mesorectal adipose tissue thickness and increase the technical difficulty of TME. This finding supports the results of the study by Meng et al.[14]. Liu et al. demonstrated that lower BMI, particularly BMI < 18.5 kg/m^2, was significantly associated with poorer overall and cancer-specific survival in patients undergoing neoadjuvant chemoradiotherapy followed by TME[15]. This highlights that not only anatomical factors but also patient-related biological characteristics may contribute to prognosis in rectal cancer[16].

In the literature, Boyle et al. found that pelvic dimensions vary by sex in healthy individuals. The anteroposterior diameter of the mesorectum and the volume of the fat area were evaluated radiologically, and it

was found that the mesorectal area was wider in men and the anterior mesorectal fat was thinner in women[16]. In our study, there was no significant difference in PI/ML between male and female patients, but BMI values were higher in female patients compared to male patients. These BMI differences could be relevant when planning treatment, as higher BMI may influence technical difficulty during surgery and post-operative outcomes. However, our study did not find a direct link between BMI and PI/ML ratio or post-operative complications, possibly due to the limited sample size.

Our findings align with recent research highlighting the role of pelvic anatomy in rectal cancer surgery. A study by Aparicio-López et al. found that specific pelvimetric measurements correlated significantly with surgical difficulty and post-operative complications, including anastomotic leakage and conversion rates during rectal cancer surgery[17]. Similarly, another review emphasized that variations in pelvic anatomy may influence not only technical aspects of TME but also functional outcomes such as LARS[18]. These reports support the potential clinical utility of anatomical indices such as the PI/ML ratio as prognostic tools for surgical planning and risk stratification in rectal cancer.

Our study has several limitations that should be acknowledged. First, it was a retrospective study conducted at a single center, which may introduce selection bias and limit the generalizability of the findings. Second, the sample size was relatively small, potentially reducing the statistical power to detect associations, especially regarding LARS outcomes. This sample size, though reflective of all eligible patients during the study period, may be underpowered to detect smaller effect sizes, particularly for outcomes such as LARS. Third, the assessment of LARS was performed via telephone interviews rather than in-person evaluations, which could introduce recall bias or variability in patient responses. Additionally, we did not assess interobserver variability for PI measurements, which may affect the reproducibility of our findings. Despite these limitations, our study provides valuable preliminary evidence on the potential role of PI/ML ratio in predicting oncological and surgical outcomes in rectal cancer patients. Future prospective multicenter studies with larger patient cohorts are needed to validate and expand upon these findings.

Conclusions

In our study, we found that the PI/ML ratio was significantly associated with anastomotic leakage and tumor recurrence in patients undergoing TME for rectal cancer. Specifically, lower PI/ML ratios were predictive of higher risk for both anastomotic leakage and tumor recurrence, with high sensitivity and moderate to high specificity. However, we did not observe a statistically significant association between the PI/ML ratio and complete mesorectal excision status or the development of LARS. Although patients with LARS had lower mean PI/ML ratios, this difference did not reach statistical significance in our analysis.

These findings suggest that pre-operative pelvic measurements and the PI/ML ratio could be useful for predicting certain oncological and surgical outcomes, such as anastomotic leakage and recurrence risk. Further research with larger cohorts is warranted to validate these findings and explore the potential of PI/ML as a prognostic tool in rectal cancer surgery.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Association of NRF-2 changes in plasma and pericardial fluid with renal injury in patients undergoing cardiac surgery

Asociación de los cambios de NRF-2 en plasma y líquido pericárdico con lesión renal en pacientes sometidos a cirugía cardiaca

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Abstract

Objective: *This study was conducted to investigate the levels of nuclear factor (erythroid derivative 2)-like 2 (NRF-2), kidney injury molecule 1 (KIM-1), and heme oxygenase-1 (HO-1) in pericardial fluid (PF) and systemic circulation of patients undergoing cardiac surgery.* **Methods:** *This study included 40 patients undergoing cardiac surgery and 40 healthy individuals. PF and venous blood samples were obtained from the patients and renal function tests, HO-1, KIM-1, NRF-2, antioxidant, and oxidative stress parameters were studied.* **Results:** *A statistically significant difference was found in the NRF-2, KIM-1, HO-1, total antioxidant status, total oxidant status, and oxidative stress index measurements in the plasma of the patient and control groups and in the PF of the patients ($p < 0.01$). Compared to the control group, NRF-2, KIM-1, and HO-1 were found to be lower in the patient's plasma and PF. In the patient group, NRF-2, KIM-1, HO-1, and KIM-1 were higher in PF compared to plasma.* **Conclusions:** *In the future, intrapericardial drug administration may improve cardiac function and prevent the adverse cardiorenal syndrome on the kidney.*

Keywords: *Kidney damage. Nuclear factor (erythroid derivative 2)-like 2. Kidney injury molecule 1. Heme oxygenase-1. Cardiopulmonary bypass. Cardiac surgery.*

Resumen

Objetivo: *Investigar los niveles del factor nuclear (derivado eritroide 2) similar 2 (NRF-2), la molécula de lesión renal 1 (KIM-1) y la hemooxigenasa 1 (HO-1) en el líquido pericárdico y en la circulación sistémica de pacientes sometidos a cirugía cardiaca.* **Métodos:** *En este estudio participaron 40 pacientes sometidos a cirugía cardiaca y 40 individuos sanos. Se obtuvieron muestras de líquido pericárdico y sangre venosa de los pacientes y se estudiaron las pruebas de función renal, HO-1, KIM-1, NRF-2 y los parámetros antioxidantes y de estrés oxidativo.* **Resultados:** *Se encontró una diferencia estadísticamente significativa en las mediciones de NRF-2, KIM-1, HO-1, estado antioxidante total (TAS), estado oxidante total (TOS) e índice de estrés oxidativo (OSI) en el plasma entre los grupos de pacientes y de sujetos control, y en el líquido pericárdico de los pacientes ($p < 0.01$). En comparación con el grupo de control, se observó que NRF-2, KIM-1 y HO-1 eran más bajos en el plasma y en el líquido pericárdico de los pacientes. En el grupo de pacientes, NRF-2, KIM-1 HO-1 y KIM-1 eran más elevados en el líquido pericárdico que en el plasma.* **Conclusiones:** *En el futuro, la administración intrapericárdica de fármacos puede mejorar la función cardiaca y prevenir el síndrome cardiorrenal adverso sobre el riñón.*

Palabras clave: *Daño renal. NRF-2. KIM-1. HO-1. Bypass cardiopulmonar. Cirugía cardiaca.*

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Introduction

Many organs, especially the heart and kidney, are affected in cardiopulmonary bypass (CPB), which allows cardiovascular surgery to be performed. Many molecules are secreted from the organs affected by this condition. Many of these secreted molecules can provide important information about the relevant organ or disease by showing biomarker properties. Recently, apart from classical kidney biomarkers such as urea, uric acid, and creatinine, such as nuclear factor (erythroid derived 2)-like 2 (NRF-2), kidney damage molecule 1 (KIM-1), and heme oxygenase-1 (HO-1) new biomarkers have been discovered.

NRF-2 is an important protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation[1]. As long as it is not exposed to reactive oxygen species, NRF-2, which is degraded, passes to the nucleus without being degraded under oxidative stress, binds to DNA and initiates the transcription of antioxidative genes[2,3]. NRF-2, which provides the stimulation of many cytoprotective proteins, is found in the kidney, as well as in the muscle, lung, heart, liver, and brain[4,5].

HO-1, an enzyme synthesized in renal tubular cells, has cell protective, anti-inflammatory, and antioxidant properties and is synthesized in response to oxidative stress[6]. HO-1, whose transcriptional regulation is dependent on NRF-2, plays a role in many diseases related to endoplasmic reticulum stress, such as cardiovascular and metabolic diseases[7,8].

In some studies, kidney injury molecule 1 (KIM-1) was found to be significantly higher in patients who developed kidney damage (KD) after cardiac surgery[9]. In damaged kidney cells, KIM-1 functions as a receptor controlling apoptotic cell phagocytosis[10]. After studies on KD, the American Food and Drug Administration and the European Medicines Agency approved KIM-1, one of the seven new biomarkers to be used for the detection of nephrotoxicity[11]. Many studies have supported that KIM-1 is a useful biomarker for the early detection and diagnosis of complications after cardiac surgery and KD caused by ischemia[12].

Although these biomarkers such as NRF-2, KIM-1, and HO-1 were investigated in human plasma, they were not investigated in pericardial fluid (PF). PF has an important place in cardiovascular research due to its anatomical proximity to cardiac tissue and rich content[13]. Changes in molecular markers in PF show strong correlations with many structural and functional parameters as well as cardiac pathophysiologies. The pericardial environment is both a potential diagnostic biomarker pool and an important location for future treatment and interventions. Due to the lack of data on the physiological composition of PF in studies conducted to date, its clinical use has been limited[14].

In our study on the change of these biomarkers, which provide valuable information in the early detection of KD, during CPB, the level of the relevant parameters in the plasma was monitored and information was obtained about the level in PF.

Methods

Ethical committee approval

The present study was approved by the local ethics committee (Approval number: 29.06.2020-20.12.26).

Patients included in the study

This study was conducted in accordance with the Helsinki Declaration, which was revised in 1989. Forty patients who underwent cardiac surgery with CPB method and 40 healthy individuals as control group were included in this study. PF and venous blood samples were obtained from the patients included in the study. Only venous blood samples were taken from the control group.

Obtaining PF

After median sternotomy was performed with standard CPB procedures in patients who underwent cardiac surgery with the CPB method, the pericardium was opened and PF aspiration was provided with a sterile syringe. The aspirated PF (5-20 mL) was then taken into sterile tubes without anticoagulant, and the sterile tube was immediately transferred into an ice-filled container. Then, the PF in a sterile tube delivered to the laboratory with an ice-filled container was centrifuged at + 4°C at 5000 rpm for 5 min, and the supernatant was taken into an RNase-free tube (ependorf tube) and stored at −80°C to be studied.

Obtaining blood plasma

In patients who underwent cardiac surgery with the CPB method, blood was drawn before, during and after CPB and put into sterile tubes with anticoagulant (heparin). The tube from which blood was drawn was

immediately transferred to an ice-filled container and transported to the laboratory. The sterile tube was then centrifuged at 5000 rpm for 5 min. After the centrifugation step, the plasma, which is the supernatant part, was taken into an RNase-free tube (ependorf tube) and stored at −80 to be studied.

Biochemistry study in plasma of patient group

Glucose, urea, albumin, alanine aminotransferase (ALT), Na, creatinine, aspartate aminotransferase (AST), direct bilirubin, gamma-glutamyl transferase (GGT), calcium (Ca), and C-reactive protein (CRP) levels were measured in the plasma of the patients included in the study before the operation (preop), after the termination of CBP and after the operation (post-operative). Siemens Atellica autoanalyzer device (USA, 2018) was used to measure these parameters.

Enzyme-linked immunosorbent assay (ELISA) study in PF and plasma

PF and plasma NRF-2 ELISA study

Human NFE2L2 (Nuclear Factor, Erythroid Derived 2, Like 2) ELISA Kit (Elabscience, USA, Catalog No: E-EL-H1564) was used for NRF-2 ELISA study in PF and Plasma. This kit used works according to the double-antibody sandwich enzyme-linked immunosorbance analysis to test the NRF-2 level in biological materials. The sensitivity (sensitivity) of the kit is 0.10 ng/mL, and the assay range (Detection Range) is 0.16-10 ng/mL.

PF and plasma HO-1 ELISA study

Human HO-1 ELISA Kit (Elabscience, USA, Cat. No: E-EL-H2172) was used for HO-1 ELISA assay in PF and plasma. This kit used works according to the double-antibody sandwich enzyme-linked immunosorbance assay to test the HO-1 level in biological materials. The sensitivity of the kit is 0.19 ng/mL, and the assay range is 0.31-20 ng/mL.

Human KIM-1 ELISA study in PF and plasma

Human KIM-1 ELISA Kit (Elabscience, USA, Catalog No: E-EL-H6029) was used for the KIM-1 ELISA study in PF and plasma. This kit used works according to the double-antibody sandwich enzyme-linked immunosorbance assay to test the level of KIM-1 in biological materials. The sensitivity of the kit is 4.69 pg/mL, and the assay range (Detection Range) is 7.81-500 pg/mL.

Measurement of antioxidant and OS parameters in PF and plasma

Total antioxidant status (TAS) measurement

Measurement of (TAS in PF and plasma was performed using Rel Assay Diagnostics total oxidant capacity measurement kit (Rel Assay Diagnostics, Lot. No: HN20106A, Turkey). Plasma TAS levels were determined using a new automated measurement method developed by Erel[15].

Total oxidant status (TOS) measurement

Rel assay diagnostics total oxidant capacity measurement kit (Rel Assay Diagnostics, Lot. No: OK20115O, Turkey) was used for the measurement of TOS in PF and plasma. Plasma TOS levels were determined using a new automated measurement method developed by Erel[16].

Oxidative stress index (OSI) measurement

OSI was calculated by dividing it as total oxidant level (TOS)/total antioxidant and expressed as arbitrary unit (AU).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) Windows version 24.0 (SPSS, Inc, Chicago, USA) package program was used for statistical analysis. The conformity of the data to the normal distribution was tested with the Shaphiro Wilk test. Mann-Whitney U test was used for comparison of numerical variables in two independent groups, one-way analysis of variance and least significant difference multiple comparison tests were used for normally distributed features, and Kruskal-Wallis test and all pairwise multiple comparison test were used for non-normally distributed features. As descriptive statistics, mean ± standard deviation for numerical variables, number, and percentage values for categorical

variables are given. P < 0.05 were considered statistically significant.

Results

Demographic data of the working group

Of the patients included in the study, 25 were male and 15 were female, with a mean age of 62.58 (years), height 160.11 (cm), weight 75.40 (kg), and body surface area (BSA) 1.83 that it is calculated as (m^2).

Biochemical results in plasma of patients

The results of biochemical examinations in the plasma of the patients included in the study before the operation (preop), after CBP and after the operation (postop) are given in table 1.

ELISA results in PF and plasma

The results of the optical density reading at 450 nm using commercial kits for the level determination of HO-1, NRF-2, and KIM-1 in PF and plasma by ELISA method and the results of OS parameters are given in table 2.

Table 2 shows the statistical analysis of different biochemical parameters in pre-operative, post-CBP, and post-operative groups. According to this analysis, glucose, urea, creatinine, albumin, ALT, AST, direct bilirubin, GGT, Na, Ca, and CRP values were statistically significant (*p < 0.05, **p < 0.001).

Glucose value which was 170.23 before CPB was 201.30 after CPB and 177 post-operative (p < 0.05). Urea value which was 37.22 before CPB was 42.07 after CPB and 47.41 post-operative (p < 0.01). Creatinine value was 0.91 before CPB, 0.98 after CPB and 1.17 post-operative (p < 0.01). Albumin value which was 41.27 before CPB decreased to 29.43 after CPB and increased to 31.22 postop (p < 0.01). While ALT value was 21.26 before CPB, it became 25.89 after CPB and 28.32 post-operative (p < 0.01). AST value was 29.12 before CPB, 49.22 after CPB and 50.30 post-operative (p < 0.01). D. bilirubin value which was 0.2 before CPB was 0.15 after CPB and 0.26 post-operative (p < 0.01). GGT value which was 27.58 before CPB decreased to 24 after CPB and increased to 29.83 post-operative (p < 0.05). Na value, which was 138.20 before CPB, became 141.78 after CPB and 141.83 post-operative (p < 0.01). Ca value which was 9.17 before CPB was 8.16 after CPB and 7.85 post-operative (p < 0.01). CRP value, which was 13.38 before CPB, was 25.4 after CPB and 132.21 post-operative (p < 0.01) (Fig. 1).

As shown in Graph 1, when HO-1, NRF-2, KIM-1, TAS, TOS, and OSI values in the plasma and PF of the patients and the plasma of the control group were compared, the highest HO-1 value was found in the plasma of the control group, while the lowest HO-1 value was found in the plasma of the patients. The highest NRF-2 value was found in the plasma of the control group, while the lowest NRF-2 value was found in the patient plasma. The highest KIM-1 value was found in the plasma of the control group, while the lowest KIM-1 value was found in the PF of the patients. The highest TAS value was found in the plasma of the control group, while the lowest TAS value was found in the PF of the patients. The highest TOS value was found in the PF of the patients, while the lowest TOS value was found in the plasma of the control group. The highest OSI value was found in the PF of the patients, while the lowest OSI value was found in the plasma of the control group.

These results were statistically significant (p < 0.001). According to these results, HO-1, NRF-2, KIM-1, and TAS values were lower in the plasma of the patients compared to the plasma of the control group, while TOS and OSI values were higher. When the PF was compared with the plasma of the patients, HO-1, NRF-2, TOS, and OSI values in the PF were higher than the plasma of the patients, while KIM-1 and TAS values were lower. HO-1, NFR-2, KIM-1, and TAS values were found to be lower in pericardium, before CPB - plasma, during CPB - plasma and after CPB-plasma compared to the control group. TOS and OSI values were found to be higher in pericardium, before CPB - plasma, during CPB - plasma and after CPB-plasma compared to the control group.

According to table 3, there is a significant positive relationship between HO-1 value and NRF-2, TOS, and OSI value. There is a significant positive relationship between NRF-2 value and KIM-1, TOS, and OSI value, and a significant negative relationship between TAS value. There is a moderately significant negative relationship between TAS value and TOS and OSI value. There is a very highly significant positive relationship between TOS value and OSI value.

As shown in figure 2, the lowest HO-1 value in patient plasma was found in Pump 1, while the highest HO-1 value was found in Pump 3. The lowest NRF-2 value was found in Pump 1, while the highest NRF-2

Table 1. Biochemical test results of the patients included in the study

Parameter	Preop CPB	After CPB	Postop	p
Plasma	**Mean ± SS**	**Mean ± SS**	**Mean ± SS**	
Glucose (mmoL/L)	170.23 ± 70.33	201.3 ± 47.78	177 ± 41.43	0.013*
Urea (mg/dL)	37.22 ± 15.29	42.07 ± 14.98	47.41 ± 19.5	0.004*
Creatinine (mg/dL)	0.91 ± 0.71	0.98 ± 0.42	1.17 ± 0.72	0.003*
Albumin (g/dL)	41.27 ± 4.95	29.43 ± 5.8	31.22 ± 5.21	0.001*
ALT (U/L)	21.26 ± 12.18	25.89 ± 13.88	28.32 ± 11.63	0.007*
AST (birim/L)	29.12 ± 20.11	49.22 ± 28.17	50.3 ± 24.34	0.001*
Total bilirubin (mg/dL)	0.55 ± 0.31	0.7 ± 0.42	0.59 ± 0.32	0.102
Direct bilirubin (mg/dL)	0.2 ± 0.09	0.15 ± 0.1	0.26 ± 0.14	0.001*
GGT (U/L)	27.58 ± 14.92	24 ± 13.81	29.83 ± 13.31	0.043*
Na (mEq/L)	138.2 ± 3.15	141.78 ± 3.08	141.83 ± 4.29	0.001*
K (mEq/L)	4.35 ± 0.35	4.46 ± 0.46	4.27 ± 0.47	0.203
Ca (mEq/L)	9.17 ± 0.68	8.16 ± 0.71	7.85 ± 0.59	0.001*
CRP (mg/L)	13.38 ± 7.25	25.4 ± 15.75	132.21 ± 78.59	0.001*

[a]Kruskal-Wallis Test.
*p < 0.05; **p < 0.001.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBP: cardiopulmonary bypass; GGT: gamma-glutamyl transferase; Na: sodium; K: potassium; Ca: calcium; CRP: C-reactive protein.

Table 2. HO-1, NRF-2, KIM-1 ELISA results, and OS parameters in PF and plasma.

Parameter	Control (Plasma)	Pericardial fluid	Preop CPB (Plasma)	After CPB (Plasma)	Postop (Plasma)	p
	Mean ± SS	**Mean ± SS**	**Mean ± SS**	**Mean ± SS**	**Mean ± SS**	
HO-1 (ng/mL)	1.35 ± 0.32	0.66 ± 0.22	0.58 ± 0.16	0.72 ± 0.28	1.12 ± 0.51	0.000
NRF-2 (ng/mL)	5.63 ± 1.26	0.85 ± 0.33	0.77 ± 0.24	4.07 ± 1.71	4.55 ± 1	0.000
KIM-1 (pg/mL)	31.54 ± 17.09	18.7 ± 9.92	26.11 ± 14.8	27.69 ± 13.81	30.66 ± 19.12	0.001
TAS (Trolox equivalent/L)	1.57 ± 0.21	1.19 ± 0.35	1.45 ± 0.17	1.34 ± 0.25	1.34 ± 0.19	0.000
TOS (μmol H_2O_2 Eqv./L)	10.79 ± 1.99	17.78 ± 2.48	14.46 ± 2.32	14.96 ± 2.52	16.55 ± 2.76	0.000
OSI (Arbitrary Unit (AU))	0.71 ± 0.19	1.69 ± 0.8	1.05 ± 0.25	1.1 ± 0.24	1.28 ± 0.34	0.000

[a]Kruskal-Wallis Test.
*p < 0.05; **p < 0.001.
HO-1: heme oxygenase-1; NRF-2: nuclear factor (erythroid derivative 2)-like 2; KIM-1: kidney injury molecule 1; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index.

value was found in Pump 3. The lowest KIM-1 value was in Pump 1, while the highest KIM-1 value was in Pump 3. The highest TAS value was in Pump 1, while the lowest TAS value was in Pump 3. The lowest TOS value was in Pump 1, while the highest TOS value was in Pump 3. The lowest OSI value was found in Pump 1, while the highest OSI value was found in Pump 3. These results were statistically significant ($p < 0.001$). According to these results, HO-1, NRF-2, KIM-1, TOS, and OSI values increased and TAS value decreased ($p < 0.001$).

There is a significant positive correlation between HO-1 value and NRF-2, TOS, and OSI value. There is a positive relationship between NRF-2 value and

Table 3. Correlation of HO-1, NRF-2, KIM-1, TAS, TOS, and OSI values in patients included in the study

Parameter	HO-1	NRF-2	KIM-1	TAS	TOS	OSI
HO-1						
r	1.000	0.543**	0.104	–0.139	0.431**	0.375**
p		0.000	0.158	0.059	0.000	0.000
NRF-2						
r	0.543**	1.000	0.172*	–0.274**	0.508**	0.511**
p	0.000		0.020	0.000	0.000	0.000
KIM-1						
r	0.104	0.172*	1.000	0.147	–0.083	–0.140
p	0.158	0.020		0.05	0.263	0.059
TAS						
r	0.139	0.274**	0.147	1.000	–0.274**	–0.740**
p	0.059	0.000	0.05		0.000	0.000
TOS						
r	–0.431**	–0.508**	–0.083	–0.274**	1.000	0.819**
p	0.000	0.000	0.263	0.000		0.000
OSI						
r	–0.375**	–0.511**	–0.140	–0.740**	0.819**	1.000
p	0.000	0.000	0.059	0.000	0.000	

*p < 0.05.
**p < 0.01.
HO-1: heme oxygenase-1; NRF-2: nuclear factor (erythroid derivative 2)-like 2; KIM-1: kidney injury molecule 1; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index.

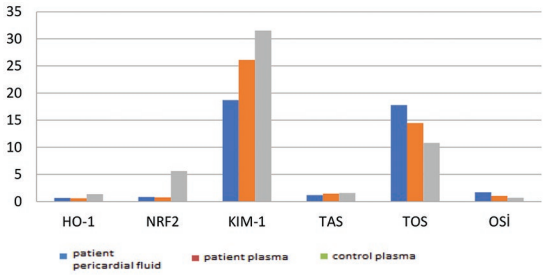

Figure 1. *Graphical display of heme oxygenase-1, nuclear factor (erythroid derivative 2)-like 2, kidney injury molecule 1, total antioxidant status, total oxidant status, and oxidative stress index values in plasma and pericardial fluid of patients and plasma of control group.*

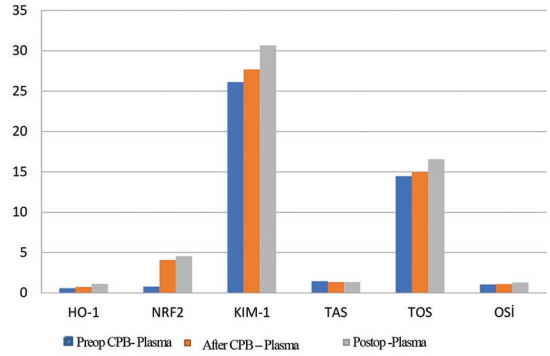

Figure 2. *Graphical representation of the changes in the heme oxygenase-1, nuclear factor (erythroid derivative 2)-like 2, kidney injury molecule 1, total antioxidant status, total oxidant status and oxidative stress index values in the plasma of the patients during before cardiopulmonary bypass (CPB) - plasma, during CPB-plasma and after CPB-plasma.*

KIM-1, TOS, and OSI values, and a negative significant relationship between TAS values. There is a moderately significant negative correlation between TAS value and TOS and OSI values. There is a highly significant positive correlation between TOS value and OSI value.

Discussion

One of the most important elements to be evaluated during CPB is the follow-up of irreversible cell and tissue damage. Before reaching this stage, the cell or tissue synthesizes biomarkers that provide information about its state. For example, in KD, NRF-2, HO-1, and KIM-1 are activated and provide information about the organ. Therefore, these parameters should be monitored during CPB and measures should be taken accordingly.

In our study, a positive correlation was found between urea, creatinine, and CRP values in the plasma of the patient group and HO-1, KIM-1, and NRF-2 values. According to this result, CPB had a negative effect on the kidneys and caused an increase in urea, creatinine, CRP, HO-1, KIM-1, and NRF-2.

In the study conducted by Magyar et al., (2019) on HO-1 and KD following cardiac surgical procedure with CPB technique, an increase in HO-1 was observed 24 h after CBP in patients who developed acute kidney injury (AKI)[17]. In another study, it was reported that AKI was associated with duration of CPB, hemolysis, inflammation, and increased HO-1 concentrations in patients after cardiac surgery[18]. In a different study, it was found that HO-1 reduces inflammation and oxidative stress, and carbon monoxide, the product of HO-1 degradation, reduces KD caused by CPB[19]. In our study, the HO-1 value, which was lower in plasma and PF of the patients compared to the control group, increased continuously during the CPB-pump ($p < 0.001$). In our study, the HO-1 value was higher in PF compared to the plasma of the same patient ($p < 0.001$). The detection of HO-1 in PF supports the view that PF is a plasma ultrafiltrate. In addition, the

detection of HO-1 in PF shows that this molecule is not only synthesized by the kidney but also by the heart tissue. A high HO-1 level during the CPB-pump period indicates that the kidney functions are affected and respond.

Some researchers believe that high KIM-1 levels can be used as an early diagnostic indicator of AKI in patients after cardiac surgery[20] and correlate with renal impairment[21]. Neyra et al., in a study of KIM-1, 23 of 106 adult patients who underwent coronary artery bypass graft (CABG) and valve surgery with CPB developed KD. In these patients, urine KIM-1/creatinine combination was found to be significantly above the optimal threshold value with post-operative KD[22]. The KIM-1 value, which was lower in plasma and PF of the patients compared to the control group, increased during the CPB process ($p < 0.001$). In our study, KIM-1 value was lower in PF compared to the plasma of the same patient ($p < 0.001$). The fact that KIM-1 was lower in PF compared to plasma indicates that this molecule is mostly synthesized in the kidneys.

In our study, the NRF-2 value, which was lower in plasma and PF of the patients compared to the control group, increased continuously during the pump ($p < 0.001$). In the same patient, NRF-2 value was higher in PF than in plasma ($p < 0.001$). While a negative significant relationship was found between NRF-2 and TAS, a positive significant relationship was found between TOS and OSI. NRF-2 value also increased in parallel with increasing OS. In this respect, NRF-2 is similar to other studies in the literature. As can be seen from the studies, promoting NRF-2-mediated protection against OS and inflammation-induced damage with different bioactive compounds may represent new therapeutic strategies. In our study, the increase of NRF-2 against the increased cellular stress and inflammatory response due to CPB was parallel to other studies in the literature.

Although NRF-2, HO-1, and KIM-1 provide important information in KD, it would not be correct to evaluate only these. Because the origin of the damage to the kidneys during CPB is multifactorial. Although CPB is the main factor in this damage, changes in hematocrit and temperature, use of vasoactive and nephrotoxic drugs, hemodynamic changes, and low cardiac output also have negative effects on the kidneys. It is interesting that some studies have reported that the incidence of KD is similar during off-pump CABG and on-pump CABG[23]. Therefore, the specific damage of CPB to the kidneys has not been clarified. However, according to studies, KD in patients with normal pre-operative renal function has a relatively low incidence compared to patients with pre-operative dysfunction. In addition, even in a patient with normal kidney function, the effect of the slightest physiological change in the heart can be felt in the kidney due to the effect of cardiorenal syndrome.

From the past to the present, different groups have tried to find treatments that can protect the kidney from damage during cardiac and non-cardiac surgery. These solutions include the use of drugs such as dopamine, furosemide, fenoldopan, atrial natriuretic factor, sodium bicarbonate, n-acetyl cysteine, enoximone, and dexmedetomidine. In addition, hypothermia and normothermia applications with high or low hematocrit during CPB are other applications to protect the kidney. However, no clear treatment or method has been found to date[24].

A 2012 study used ulinastatin, a protease inhibitor that can suppress the harmful effects of inflammatory reactions and free radicals on kidney cells during CPB[25].

As can be understood from these studies, promoting NRF-2-mediated protection against OS and inflammation-induced damage with different bioactive compounds may represent new therapeutic strategies. In our study, the high level of NRF-2 against increased cellular stress and inflammatory response due to CPB was in parallel with other studies in the literature. In particular, the level of NRF-2 increased rapidly in response to ischemia/reperfusion after cross-clamping of the aorta during CPB. This shows that NRF-2 responds rapidly to cellular reactions and is a diagnostically important parameter. It is important to follow the NRF-2 level especially in the detection of BD that may occur during CPB and to get support from the nephrology clinic to make the necessary treatment according to the level. During CPB, tissue perfusion may also be impaired due to pump pressure and ischemia/reperfusion injury may occur especially in the kidney due to insufficient blood supply. In such cases, NRF-2 may protect the kidney from damage by supporting antioxidant capacity.

Conclusions

In our study population, urea, creatinine, CRP, HO-1, NRF-2, KIM-1, TOS, and OSI increased continuously in correlation with each other during CPB and postoperatively. Compared to the plasma of the control group, HO-1, NRF-2, KIM-1, and TAS were found to be lower in the plasma of the patient group, while TOS

and OSI were found to be higher. In the patient group, HO-1, NRF-2, TOS, and OSI were higher in PF compared to plasma, while KIM-1 and TAS values were lower. It is important that all molecules in plasma were detected in PF for the first time in the study, and this supports the view that PF is a plasma ultrafiltrate. In addition, we can say that KIM-1, which is lower in Pf compared to plasma, is a molecule released mostly by the kidneys.

In CPB, KD can be prevented or reduced with therapeutic strategies that reduce the adverse effects on the kidneys. For this, it is important to develop and implement the most appropriate strategies that increase NRF-2/HO-1 and decrease KIM-1 by following the relevant parameters during CPB and postoperatively.

Two different terms can be used to describe the pathophysiologic interaction between the heart and kidney. The first one, cardiorenal, is used when cardiac dysfunction causes renal dysfunction. The second term, renocardiac, is used when renal dysfunction causes cardiac dysfunction. Future studies may examine the relationship between cardiac and renal biomarkers to determine whether the interaction between the two organs is cardiac or renal (cardiorenal or renocardiac).

The fact that PF was studied and compared with plasma for the first time, that three important parameters such as HO-1, NRF-2, and KIM-1, which are related to each other, were studied together and that the data obtained were compatible with the clinic made our study powerful.

Limitations

Our study has some limitations. This was a prospective study and included a limited number of patients. We had limitations such as not being able to analyze NRF-2, HO-1 and KIM-1 in healthy individuals because PF could not be obtained from healthy individuals, not being able to analyze the relevant parameters in urine due to budget problems and not being able to perform gene expression studies. Our main aim in this study was to investigate the prognostic value of NRF-2. Different designed studies on pathophysiologic processes are needed to elucidate the mechanisms underlying our findings.

Funding

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

The effect of genetic amniocentesis on Doppler measurements of utero-placental and feto-placental circulations

Efecto de la amniocentesis genética en las mediciones Doppler de las circulaciones útero-placentaria y feto-placentaria

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Abstract

Objective: *The objective of this study was to determine whether there is a change in feto-maternal circulation after amniocentesis (AS) using Doppler ultrasonography.* **Methods:** *In this prospectively designed study, fetuses with singleton pregnancies between 16 and 22 weeks of gestational age with an indication for invasive testing and a healthy AS result were included. Twin pregnancies, fetuses with major anomalies as determined by ultrasound evaluation, and fetuses with chromosomal or genetic diseases resulting from AS were excluded from the study.* **Results:** *A total of 73 patients who underwent AS according to the risky screening result were included in the study. Fetal Doppler measurements were performed at three different time periods. The parameters that were analyzed included the fetal umbilical artery, the ductus venosus, and the maternal right and left uterine arteries. The analysis revealed no statistically significant differences between the measurements.* **Conclusions:** *It has been observed that AS, the most commonly used invasive diagnostic procedure in clinical practice, does not affect feto-maternal circulation and fetal heart function.*

Keywords: *Amniocentesis. Doppler ultrasonography. Placental circulation.*

Resumen

Objetivo: *Determinar si existe un cambio en la circulación feto-materna tras la amniocentesis mediante ultrasonografía Doppler.* **Métodos:** *Estudio de diseño prospectivo en el que se incluyeron fetos de embarazos únicos de entre 16 y 22 semanas de edad gestacional con indicación de pruebas invasivas y un resultado sano de la amniocentesis. Se excluyeron del estudio los embarazos gemelares, los fetos con anomalías importantes determinadas mediante ecografía y los fetos con enfermedades cromosómicas o genéticas derivadas de la amniocentesis.* **Resultados:** *Se incluyeron en el estudio 73 pacientes que se sometieron a amniocentesis según el resultado del cribado de riesgo. Se realizaron mediciones de Doppler fetal en tres periodos de tiempo diferentes. Los parámetros analizados fueron la arteria umbilical fetal, el conducto venoso y las arterias uterinas derecha e izquierda de la madre. El análisis no reveló diferencias estadísticamente significativas entre las mediciones.* **Conclusiones:** *Se ha observado que la amniocentesis, el procedimiento diagnóstico invasivo más utilizado en la práctica clínica, no afecta a la circulación feto-materna ni a la función cardiaca fetal.*

Palabras clave: *Amniocentesis. Ultrasonografía Doppler. Circulación placentaria.*

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Introduction

Prenatal diagnosis is a medical procedure used to identify fetal chromosomal abnormalities, single-gene disorders, and congenital infections in the antenatal period. Invasive prenatal diagnostic tests include amniocentesis (AS), chorionic villus sampling, and cordocentesis[1,2]. AS is an invasive procedure in which amniotic fluid is obtained using a 20-22-gauge spinal needle under ultrasonography (USG) guidance through a transabdominal approach[2]. The first documented case of AS was performed by Fuchs and Riis in 1956 with the objective of determining antenatal sex chromosomes[3]. AS, when performed by experienced clinicians under outpatient clinic conditions, can be utilized not only for prenatal diagnosis but also for treatment in certain cases[4,5]. The advent of advanced technology has led to a substantial decrease in the incidence of complications associated with the AS procedure. While transient vaginal bleeding and amniotic fluid leakage may occur in some cases, the risk of miscarriage, the most serious complication, has been reported to be approximately 0.2%[6,7].

The potential hemodynamic changes in the feto-maternal circulation following AS are a source of concern. Doppler USG can be used safely as a non-invasive method to detect these changes. The findings from Doppler USG of the fetal umbilical artery, ductus venosus (DV), middle cerebral artery, and maternal uterine artery can provide crucial insights into placental perfusion[8].

There are very few studies on maternal and fetal perfusion after AS. Previous studies on this subject have reported that fetal circulation was not affected after the procedure[9,10]. In this study, we tried to investigate whether there is a change in feto-maternal circulation after AS procedure using Doppler USG.

Methods

This prospective study was conducted in the Department of Obstetrics and Gynecology between June 2022 and January 2025. The study was planned in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Local Ethics Committee of (Ethics Committee number: 2022/309) before the study. Written informed consent was obtained from all patients included in the study.

A total of 73 patients with singleton pregnancies between 16 and 22 weeks of gestation were included in the study. Fetuses with an indication for invasive testing and a healthy AS result were included in the study. Twin pregnancies, fetuses with major anomalies on USG evaluation, and fetuses with AS results of chromosomal or genetic disorders were excluded from the study.

All procedures were carried out by clinicians specializing in perinatology, utilizing a Voluson E6 (GE Medical Systems, Milwaukee, WI) equipped with a transabdominal 2D convex probe. Fetal Doppler measurements were obtained at three distinct time points: before AS (1st measurement), immediately after AS (2nd measurement), and 1 h after AS (3rd measurement). The parameters that were analyzed included the fetal umbilical artery, the DV, and the maternal right/left uterine artery. The recorded values were then subjected to statistical analysis to determine the presence of any significant differences between them.

Statistical analysis

The analyses were evaluated in Statistical Package for Social Sciences (SPSS) (SPSS Inc., Chicago, IL) 22. Descriptive data were presented as n and % values for categorical data and mean ± standard deviation (mean ± standard deviation) and median (minimum-maximum) values for continuous data. The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous variables. For comparison between measurements, the Wilcoxon analysis was employed for paired comparisons, and the Friedman analysis was used for comparisons involving three measurements. The statistical significance level was set at $p < 0.05$.

Results

A total of 73 patients who underwent AS according to high-risk screening results (n = 57; 78%), minor soft markers (hyper echogenic cardiac focus, hyperechogenic bowel, nuchal fold thickness, pelviectasia) (n: 9; 12%), and advanced maternal age (n: 7; 10%) were included in the study. The mean maternal age was 31.9 ± 6.1 (min 21-max 38), and the mean maternal body mass index was 28.0 ± 5.5 kg/m^2 (min 23-max 33). The mean gestational week at which AS was performed was 18.4 ± 2.0 (min 16-max 22), while the mean estimated fetal weight of the fetuses was 273.8 ± 134.0 g (min 168-max 420).

The first and second Doppler measurements of the umbilical artery, DV, and right and left uterine artery

Table 1. Comparison of first and second Doppler measurements

Doppler measurements	1st	2nd	p*
	Mean ± SD	Mean ± SD	
Umbilical artery	3.71 ± 1.13	3.90 ± 1.32	0.360
S/D	1.32 ± 0.47	1.39 ± 0.54	0.510
PI	0.75 ± 0.20	0.78 ± 0.21	0.405
RI			
Right uterine artery			
S/D	3.20 ± 1.26	3.05 ± 1.30	0.220
PI	1.32 ± 0.66	1.23 ± 0.50	0.843
RI	0.65 ± 0.18	0.64 ± 0.17	0.998
Left uterine artery			
S/D	3.00 ± 0.97	3.12 ± 1.29	0.997
PI	1.25 ± 0.58	1.28 ± 0.65	0.999
RI	0.66 ± 0.22	0.65 ± 0.23	0.987
DV			
PI	0.77 ± 0.32	0.78 ± 0.32	0.998

*Wilcoxon analysis was applied.
S/D: systolic/diastolic; PI: pulsatility index; RI: resistance index; DV: ductus venosus; SD: standard deviation.

Table 2. Comparison of the first and third Doppler measurements of the patients

Doppler measurements	1st	3rd	p*
	Mean ± SD	Mean ± SD	
Umbilical artery			
S/D	3.71 ± 1.13	3.65 ± 0.76	0.998
PI	1.32 ± 0.47	1.36 ± 0.51	0.936
RI	0.75 ± 0.20	0.77 ± 0.26	0.684
Right uterine artery			
S/D	3.20 ± 1.26	3.07 ± 0.97	0.998
PI	1.32 ± 0.66	1.25 ± 0.51	0.999
RI	0.65 ± 0.18	0.67 ± 0.20	0.987
Left uterine artery			
S/D	3.00 ± 0.97	3.37 ± 1.32	0.099
PI	1.25 ± 0.58	1.31 ± 0.52	0.819
RI	0.66 ± 0.22	0.68 ± 0.18	0.237
DV			
PI	0.77 ± 0.32	0.73 ± 0.18	0.887

*Wilcoxon analysis was applied.
S/D: systolic/diastolic; PI: pulsatility index; RI: resistance index; DV: ductus venosus; SD: standard deviation.

are shown in table 1. There was no statistically significant difference in the Doppler parameters before and immediately after AS ($p > 0.05$ for all).

The data regarding the first and third Doppler measurements of the umbilical artery, DV, and right and left uterine artery are shown in table 2. There was no statistically significant difference in Doppler parameters before and 1 h after the procedure ($p > 0.05$) ($p > 0.05$) (Table 2).

The first, second, and third Doppler measurements of the umbilical artery, DV, right, and left uterine artery are shown in table 3. The umbilical artery systolic/diastolic ratio and pulsatility index (PI) value increased immediately after the procedure and returned to the pre-procedure level at 1 h. However, these findings were not statistically significant.

Table 3. Comparison of three different Doppler measurements of the cases

Doppler measurements	1st	2nd	3rd	p*
	Mean ± SD	Mean ± SD	Mean ± SD	
Umbilical artery				
S/D				
PI	3.71 ± 1.13	3.90 ± 1.32	3.65 ± 0.76	0.397
RI	1.32 ± 0.47	1.39 ± 0.54	1.36 ± 0.51	0.286
	0.75 ± 0.20	0.78 ± 0.21	0.77 ± 0.26	0.206
Right uterine artery				
S/D				
PI	3.20 ± 1.26	3.05 ± 1.30	3.07 ± 0.97	0.287
RI	1.32 ± 0.66	1.23 ± 0.50	1.25 ± 0.51	0.805
	0.65 ± 0.18	0.64 ± 0.17	0.67 ± 0.20	0.494
Left uterine artery				
S/D				
PI	3.00 ± 0.97	3.12 ± 1.29	3.37 ± 1.32	0.132
RI	1.25 ± 0.58	1.28 ± 0.65	1.31 ± 0.52	0.463
	0.66 ± 0.22	0.65 ± 0.23	0.68 ± 0.18	0.133
DV				
PI	0.77 ± 0.32	0.78 ± 0.32	0.73 ± 0.18	0.805

*Friedman analysis was applied.
S/D: systolic/diastolic; PI: pulsatility index; RI: resistance index; DV: ductus venosus; SD: standard deviation.

Discussion

AS is the most commonly performed prenatal invasive diagnostic test, and the incidence of associated complications is very rare when performed by experienced clinicians with superior equipment. However, our understanding of the short-term effects of AS on the feto-maternal circulation and their implications for the fetus remains limited. While numerous studies have examined the indications and complications of AS[11-14], there is a paucity of research investigating the potential changes in the feto-maternal circulation resulting from AS procedures[9,10]. Consequently, we sought to elucidate the effects of AS on feto-maternal circulation by employing Doppler USG, a non-invasive methodology.

DV is one of the shunt mechanisms that provide oxygen-rich blood to the fetus in intrauterine life, which makes fetal life different from adult life. The DV carries a substantial proportion of the blood flow from the umbilical vein directly to the inferior vena cava, thereby ensuring the delivery of oxygenated blood to the fetal body, particularly the fetal heart and brain[15]. Consequently, DV assumes a pivotal role in the assessment of fetal heart function[16,17]. To date, only two studies have examined the relationship between DV Doppler parameters and AS. One of these studies was conducted by Helbig and Haugen, who evaluated 99 patients who underwent AS for genetic diagnosis. The pre-procedure DV PI measurements of the fetuses were calculated as mean:1.07; min 0.54-max 2.42, and the post-procedure DV PI measurements were calculated as mean:1.03; min 0.51-max 3.27. No significant difference was observed between the two measurements[10]. In a subsequent study, DV PI parameters were examined immediately before and after the AS procedure, and the mean and mean values were calculated as 1.050 and 1.050, respectively. 1.050 and 0.930, respectively, and no statistically significant difference was found between these two values. The findings of the present study are consistent with the extant literature; the mean DV PI measurements before AS were 0.77 ± 0.32, immediately after AS were 0.78 ± 0.32, and 1 h after AS were 0.73 ± 0.18. The results were analogous, and no statistically significant difference was identified between them.

In their study, Ulkumen et al. compared the Doppler USG parameters of the umbilical artery, middle cerebral artery, right uterine artery, and left uterine artery before and after the procedure in 56 patients who underwent AS in their clinic. The researchers reported that the results of all parameters before and after the procedure were similar[9]. In a related study, 200 patients who underwent AS for genetic diagnosis were examined, and the patient group who underwent transplacental AS during the procedure and the patient group who did not undergo transplacental needle passage were compared. The umbilical artery Doppler parameters and fetal heart rate were compared between these two groups before and after the procedure. The results showed that both measurements were similar in both groups[18]. In a subsequent study by Iskender et al., the Doppler parameters of the middle cerebral artery and umbilical artery were compared before and after the procedure in patients with bleeding into the amniotic fluid during the AS procedure and in patients without such bleeding. The study revealed that the Doppler parameter measurements were comparable between the two groups[19]. The present study involved the performance of uterine artery, umbilical artery, and DV Doppler flow examinations on 73 patients before, immediately following, and 1 h after the AS procedure. The results of the present study corroborate the extant literature, and no statistically significant difference was observed between the groups in Doppler USG parameters evaluating feto-maternal circulation and fetal cardiac function.

The strengths of this study are its prospective design, the expertise of the clinicians, the utilization of advanced technological devices, and the inclusion of only live, healthy fetuses. The limitations of the study are its single-center design and the limited number of patients.

Conclusion

In this research, it was observed that AS, the most commonly used invasive diagnostic procedure in clinical practice, does not affect feto-maternal circulation and fetal cardiac function. Therefore, AS can be safely recommended by experienced clinicians under appropriate conditions.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Concordance of CO_2 gaps measured using peripheral and central venous blood in patients diagnosed with septic shock

Concordancia de las brechas de CO_2 medidas en sangre venosa periférica y central en pacientes diagnosticados de choque séptico

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Abstract

Objective: *This study evaluates the venous-arterial CO_2 difference ($Pv\text{-}aCO_2$) from peripheral venous blood ($Pv\text{-}aCO_2p$) as a less invasive alternative to central venous $Pv\text{-}aCO_2$ for assessing tissue perfusion in septic shock.* **Methods:** *A prospective, single-center study included 54 septic shock patients with central venous catheters placed within 24 h of intensive care unit admission. Blood samples from arterial, central venous, and peripheral venous sources were analyzed. Correlation analyses and Bland-Altman plots were used to assess agreement between $Pv\text{-}aCO_2p$ and central $Pv\text{-}aCO_2$.* **Results:** *Patients had a mean age of 70 years, and 51.9% were male. The median SOFA score was 8.5, and the mean APACHE-II score was 22.7. The $Pv\text{-}aCO_2p$ gap was 8 mmHg, whereas the central $Pv\text{-}aCO_2$ gap was 6 mmHg. A moderate correlation was found between $Pv\text{-}aCO_2p$ and central $Pv\text{-}aCO_2$ ($r = 0.593$, $p < 0.001$), with stronger correlations observed in patients with arterial lactate ≥2 mmol/L ($r = 0.673$) and hemoglobin <8 g/dL ($r = 0.625$). Bland-Altman analysis revealed a mean difference of 8.278 mmHg between arterial and peripheral pCO_2.* **Conclusions:** *Peripheral $Pv\text{-}aCO_2p$ correlates well with central $Pv\text{-}aCO_2$ and can serve as a less invasive alternative for assessing tissue perfusion in septic shock patients. It offers practical utility when central venous access is not available, aiding in early clinical decisions.*

Keywords: *$Pv\text{-}aCO_2$. Tissue perfusion. Septic shock. Veno-arterial CO_2 difference. Hemodynamic monitoring.*

Resumen

Objetivo: *Evaluar la diferencia venosa-arterial de CO_2 ($Pv\text{-}aCO_2$) medida en sangre venosa periférica ($Pv\text{-}aCO_2p$) como una alternativa menos invasiva a la $Pv\text{-}aCO_2$ venosa central para evaluar la perfusión tisular en el choque séptico.* **Métodos:** *Estudio prospectivo, unicéntrico, que incluyó 54 pacientes con choque séptico y catéter venoso central colocado dentro de las primeras 24 horas de ingreso a la UCI. Se analizaron muestras de sangre arterial, venosa central y venosa periférica. Se realizaron análisis de correlación y gráficos de Bland-Altman para evaluar la concordancia entre la $Pv\text{-}aCO_2p$ y la $Pv\text{-}aCO_2$ central.* **Resultados:** *Los pacientes tenían una edad promedio de 70 años y el 51.9% eran hombres. La mediana del puntaje SOFA fue de 8.5 y el puntaje APACHE-II promedio fue de 22.7. La brecha de $Pv\text{-}aCO_2p$ fue de 8 mmHg, mientras que la brecha de $Pv\text{-}aCO_2$ central fue de 6 mmHg. Se encontró una correlación moderada entre la $Pv\text{-}aCO_2p$ y la $Pv\text{-}aCO_2$ central ($r = 0.593$; $p < 0.001$), con correlaciones más fuertes en los pacientes con lactato en sangre arterial ≥ 2 mmol/l ($r = 0.673$) y hemoglobina < 8 g/dl ($r = 0.625$). El análisis de Bland-Altman reveló una diferencia promedio de 8.278 mmHg entre la pCO_2*

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en sangre arterial y en sangre periférica. **Conclusiones:** *La Pv-aCO$_2$p se correlaciona bien con la Pv-aCO$_2$ central y puede servir como una alternativa menos invasiva para evaluar la perfusión tisular en pacientes con choque séptico. Es de utilidad práctica cuando no se dispone de acceso venoso central, ayudando en las decisiones clínicas tempranas.*

Palabras clave: *Pv-aCO$_2$. Perfusión tisular. Choque séptico. Diferencia venosa-arterial de CO$_2$. Monitoreo hemodinámico.*

Introduction

Early identification of tissue hypoperfusion and prompt, effective resuscitation are crucial for the successful management of patients with septic shock[1]. The latest guidelines from the Surviving Sepsis Campaign (SSC) for managing patients with septic shock emphasize hemodynamic support using a structured protocol of fluid administration and vasopressor therapy. The objective is to enhance tissue perfusion and fulfill tissue oxygen requirements[2]. The veno-arterial partial pressure of carbon dioxide difference (Pv-aCO$_2$ or ΔpCO$_2$) has been suggested as a marker for tissue hypoperfusion[3]. These findings have immediate clinical relevance, as they can alter the treatment strategy at the patient's bedside. Under physiological conditions, the Pv-aCO$_2$ typically does not exceed 0.8 kPa (6 mmHg) and reflects the adequacy of venous blood flow and cardiac output (CO)[4].

Several researchers have emphasized a linear relationship between Pv-aCO$_2$ determined from mixed or central venous blood[5,6]. However, the studies conducted so far have been performed in an intensive care setting using central venous catheters. Evaluating the CO$_2$ gap using peripheral venous blood samples outside/inside the intensive care environment is important for its potential to aid daily practice as well. The objective of this study was to determine whether a linear correlation exists between Pv-aCO$_2$ measured from peripheral venous blood (Pv-aCO$_2$p) and Pv-aCO$_2$ measured from central venous blood.

Methods

We conducted a prospective, observational single-center study at Level-3 medical ıntensive care unit (ICU) of Marmara University Hospital, focusing on patients diagnosed with septic shock according to SSC: International Guidelines for Management of Sepsis and Septic Shock 2021 recommendations (e.g., for patients with sepsis induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 h of resuscitation) who were admitted between December 2023 and June 2024[7].

The study specifically targeted patients who had a central venous catheter inserted within the first 24 h following their diagnosis and with at least one site of peripheral venous access. Patients were excluded if they were under 18 years of age, or if they presented with trauma, burns, thrombosis, or other contraindications to jugular vein catheterization, were undergoing extracorporeal membrane oxygenation, continous renal replacement therapy, or extracorporeal CO$_2$ removal therapy, or had a prior diagnosis of congestive heart failure and patients with < 24 h of ICU stay (Fig. 1).

Patient management

All evaluations were performed within 24 h of identifying septic shock in eligible ICU patients. Peripheral blood samples were obtained using a needle cannula in one of the upper extremities, typically in the ICU, with a tourniquet applied. Simultaneously, central venous blood samples were collected under ultrasound guidance following the placement of an internal jugular vein catheter. Patients were thoroughly assessed, with blood samples taken for complete blood count, arterial blood gas analysis, venous blood gas analysis, metabolic panel, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and calculation of Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and the Sequential Organ Failure Assessment (SOFA) scores.

Consent for the hospital's clinical management was requested from each patient, ensuring alignment with their clinical condition. Data were anonymously collected and stored in secure databases accessible solely to investigators specified in the protocol.

Calculation of the venous-to-arterial CO$_2$ tension difference

Blood samples were collected from central and peripheral veins, as well as arterial blood, to determine CO$_2$ values in a cohort of 54 patients. The v-a CO$_2$ gap was calculated by subtracting the arterial pCO$_2$

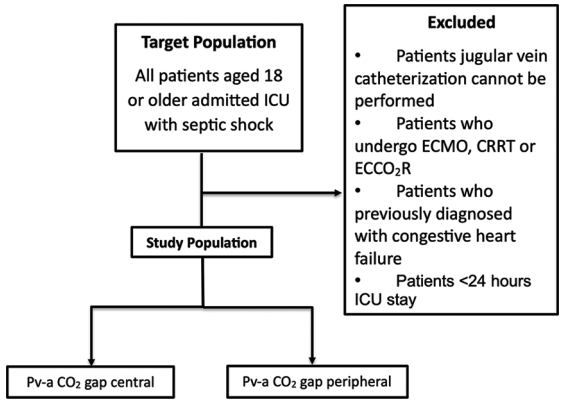

Figure 1. *Flowchart of the study.*

values from the pCO_2 values obtained from the central and peripheral venous blood samples.

Outcomes

The primary aim was the evaluation of the linear correlation and agreement between the Pv-aCO_2 measured with peripheral venous and central venous blood. The secondary objective of the study was to identify patient subgroups or specific laboratory parameters associated with a potentially stronger correlation. To accomplish this, we aimed to stratify patients based on their mean arterial pressures, heart rates, mottling scores, capillary refilling times (CRT), arterial lactate levels, APACHE-II scores, SOFA scores, NT-proBNP values, as well as the type and dosage of vasopressors initiated at the time of septic shock diagnosis.

Statistical analysis

To determine the sample size for this study, literature data were utilized (with a significance level of $\alpha = 0.05$ and power = 90%), leading to the inclusion of a total of 50 patients, with calculations performed using G-Power version 3.1.9.7.8.

The data analysis was conducted using IBM Statistical Package for the Social Sciences Statistics Version 23. Normality of the data distribution was assessed using the Shapiro–Wilk test. Analysis results were presented as mean ± standard deviation or median (minimum–maximum). The paired samples t-test was employed for normally distributed data in two dependent groups, whereas the Wilcoxon test was used for data that did not follow a normal distribution. Pearson correlation coefficient was used to examine the relationship between normally distributed continuous parameters, whereas Spearman's ρ correlation coefficient was employed for non-normally distributed continuous parameters.

In the comparative analysis of methods, the robust Bland-Altman analysis was utilized, renowned for its effectiveness in assessing agreement between two measurement techniques or observers. This method offers insights into the agreement and potential biases between two quantitative measurements, contributing valuable information on the degree of agreement and any systematic differences.

Furthermore, the intra-class correlation coefficient (ICC) was utilized to assess the concordance of pCO_2 differences across regions. The ICC is a widely used statistical measure for evaluating the agreement or consistency between multiple measurements or observations. Specifically, in the context of regional PCO_2 differences, ICC sheds light on the overall consistency of measurements across different regions.

By employing these rigorous statistical methods and adhering to established significance levels, the study ensures robustness and reliability in its findings, thereby contributing to the advancement of knowledge in the field and facilitating informed decision-making in clinical practice.

The significance level of $p < 0.050$ was established to determine statistical significance, aligning with conventional practices in hypothesis testing. This threshold ensures that findings with a p-value below 0.050 are considered statistically significant, indicating a high likelihood of rejecting the null hypothesis.

Results

Among the participants, 28 (51.9%) were male. Diabetes mellitus was present in 12 (22.2%) individuals, whereas 22 (40.7%) had hypertension. Coronary arterial disease was found in 9 (16.7%) participants, and chronic renal failure was reported in 12 (22.2%) individuals. The mean age of the participants was 70 ± 15 years. The mean SOFA score was 8.52 ± 3.65, and the mean APACHE score was 22.7 ± 5.89. The median CRT was determined to be 3 (1-8) s. The median mottling score was 0 (0-5). Patients' characteristics and baseline laboratory findings are shown in table 1.

Out of 54 determinations, the mean difference in PCO_2 values obtained from arterial and central regions (Pv-aCO_2) was found to be 6.81, with this difference being statistically significant from zero ($p < 0.001$). The lower limit of agreement was −0.848, whereas the upper limit was 14,478. In addition, a statistically significant

Table 1. Main characteristics, laboratory results, and clinical scores of the study population on ICU admission

Characteristics	Patients
Male sex, n (%)	28 (51.9)
Age (mean value ± SD)	70 ± 15
Comorbid diseases	
DM, n (%)	12 (22.2)
HT, n (%)	22 (40.7)
CAD, n (%)	9 (16.7)
CKD, n (%)	12 (22.2)
COPD, n (%)	4 (7.4)
Hematologic malignancy, n (%)	4 (7.4)
Solid tumor, n (%)	16 (29.6%)
Mean arterial pressure (mmHg), (mean value ± SD)	71.15 ± 10.54
Heart rate (bpm), (mean value ± SD)	96.11 ± 20.88
SOFA score, (median [25-75])	8.5 (1-17)
APACHE-II score, (mean value ± SD)	22.7 ± 5.89
NT-ProBNP (pg/mL), (median [25-75])	4034 (10-35000)
Hgb (g/dL), (mean value ± SD)	9.06 ± 2.05
Htc (%), (mean value ± SD)	27.7 ± 6.36
Noradrenaline dose (mcg/kg/min), (median [25-75])	0.18 (0.02-1)
Capillary refilling time (seconds), (median [25-75])	3 (1-8)
Mottling score, (median [25-75])	0 (0-5)

ICU: intensive care unit; SD: standard deviation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; SOFA: the sequential organ failure assessment; APACHE-II: acute physiology and chronic health evaluation-II; Hgb: hemoglobin; Htc: hematocrit; NT-ProBNP: n-terminal pro-B-type natriuretic peptide.

Table 2. Blood gas analysis of the study population

Parameter	Arterial	Central	Peripheral
pH, (min-max)	7.45 (7.06-7.74)	7.4 (6.98-7.65)	7.38 (7.02-7.58)
pO_2, mmHg, (min-max)	92.5 (51-289)	41 (24-137)	36 (15-104)
pCO_2, mmHg, (min-max)	36 (14-73)	43.5 (20-84)	46 (23-81)
HCO_3, mEq/L, (min-max)	25.1 (8.5-38.8)	25.05 (9.9-39.2)	24.45 (9-38.1)
BE, (min-max)	0.6 (−22.5-15.5)	1.15 (−18.9-16.5)	1.65 (−19.3-13.9)
Lactate, mmol/L, (min-max)	1.9 (0.3-8.6)	2.05 (0.1-14.8)	2.2 (0.2-13.7)
sO_2, %, (min-max)	98 (80-100)	70.72 ± 11.98	60 (24-95)
Pv-aCO_2 (mmHg), (Median [25-75])		6.81 ± 3.91	
Pv-aCO_2p (mmHg), (Median [25-75])		8.27 ± 4.60	

Table 3. Analysis results of Bland-Altman and examination of agreement between Pv-aCO_2 and Pv-aCO_2p

Variable	Median difference (95% CI)	SD	ICC (95% CI)	p
Pv-aCO_2	6.815 (5.75-7.882)	3.910	0.942 (0.902-0.966)	< 0.001
Pv-aCO_2p	8.278 (7.02-9.53)	4.595	0.914 (0.856-0.949)	< 0.001

CI: confidence interval; SD: standard deviation; ICC: intra-class correlation coefficient.

strong agreement was observed between arterial and central regions (ICC = 0.942; p < 0.001). Similarly, the mean difference in pCO_2 values obtained from arterial and peripheral regions (Pv-aCO_2p) was 8.27, with this difference being statistically significant from zero (p < 0.001) (Table 2). The lower limit of agreement was -0.728, whereas the upper limit was 17,283. Furthermore, a statistically significant strong agreement was observed between arterial and peripheral regions (ICC = 0.914; p < 0.001) (Table 3). These findings indicate a consistent and reliable agreement between pCO_2 measurements taken from arterial and central regions, as well as between arterial and peripheral regions. This strong agreement highlights the robustness of comparing pCO_2 values across different regions (Fig. 2).

Among individuals with arterial lactate levels of 2 or higher, there was a strong positive correlation between Pv-aCO_2 and Pv-aCO_2p (r = 0.673, p < 0.001). Similarly, individuals with NT-proBNP values < 2000, Hgb values < 8, and noradrenaline values < 0.1 exhibited high positive correlations between Pv-aCO_2 and Pv-aCO_2p values (r = 0.637, p = 0006; r = 0.625, p = 0.004; r = 0.620, p = 0.032, respectively) (Table 4).

Discussion

Our study focused on analyzing the Pv-aCO_2 gap obtained from central venous catheters and comparing it to the Pv-aCO_2p gap obtained from peripheral venous catheters. The outcomes of our study reveal useful insights into the relationship between these two types of venous access methods and their corresponding Pv-aCO_2 measurements. The research showed a statistically significant relationship between the Pv-aCO_2 gaps measured at central and peripheral venous sites, showing that measurements obtained from peripheral venous access are similarly reflective of those obtained from central venous access.

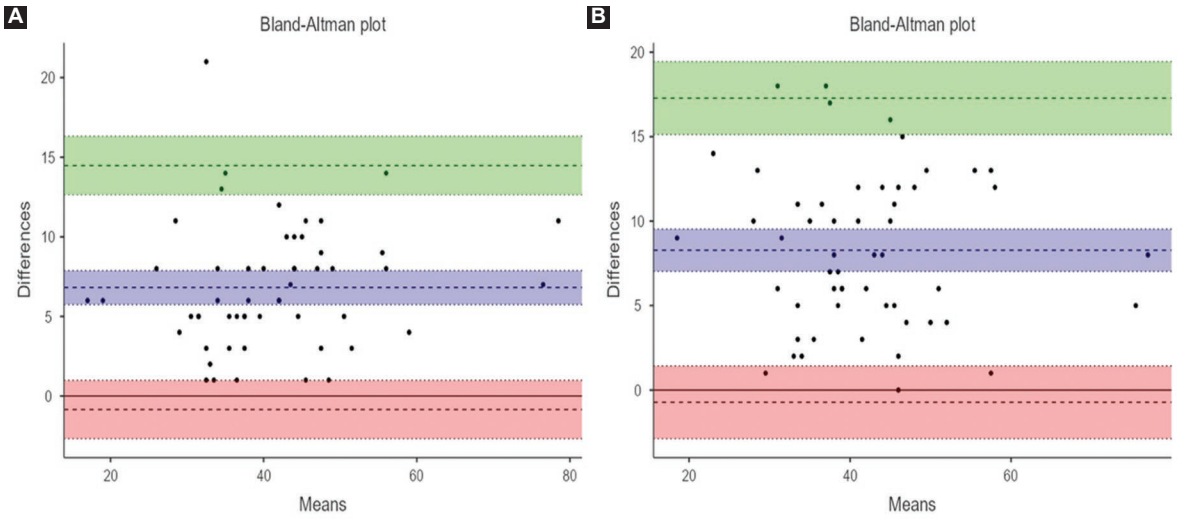

Figure 2. *The Bland-Altman plot comparison shows the agreement between two measurement methods. Each plot presents differences in measurements on the y-axis against their mean values on the x-axis, and includes limits of agreement, typically set at ± 1.96 standard deviations from the mean difference.* **A:** *the mean difference of PCO values obtained from arterial and central regions was found to be 6.815, with a statistically significant difference from 0 ($p < 0.001$). In this plot, the lower limit of agreement was approximately –0.848, and the upper limit was about 14.478. Most data points lie within these limits, indicating a strong agreement between the arterial and central regions. The shaded areas (green for the upper limit and red for the lower limit) emphasize the range within which the majority of measurements fall, with only a few outliers observed. The intraclass correlation coefficient (ICC) was 0.942, showing a statistically significant and very strong agreement ($p < 0.001$).* **B:** *which illustrates the comparison between arterial and peripheral regions, the mean difference of PCO values was calculated as 8.278, also showing a statistically significant difference from 0 ($p < 0.001$). Here, the lower limit of agreement was approximately –0.728, and the upper limit was around 17.283. While most data points again fall within the shaded limits, the wider spread indicates a slightly greater variability in measurements between the arterial and peripheral regions compared to the central region. Nevertheless, a very strong agreement was still observed between the arterial and peripheral regions, with an ICC of 0.914 ($p < 0.001$), underscoring the statistically significant agreement in this comparison as well.*

This finding has significant therapeutic effects, as central venous access, despite its frequent utilization for precise hemodynamic monitoring, is associated with risks such as infection, thrombosis, and pneumothorax, especially in critically ill individuals[8]. On the other hand, peripheral venous access is a minimally invasive treatment that is easier to perform and has a lower risk of problems. If the measurements of the peripheral Pv-aCO_2p gap show a strong correlation with those obtained via central venous access, as shown by our findings, then peripheral venous sampling could be considered a feasible option in cases where central venous access is not possible or considered risky.

The practical applications of using peripheral venous Pv-aCO_2p gap measurements as a substitute for central venous measurements are numerous. In emergency settings or resource-limited environments where central venous catheterization may not be easily accessible or feasible, peripheral venous sampling can be used to effectively monitor tissue perfusion and provide guidance for vital actions. Furthermore, this approach can be especially beneficial for patients who are unable to have central venous access due to anatomical or physiological limitations.

Another crucial factor to take into consideration is the potential impact on patient comfort and overall treatment. Peripheral venous catheterization is characterized by lower pain, better tolerance, and the ability to be performed with fewer assets and staff when compared to central venous catheterization[9]. This has the potential to improve patient outcomes by decreasing problems associated with procedures and enabling faster implementation of monitoring, particularly in urgent situations such as septic shock.

The strong correlations shown in our study have not been thoroughly investigated in previous studies, and the provided values have been isolated from statistical analysis[10,11]. Although our research provides valuable data in this relatively unexplored field, larger-scale investigations are necessary to validate our findings and identify specific clinical conditions in which peripheral venous sampling might effectively replace a central venous sample.

Various clinical settings are involved in managing septic patients, particularly in the initial stages of the syndrome, including pre-hospital medicine, emergency medicine, and hospital medicine. In these contexts, obtaining a central venous line may pose

Table 4. Comparison of pCO_2 differences in regions by groups

Clinical variable	Pv-aCO2p (mmHg)		Pv-aCO2 (mmHg)		r/p	Test statistic	p
	Mean value ± SD	Median (Min-Max)	Mean value ± SD	Median (Min-Max)			
Arterial lactate level, mmol/L							
≥ 2	8.1 ± 4.67	7 (2-18)	6.21 ± 3.34	6 (1-14)	0.433/0.019***	2.316	0.028*
< 2	8.48 ± 4.59	9 (0-18)	7.52 ± 4.45	8 (1-21)	0.673/< 0.001***	1.313	0.202*
NT-proBNP, pg/mL							
< 2000	7.18 ± 4.08	7 (1-13)	7.35 ± 4.7	6 (1-21)	0.637/0.006****	–0.032	0.975**
≥ 2000	9.22 ± 4.67	9.5 (0-18)	6.94 ± 3.51	6.5 (1-14)	0.516/0.003***	3.108	0.004*
Hgb, g/dL							
< 8	7.21 ± 3.74	7 (2-14)	5.0 ± 3.09	5 (1-12)	0.625/0.004***	3.2	0.005*
≥ 8	8.86 ± 4.95	9 (0-18)	7.8 ± 3.99	8 (1-21)	0.545/0.001****	–1.107	0.268**
HR, beats/min							
< 100/min	8.87 ± 4.76	10 (0-18)	6.71 ± 3.36	6 (1-14)	0.600/< 0.001***	3.134	0.004*
≥ 100/min	7.27 ± 4.32	6.5 (1-17)	6.82 ± 4.69	5.5 (1-21)	0.562/0.007****	–0.328	0.743**
Noradrenaline dose (mcg/kg/dak)							
< 0.1	5.75 ± 3.47	6 (1-13)	5.33 ± 3.17	5 (1-11)	0.620/0.032***	0.497	0.629*
≥ 0.1	9.18 ± 4.93	10 (0-18)	7.21 ± 4.36	6 (1-21)	0.540/0.001***	2.524	0.017*

*Paired two-sample t-test.
**Wilcoxon test.
***Pearson correlation coefficient.
****Spearman's rho correlation coefficient.
NT-proBNP: n-terminal pro-B-type natriuretic peptide; Hgb: hemoglobin; HR: heart rate; SD: standard deviation.

challenges. Early assessment of the CO_2 gap could prompt earlier initiation of inotropic medications, which have been demonstrated to be safely administered via peripheral venous access[12].

To the best of our knowledge, only two studies in the literature have explored the association between standard Pv-aCO_2 and Pv-aCO_2p. Gao et al.[11] reported a correlation of 90%, and Orso et al.8 reported a correlation of 70%.

In the present study, we observed a direct correlation between Pv-aCO_2 and Pv-aCO_2p. The ICC value of 0.914 underscores the strong consistency and reliability of these measurements, affirming their robust agreement and reliability in clinical assessment.

Beyond the primary findings regarding the correlation between Pv-aCO_2 and Pv-aCO_2p gaps, our study revealed several additional correlations that hold important clinical implications and have not been previously addressed in the literature. Among patients with arterial lactate levels of 2 mmol/L or higher, we observed a robust positive correlation between Pv-aCO_2 and Pv-aCO_2p ($r = 0.673$, $p < 0.001$). Elevated lactate is often associated with impaired tissue oxygenation and metabolic stress, yet our findings suggest that even in this physiologically challenging condition, peripheral venous measurements remain reliably reflective of central venous values[13]. This could potentially offer a safer, less invasive alternative for hemodynamic monitoring in patients where elevated lactate levels would traditionally necessitate central venous access.

In addition, in patients with NT-proBNP levels under 2000, hemoglobin values below 8 g/dL, and noradrenaline doses < 0.1 μg/kg/min, we found similarly high positive correlations between Pv-aCO_2 and Pv-aCO_2p ($r = 0.637$, $p = 0.006$; $r = 0.625$, $p = 0.004$; $r = 0.620$, $p = 0.032$, respectively). The ability of peripheral Pv-aCO_2p measurements to align with central values across these diverse clinical markers reinforces its potential role as a practical alternative, particularly in situations where central venous access may be risky or infeasible.

Furthermore, our research revealed a statistically significant moderate positive correlation between capillary refill time and mottling score ($p < 0.001$), which are both simple bedside measurements of peripheral perfusion[13,14]. The correlation between these two non-invasive indicators enhances the significance of their combined utilization in evaluating the degree of circulatory failure in critically ill patients.

The results of our study show that peripheral venous measures can be reliably accurate under a variety of clinical situations, including those marked by increased lactate levels, decreased hemoglobin levels, impaired cardiac function, and the administration of low doses of vasopressors. This emphasizes the broader relevance

of peripheral venous sampling as a less invasive, but accurate option for central venous access in critically ill patients. Our investigation offers new insights into the correlations between Pv-aCO_2 and Pv-aCO_2p in different conditions. This gives a basis for future research to assess and expand upon these findings, potentially leading to modifications in the approach to venous sampling and hemodynamic monitoring in critical care.

Our study presents several limitations. First, it is a single-center study, so the results might not universally apply. Second, we did not measure cardiac index, and we excluded patients with a prior diagnosis of heart failure from our study to avoid potential confusion with cardiac dysfunction that could develop secondary to sepsis. Finally, our patient group received only single-agent vasopressor therapy with noradrenaline. Therefore, our results should be validated in future studies with a larger sample size.

Conclusion

The significant linear correlation observed between Pv-aCO_2 levels from central and peripheral venous catheters in patients with septic shock underscores the potential benefits of using peripheral venous access. This approach offers a less invasive alternative for Pv-aCO_2 measurement, simplifying patient management while still providing valuable physiological insights. Further controlled clinical trials are necessary to explore whether Pv-aCO_2p could be utilized in broader clinical settings beyond ICUs, aiming to assess whether CO adequately meets tissue metabolic demands during early sepsis stages.

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Conflicts of interest

The authors declare no conflicts of interest.

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study. The protocol for this study was approved by the Marmara University School of Medicine Ethics Committee (Approval No: 09.2023.566, date: 07.04.2023). The study was carried out in strict adherence to the principles outlined in the Declaration of Helsinki.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Perirenal fat Hounsfield units: not only for renal stones but also for renal cell carcinoma

Unidades Hounsfield de grasa perirrenal: no solo para los cálculos renales, sino también para el carcinoma de células renales

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Abstract

Objective: *We aimed to evaluate the role of attenuation values of perirenal fat calculated by computed tomography (CT) in differentiating aggressive renal masses.* **Methods:** *The data of 83 patients with histologically confirmed local stage renal cell carcinoma (RCC), who were treated with nephrectomy in our center, and 78 control group cases were analyzed. All measurements including renal mass volume, abdominal subcutaneous fat area and subcutaneous fat area pelvic subcutaneous fat area, and perirenal fat thickness and Hounsfield unit (perirenal fat tissue thickness [PFT]-hounsfield unit of perirenal fat [PFHU]) were performed on CT by the same radiologist.* **Results:** *In the statistical analysis of PFT and PFHU measurements between the groups, fat thickness was found to be lower in the patient group compared with the control group. However, hounsfield unit measurements were statistically significantly higher in the patient group ($p < 0.0001$). A cutoff value of –98.1 for the PFHU can identify the patient group with a sensitivity of 89.2% and a specificity of 84.6% (area under the curve = 0.9; 95% confidence interval: 0.86-0.95 $p < 0.0001$). In the multivariate logistic regression analysis, a PFHU ≥ –98.1 was independently associated with RCC after accounting for clinical and radiologic parameters.* **Conclusion:** *We believe that measurement of the HU values of perirenal adipose tissue with the CT may be useful in differentiating aggressive renal masses and therefore in determining the appropriate treatment selection.*

Keywords: *Computed tomography. Hounsfield. Kidney. Perirenal fat. Renal cell carcinoma.*

Resumen

Objetivo: *Evaluar el papel de los valores de atenuación de la grasa perirrenal calculados por tomografía computarizada (TC) en la diferenciación de masas renales agresivas.* **Métodos:** *Se analizaron los datos de 83 pacientes con carcinoma de células renales en estadio local confirmado histológicamente, que fueron tratados con nefrectomía en nuestro centro, y de 78 casos del grupo control. Todas las mediciones, incluido el volumen de masa renal, el área de grasa subcutánea abdominal y pélvica (SFA_A-SFA_P), el espesor de la grasa perirrenal y las unidades Hounsfield (PFT-PFHU), fueron realizadas en TC por el mismo radiólogo.* **Resultados:** *En el análisis estadístico de las mediciones de PFT y PFHU entre los grupos se encontró que el espesor de la grasa era menor en los pacientes en comparación con los controles. Sin embargo, las mediciones de las unidades Hounsfield fueron mayores, con significación estadística, en el grupo de pacientes ($p < 0.0001$). Un valor de corte de –98.1 para la PFHU puede identificar el grupo de pacientes con una sensibilidad del 89.2% y una especificidad del 84.6% (AUC = 0.9; IC 95%: 0.86-0.95; $p < 0.0001$). En el análisis de regresión logística multivariado, una PFHU ≥ –98.1 se asoció de manera independiente con el carcinoma de células renales después de tener en cuenta los parámetros clínicos y radiológicos.*

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Conclusiones: *Creemos que la medición de los valores de unidades Hounsfield del tejido adiposo perirrenal con TC puede ser útil para diferenciar masas renales agresivas y, por tanto, para determinar la selección del tratamiento adecuado.*

Palabras clave: *Tomografía computarizada. Unidades Hounsfield. Riñón. Grasa perirrenal. Carcinoma de células renales.*

Introduction

Renal cell carcinoma (RCC) is the most common solid lesion in the kidney and accounts for approximately 90% of all renal malignancies and is associated with the highest mortality[1,2]. The three main subtypes with specific histopathologic and genetic features are clear cell RCC (ccRCC), papillary RCC (pRCC types I and II), and chromophobe cell RCC (chRCC)[3]. The diagnosis of early stage RCCs is increased with the widespread use of imaging methods.

There is numerous epidemiologic evidence showing that long-term obesity is one of the major causes of some types of cancers, such as breast, colon, esophageal, pancreatic, and renal cancers[4]. Although the exact etiology of RCC remains unclear, the association of obesity with RCC development was reported in some previous studies[5,6]. In addition, perirenal fat may promote migration of the ccRCC cells[7]. A recent study showed that renal neoplasms were more common in patients with a high perirenal fat tissue thickness (PFT) than in those with a low PFT[8]. It is also reported that the density of the perirenal fat is a negative factor for the progression-free survival of localized renal cancer[9].

The hounsfield unit (HU) measurement on computed tomography (CT) is routinely performed in clinical practice to define the hardness and composition of kidney stones and to predict the outcome of the stone treatment[10-12]. It is known that CT has high sensitivity and specificity in the diagnosis and extension of renal tumors[13]. In patients with suspected RCC undergoing routine abdominal CT imaging, the HU can be easily measured and reported without the need for extra procedures. Detection of the radiologic and histopathologic association of the high PFT and high perirenal fat density (hounsfield unit of perirenal fat [PFHU]) with renal masses may help in planning appropriate treatment at the right time.

Methods

Patients and data collection

Patients, who were treated with partial or radical nephrectomy between January 2020 and December 2023 in two centers of University of Health Sciences, were included in the study. Those, whose pre-operative CT images were unavailable, who underwent the surgery in another hospital, and whose tumor location may have affected the subcutaneous fat thickness (SFT) measurement (posterior in the renal hilus) were excluded. Individuals, who were under 45 or over 80 years of age, had experienced a previous intra-abdominal surgery, had a history of kidney stones, a malignancy other than RCC, and infection around the kidney, and had incomplete data were excluded. Numbers of patients with pRCC and chRCC subtypes were insufficient for statistical analysis, and therefore, they were also excluded. A total of 100 cases were picked randomly and included as the control group among the participants who underwent a CT imaging for screening in the above-mentioned time period at our center and had similar descriptive characteristics such as age, gender, body mass index (BMI), and comorbidities. A total of 22 individuals, who had a history of intra-abdominal surgery or kidney stones, and had kidney stones, malignancy or infection around the kidney in the admission were excluded. The study was completed with a total of 83 patients with clinically and histologically confirmed local stage ccRCC and 78 patients are the control group (Fig. 1).

Age at the diagnosis, BMI, tumor location (right and left kidney), and the presence of systemic diseases (hypertension and diabetes mellitus) were retrospectively obtained from medical records. T stage based on the American Joint Committee on Cancer (T1vs. T2), Fuhrman grade, RCC subtype, histological necrosis, and presence of sarcomatoid component were reported by our uropathologist[14]. All measurements including the renal mass volume, abdominal subcutaneous fat area (SFA_A), pelvic subcutaneous fat area (SFA_P), PFT, and PFHU were performed on CT by the same radiologist Dr. Esin Derin-Çiçek (third author).

Regional Ethic Committee (Hamidiye-BAEK 20/268) reviewed and approved the study protocol and the study's protocol was in accordance with by the 1964 Declaration of Helsinki and its later changes. All participants included in the study obtained informed consent form.

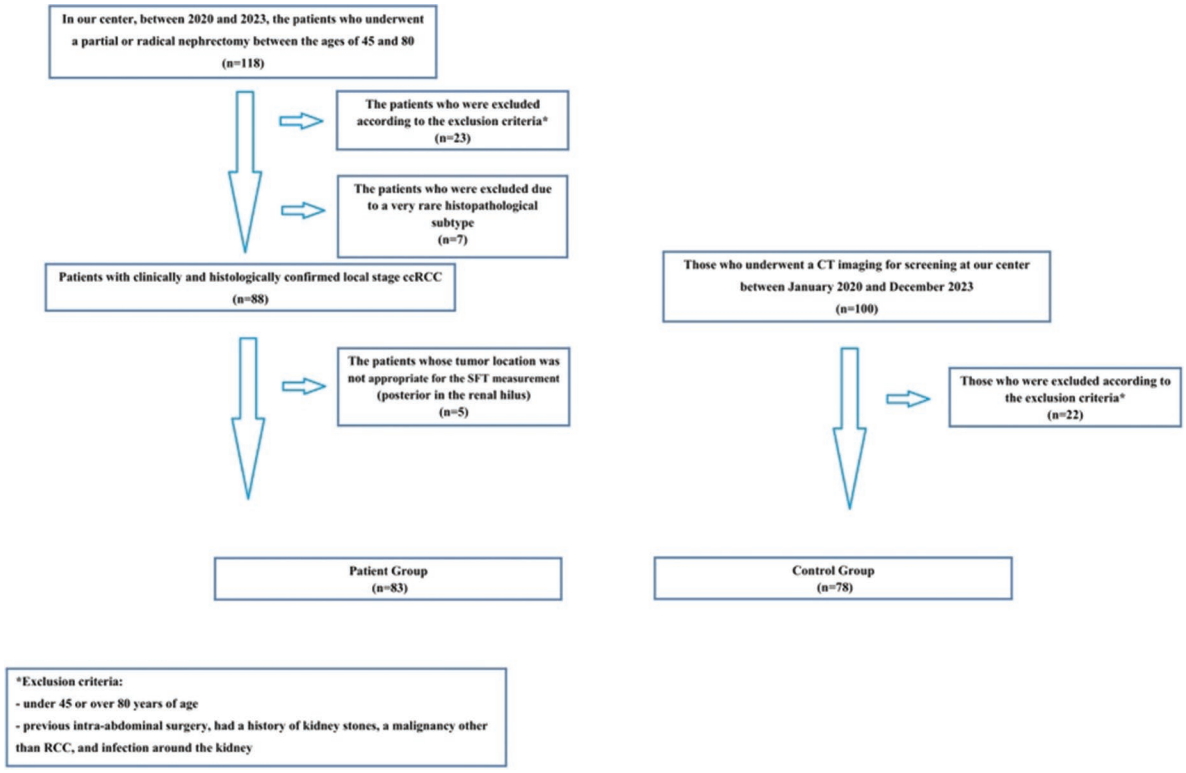

Figure 1. *Flowchart of patients who met inclusion/exclusion criteria for the study.*

The measurement of the SFA, PFT, and PFHU

A non-contrast CT scan of abdomen (Optima 660 SE, GE Healthcare/Aquilion Lightning Ultra Helical CT, Canon Medical) was performed for all individuals in the preoperative period. The SFA_A and SFA_P (Fig. 2) calculations were consistent with those reported in the previous studies[15,16]. First, the border between the visceral and subcutaneous compartment was defined manually along with the contour of the abdominal muscular wall at the umbilical level. Then, to identify the fat containing pixels, an image display window width between −195 and −45 HUs was utilized. A software analysis program (RAD-X® PACS software, Simplex, Ankara, Turkey) evaluated the values of the SFA_A and SFA_P automatically.

The PFT and PFHU were also calculated with the same method as in the previous studies[8,16]. In the CT images, the linear ruler tool of the software was used to measure the distance from the posterior surface of the kidney to the external edge of the iliopsoas at the renal hilum level (Fig. 3). The same radiologist Dr. Esin Derin-Çiçek (third author), who was unaware of the clinical and pathological data, assessed the all preoperative scans.

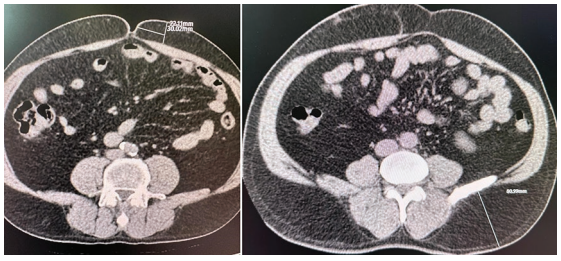

Figure 2. A: *evaluation of the subcutaneous fat area of the abdomen.* **B:** *evaluation of the subcutaneous fat area of the pelvis.*

Statistical analysis

IBM Statistical Package for the Social Sciences Statistics 22 program was used for statistical analysis of the findings. The conformity of the parameters to normal distribution was evaluated by Kolmogorov–Smirnov test. In addition to descriptive statistical methods (minimum, maximum, mean, standard deviation, median, and frequency), t-test was used for comparisons of quantitative data between two groups

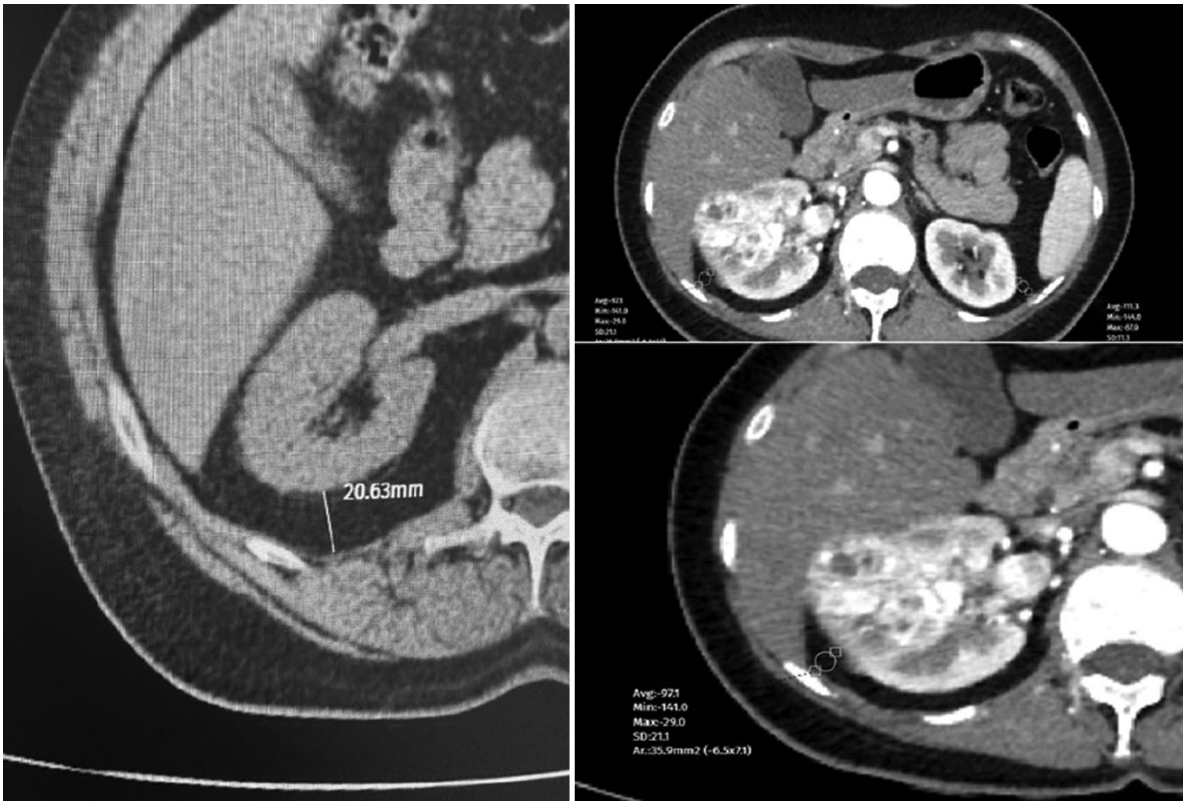

Figure 3. *The evaluation of the perirenal fat thickness and perirenal fat hounsfield unit.*

for normally distributed parameters and Mann-Whitney U test was used for comparisons of non-normally distributed parameters between two group receiver operating characteristics (ROC). Chi-square and Fisher's Exact test were used to compare qualitative data. Spearman's rho correlation analysis, ROC for discrimination, and logistic regression analysis for effect were used to analyze the relationships. Analysis of covariance was performed to control/refine the SFA values. Significance was evaluated at $p < 0.05$ level.

Results

The study was conducted with a total of 161 patients, 59 (36.7%) women and 102 (63.3%) men, aged between 45 and 79 years. The mean age was 58.5 ± 8.56 years. The cases were evaluated in two groups as "Patient" (n = 83) and "Control" (n = 78). There was no statistically significant difference between the two groups in terms of descriptive characteristics ($p > 0.05$; Table 1).

The pre-operative SFA_A and SFA_P measurements were not statistically significantly different between the groups ($p > 0.05$). In the pre-operative PFT measurement analysis in both groups, fat thickness was found to be lower in the patient group compared with the control group; however, this difference was not statistically significant ($p > 0.05$). In separate comparisons of both kidneys, fat thickness was found to be lower in the patient group than in the control group according to the PFT (PFT_R) measured in the right kidney and the PFT (PFT_L) measured in the left kidney; however, these differences were not statistically significant ($p > 0.05$). After eliminating the effect of the SFA_A and SFA_P values in our study, the PFT measurements were re-evaluated between the two groups; however, no statistically significant difference was found ($p > 0.05$; Table 1).

The analysis of the pre-operative PFHU measurements revealed higher perirenal fat densities in the patient group compared with the control group; this difference was statistically significant ($p < 0.0001$). In separate comparisons for both kidneys, perirenal fat densities were found to be higher in the patient group than in the control group according to the analysis of the PFHU ($PFHU_R$) measured in the right kidney and the PFHU ($PFHU_L$) measured in the left kidney; these

Table 1. Demographic data and the radiological measurements of the participants among the groups

Data and measurements	Patient (mean) (%)	Control (mean) (%)	Total (mean) (%)	p
Age	59.10 ± 9.29	57.87 ± 7.71	58.50 ± 8.56	0.451[1]
Sex				
Male	54 (65)	102 (63)	48 (61)	0.643[1]
Female	29 (35)	59 (37)	30 (39)	
BMI				
< 25	37 (45)	72 (45)	35 (45)	0.97[1]
≥ 25	46 (55)	89 (55)	43 (55)	
HT				
+	46 (55)	80 (50)	34 (44)	0.133[1]
–	37 (45)	81 (50)	44 (56)	
DM				
+	24 (29)	40 (25)	16 (20)	0.218[1]
–	59 (71)	121 (75)	62 (80)	
SFA_A	25.65 ± 8.79	25.10 ± 7.49	25.38 ± 8.17	0.671[2]
SFA_P	61.96 ± 16.28	59.61 ± 13.64	60.82 ± 15.06	0.325[2]
PFT	16.31 ± 9.12	17.78 ± 7.07	17.02 ± 8.2	0.256[2]
PFT_R	15.53 ± 9.41	16.58 ± 7.01	16.04 ± 8.33	0.423[2]
PFT_L	17.09 ± 10.05	18.99 ± 8.07	18.01 ± 9.17	0.187[2]
PFHU	–92.63 ± 6.43	–103.63 ± 7.03	–97.96 ± 8.68	0.0001[2]*
$PFHU_R$	–92.88 ± 8.55	–103.03 ± 8.06	–97.8 ± 9.73	0.0001[2]*
$PFHU_L$	–92.38 ± 8.47	–104.24 ± 7.99	–98.13 ± 10.14	0.0001[2]*

[1]Mann-Whitney U-test.
[2]t-test.
*p < 0.05.
BMI: body mass index; HT: hypertension; DM: diabetes mellitus; SFA: subcutaneous fat area; SFA_A: subcutaneous fat area of abdomen; SFA_P: subcutaneous fat area of pelvis; PFT: perirenal fat thickness; PFT_R: perirenal fat thickness of right kidney; PFT_L: perirenal fat thickness of left kidney; PFHU: kounsfield unit of perirenal Fat; $PFHU_R$: hounsfield unit of right kidney perirenal fat; $PFHU_L$: hounsfield unit of left kidney perirenal fat.

Table 2. Histopathologic data of the patient group

Characteristics	Tumor Location		p
	L (%)	R (%)	
T Stage			
1	36 (64)	20 (36)	0.059[1]
2	5 (42)	7 (58)	
3	5 (33)	10 (67)	
Fuhrman Grade			
1	7 (64)	4 (36)	0.587[1]
2	26 (51)	25 (49)	
3	13 (62)	8 (38)	
Tumor necrosis			
+	15 (71)	6 (29)	0.088[1]
–	31 (50)	31 (50)	
Sarcomatoid component			
+	1 (50)	1 (50)	0.99[2]
–	45 (56)	36 (44)	

[1]Ki-Kare test.
[2]Fisher's exact test.

differences were statistically significant (p < 0.0001; Table 1).

The histopathologic data of the patient group are shown in table 2. According to T staging, the rates of stage 1, 2, and 3 were 67.5%, 14.5%, and 18%, respectively. Fuhrman grades 1, 2, and 3 were 11%, 51%, and 21%, respectively. Tumor necrosis was positive in 21% of patients and sarcomatoid component was positive in 2.5%. T stages, Fuhrman grades, tumor necrosis, and presence or absence of the sarcomatoid component were not significantly different in the analysis of the tumor formation sides (left/right) (p > 0.05) (Table 2).

In the analysis of radiologic measurements (Table 3), there was no statistically significant difference between the right and left kidney for the SFA_A, SFA_P and PFHU values in the patient group (p > 0.05). There was a statistically significant difference between the PFT_L and PFT_R in both patient and control groups (p < 0.0001). In the patient group, the measurement of the tumor side and in the control group and the mean of the measurements of the right and left sides were taken for further comparison. While the difference in the PFT measurements between the two groups was not statistically significant, the difference in the PFHU measurements was statistically significant (p = 0.0001).

The PFHU measurement was found to be highly differentiative for the patient group, the cutoff point was set as –98.1 and the participants were divided into two groups. Those with a PFHU value < –98.1 had 6.7 times more risk than those with a PFHU value < –98.1 (Exp(B) = 6.725; 95% confidence ınterval [CI] 4.2-10.6 p < 0.0001). A cutoff value of –98.1 for the PFHU can identify the patient group with a sensitivity of 89.2% and a specificity of 84.6% (area under the curve = 0.9; 95% CI: 0.86-0.95 p < 0.0001) (Fig. 4). In multivariate logistic regression analysis, a PFHU ≥ –98.1 was independently associated with RCC after clinical and radiological parameters were added to the analysis.

Discussion

The relationship between ccRCC, the most common histologic subtype of RCC, and obesity has been emphasized in previous studies[16,17]. Obesity is highly associated with an increased risk of RCC development; therefore, it is considered to be one of the best known etiologic factors of RCC[5,6]. A high BMI appears to be associated with poor survival outcomes in both

Table 3. Data on radiological measurement

Outcomes	L	R	p
SFA_A	26.05 ± 9.14	25.15 ± 8.45	0.647[1]
SFA_P	61.71 ± 16.64	62.27 ± 16.05	0.877[1]
PFT			
Patient	17.09 ± 10.05	15.53 ± 9.41	0.04[2]*
Control	18.99 ± 8.07	16.58 ± 7.01	0.001[2]*
PFHU			
Patient	−92.38 ± 8.47	−92.88 ± 8.55	0.685[2]
Control	−104.24 ± 7.99	−103.03 ± 8.06	0.172[2]

[1]t-test.
[2]paired sample t-test.
*p < 0.05.
SFA_A: subcutaneous fat area of abdomen; SFA_P: subcutaneous fat area of pelvis; PF%rirenal fat thickness; PFHU: hounsfield unit of perirenal fat.

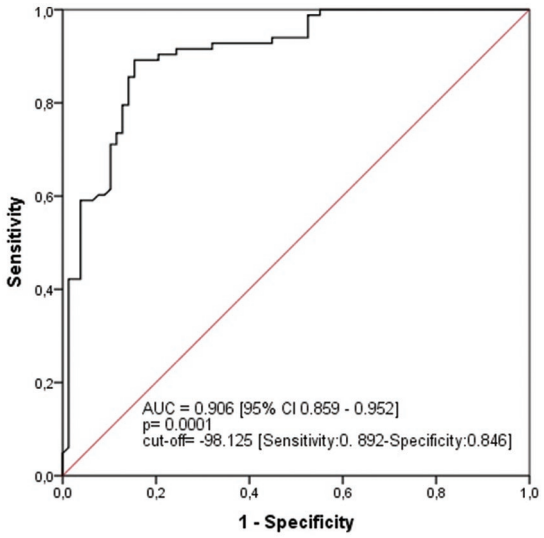

Figure 4. *Cutoff point determination for perirenal fat thickness hounsfield unit in radiologic imaging of renal cell carcinoma.*

non-metastatic and metastatic RCC[18,19]. There are also studies on the role of body composition indices measured on cross-sectional imaging, such as sarcopenia and fat accumulation, in the prognosis of RCC[20,21].

Visceral and subcutaneous fat thickness measurements are quantitative methods calculated on CT. These measurements, which have been emphasized recently, may provide more objective results than BMI. The visceral fat, which increases with age, has been shown to increase the risk of metabolic diseases as well as prostate cancer (PCa) in men[22]. Another study showed that PCa patients with higher periprostatic fat levels had more aggressive PCa[23]. In studies on RCC, Zhu et al. reported a positive correlation between the percentage of visceral adipose tissue and the Fuhrman tumor grade[24]. Huang et al. revealed that high visceral fat accumulation played a positive role on the progression of ccRCC[16]. On the contrary, there are also studies reporting that high visceral fat deposition is associated with relatively long cancer-specific survival in RCC patients[15].

Perirenal fat accumulation is an ectopic fat accumulation and has been reported to be associated with high diastolic blood pressure, diabetes mellitus, metabolic syndrome, and chronic renal failure[25,26]. In 2012, Okhunov et al. revealed that perirenal fat accumulation was an important predictor of ccRCC histopathology[8]. They showed that WNT signaling pathway-related factors secreted from perirenal adipose tissue affected the oncogenic pathways critical for ccRCC (migration of ACHN and CaKi-2 cells) and promoted the progression of local ccRCC to locally advanced (T3 stage) disease[7]. Huang et al. reported that the high PFT was associated with lower progression-free survival for ccRCC in both sexes[16]. In our study, we compared the images of histologically confirmed ccRCC patients with those of control group participants who were equivalent to them in terms of descriptive characteristics such as age, gender, BMI, and comorbidity (we measured the PFT using the technique described by Okhunov et al. and Huang et al., due to the lack of any standardized measurement method). The PFT was lower in the patient group compared with the control group; however, this difference was not statistically significant. The PFT was again compared by separating the right and left kidneys according to the side of the cancerous kidney, and again the PFT was found to be lower in the patient group. The PFT measurements were re-evaluated by eliminating the effect of the SFA_A and SFA_P values; however, again, no statistically significant difference was found. The PFT measurements for both genders were compared again separately; no significant difference was found between the PFTs for male and female genders in all cases and in the control group. However, the mean PFT measurement of women in the patient group was statistically significantly lower (13.2 ± 7.9, 17.9 ± 9.3; p = 0.023).

So far, most studies on the perirenal fat have focused on the thickness and volume of the adipose tissue[16,27]. However, several experimental studies suggest that the fat quality (HU) measurements may also be important[28,29]. They have shown that a lower HU is associated with an adipose tissue containing higher levels of lipid content and the range of HU typically

attributed to fat is in the range of −195 to −45[27]. The fat depots with higher lipid content and lipolytic activity can cause endothelial dysfunction and high insulin resistance[30]. These studies also suggest that adipocyte hypertrophy is associated with vascularity; decreased perfusion may lead to hypoxia and inflammation in adipose tissue[31].

In characterization of the renal masses, the CT still remains as the first-line imaging modality[32]. Based on the above mentioned studies, we think that the perirenal fat tissue density (PFHU), which can be easily measured by non-contrast CT, may be associated with RCC independently of the abdominal adipose tissue. In our study, the mean PFHU value of the RCC group was significantly higher than that of the control group (−92.6 ± 6.4 vs. −103.6 ± 7; p = 0.0001). Right and left kidney measurements were also compared and similar results were obtained. In our study, gender-specific PFHU was also evaluated; the mean PFHU value for males was found to be higher (denser) in both the patient group and the control group, but this difference was not significant. According to the results of our study, those with a PFHU value < −98.1 were 6.7 times more likely to have RCC than those with a PFHU value > −98.1. In multivariate logistic regression analysis, a PFHU ≥ −98.1 was independently associated with RCC after accounting for clinical and radiologic parameters.

The main limitations of our study are its retrospective nature, relatively small sample size and the lack of survival analysis. Second, only histologically confirmed localized ccRCC patients were included in this study, as the numbers of patients with other histological subtypes were not sufficient for statistical study. Third, our study may not include different ethnic groups. However, to our knowledge, our study is the first to examine the association between the PFHU and ccRCC, in English literature.

Conclusion

Although potential mechanisms for the association of the perirenal adipose tissue thickness with RCC are known, its exact role remains unclear. We suggest that the measurement of the perirenal adipose tissue HU by CT may be useful in differentiating the aggressive renal masses and therefore in determining the appropriate treatment selection. The effects of the PFT and PFHU need to be clarified by further research.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

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

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

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

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

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ORIGINAL ARTICLE

Neoadjuvant chemo(radio)therapy and anastomotic leakage risk in patients with esophageal squamous cell carcinoma

Quimio(radio)terapia neoadyuvante y riesgo de fuga anastomótica en pacientes con carcinoma de células escamosas esofágico

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Abstract

Objective: *To investigate the different impacts of neoadjuvant chemotherapy (NCT) and neoadjuvant chemoradiotherapy (NCRT) on anastomotic leakage after esophageal cancer resection.* **Methods:** *The data of three clinical studies (222 patients) launched were retrospectively collected, including 113 patients in the NCRT group and 109 patients in the NCT group. The NCT group received platinum-based doublet chemotherapy once every 3-4 weeks, whereas the NCRT group received platinum-based doublet chemotherapy weekly (taxane-containing regimen) or once every 3-4 weeks (5-Fu-containing regimen) concurrently with thoracic radiotherapy. After neoadjuvant therapy, all patients underwent Ivor-Lewis or McKeown esophagectomy. The study compared the pathologic complete remission (pCR) rate, 30-day post-operative mortality rate, incidence of anastomotic leakage, post-operative complications, and survival rates between the two groups.* **Results:** *The pCR rate, 30-day post-operative mortality rate, and the incidence of anastomotic leakage were 39.8% versus 5.5% ($p < 0.001$), 2.7% versus 0% ($p = 0.043$), and 28.3% versus 5.5% ($p < 0.001$) in the NCRT group and NCT group, respectively. Multivariate analysis showed that only NCRT significantly increased the incidence of anastomotic leakage (odds ratio 7.28, 95% confidence interval 2.44-21.78, $p < 0.001$).* **Conclusions:** *The results show that NCRT can improve the pathological response rate but will increase the incidence of anastomotic leakage. Radiation dose-volume parameters were not associated with anastomotic leakage risk.*

Keywords: *Malignant esophageal tumor. Neoadjuvant therapy. Anastomotic leak. Risk factors. Chemoradiation.*

Resumen

Objetivo: *Investigar el diferente impacto de la quimioterapia neoadyuvante (QTN) y la quimiorradioterapia neoadyuvante (QRTN) en la fuga anastomótica después de la resección de cáncer de esófago.* **Métodos:** *Se recopilaron retrospectivamente los datos de tres estudios clínicos (222 pacientes), incluyendo 113 pacientes en el grupo de QRTN y 109 pacientes en el grupo de QTN. El grupo de QTN recibió quimioterapia de doblete a base de platino una vez cada 3-4 semanas, mientras que el grupo de QRTN recibió quimioterapia de doblete a base de platino semanal (régimen que contiene taxano) o una vez cada 3-4 semanas (régimen que contiene 5-fluorouracilo) de forma concurrente con radioterapia torácica. Después del tratamiento neoadyuvante, todos los pacientes se sometieron a esofagectomía de Ivor-Lewis o McKeown. El estudio comparó las tasas de remisión completa patológica, mortalidad posoperatoria a 30 días, incidencia de fuga de anastomosis, complicaciones posoperatorias y tasas de supervivencia entre los dos grupos.* **Resultados:** *Las tasas de remisión completa patológica, mortalidad posoperatoria a 30 días e incidencia de fuga de anastomosis fueron del 39.8% frente al 5.5% ($p < 0.001$), del 2.7% frente al 0% ($p = 0.043$) y del 28.3% frente al 5.5% ($p < 0.001$) en el grupo de QRTN y en el grupo de QTN, respectivamente.*

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El análisis multivariado mostró que solo la QRTN aumentó significativamente la incidencia de fuga anastomótica (OR: 7.28; IC 95%: 2.44-21.78; p < 0.001). **Conclusiones:** *Los resultados muestran que la QRTN puede mejorar la tasa de respuesta patológica, pero aumentando la incidencia de fuga anastomótica. Los parámetros de dosis-volumen de radiación no estuvieron asociados con el riesgo de fuga anastomótica.*

Palabras clave: *Tumor maligno de esófago. Tratamiento neoadyuvante. Fuga de anastomosis. Factores de riesgo. Quimiorradioterapia.*

Introduction

Esophageal carcinoma has a poor prognosis after surgery alone, neoadjuvant chemoradiotherapy (NCRT) is currently considered the standard care for locally advanced esophageal carcinoma[1,2]. Neoadjuvant chemotherapy (NCT) is also a common practice in multimodality treatment due to the fear of excessive toxicity associated with NCRT, especially after the JCOG1109 NExT study[3] and the CMISG1701 trial[4]. Neoadjuvant therapy may increase the incidence of post-operative complications and even mortality[5]. Anastomotic leakage refers to the rupture of the anastomosis after esophageal cancer (EC) surgery, resulting in the leakage of gastric contents[6]. It is one of the most common complications after EC surgery and can lead to serious infection and even death. Radiation therapy in NCRT can damage tissue, affect wound healing, and increase the risk of anastomotic leakage. In addition, NCRT may lead to malnutrition, affect the patient's immune function, increase the risk of infection, and thereby increase the risk of anastomotic leakage[7]. Studies have shown that anastomotic leakage is closely related to both tumor recurrence and poor survival[8,9]. However, the impact of different neoadjuvant treatment patterns on anastomotic leakage is not well studied.

Radiotherapy can cause damage to microvessels and has a negative effect on irradiated tissue healing. Theoretically, the incidence of anastomotic leakage may be increased when radiotherapy is added to NCT, but rare data were reported from past studies. Most of the studies involve the comparison of anastomotic complications between NCRT and surgery alone, and the conclusions are inconsistent. Some studies have reported a higher incidence of anastomotic leakage in the NCRT group, whereas others have found no significant difference compared with surgery alone. This inconsistency may arise from variations in study design, patient populations, surgical techniques, and definitions of anastomotic leakage[10-12]. Unlike EC in Western countries, which has a high prevalence of esophagogastric junction adenocarcinoma, esophageal squamous cell carcinoma (ESCC) is the most common pathological type in East Asia, and most of the lesions are located in the upper middle portion of the chest. As a result, the radiation field is more closely related to the anastomotic region. In addition, the optimal radiation dose of NCRT has not yet been determined. In recent years, great progress has also been made in the technology of radiotherapy. Based on the above reasons, the risk factors for anastomotic leakage in multimodality treatment should be re-analyzed.

Therefore, clinical data from three prospective trials in neoadjuvant therapy were collected to evaluate whether adding radiotherapy to NCT would increase the incidence of anastomotic leakage, and the effect of radiation dose-volume parameters on rates of anastomotic leakage was also analyzed.

Methods

Clinical data

This study is a retrospective study. A total of 222 cases of clinical data from three prospective clinical studies (NCT01258192, NCT01463501, and NCT03381651) from February 2013 to December 2017 were selected. According to the choice of treatment, the NCT group formed the control group (n = 109), and the NRCT group formed the observation group (n = 113). The pre-treatment evaluation included chest and upper abdominal enhanced computed tomography (CT) scan and cervical B-ultrasound. Informed consent was waived due to the retrospective nature of the study.

Main inclusion criteria: (1) ECOG PS 0-1; (2) operable or potentially operable (cT2-4N0 or cN1) thoracic ESCC; (3) number of NCT cycles ≥ 2; (4) Ivor-Lewis esophagectomy or McKeown esophagectomy (open or laparoscopic) was mandatory; (5) intensity-modulated radiation therapy (IMRT) was mandatory. Exclusion

criteria: (1) salvage esophagectomy after chemoradiotherapy; (2) prophylactic cervical lymph node dissection; (3) jejunal or colon interposition for esophageal replacement; (4) exclude patients with chronic diseases such as malnutrition, diabetes, hypertension, coronary heart disease; (5) exclude patients who have received other anti-tumor treatments.

Data collection

The following data were collected: age, gender (male/female), smoking history (yes/no), drinking (yes/no), lesion location (upper/middle lower of the chest), lesion length, body mass index (BMI) before neoadjuvant treatment, types of neoadjuvant therapy (NCRT/NCT), time from the end of neoadjuvant therapy to surgery, pre-operative BMI, surgical approach (laparoscopic/open), intraoperative blood loss, anastomotic location (cervical/thoracic), residual esophageal length, degree of pathological remission (complete/incomplete), 30-day post-operative mortality rate, radiation prescribed dose, residual esophageal dose (maximum dose and average dose), and anastomotic region dose-volume parameters (V10, V20, V30, V40, V50, average dose, and maximum dose).

Treatment

Neoadjuvant therapy

The platinum-based doublet chemotherapy regimen was delivered once every 3-4 weeks in the NCT group, and few patients received a platinum-based triplet regimen[13,14]. In the NCRT group, platinum-containing doublet chemotherapy was given weekly (taxane-containing regimen) or once 3-4 weeks (5-Fu-containing regimen) concurrently with thoracic radiotherapy. IMRT was delivered in all patients, GTV included primary tumor and metastatic lymph node (> 5-10 mm in maximum diameter), which was contoured on the planning CT scans. The PTV was defined as GTV plus a 3-4 cm margin superior and inferior to the primary tumor and a 1-1.5 cm radial margin. For patients with lesions in the upper chest or lymph node metastasis in the superior mediastinum, prophylactic irradiation of para-recurrent laryngeal nerve lymph chain and lower neck lymph node was preferred, but the cervical esophagus and the bilateral lower neck should be protected from radiation as much as possible. The radiation dose was 40-50.4 Gy at 1.8-2 Gy per fraction.

Delineation of the residual esophagus and anastomotic region, and evaluation of dosimetry: a diagnostic CT scan which was performed within half a year after surgery with the same body position and layer thickness as planning CT scan was selected. Anastomosis was recognized in diagnostic CT slices through anastomosis staples and was uniformly expanded by 5 mm to create a so-called “anastomotic region,” which was then copied to the corresponding planning CT image. Delineation of the residual esophagus: the upper boundary was at the level of the cricothyroid membrane, and the lower boundary was at the level of the anastomotic region. To reduce the contour error, the delineation of the anastomotic region and residual esophagus were all completed by the first author. The evaluation of anastomotic region dose-volume parameters included V10, V20, V30, V40, V50, mean dose, and maximum dose. The evaluation of residual esophageal dose included the maximum dose and mean dose. The length of the residual esophagus was measured on the CT slice.

Surgery

Ivor-Lewis esophagectomy or McKeown esophagectomy was performed around 1.5 months after the completion of neoadjuvant therapy. Laparoscopic resection was also allowed. Jejunal or colon interposition for esophageal replacement was not allowed.

Definition of anastomotic leakage

Esophageal-gastric anastomotic leakage was diagnosed through clinical and/or adjuvant examination, including esophagography, digestive endoscopy, and diagnostic CT. The incidence of anastomotic leakage is usually highest within 5-7 days after surgery, but it also occurs in approximately 12% of patients 30 days after surgery. Therefore, we followed up with patients after surgery for EC for 60 days to monitor the occurrence of anastomotic leakage[15].

Definition of pathologic complete remission (pCR) rate

In patients with EC, the pCR rate usually refers to surgical resection after NCT or chemoradiotherapy, and pathological examination finds no residual tumor, including carcinoma *in situ* and invasive carcinoma.

PCR is one of the important indicators to evaluate the effect of neoadjuvant therapy for EC.

Statistical analysis

Detailed statistical analysis of the collected data was conducted using Statistical Package for Social Sciences 18.0 statistical software. Continuous numerical variables that conform to normal distribution are statistically described by mean standard deviation (x s), and a two-sample t-test is used for comparison between groups. Numerical variables that do not conform to the normal distribution are described by median (minimum–maximum), and Mann-Whitney U test is used for comparison between groups. Categorical data were statistically described using the number of cases (%), and X^2 tests were used for comparisons between groups. Univariable logistic regression model and multivariable Cox regression model analysis were used to evaluate risk factors associated with anastomotic leakage. $P < 0.05$ indicates that the difference is statistically significant.

Results

General information description

About 113 patients received NCRT, and 109 received NCT. The median age was 60 years (42-77 years old). There were 60 cases in stage IIA, 26 cases in stage IIB, 122 cases in stage III, and 14 cases in stage IVA. Among them, 38 (17.1%) patients had lesions in the upper thoracic region, 144 (64.9%) in the middle thoracic region, and 40 (18.0%) in the lower thoracic region. Compared with the NCT group, patients in the NCRT group had younger ages, longer time from the end of neoadjuvant therapy to surgery, shorter residual esophagus, less blood loss, and more laparoscopic surgery (Table 1). The dose of radiation was between 3,400 to 5,220 cGy (median radiation dose was 4,500 cGy). 89% of patients received taxane + platinum chemotherapy regimen, and other regimens included 5-Fu+platinum, NVB+ platinum.

Post-operative results between NCRT group and NCT group

The pathological complete remission rate (pCR) in the NCRT group and NCT group was 39.8% and 5.5%, respectively ($p < 0.001$), and the 30-day post-operative morality was 2.7% and 0%, respectively, the log-rank test showed that there was a significant difference in survival between the two groups ($p = 0.019$). One patient in the NCRT group died from major bleeding caused by anastomotic leakage (Table 2).

About 38 patients had a post-operative anastomotic leakage, 27 of which were diagnosed by clinical plus adjuvant examination, nine were diagnosed according to clinical examination, and two were confirmed by adjuvant examination. The median time of leakage occurrence after surgery was 13 days (4 days-57 days). The incidence of anastomotic leakage in the NCRT group and NCT group was 28.3% and 5.5%, respectively, with a statistically significant difference ($p < 0.001$) (Table 2).

Univariate and multivariate analysis of clinicopathologic factors associated with anastomotic leakage incidence in whole group

Univariate analysis showed that NCRT ($p < 0.001$), cervical anastomosis ($p = 0.002$), laparoscopic surgery ($p = 0.017$), longer time from the end of neoadjuvant therapy to surgery ($p = 0.010$), and shorter residual esophageal length ($p = 0.001$) were significantly associated with the risk of anastomotic leakage. The multivariate analysis showed that NCRT was an independent risk factor for anastomotic leakage (odds ratio 7.28, 95% confidence interval 2.44-21.78, $p < 0.001$). However, this study only included patients in the NCT and NCRT groups, and the impact of other factors on anastomotic leakage requires further study (Table 3).

Univariate and multivariate analysis of risk factors associated with anastomotic leakage in NCRT group

Further analysis of the dosimetry parameters related to anastomotic leakage in the NCRT group found no significant association between anastomotic leakage incidence and the radiation prescribed dose, anastomotic region dose-volume parameters (V10, V20, V30, V40, V50, mean dose, and maximum dose), and residual esophageal dose (mean dose and maximum dose) based on univariate and multivariate analysis (Table 4).

Table 1. Baseline characteristics between NCRT group and NCT group

Characteristics	NCRT (n = 113)	NCT (n = 109)	u/X^2	p
Gender, n (%)			0.005	0.944
Male	106 (93.8)	102 (93.6)		
Female	7 (6.2)	7 (6.4)		
Smoking, n (%)			0.059	0.808
Yes	84 (74.3)	84 (77.1)		
No	29 (25.7)	25 (22.9)		
Drinking, n (%)			0.073	0.797
Yes	89 (78.8)	85 (78.0)		
No	24 (21.2)	23 (21.1)		
Lesion location, n (%)			0.055	0.815
Upper chest	20 (17.7)	18 (16.5)		
Middle-lower chest	93 (82.3)	91 (83.5)		
cTNM stage, n (%)			1.348	0.717
IIA	27 (23.9)	33 (30.3)		
IIB	13 (11.5)	13 (11.9)		
III	66 (58.4)	56 (51.4)		
IVA	7 (6.2)	7 (6.4)		
Surgery approach, n (%)			51.061	0.000
Open	45 (39.8)	94 (86.2)		
Laparoscopic	68 (60.2)	15 (13.8)		
Anastomotic location, n(%)			110.47	0.000
Cervical	113 (100)	37 (33.9)		
Intrathoracic	0 (0)	72 (66.1)		
Median age (years)	59 (42-77)	61 (43-73)	8.371	0.009
Lesion length (cm), mean ± SE	6.05 ± 0.18	5.94 ± 0.23	0.427	0.191
BMI before neoadjuvant therapies (kg/m^2), mean ± SE	21.82 ± 0.27	22.23 ± 0.27	0.401	0.204
Median time from the end of neoadjuvant therapy to surgery (days)	35 (15-80)	29 (11-55)	11.745	0.000
Pre-operative BMI (kg/m^2), mean ± SE	21.38 ± 0.29	22.00 ± 0.23	2.355	0.060
Intraoperative blood loss (mL), mean ± SE	219.42 ± 13.61	240.54 ± 17.03	3.597	0.034
Residual esophageal length (cm), mean ± SE	3.76 ± 0.09	6.25 ± 0.23	9.471	0.000
TNM stage			0.821	0.365
II	43	48		
III	70	61		
T staging of tumor			0.427	0.514
T2	18	21		
T3	95	88		

cTNM: clinical tumor node metastasis; TNM: tumor node metastasis; BMI: body mass index; SE: standard error.

Table 2. Post-operative results between NCRT group and NCT group

Characteristics	NCRT (n = 113)	NCT (n = 109)	X^2	p
R0, n (%)	106 (93.8)	105 (96.3)	0.751	0.386
pCR, n (%)	45 (39.8)	6 (5.5)	36.927	0.000
pT0, n (%)	61 (54.0)	7 (6.4)	59.063	0.000
pN0, n (%)	66 (58.4)	47 (43.1)	5.189	0.022
Anastomotic leakage, n (%)	32 (28.3)	6 (5.5)	20.354	0.000
30-day post-operative mortality rate, n (%)	3 (2.7)	0 (0)	-	-

NCT: neoadjuvant chemotherapy; NCRT: neoadjuvant chemoradiotherapy; R0: macroscopic complete resection; pCR: pathologic complete remission; pT0: pathologic T0; pN0: pathologic n0.

Discussion

This study compared the impact of NCT and NCRT on anastomotic leakage after EC resection. The results showed that compared with NCT, NCRT significantly increased the rate of pCR but also increased the incidence of anastomotic leakage. Multivariate analysis confirmed that NCRT was an independent risk factor for anastomotic leakage. Further dosimetry analysis showed no significant association between anastomotic leakage risk and radiation dose to the residual esophagus and anastomotic region.

Our findings are similar to those of previous studies[2,9,15-23]. For example, the CROSS study reported

Table 3. Univariate and multivariate analysis of clinicopathologic factors associated with anastomotic leakage incidence in whole group

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Gender, male/female	0.29	0.04-2.28	0.241			
Smoking, yes/no	1.56	0.64-3.76	0.325			
Drinking, yes/no	1.08	0.46-2.53	0.866			
Tumor location, proximal third/middle-lower third	2.23	1.00-5.00	0.050			
Type of neoadjuvant therapy, NCRT/NCT	7.51	3.01-18.75	< 0.001	7.28	2.44-21.78	< 0.001
Surgery approach, open/laparoscopic	0.43	0.21-0.86	0.017	0.47	0.33-1.17	0.144
Anastomosis location, cervical/thoracic	25.07	3.37-186.54	0.002	10.381	0.84-65.41	0.082
Age (years)	0.98	0.94-1.04	0.532			
Lesion length (cm)	1.15	0.99 ± 1.33	0.068			
BMI before neoadjuvant therapies (kg/m^2)	0.94	0.83-1.06	0.301			
Time from the end of neoadjuvant therapy to surgery (days)	1.04	1.01-1.07	0.010	1.28	0.87-1.36	0.085
Pre-operative BMI (kg/m^2)	0.98	0.87-1.11	0.767			
Intraoperative blood loss (mL)	1.00	1.00-1.00	0.288			
Residual esophageal length (cm)	0.71	0.58-0.87	0.001	0.62	0.64-1.22	0.064

OR: odds ratio; CI: confidence interval; BMI: body mass index.

an anastomotic leakage rate of 22% in the NCRT group[2]. A retrospective study of 686 ESCC patients in Japan showed that the incidences of anastomotic leakage were 27.9% in the NCRT group (376 patients with a radiation dose of 30-42 Gy) and 16.5% in the surgery group (310 patients)[9]. The incidence of anastomotic leakage in the NCT group was similar to that reported in the surgery-alone groups in other studies[17-19], suggesting that NCT does not significantly increase the incidence of anastomotic leakage.

The current results suggest that factors other than NCRT and tumor size may contribute to anastomotic leakage. Although the dose parameters V20, V30, and V40 have been shown to be associated with anastomotic leakage, the underlying mechanisms are unclear. Patient-specific factors such as comorbidities or nutritional status may play a role. The surgical technique itself, such as the type of anastomosis or the use of drains, may also have an impact.

The relationship between radiation dose and anastomotic leakage is more complicated. Despite the high pre-operative radiation dose given (50.4 Gy/28 F), the CALGB9781 study reported a low leakage incidence of 8%[22], which was similar to that in the NEOCRTEC5010 study (8.6%)[16], but lower than that in the CROSS study (22%)[2]. A lower irradiation dose was prescribed in both NEOCRTEC 5010 (40Gy) and CROSS study (41.4Gy). Our study also found a non-significant relationship between radiation dose and leakage. When the influence of radiation dose on leakage was investigated, the relationship between radiation fields and the location of anastomosis should also be considered. A retrospective study from MD Anderson revealed that the incidence of anastomotic leakage was 11% in NCRT (radiation dose: 50.4Gy/28F), and the incidence of leakage was increased significantly (39% vs. 2.6%) when the anastomosis was placed within the pre-operative radiation field[24]. Another study from France showed that although the anastomosis was within the radiation field, the leakage incidence did not rise significantly when thoracic anastomosis was performed[17]. Since a wide range of irradiation doses was delivered in NCRT and the spatial relationship between the radiation field and the anastomosis location was sometimes difficult to define accurately, it is more reasonable to explore the relationship between radiation dose of the anastomotic region and leakage incidence. Our results indicated

Table 4. Univariate analysis of risk factors associated with anastomotic leakage in NCRT group

Characteristics	Univariate analysis		
	OR	95% CI	p
Gender, male/female	2.56	0.30-22.13	0.393
Smoking, yes/no	1.19	0.45-3.17	0.727
Drinking, yes/no	1.44	0.54-3.84	0.461
Tumor location, proximal third/ middle-lower third	1.84	0.67-5.03	0.234
Surgery approach, open/laparoscopic	1.13	0.50-2.57	0.773
Age (years)	1.02	1.00-1.09	0.427
Lesion length (cm)	1.15	0.94-1.42	0.181
BMI before neoadjuvant therapies (kg/m^2)	0.99	0.86-1.13	0.846
Time from the end of neoadjuvant therapy to surgery (days)	1.02	0.98-1.05	0.349
Pre-operative BMI (kg/m^2)	1.04	0.91-1.18	0.610
Intraoperative blood loss (mL)	1.00	1.00-1.01	0.038
Residual esophageal length (cm)	1.12	0.73-1.74	0.601
Anastomotic region			
V10	1.00	0.99-1.01	0.893
V20	1.00	0.99-1.01	0.891
V30	1.00	0.99-1.01	0.592
V40	1.00	0.99-1.01	0.432
V50	0.99	0.99-1.01	0.298
Average dose	1.00	1.00-1.00	0.565
Maximum dose	1.00	1.00-1.00	0.586
Residual esophagus			
Average dose	1.00	1.00-1.00	0.586
Maximum dose	1.00	1.00-1.00	0.537
Radiation dose	1.00	1.00-1.00	0.968

NCRT: neoadjuvant chemoradiotherapy; OR: odds ratio; CI: confidence interval; BMI: body mass index.

that there was no significant relationship between the dose-volume parameters of the anastomotic region and leakage incidence. In MD Anderson's study, the anastomotic region should have been exposed to a dose of ≥ 50Gy in those patients whose anastomosis was completely placed within the irradiation field. In our study, we tried to protect the lower neck or cervical esophagus from being irradiated when a higher dose was prescribed, and neck anastomosis was performed in all patients receiving NCRT. Thus, the average dose in the anastomosis was only 37Gy, and V40, V45, and V50 were 64%, 41%, and 22%, respectively, suggesting that good communication between the surgeon and radiotherapist is indispensable in irradiation field design.

Our study had some limitations, as all retrospective studies did. Although the anastomotic region was delineated by the same investigator, there still might be some deviations in identifying the location of the anastomosis and delineating it on the corresponding planning CT slices, especially for patients with manual anastomosis. Moreover, mixed factors were thought to work together in the development of leakage, posing some potential confounding factors that could not be included in this retrospective analysis. Furthermore, the relatively few studies included in our analysis may limit the generalizability of our findings. Future studies of a larger sample size and a more diverse patient population are needed to further validate our results.

Conclusion

Our results confirmed that NCRT could improve the pathologic response rate but also increase the incidence of anastomotic leakage simultaneously. However, neither the prescribed radiation dose nor the doses to the anastomotic site and residual esophageal tissue were significantly associated with anastomotic leakage risk.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of Humans and Animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, Informed Consent, and Ethical Approval. The authors have followed their institution's confidentiality protocols and obtained informed consent from patients. The authors have obtained approval from the Ethics Committee for the analysis of routinely

obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the Use of Artificial Intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Evaluation of mediastinal lymphadenopathy from long-term radiological findings in COVID-19

Evaluación de la linfadenopatía mediastínica a partir de hallazgos radiológicos a largo plazo en COVID-19

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Abstract

Objective: *Mediastinal lymphadenopathy (MLAP) has been reported in post-COVID-19 patients. In this study, the relationship between post-COVID-19 infection and MLAP was investigated in patients who had been diagnosed with MLAP and decided to undergo surgery.* **Methods:** *The study included the records of 140 patients who had been diagnosed with MLAP and were decided for surgical treatment. Demographic findings, reverse transcription-polymerase chain reaction (PCR) test results, chest X-ray, thorax computed tomography (CT) findings, positron emission tomography (PET)-CT findings, and histopathological results were recorded.* **Results**: *SUV_{max} value above 2.5 was 15 times more common in patients with positive PCR test results than in patients with negative results. Abnormal chest X-ray results were associated with a 9.3-fold increase in the number of patients, and the number of patients with abnormal pathology results was 33.9 times higher than those with normal results.* **Conclusions:** *Post-COVID-19 and MLAP (SUV_{max} 3-5) were shown to be associated independently of age, gender, comorbidities, and disease outcomes. MLAP lesions in patients with COVID-19 demonstrated SUVmax values that were 10-fold higher compared to patients without COVID-19. Determining reliable SUV_{max} values in patients with severe COVID-19 may help guide clinical decisions, tailor therapeutic approaches, and avoid unnecessary surgical indications.*

Keywords: *Mediastinal lymphadenopathy. SUV_{max}. Surgical indication. Positron emission tomography. Post-COVID-19.*

Resumen

Objetivo: *Se ha informado linfadenopatía mediastínica en pacientes que se recuperan de COVID-19. Nuestro objetivo fue investigar si la linfadenopatía mediastínica encontrada en pacientes con neumonía grave por COVID-19 al menos 6 meses después de la infección está asociada con la enfermedad.* **Métodos:** *El estudio incluyó los registros de 140 pacientes a quienes se les había diagnosticado MLAP y se decidió que recibirían tratamiento quirúrgico. Los hallazgos demográficos se compararon mediante los resultados de RT-PCR, TC de tórax y PET-CT.* **Resultados:** *Un valor de SUV_{max} superior a 2,5 fue 15 veces más frecuente en pacientes con resultados positivos en la prueba PCR que en aquellos con resultados negativos. Los resultados anormales en la radiografía de tórax se asociaron con un aumento de 9,3 veces en el número de pacientes, y el número de pacientes con resultados anormales en las pruebas de anatomía patológica fue 33,9 veces mayor que el de aquellos con resultados normales.* **Conclusiones:** *Se demostró que la presencia de MLAP (SUV_{max} 3-5) tras la COVID-19 se asocia independientemente de la edad, el sexo, las comorbilidades y la evolución de la enfermedad. Las lesiones de MLAP en pacientes con COVID-19 mostraron valores de SUV_{max} 10 veces superiores a los de los pacientes sin COVID-19. Determinar valores fiables de SUV_{max} en pacientes con COVID-19 grave puede ayudar a orientar las decisiones clínicas, personalizar los enfoques terapéuticos y evitar indicaciones quirúrgicas innecesarias.*

Palabras clave: *Linfadenopatía mediastínica. SUV_{max}. Indicación quirúrgica. Tomografía por emisión de positrones. Post-COVID-19.*

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Introduction

Mediastinal lymph node enlargement is a critical computed tomography (CT) finding that can range from benign to malignant in patients with respiratory complaints and may require further examination. Since the presence of mediastinal lymphadenopathy (MLAP) is related to the severity of the disease in post-COVID patients who have had and recovered from severe COVID-19 infection, the presence of MLAP should be carefully examined in subsequent examinations, even in patients without lung involvement on admission CT[1]. The detection of MLAP in patients with idiopathic pulmonary fibrosis (IPF) is thought to be a result of high-grade chronic inflammation, and a correlation between the severity of IPF disease and MLAP has been shown in the literature[2].

When the current literature on MLAP and COVID-19 were examined, studies were conducted in the acute and active period of COVID-19 pneumonia. However, in our study, MLAP in the controls was performed 6-12 months after the patients had COVID-19 pneumonia. After suffering severe COVID-19 pneumonia, the mediastinal lymph nodes begin to enlarge during acute inflammation, which is considered a poor-prognosis marker at that time. After 6 months, this turns into chronic inflammation, and MLAP occurs. It is thought that there may be a correlation between the severity of chronic inflammation and mediastinal lymph node enlargement in patients with severe COVID-19 pneumonia, just as in IPF.

MLAP can be caused by infectious or non-infectious causes and is defined as a measurement of the lymph node short axis ≥ 10 mm. SUV_{max} value ≥ 2.5 was defined as pathological MLAP[3]. The most common atypical CT features of COVID-19 pneumonia are MLAP, linear opacities, tree bud sign, interlobular and intralobular septal thickening, cavitation, and pleural effusion[4]. MLAP is frequently associated with benign diseases such as heart failure, sarcoidosis, and diseases accompanying malignant diseases. Although MLAP is not the typical chest finding in COVID-19 pneumonia, it is associated with the prognosis of COVID-19 patients. The mortality rate in hospitalized COVID-19 patients with MLAP was found to be higher than in those without MLAP, and it has been reported in the literature that it should be investigated as a prognostic factor for severe disease. The literature shows a correlation between the severity of IPF disease and the presence of MLAP, suggesting that MLAP results from severe chronic inflammation in these patients[1,5,6].

For MLAP, the size and number of lymph nodes are essential for surgical treatment and follow-up. MLAP, usually over 2 cm in size, should be closely monitored regardless of the cause[6]. The radiological findings of one of our patients are shown in figure 1.

COVID-19 is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this study, we aimed to determine whether MLAP, which was detected in patients with severe COVID-19 pneumonia in the controls at least 6 months after the disease (post-COVID-19 period), was related to having the disease. If the detected MLAP formation is determined to be secondary to COVID-19 pneumonia, then immediate referral to the surgery clinic for further examination may be unnecessary. At the same time, by closely monitoring the patients in whom we detect MLAP, we can protect them from surgical complications and not be late in making the diagnosis.

Methods

This study was approved by the Ethical Committee of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital. Ethics Committee approval was granted by our institution on September 06, 2022, protocol number 2137. It was conducted according to the Declaration of Helsinki and Good Clinical Practice. The authors have obtained the approval of the Ethics Committee for the analysis and publication of clinical data obtained routinely. The informed consent of the patients was not required because it was a retrospective observational study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Study population and data collection

Our study was a single-center, retrospective, case–control study. Our study analyzed the data of 140 patients who applied to our hospital's Şişli Hamidiye Etfal Training and Research Hospital Chest Diseases Outpatient Clinic between January 01, 2022, and August 01, 2022, and were reviewed retrospectively. During etiological investigations, individuals over 18 years old, regardless of gender, who applied to our hospital's chest diseases outpatient clinics with the MLAP, who had not been diagnosed with lymphoma and sarcoidosis, immunodeficiency, cancer,

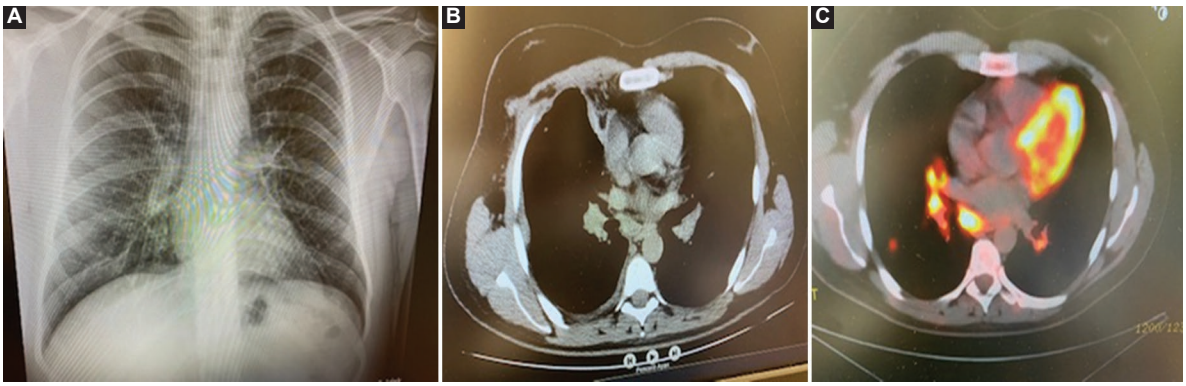

Figure 1. *A view from the chest radiograph of the patients*.* **A:** *a section with Hilar fullness from the chest X-ray findings of the patients.* **B:** *a section from the mediastinal window view with mediastinal lymphadenopathy.* **C:** *a section with positive fluorodeoxyglucose from positron emission tomography-computed tomography findings. *It was taken from the hospital file archives of the patients in our study, and their permission was obtained.*

tuberculosis, asthma, chronic obstructive pulmonary disease, and had no previous mediastinal pathology. Patients with MLAP detected in thorax CT examinations were included in the study. Patients with lung and other malignancies, under 18 years of age, pregnant women, and patients who had image artifacts on their CT scans were excluded from the study. A total of 140 cases who were followed up in our clinic and diagnosed with chest MLAP by CT were included in the study. These cases were divided into two categories: 83 cases with COVID-19 who had COVID-19 pneumonia and recovered, and 57 cases without COVID-19. The two categories were compared using data obtained from demographic characteristics, clinical findings, reverse transcription-polymerase chain reaction (RT-PCR) results, chest radiography findings, thorax CT findings, positron emission tomography (PET)-CT findings, histopathological results, and treatment approaches. Data were collected from the hospital automation system and analyzed with Statistical Package for the Social Sciences (SPSS) 24.

Sample size

The sample of the study was determined as a total of 140 patients, at least 51 in both groups, with an effect size of 0.40, a = 0.05, and power (1-b) = 0.85, using the G-power program. There were two groups: 57 patients without covid-19 and 83 patients with RT-PCR (+)

Image analysis

Demographic information, clinical findings, comorbidities, thorax CT, and PET-CT images were obtained from hospital computer records and Picture Archiving and Communication System. RT-PCR testing was performed using nasopharyngeal or oropharyngeal swabs using the Biospeedy SARS-CoV-2 Dual Gene RT-qPCR Kit (Bioeksen). Chest CT scans were performed with patients in the supine position, during last inspiration, and without intravenous contrast administration. The protocol included a peak voltage of 100 kV and an effective milliampere-second setting of 20 mA-s, resulting in unenhanced chest CT scans. These scans used a 512 × 512 pixel image matrix with 2 mm thin sections taken in the axial plane.

In this study, adjustments were applied to the mediastinal windows (width: 400 HU; level: 100 HU) and lung windows (width: 1500 HU; level: –500 HU). Tomography findings were evaluated by two experienced radiologists who agreed on the CO-RADS value. In routine axial CT images, the short axis of the mediastinal lymph node was measured, and if the short axis was 10 mm or more, it was considered MLAP. When the SUVmax value was ≥ 2.5 in the PET-CT examination of patients diagnosed with MLAP, fluorodeoxyglucose (FDG) uptake was considered pathological and was called “FDG positive”.

Statistical analysis

Patient data collected within the scope of the study were analyzed with the IBM SPSS for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage were given for categorical data, and median, minimum, and maximum descriptive values for continuous data. The normality test of the data was conducted with the Kolmogorov–Smirnov Test. In the comparisons between the groups, the “Independent

Table 1. Distribution of demographic characteristics of all patients according to MLPA (lymph node short axis, SUV_{max} value)

Characteristics	Lymph node short axis			p	SUV_{max}			p
	10-20 (n = 103)	21-30 (n = 27)	> 30 (n = 10)		< 2.5 (n = 22)	2.5-5.0 (n = 51)	> 5.0 (n = 49)	
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
Age (years)				0.553				0.432
18-64	62 (60.2)	19 (70.4)	7 (70)		16 (72.7)	33 (64.7)	28 (57.1)	
65-94	41 (39.8)	8 (29.6)	3 (30)		6 (27.3)	18 (35.3)	21 (42.9)	
Gender				0.696				0.428
Male	64 (62.1)	15 (55.6)	7 (70)		16 (72.7)	29 (56.9)	29 (59.2)	
Female	39 (37.9)	12 (44.4)	3 (30)		6 (27.3)	22 (43.1)	20 (40.8)	
Smoking status				0.988				0.276
Smoker	44 (42.7)	13 (48.1)	4 (40)		13 (59.1)	22 (43.1)	20 (40.8)	
Non-smoker	38 (36.9)	9 (33.3)	4 (40)		8 (36.4)	21 (41.2)	17 (34.7)	
Ex-smoker	21 (20.4)	5 (18.5)	2 (20)		1 (4.5)	8 (15.7)	12 (24.5)	
Symptoms				0.058				0.275
Dyspnea	17 (16.5)	1 (3.7)	5 (50)		4 (18.2)	5 (9.8)	12 (24.5)	
Chest pain	14 (13.6)	5 (18.5)	1 (10)		1 (4.5)	9 (17.6)	7 (14.3)	
Cough	61 (59.2)	17 (63)	4 (40)		13 (59.1)	33 (64.7)	26 (53.1)	
Back pain	11 (10.7)	4 (14.8)	0 (0)		4 (18.2)	4 (7.8)	4 (8.2)	
Concomitant disease				0.118				0.950
Asthma	36 (38.7)	4 (15.4)	2 (20)		5 (27.8)	13 (26)	15 (34.1)	
DM	7 (7.5)	3 (11.5)	0 (0)		1 (5.6)	5 (10)	2 (4.5)	
GIS	5 (5.4)	3 (11.5)	2 (20)		2 (11.1)	6 (12)	2 (4.5)	
HT	13 (14)	4 (15.4)	1 (10)		3 (16.7)	7 (14)	8 (18.2)	
HD	6 (6.5)	2 (7.7)	3 (30)		2 (11.1)	5 (10)	3 (6.8)	
COPD	26 (28)	10 (38.5)	2 (20)		5 (27.8)	14 (28)	14 (31.8)	

DM: diabetes mellitus; GISD: gastrointestinal system diseases; HT: hypertension; COPD: chronic obstructive pulmonary disease; HD: heart disease; MLAP: mediastinal lymphadenopathy.

Sample T-Test" was used for those with normal distribution for the two groups, the "Mann-Whitney U Test" for those who did not show normal distribution, and the "Fisher's Exact Test or Chi-Square Test" was used for the comparison of categorical variables. Logistic regression analysis was used to examine the risk factors affecting the SUV_{max} value of ± 2.5. The results were considered statistically significant when $p < 0.05$.

Results

A total of 140 patients, 38.6% (n = 54) female and 61.4% (n = 86) male, were included in the evaluation. 40.7% (n = 57) of the patients were diagnosed without COVID-19, and 59.3% (n = 83) had positive RT-PCR test results, and it was determined that they had COVID-19. The distribution of demographic characteristics of all patients according to MLAP (lymph node short axis, SUV_{max} value) is shown in table 1. When table 1 was examined, no statistically significant difference was detected between demographic characteristics and mediastinal lymph node short axis and SUV_{max} values $p > 0.05$).

The distribution of demographic characteristics of the patients with COVİD-19 and without COVID-19 is denoted in table 2. When the table was examined, there was only a statistically significant difference between the two groups regarding age ($p < 0.05$).

Significant differences were observed between the two groups in all clinical findings ($p < 0.05$) (Table 3). Peripheral lymphadenopathy was in the intra-abdominal region in 24.1% (n = 20) of RT-PCR-positive with COVİD-19 patients and 3.5% (n = 2) of those without COVİD-19 patients ($p < 0.001$). Mediastinal width and lymph node size were higher in COVİD-19 patients than in non-COVID-19 patients ($p = 0.008$; $p < 0.001$). The pathology result of the majority of COVID-positive patients with COVİD-19 was benign (65%), whereas this rate was 22.8% in patients without COVİD-19 ($p < 0.001$). As a result, 77.2% of the patients without COVİD-19 PCR results regressed in the follow-up, whereas this rate was 24.1% in the patients with COVİD-19 ($p < 0.001$).

Table 4 elaborates on the logistic regression analysis results, examining the factors causing the SUV_{max}

Table 2. Distribution of demographic characteristics of patients with COVİD-19 and without COVİD-19

Characteristics	Total (n = 140)	without COVID-19 (n = 57)	with COVID-19 (n = 83)	p
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Age (years)	61 (20-94)	55 (22-78)	62 (20-94)	0.006
Gender				0.477
Male	86 (61.4)	33 (57.9)	53 (63.9)	
Female	54 (38.6)	24 (42.1)	30 (36.1)	
Smoking status				0.115
Smoker	61 (43.6)	25 (43.9)	36 (43.4)	
Non-smoker	51 (36.4)	25 (43.9)	26 (31.3)	
Exsmoker	28 (20)	7 (12.3)	21 (25.3)	
Symptoms				0.656
Dyspnea	23 (16.4)	8 (14)	15 (18.1)	
Chest pain	20 (14.3)	7 (12.3)	13 (15.7)	
Cough	82 (58.6)	34 (59.6)	48 (57.8)	
Back pain	15 (10.7)	8 (14)	7 (8.4)	
Concomitant disease	129 (92.1)	50 (87.7)	79 (95.2)	0.122
Asthma	42 (32.6)	19 (38)	23 (29.1)	
DM	10 (7.8)	5 (10)	5 (6.3)	
GIS	10 (7.8)	4 (8)	6 (7.6)	
HT	18 (14)	8 (16)	10 (12.7)	
HD	11 (8.5)	2 (4)	9 (11.4)	
COPD	38 (29.5)	12 (24)	26 (32.9)	

DM: diabetes mellitus; GISD: gastrointestinal system diseases; HT: hypertension; COPD: chronic obstructive pulmonary disease; HD: heart disease.

value to be ≥ 2.5 in the patients included in the study. COVİD-19 patients caused a 15-fold SUV_{max} value of ≥ 2.5. In addition, peripheral lymphadenopathy caused a 3.9-fold SUVmax value of ≥ 2.5, abnormal chest X-rays caused a 9.3-fold SUVmax value of ≥ 2.5, and abnormal pathology results led to a 33.9-fold SUV_{max} value of ≥ 2.5.

The statistically significant variables in the univariate model were re-evaluated in the multivariate model. RT-PCR positivity with COVİD-19 and abnormal pathology findings were statistically significant. Accordingly, it was determined that positive RT-PCR test results with COVİD-19 were 5.9 times higher than without COVİD-19 outcomes, and abnormal pathology results were found to be 13.4 times more frequently in SUV_{max} value being ≥ 2.5 compared to normal samples.

Discussion

In the study, MLAP was detected in the 6-month follow-up of patients with severe COVID-19, and the aim was to evaluate the relationship between these MLAP SUV_{max} values and having COVID-19 disease. While the frequency of MLAP in patients with COVID-19 pneumonia is 0-66% in the literature, the frequency of MLAP in this study (965 patients with COVID-19 pneumonia were scanned, and MLAP was detected in 83 and included in the study) was found to be 11.6%, similar to the literature[1,6,7].

Thorax tomography and PET-CT scans were performed on our patients who applied to us with respiratory complaints at least 6 months to 1 year after COVID-19, that is, during the post-COVID-19 patient controls. Diagnostic PET-CT was performed in patients with MLAP detected in thorax CT examination. In addition, we evaluated that MLAP size (SUV_{max} value) and FDG uptake are not associated with malignancy in patients with severe COVID-19, but may be associated with the severity of chronic inflammation.

Our results showed that mediastinal width and lymph node size were higher in patients with COVID-19 than in those without COVID-19. The pathology result of most COVID-19-positive patients was benign (65%), whereas this rate was 22.8% in patients without COVID-19. As a result, 77.2% of the patients without COVID-19 regressed in the follow-up, whereas this rate was 24.1% in the patients with COVID-19.

COVID-19-positive patients included in the study increased the incidence of MLAP ≥ 2.5 above the SUV_{max} value 15 times more than those without COVID-19. In addition, detecting peripheral lymphadenopathy in PET-CT increased the incidence of ≥ 2.5 times above the SUV_{max} value, 3.9 times more. Abnormal chest X-rays of the patients increased the incidence of ≥ 2.5 above the SUV_{max} value 9.3 times, and abnormal pathology results increased the incidence of ≥ 2.5 above the SUV_{max} value 33.9 times.

In our study, the chest X-ray findings of the patients without COVID-19 were mostly expected. In contrast, the chest X-ray of the patients with COVID-19-positive patients was found to be more abnormal, resulting in mediastinal enlargement and hilar lymphadenopathies[8-10]. The most common thorax CT finding detected in our study was M4R right lower paratracheal lymph node enlargement. Pulmonary parenchyma findings were deficient, and sequelae were reported as changes[11].

Regarding the results of our study, the presence of aggravated COVID-19 is linked with the occurrence of MLAP. COVID-19-positive patients and abnormal pathology results have indicated higher SUV_{max} values, thus the presence of lymphadenopathy. To date, MLAP has been observed widely in COVID-19 (0-66%).

Table 3. Distribution of clinical characteristics of patients with COVİD-19 and without COVİD-19

Characteristics	Total (n = 140)	Without COVID-19 (n = 57)	With COVID-19 (n = 83)	p
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Peripheric LAP				< 0.001
None	55 (39.3)	35 (61.4)	20 (24.1)	< 0.001
Cervical	43 (30.7)	15 (26.3)	28 (33.7)	0.454
Intraabdominal	22 (15.7)	2 (3.5)	20 (24.1)	< 0.001
Pelvic	4 (2.9)	1 (1.8)	3 (3.6)	0.646
Diffuse	16 (11.4)	4 (7)	12 (14.5)	0.276
Chest X-ray				0.002
Normal	78 (55.7)	42 (73.7)	36 (43.4)	< 0.001
Enlarged mediastinum	50 (35.7)	13 (22.8)	37 (44.6)	0.008
Hilar fulness	12 (8.6)	2 (3.5)	10 (12)	0.122
Computerize tomografi				0.024
M2R right upper paratracheal	39 (27.9)	14 (24.6)	25 (30.1)	0.597
M3 prevascular	20 (14.3)	12 (21.1)	8 (9.6)	0.099
M4R right lower paratracheal	39 (27.9)	21 (36.8)	18 (21.7)	0.049
M4L lower left paratracheal	14 (10)	3 (5.3)	11 (13.3)	0.207
M7 subcarinal	28 (20)	7 (12.3)	21 (25.3)	0.093
Lymph node size (mm)	17 (10-51)	15 (10-44)	18 (10-51)	< 0.001
SUV_{max}				< 0.001
FDG (-)	18 (12.9)	15 (26.3)	3 (3.6)	< 0.001
< 2.5	22 (15.7)	18 (31.6)	4 (4.8)	< 0.001
2.5-5.0	51 (36.4)	15 (26.3)	36 (43.4)	0.039
> 5.0	49 (35)	9 (15.8)	40 (48.2)	< 0.001
Pathology				< 0.001
None	57 (40.7)	40 (70.2)	17 (20.5)	< 0.001
Benign	67 (47.9)	13 (22.8)	54 (65.1)	< 0.001
Malign	16 (11.4)	4 (7)	12 (14.5)	0.276
Pathology result				< 0.001
Granulomatous lymphadenitis (benign)	20 (14.3)	4 (7)	16 (19.3)	0.073
Regressed at follow-up (benign)	64 (45.7)	44 (77.2)	20 (24.1)	< 0.001
Reactive lymph node (benign)	37 (26.4)	5 (8.8)	32 (38.6)	< 0.001
Anthracosis (benign)	3 (2.1)	0 (0)	3 (3.6)	0.271
Cancer metastasis (malignant)	16 (11.4)	4 (7)	12 (14.5)	0.276

LAP: lymphadenopathy; FDG: fluorodeoxyglucose.

However, it should be emphasized that not all lymphadenopathies are located in the mediastinal region. In published case reports, two cases (both female) are reported to have MLAP at the initial and repeated CT scan on the 6th day (1/6/10R and 2R/4R/4L)[12,13].

However, there are controversial data on this subject. Bayramoglu et al. indicated the presence of MLAP as 0-8.1% in their retrospective analysis[14]. In another retrospective research, no MLAP was found during pregnancy[15]. Grassi et al. found the incidence of MLAP as 1.3% in a cohort of 80 patients from Italy[16]. In two different studies (n = 418 and n = 134), the rate of MLAP was reported as 18.2% and 54.8%[16-18]. Fang et al. did not detect any association between MLAP and gender, age, cancer history, intensive care unit (ICU) admission, length of hospital stays, and laboratory parameters, but with cobblestone imaging findings[19]. In a French study, Valette et al. published that MLAP existed in six of nine individuals with severe COVID-19 in the ICU[20]. Studies from Chinese patients indicated the presence of MLAP at 43.5%, 41.7%, and 19.8%[18,19,21].

Kaya and Akman investigated the relationship between MLAP and ICU hospitalization and mortality in COVID-19 patients and found a statistical significance between the three parameters[6]. They claimed that the more severe findings on CT scans predict the prognosis. In addition, they stated that increased bronchial wall

Table 4. Laboratory parameters affecting $SUV_{max} \geq 2.5$

Characteristics	Univariant		Multivariant	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age	1.013 (0.990-1.037)	0.271		
Gender				
Male	Reference	-		
Female	1.690 (0.771-3.702)	0.190		
RT-PCR				
Negative	Reference	-	Reference	-
Positive	15.000 (5.856-38.058)	< 0.001	5.964 (1.937-18.370)	0.002
Peripheric LAP				
No	Reference	-	Reference	-
Yes	3.890 (1.801-8.398)	< 0.001	1.451 (0.491-4.289)	0.500
Chest X-Ray				
Normal	Reference	-	Reference	-
Abnormal	9.280 (3.355-25.662)	< 0.001	2.777 (0.758-10.165)	0.123
Pathology	Reference	-	Reference	-
Normal	33.857 (10.833-105.818)	< 0.001	13.452 (3.864-46.831)	< 0.001
Abnormal				

RT-PCR: reverse transcription-polymerase chain reaction; LAP: lymphadenopathy.

thickness was more common in patients with MLAP. The mortality rate was higher in patients with MLAP[1].

In another study, Satici et al.[22] reported that mediastinal lymphadenopathies were detected more in elderly patients with comorbid diseases and were significantly associated with mortality. The rate of MLAP was 9.2% in the whole study population but 19.65% in deceased individuals[21]. Both studies declared that the presence of MLAP led to increased mortality. Similar to our findings, mediastinal lymph node involvement has been an essential factor in COVID-19.

In the study of Bhatti et al.,[23] MLAP was detected in 131 (62.4%) of 210 patients included in the study. Covid-19 patients with MLAP had a higher mean and median severity score than those without MLAP. This study documents the high prevalence of MLAP in hospitalized COVID-19 patients and shows that the severity score, which represents the more severe course of the disease, is higher[22].

Limitations of our study

Since our study was retrospective, some laboratory findings and respiratory function findings could not be obtained. In this regard, a study can be organized to investigate the laboratory findings showing the severity of chronic inflammation in patients with severe COVID-19 pneumonia, respiratory functional characteristics, and the relationship between radiological imaging and MLAP features. Although this study is a retrospective observational study and provides valuable information about the potential etiology of the disease, it typically cannot definitively determine causality.

Conclusions

This study showed that severe COVID-19 and mediastinal lymph node involvement (SUV_{max}: 3-5) were associated regardless of age, gender, comorbidities, and disease outcomes. Establishing reliable SUVMAX values in severe post-COVID-19 patients will help guide clinical decisions, adapt therapeutic approaches, and avoid unnecessary surgical interventions for patients with MLAP who require surgical diagnosis and treatment, and will help these patients avoid surgery complications.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed. The study was carried out with the permission of Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Date: September 06, 2022, Decision No:2137).

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

An evaluation of factors which affect recurrence and malignancy of sinonasal papillomas

Evaluación de los factores que afectan la recurrencia y la malignidad de los papilomas sinonasales

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Abstract

Objective: *Sinonasal papillomas are rare benign tumors. They challenge otorhinolaryngologists due to their high recurrence rate and malignant transformation. The aim of this study was to investigate the clinical and demographic factors associated with recurrence and/or malignancy of sinonasal papillomas.* **Methods:** *This retrospective study included 49 patients who were operated on between 2014 and 2020. Clinical and demographic characteristics of the patients were retrieved from the patients' records.* **Results:** *The recurrence rate was determined to be 12.2% and the malignancy rate was 8.2%. Recurrence was significantly higher in females, the advanced stage (T3 and T4), and papillomas located in the maxillary sinus. The recurrence rate was significantly lower in patients treated with the endoscopic surgery. Factors affecting malignancy were the presence of dysplasia and extension out of the paranasal sinuses.* **Conclusions:** *The results of this study showed that the factors affecting recurrence were gender, papilloma stage, type of surgery performed, and whether the tumor extended to the paranasal sinuses.*

Keywords: *Sinonasal papilloma. Inverted papilloma. Paranasal sinus.*

Resumen

Objetivo: *Los papilomas sinonasales son tumores benignos poco frecuentes. Suponen un reto para los otorrinolaringólogos por su elevada tasa de recurrencia y transformación maligna. Investigar los factores clínicos y demográficos asociados con la recurrencia y con la malignidad de los papilomas sinonasales.* **Métodos:** *Estudio retrospectivo que incluyó 49 pacientes operados entre 2014 y 2020. Las características clínicas y demográficas se recuperaron de los registros de los pacientes.* **Resultados:** *Se determinó una tasa de recurrencia del 12.2% y una tasa de malignidad del 8.2%. La recurrencia fue significativamente mayor en las mujeres, en los estadios avanzados (T3 y T4) y en los papilomas localizados en el seno maxilar. La tasa de recidiva fue significativamente menor en los pacientes tratados con cirugía endoscópica. Los factores que afectaron a la malignidad fueron la presencia de displasia y la extensión fuera de los senos paranasales.* **Conclusiones:** *Los resultados de este estudio muestran que los factores que afectaron la recidiva fueron el sexo, el estadio del papiloma, el tipo de cirugía realizada y si el tumor se extendía a los senos paranasales.*

Palabras clave: *Papiloma sinonasal. Papiloma invertido. Seno paranasal.*

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Introduction

Sinonasal papillomas are benign tumors originating from the Schneiderian membrane of the nasal cavity and paranasal sinuses. There are three types of sinonasal papillomas; exophytic, oncocytic, and inverted, with the latter being the most common type. The most important features that distinguish inverted papilloma (IP) from other benign sinonasal tumors are; high recurrence, malignancy potential, and significant local bone erosion[1]. The recurrence rate has been reported to be between 15% and 20%[2-7]. Recurrences usually occur within the first 3 years after incomplete excisions. IP may be histopathologically associated with varying degrees of dysplasia, carcinoma *in situ,* and squamous cell carcinoma (SCC)[8]. The malignancy rate has been reported to be approximately 1.9-27%[9-13]. Malignancy may coexist with the IP in the same lesion or may develop years after excision of the papilloma.

Many factors, including smoking, size of the papilloma, type of surgery, the presence of squamous hyperplasia, high hyperkeratosis, increased mitosis, HPV positivity, bilateral papilloma and localization of IP have been associated with recurrence or malignancy in the literature[9,10,14]. In the majority of case series, the limited number of patients makes it difficult to draw reliable conclusions from these data, as sinonasal papillomas are rare and it can take many years to gather a large number of cases. Each institution should share their experiences to increase the number of the patients to be able to make an additional contribution to the literature on this subject. The aim of this study was to investigate the clinical and demographic factors associated with recurrence and/or malignancy in sinonasal papillomas. Furthermore, with the results obtained from this study, it was aimed to contribute to the pool of knowledge on this subject, which has many controversies and uncertainties.

Methods

The study was initiated following the approval of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Date: September 21, 2020, Number: 96/6). The study cohort included 61 patients who underwent surgery for sinonasal papilloma between 2014 and 2020. After the exclusion of 12 patients who were first operated on another center or who did not have complete follow-up data, the analyses were completed with 49 patients. The parameters evaluated in this study were patient age, gender, smoking and alcohol consumption, follow-up time, type of surgery, papilloma side and localization of origin, the presence extranasal extension, the type and stage of the papilloma, and recurrence and malignancy rates. The Krouse Staging System[15] was used for staging. The stage, localisation, origin, and invasion site of papillomas were determined according to the intraoperative findings and paranasal sinus tomography images.

The post-operative regular follow-up examinations included nasal endoscopic examination every 3 months in the 1st year, every 6 months in the 2nd year, and annually thereafter for up to 7 years. In the follow-up examinations, all cavities and sinuses were checked with straight and angled telescopes. In cases with suspicious lesions in the frontal sinus or in the anterior wall of the maxillary sinus, imaging was performed to view the areas that could not be seen with endoscopy. Patients with suspicious lesions identified in endoscopic examination underwent biopsies.

The Chi-square test was used in the statistical analysis. Parameters with a $p < 0.05$ were considered statistically significant.

Results

Demographic and clinical parameters of patients

The patients comprised 43 (87.8%) males and 6 (12.2%) females with a mean age of 48.96 ± 15.9 years (Range, 15-78 years) and a mean follow-up period of 39.16 ± 20.4 months (Range, 8-88 months). The demographic and clinical parameters of the patients are summarized in table 1.

Factors associated with recurrence

The overall recurrence rate of this cohort was 12.2%. The earliest time to recurrence was 9 months, and the latest was 72 months (Mean, 39.5 ± 21.6 months). All recurrences occurred in the same localisation as the original tumor. The relationships between the demographic and clinical parameters and recurrence are shown in table 2. Recurrence was observed in 7% of male and 50% of female patients. The difference between the gender in terms of recurrence rates was statistically significant ($p = 0.003$).

Table 1. Demographic and clinical parameters of patients

Parameters	Number of patients (%)
Age	
Mean ± standard deviation (SD)	48.96 ± 15.9
≤ 45	16 (32.7)
> 45	33 (67.3)
Gender	
Male	43 (87.8)
Female	6 (12.2)
Follow-up time (months)	
Min-Max	8-88
Mean ± SD	39.16 ± 20.4
Side of papilloma	
Right	34 (69.4)
Left	15 (30.6)
Type of papilloma	
Inverted	44 (89.8)
Non-inverted	5 (10.2)
Exophytic	5 (10.2)
Oncocytic	0
Originated site	
Paranasal sinus	27 (55.1)
Maxillary sinus	23 (46.9)
Frontal sinus	2 (4.1)
Sphenoid sinus	2 (4.1)
Ethmoid sinus	0
Nasal cavity	22 (44.9)
Lateral nasal wall	12 (24.5)
Middle turbinate	9 (18.4)
Inferior turbinate	1 (2)
Stage of papilloma	
Early (T1-T2)	18 (36.7)
T1	8 (16.3)
T2	10 (20.4)
Advanced (T3-T4)	31 (63.3)
T3	26 (53.1)
T4	5 (10.2)
Malign transformation	
Yes	4 (8.2)
No	45 (91.8)
Displasia	
Yes	5 (10.2)
No	44 (89.8)
Smoking	
Yes	20 (40.8)
No	29 (59.2)
Alcoholism	
Yes	3 (6.1)
No	46 (93.8)
Type of surgery	
Endoscopic	42 (85.7)
Open	0
Combine	7 (14.3)

Endoscopic surgery was performed on 42 (85.7%) patients, and 7 patients (14.3%) underwent combined surgery (Maxillary trocar, Caldwell Luc, and Bicoronal Forehead flap in 4, 2, and 1 patients, respectively). The recurrence rate in patients who underwent only endoscopic surgery was found to be significantly lower than those who underwent combined surgery ($p = 0.008$).

The sinonasal papillomas were separated into two groups according to localisation in the paranasal sinus or nasal cavity. The distribution of the sinonasal papillomas according to localisations is summarized in table 3. Sinonasal papillomas most commonly originated from the maxillary sinus in this cohort. Recurrence occurred in 6 of 27 patients (22.2%) with papilloma located in the paranasal sinus, and no recurrence was observed in any of the papillomas located in the nasal cavity. The difference between the two groups was statistically significant ($p = 0.018$). All the recurrences originated from the maxillary sinus.

In this study, the patients were evaluated in two groups. Those with Krouse stage T1 and T2, in which the papilloma is limited to the nasal cavity, ethmoid sinuses, and medial wall of maxillary sinus, were defined as early stage (Group 1). Patients with papilloma, which are more difficult to reach surgically, such as in the other walls of the maxillary sinus, sphenoid, and/or frontal sinuses (Krouse T3 and T4), were accepted as advanced stage (Group 2). Patients with malignancy and/or with extension out of the nasal cavity and paranasal sinus were also included in Group 2. The distribution of papilloma types according to the Krouse Staging System is shown in table 4. More than half of the patients were at the advanced stage (53.1% T3 and 10.2 % T4). All patients with recurrence were at T3 stage. There was a statistically significant difference between the two groups in terms of recurrence ($p = 0.046$). In five patients, the papilloma extended out of the nasal cavity and paranasal sinus. IP extended to the orbit in two of these patients, to the orbit and intracranial region in one patient, and to the parapharyngeal region in one patient. Another patient had an oroantral fistula stemming from IP invasion.

The study results showed that patient age, smoking and alcohol consumption, papilloma side and type, and the extension of sinonasal papilloma out of the nasal cavity and paranasal sinuses had no significant effect on recurrence ($p > 0.05$).

Table 2. The effects of demographic and clinical parameters of patients on recurrence

Parameters	Patients with Recurrence (number of patients [%])	Patients without recurrence (number of patients [%])	Total (number of patients [%])	p
Age Min-Max (mean±standard deviation)	16-59 (44.83 ± 15.2)	15-78 (49.53 ± 16)	15-78 (48.96 ± 15.9)	
≤ 45	2 (12.5)	14 (87.5)	16 (32.7)	0.97
> 45	4 (12.1)	29 (87.9)	33 (67.3)	
Side of papilloma				
Right	5 (14.7)	29 (85.3)	34 (69.4)	0.43
Left	1 (6.7)	14 (93.3)	15 (30.6)	
Gender				
Female	3 (50)	3 (50)	6 (12.2)	0.003*
Male	3 (7)	40 (93)	43 (87.8)	
Type of papilloma				
Inverted	6 (13.6)	38 (86.4)	44 (89.8)	0.38
Non-inverted	-	5 (100)	5 (10.2)	
Papilloma's originated site				
Intra-paranasal sinus	6 (22.2)	21 (77.8)	27 (55.1)	0.018*
Nasal cavity	-	22 (100)	22 (44.9)	
Extension out of the paranasal sinus				
Yes	-	5 (100)	5 (10.2)	0.38
No	6 (13.6)	38 (86.4)	44 (89.8)	
Stage of papilloma				
Early (T1-T2)	-	18 (100)	18 (36.7)	0.046*
Advanced (T3-T4)	6 (19.3)	25 (80.7)	31 (63.3)	
Smoking				
Yes	3 (15)	17 (85)	20 (40.8)	0.63
No	3 (10.3)	26 (89.7)	29 (59.2)	
Alcohol use				
Yes	-	3 (100)	3 (6.1)	0.71
No	6 (13)	40 (87)	46 (93.9)	
Type of surgery				
Endoscopic surgery	3 (7.1)	39 (92.9)	42 (85.7)	0.008*
Combined surgeries	3 (42.9)	4 (57.1)	7 (14.3)	

*p < 0.05, statistically significant values.

Table 3. Distribution of sinonasal papillomas according to originated site

Originated site	Number of patients (%)
Paranasal sinus	27 (55.1)
Maxillary sinus	23 (46.9)
Ethmoid sinus	-
Frontal sinus	2 (4.1)
Sphenoid sinus	2 (4.1)
Nasal cavity	22 (44.9)
Lateral nasal wall	12 (24.5)
Middle turbinate	9 (18.4)
Inferior turbinate	1 (2)

Factors associated with malignancy

The malignancy rate of this study was found to be 8.2% (4/49). All the patients who developed malignancy had inverted type and synchronous SCC. All patients with malignancy were male with a mean age of 54.75 years. All four patients with malignancy were treated with endoscopic surgery, and the follow-up time of these patients was 8, 22, 23, and 37 months, respectively. Recurrence was observed in only one patient with malignancy.

Of the 5 patients (40%) with dysplasia, malignancy was determined in 2 (40%). The malignancy rate of IP with dysplasia was significantly higher than that of IP without dysplasia (p = 0.006). The rate of malignancy

in IP extending out of the nasal cavity and paranasal sinuses was statistically significantly higher than in those without extension (3 of 5 patients, $p < 0.001$). In this cohort, no other parameters had any effect on malignancy.

Discussion

The overall recurrence rate in this study was 12.2% (6 of 49 patients), which was consistent with the literature. Some studies have reported significantly higher rates of recurrence[16-18]. The high rate of recurrence in one of these studies was explained by the fact that their hospital was a tertiary health-care center which treated more complex patients[18]. However, the development of recurrence in sinonasal papillomas is a multifactorial event and should not be attributed to a single factor. Factors such as the type of surgery applied, the surgeon's experience, the localization and stage of the papilloma, and the presence of residue may also affect recurrence. Many studies have been conducted on the recurrence and malignancy of sinonasal papillomas, but no consensus has been reached. In the current study, the factors with significant effect on the recurrence of sinonasal papillomas were determined to be; female gender, the stage and localization of the papilloma, and the type of surgery applied. Recurrence rates were found to be increased by a younger patient age and smoking according to Jardine et al.[19], whereas Roh et al.[20] and Moon et al.[21] reported that smoking, Suh et al.[22] stated that female gender, and Katori et al.[23] that some histopathological features of papilloma (increased mitotic activity, hyperkeratosis, and the presence of squamous hyperplasia) increased recurrence. In other studies, residual papilloma tissue following surgery has also been blamed for recurrence[10,24].

In many studies, the recurrence rate in males has been reported to be higher than in females[18,24]. In contrast, the recurrence rate in the current study was significantly higher in females than in males. Suh et al.[22] also reported the relationship between recurrence and gender, with a recurrence rate in female patients of 50% (4 of 8 patients), similar to the current study. However, to be able to more clearly state that female gender increases recurrence, there is a need for further studies to be conducted with more female patients.

It has been reported that recurrence is more common in IP located in the frontal sinus, which is due to the difficulty in visualization of the sinus[6,18,25-27]. Recurrence in IP with frontal sinus localization has been reported to be 22.4%[28]. In the two patients with frontal sinus localization in the current study, no recurrence developed. In some studies, it has been reported that maxillary sinus localisation increases recurrence[7,29] and the results obtained in the current study were similar to those studies. In all the patients with recurrence, the IP was located in the maxillary sinus, and there was invasion of the anterior and lateral walls of the maxillary sinus. Just like the lateral wall of the frontal sinus, the anterior wall of the maxillary sinus is an area where papilloma can be overlooked, and residual tissue may remain. Although Caldwell-Luc and/or gingival trocar surgery was added to the endoscopic surgery in these cases; unfortunately, recurrence was still observed in some patients. In these cases, the inside of the sinus should be carefully checked with straight and angled telescopes to ensure that no residual tissue remains. The mucosa invaded by the papilloma should be curetted, and the bone tissue should be removed by drilling. When there is frontal sinus lateral wall invasion, it is difficult to reach this area with endoscopic surgery alone, so adding open surgeries such as bicoronal forehead flap and/or osteoplastic flap to the endoscopic surgery allows the papilloma to be removed without residue.

There are different opinions about the relationship between the stage of the IP and recurrence. Some studies have highlighted an association between recurrence and Krouse classification[30], while others have not[4,5,7,17,24-26]. A meta-analysis revealed an increased risk of recurrence between Krouse T2 and T3 stages,[31] and another study showed a significant relationship only between Krouse T4 stage and recurrence[21]. In most studies, the four stages have been compared with each other in terms of recurrence. In the current study, T1 and T2 stage papillomas, which are easier to reach surgically, were defined as early stage, and T3 and T4 stage papillomas, which are more difficult to reach, as advanced stage. Thus, it was aimed to compare 2 more homogeneous groups. The results showed that advanced-stage papillomas significantly increased recurrence.

In this cohort, the malignancy rate was observed to be 8.2% (4/49), which was consistent with the literature. All four patients had synchronous SCC, and no metachronous malignancy was observed during follow-up. Metachronous malignancy may develop many years after excision of the IP. Lesperance et al.[32] described an average interval of 63 months between the onset of IP and the development of malignancy.

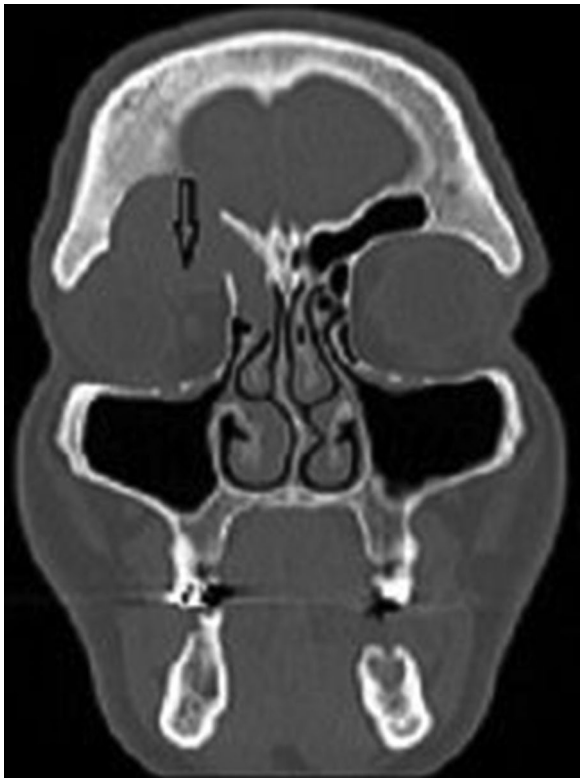

Figure 1. *In the coronal paranasal sinus tomography, inverted papilloma + squamous cell carcinoma extending to the orbit by eroding the frontal sinus wall on the right side (the arrow shows erosion in frontal sinus wall).*

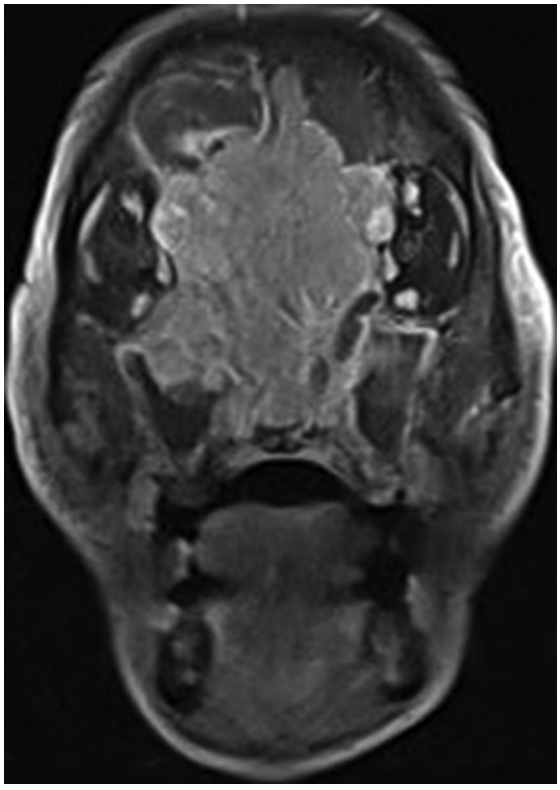

Figure 2. *In the coronal paranasal sinus magnetic resonance T1 image, an inverted papilloma + squamous cell carcinoma that fills both nasal passages and all sinuses and extends to the orbit and intracranial area.*

Another study showed that the development of metachronous malignancy occurred approximately 10 years after undergoing IP surgery[33]. These data reveal the importance of long-term follow-up of patients with IP. Therefore, these patients should be checked at regular intervals, their complaints should be questioned, and endoscopic nasal examinations should be performed. If a suspicious mass is detected, radiological imaging should be performed and a biopsy should be taken.

Malignancy of IPs may present with different clinical scenario. They may present with limited eye movements without a mass in the nasal passage and complaints of nasal congestion, as in one of the current study patients (Fig. 1). Or, as in the other patient, they may present with visual loss and loss of consciousness due to bilateral nasal mass that has invaded the orbit and intracranial area (Fig. 2). Clinicians must be alert to such cases.

Many factors affecting the malignancy of IPs have been reported. Hong et al. reported that smoking significantly affects malignancy[34]. In a literature review, some biochemical and immunohistochemical markers were found to play a role in malignant transformation[13]. In this cohort, the presence of dysplasia and invasion of papilloma outside the nasal cavity and paranasal sinus had a significant effect on malignancy in IPs. The rate of malignancy in IPs extending out of the paranasal sinus was significantly higher than those that did not. This result can be explained in 2 ways. First, papillomas that tend to extension outside the nasal cavity and the paranasal sinus are perhaps more aggressive and have higher malignant potential. The second reason may be the malignant and aggressive characteristics of the malignant tumor accompanying the IP. More research is needed of IPs that tend to invade to be able to predict which papillomas may behave more aggressively or become malignant.

For treatment of IPs, more experienced surgeons prefer the classical open surgery, whereas younger surgeons tend to perform endoscopic surgery[22]. In 2019, a meta-analysis stated that open surgeries are no longer the “gold standard” for surgery of IPs[6]. Goudakos et al.[35] stated that endoscopic surgery is the first choice for IPs, regardless of the stage of

Table 4. Distribution of papilloma types according to krouse staging system

Stage	Inverted (number of patients [%])	Exophytic (number of patients [%])	Oncocytic (number of patients [%])	Total (number of patients [%])
Early stage T1	8 (18.2%)	-	-	8 (16.3%)
T2	9 (20.4%)	1 (20%)	-	10 (20.4%)
Advanced stage T3	22 (50%)	4 (80%)	-	26 (53.1%)
T4	5 (11.4%)	-	-	5 (10.2%)
Total	44 (100%)	5 (100%)	0	49

papilloma. Endoscopic surgery provides better surgical results than open and combined surgeries[3]. In a meta-analysis by Peng et al., it was stated that the recurrence rate of the endoscopic surgery group was significantly lower compared to the open surgery group[6]. Bugter et al.[17] also confirmed the superiority of endoscopic surgery over open and combine surgery. In the current cohort, 85.71% of the patients were treated with the endoscopic approach and 14.29% with combined surgery. Open surgery alone was not performed in any patient. It can be considered that every surgeon experienced in endoscopic sinus surgery can treat most patients with sinonasal papilloma, even malignant cases, with an endoscopic approach. Open surgeries can be added to the endoscopic approach, especially in cases that are difficult to reach endoscopically, such as localisation in the lateral wall of the frontal sinus, or anterior and lateral wall of the maxillary sinus. In appropriately selected patients, endoscopic surgery allows removal of the tumor without residue. In summary, endoscopic surgery; facilitates the treatment of sinonasal papillomas, decreases the complication and recurrence rates, shortens the hospitalization time, and accelerates post-operative recovery.

The present study had some limitations primarily that the retrospective nature of the study had a negative impact on the quantity and quality of the information, and this should be taken into account when interpreting the results. The number of patients was not very high. Because sinonasal papilloma is a rare disease and it takes a long time to gather a large case series. Further limitations could be said to be that the study was conducted in a single center and patients who had previously undergone surgery in another center were excluded. Therefore, there is a need for further studies with more patients to support the values that were found to be significant.

Conclusions

Although many factors affecting the recurrence of sinonasal papillomas have been identified, there is no definite consensus on this issue. In this study, the factors with a significant effect on recurrence were determined to be female gender, localization and stage of papilloma, and type of surgery. Factors affecting malignancy were the presence of dysplasia and extension out of the paranasal sinuses. Most sinonasal papillomas, including malignant cases, can be treated with endoscopic surgery regardless of stage. When necessary, open surgical approaches can be added to the endoscopic approach. Nevertheless, there is a need for more extensive research, especially molecular research, to further elucidate this complex issue.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Índices celulares y reactantes de fase aguda como predictores de absceso tras apendicectomía

Cellular indices and acute phase reactants as predictors of abscess after appendectomy

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Resumen

Objetivo: *Comparar la precisión de cuatro biomarcadores como predictores de absceso abdominal posapendicectomía (APA).* **Métodos:** *Estudio diagnóstico de los pacientes menores de 15 años intervenidos por apendicitis en un hospital pediátrico entre 2010 y 2022. Se compararon el índice neutrófilo-linfocito (INL), el índice plaqueta-linfocito (IPL), la proteína C reactiva (PCR) y la procalcitonina (PCT) entre los pacientes con APA y los que no presentaron dicha complicación (NAPA).* **Resultados:** *Se incluyeron 86 pacientes con APA (64% hombres; edad media: 9.4 ± 3.5 años) y 91 pacientes NAPA (65% hombres; edad media: 10.2 ± 2.9 años). Los valores de INL, IPL, PCR y PCT fueron significativamente mayores en el grupo APA que en el grupo NAPA ($p < 0.0001$). La PCT tuvo el mayor área bajo la curva ROC (0.761), un punto de corte de 0.37, sensibilidad del 74%, especificidad del 75% y valor predictivo positivo del 74% para predecir la aparición de APA.* **Conclusiones:** *La PCT es un buen predictor de absceso abdominal tras una apendicectomía. Tener en cuenta los valores preoperatorios de PCT para optimizar el manejo y la antibioticoterapia en el posoperatorio podría ser una herramienta adicional en la prevención de esta complicación.*

Palabras clave: *Apendicitis. Absceso abdominal. Procalcitonina. Índice neutrófilo-linfocito. Proteína C reactiva. Índice plaqueta-linfocito.*

Abstract

Objective: *To compare the accuracy of four biomarkers as predictors of post-appendectomy abdominal abscess (PAA).* **Methods:** *Diagnostic study of patients under 15 years of age operated for appendicitis in a pediatric hospital between 2010 and 2022 was analyzed. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP) and procalcitonin (PCT) were compared between patients with PAA and those without such complication (NPAA).* **Results:** *86 patients with PAA (64% men; mean age: 9.4 ± 3.5 years) and 91 patients NPAA (65% men; mean age: 10.2 ± 2.9 years) were included. NLR, PLR, CRP and PCT values were higher in the PAA group than in the NPAA group ($p < 0.0001$). PCT had the highest area under the ROC curve (0.761), a cutoff point of 0.37, sensitivity 74%, specificity 75%, and positive predictive value of 74% for predicting the occurrence of PAA.* **Conclusions:** *PCT is a good predictor of abdominal abscess after appendectomy. Considering preoperative PCT values to optimize postoperative management and antibiotics could be an additional tool in the prevention of this complication.*

Keywords: *Appendicitis. Abdominal abscess. Procalcitonin. Neutrophil-lymphocyte ratio. C-reactive protein. Platelet-lymphocyte ratio.*

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Introducción

La apendicitis aguda es la urgencia quirúrgica más frecuente en pediatría, con un riesgo acumulado a lo largo de la vida del 9%[1]. Su diagnóstico depende fundamentalmente de la evaluación clínica abdominal y general, aunque en la edad pediátrica a menudo es difícil realizar un diagnóstico precoz debido a dificultades en la anamnesis y la ausencia de síntomas clásicos[2]. La apendicitis requiere un diagnóstico y un tratamiento oportunos, ya que su retraso puede conducir a perforación apendicular y desarrollo de complicaciones.

Los pacientes intervenidos quirúrgicamente por apendicitis evolucionada tienen mayor riesgo de presentar complicaciones, como el absceso abdominal posapendicectomía (APA). Esta complicación ocurre en aproximadamente el 4% de las apendicitis no perforadas y en el 6-28% de las perforadas, y se asocia un aumento significativo de la morbimortalidad[3,4]. Aunque se ha investigado el valor de diferentes parámetros de laboratorio como posibles predictores de APA, los resultados han sido diversos[5].

Recientemente se ha evaluado la utilidad de diversos biomarcadores, como el índice bilirrubina directa-linfocito, el índice neutrófilo-linfocito (INL) y el índice plaqueta-linfocito (IPL) como predictores de APA y en otras condiciones quirúrgicas, con resultados dispares[6-8]. Sin embargo, la evidencia científica es aún limitada y no existen estudios comparativos de la utilidad de estos índices y otros parámetros inflamatorios como predictores de esta complicación. El objetivo de este estudio es comparar la precisión de cuatro biomarcadores como predictores de APA.

Métodos

Se llevó a cabo un estudio diagnóstico retrospectivo en una serie consecutiva de pacientes menores de 15 años que desarrollaron APA, comparándolos con una muestra aleatoria de sujetos intervenidos por apendicitis aguda que no presentaron esta complicación (NAPA), en un hospital materno-infantil de segundo nivel de complejidad, entre enero de 2010 y diciembre de 2022. Los pacientes del grupo control (NAPA) fueron seleccionados secuencialmente de la misma población objeto de estudio y durante el mismo periodo de tiempo que los pacientes con APA, sin importar el tipo de apendicitis, siendo la única característica obligatoria la ausencia de APA, para así controlar posibles sesgos de selección y hacer los grupos comparables. Se recolectaron diferentes variables de la historia clínica informatizada, incluyendo edad, sexo, peso en kilogramos, tipo histológico de apendicitis, días de estancia hospitalaria valores de proteína C reactiva (PCR) y de procalcitonina (PCT), INL e IPL en el momento del ingreso hospitalario (estos índices se presentan como valores numéricos continuos y no tienen unidades de medida). Los recuentos celulares se realizaron con el analizador hematológico Beckman Coulter y en todos los casos el facultativo del área de anatomía patológica desconocía los resultados analíticos de los sujetos y la aparición de APA. Los pacientes sometidos a apendicectomía incidental, con líquido libre no organizado o con un registro clínico incompleto, fueron excluidos del estudio.

El INL y el IPL se calcularon dividiendo el número absoluto de neutrófilos y de plaquetas entre el número de linfocitos, respectivamente. El diagnóstico clínico de apendicitis aguda se basó en la anamnesis, la exploración física y los hallazgos ecográficos y analíticos; el diagnóstico definitivo se fundamentó en el análisis histopatológico, clasificado en apendicitis congestiva, flemonosa, gangrenosa, perforada o peritonitis. El diagnóstico de plastrón apendicular se estableció durante la intervención quirúrgica al identificar el apéndice cecal con signos inflamatorios primarios y cubierto por una masa de asas intestinales con fibrina adyacente o epiplón edematoso. Se definió peritonitis localizada como la contaminación purulenta o fecaloide de uno o dos cuadrantes de la cavidad abdominal, y generalizada si existía contaminación en tres o más cuadrantes. El absceso se definió como una colección delimitada de líquido ecogénico o purulento dentro de la cavidad abdominal durante el primer mes tras una apendicectomía, confirmado radiológicamente y acompañado de signos clínicos de infección. Todos los pacientes recibieron tratamiento antibiótico intravenoso con cefotaxima (150 mg/kg al día) y metronidazol (30 mg/kg al día) desde el momento del diagnóstico de apendicitis aguda y durante el posoperatorio de acuerdo con el tipo de apendicitis: tres dosis en la flemonosa, 3-5 días en la gangrenosa y 7 días en el resto de las apendicitis.

Las variables cualitativas se expresaron como frecuencias relativas y absolutas, mientras que las variables cuantitativas se presentaron como media y desviación estándar o como mediana y rango intercuartil (RIC). La distribución de las variables

cuantitativas se determinó mediante el test de Kolmogórov-Smirnov para definir la prueba de contraste de hipótesis a utilizar (U de Mann-Whitney o t de Student), y las variables cualitativas se analizaron mediante la prueba de χ^2 o la prueba exacta de Fisher. Se estableció la significancia estadística como un valor $p < 0.05$ para un error tipo I permitido del 5%. La PCR, la PCT, el INL y el IPL se evaluaron para calcular su sensibilidad, especificidad, valor predictivo positivo (VPP) y negativo (VPN), y *odds ratio* (OR). Mediante el área bajo la curva característica operativa del receptor (AUC-ROC) se obtuvo el punto de corte óptimo para predecir la aparición de APA. De acuerdo con el AUC-ROC, se consideró que la precisión de la prueba fue deficiente (0.5-0.6), regular (0.61-0.7), aceptable (0.71-0.8), buena (0.81-0.9) o sobresaliente (> 0.9). Si bien se han descrito valores de referencia para algunos de estos índices en la población pediátrica, en este estudio se ha calculado el punto de corte propio para cada uno de ellos, ya que se trata de una situación patológica particular (APA)[9].

Los datos recolectados se anonimizaron y tabularon en Microsoft Excel (Versión 16.66.1) y se analizaron mediante el *software* estadístico SPSS (IBM Corp., Armonk, NY, USA). Este trabajo fue aprobado por el Comité Ético de Investigación Clínica (No. Registro 3318-0000200) y ha seguido las recomendaciones de la guía STARD (*Standards for Reporting Diagnostic accuracy studies*)[10].

Resultados

Durante el periodo de 2010 a 2022 se realizaron 1766 apendicectomías en pacientes menores de 15 años en el hospital que fue objeto de estudio. La tasa de APA fue del 5% (n = 89). En este análisis se incluyeron 86 niños con APA que cumplían con los criterios de inclusión y 91 pacientes apendicectomizados sin colección posoperatoria como muestra comparativa (Fig. 1). Del total de los sujetos con APA, el 64% eran varones, similar al 64.8% en el grupo de pacientes apendicectomizados sin complicaciones ($p = 0.903$). La edad media de los pacientes con APA fue de 9.4 ± 3.5 años, mientras que en el grupo NAPA fue de 10.2 ± 2.9 años ($p = 0.166$). Los participantes con APA tuvieron un peso de 35.8 ± 14.9 kg, mientras que en el grupo NAPA el peso promedio fue de 41.4 ± 17.1 kg ($p = 0.021$). Ningún paciente presentaba antecedentes quirúrgicos ni comorbilidad relevante, y todos fueron operados dentro de las primeras 24 horas desde el ingreso (Tabla 1).

El principal tipo de apendicitis en los pacientes con APA frente al grupo NAPA fue la peritonitis generalizada, en el 32.6% (n = 28/86) vs. 2.2% (n = 2/91), seguida de peritonitis localizada en el 31.4% (n = 27/86) vs. 8.8% (n = 8/91), perforación en el 18.6% (n = 16/86) vs. 6.6% (n = 6/91), plastrón apendicular en el 10.5% (n = 9/86) vs. 2.2% (n = 2/91), gangrena en el 3.5% (n = 3/86) vs. 13.2% (n = 12/91), e inflamación flemonosa del apéndice en el 3.5% (n = 3/86) vs. 61.5% (n = 56/91); solo en el grupo NAPA hubo apendicitis congestivas (5.5%, n = 5/91). Estas diferencias fueron estadísticamente significativas ($p < 0.0001$).

El abordaje quirúrgico más utilizado fue el transumbilical videoasistido en el 72% de los pacientes NAPA y el 73% de los pacientes con APA, seguido por el acceso por vía laparotomía (9% vs. 8%) y por el laparoscópico (5% vs. 2%), con una tasa similar de conversión a laparotomía desde el abordaje laparoscópico o videoasistido (14% en pacientes NAPA vs. 17% en pacientes con APA; $p > 0.05$). En ningún caso se colocó drenaje quirúrgico. La estancia hospitalaria de los pacientes con APA fue de 14 días (RIC: 5 días), mientras que en el grupo NAPA fue de 2 días (RIC: 4 días) ($p < 0.0001$).

El valor de INL en el grupo con APA frente a la cohorte NAPA fue de 12.2 vs. 6.4, el IPL fue de 260.8 vs. 153.1, la PCR fue de 74.1 vs. 11.4 mg/l, y la PCT fue de 0.90 vs. 0.10 ng/ml, respectivamente. Todos los marcadores inflamatorios fueron significativamente mayores en los pacientes con APA frente a aquellos sin colección posoperatoria ($p < 0.0001$) (Tabla 1).

La PCT fue el marcador inflamatorio con mejor rendimiento y mayor AUC-ROC para predecir la aparición de APA (Fig. 2), con un punto de corte de 0.37 ng/ml, sensibilidad del 74%, especificidad del 75%, VPP del 74% y VPN del 76%. La capacidad predictiva de cada uno de los biomarcadores analizados se muestra detalladamente en la tabla 2.

Discusión

Los abscesos abdominales ocurren hasta en el 20% de los pacientes después de una apendicectomía, especialmente en aquellos con apendicitis complicadas[11,12]. Aunque se han evaluado diferentes variables clínicas y analíticas pronósticas en la población pediátrica, incluyendo el peso, la presencia de apendicolito o la intolerancia a la vía oral en el postoperatorio, entre otros, aún hay brechas en la literatura actual sobre la utilidad de algunos parámetros

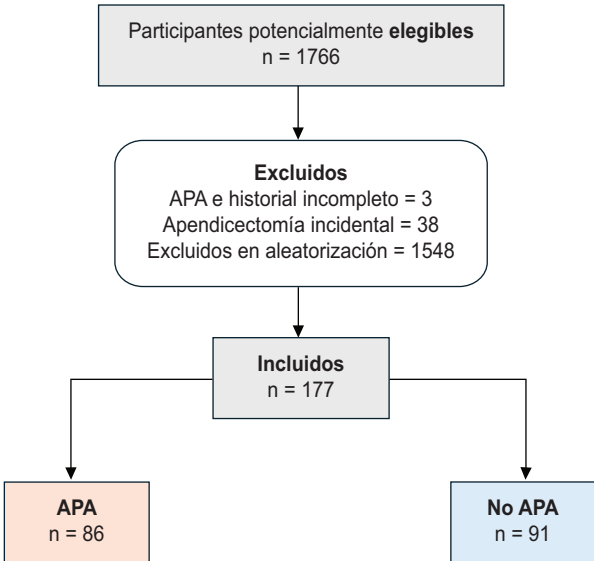

Figura 1. *Diagrama de flujo que muestra la población potencialmente elegible, excluida e incluida en cada uno de los dos grupos objeto de análisis. APA: absceso abdominal posapendicectomía.*

Tabla 1. Características demográficas y valores de biomarcadores en la población estudiada

Variable	APA (n = 86)	NAPA (n = 91)	p
Mujer	36%	35%	0.903
Hombre	64%	65%	
Edad (años)	9.4 ± 3.5	10.2 ± 2.9	0.166
Peso (kg)	35.8 ± 14.9	41.4 ± 17.1	0.021
Horas desde el ingreso a la cirugía	7.2 ± 3.6	8.1 ± 3.1	0.178
PCR (mg/l)	74.1 ± 170.3	11.4 ± 42.5	< 0.0001
PCT (ng/ml)	0.9 ± 4.8	0.1 ± 0.26	< 0.0001
INL	12.2 ± 12.7	6.4 ± 6.2	< 0.0001
IPL	260.8 ± 150.7	153.1 ± 260.8	< 0.0001

APA: absceso abdominal posapendicectomía; INL: índice neutrófilo-linfocito; IPL: índice plaqueta-linfocito; NAPA: no APA; PCR: proteína C reactiva; PCT: procalcitonina.
Los valores se presentan como mediana y rango intercuartil.

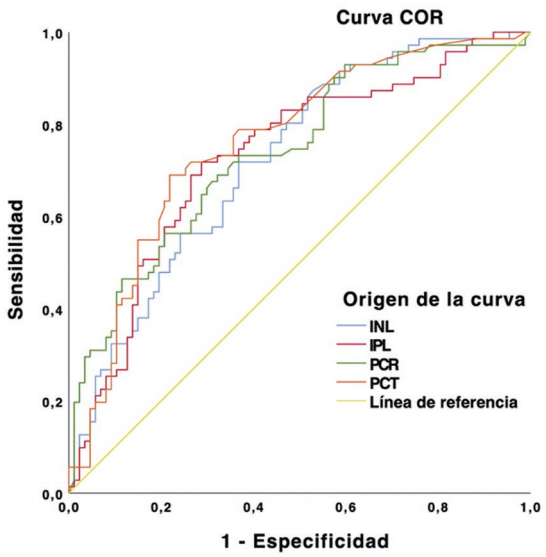

Figura 2. *Área bajo la curva curva característica operativa del receptor de los parámetros analizados. INL: índice neutrófilo-linfocito; IPL: índice plaqueta-linfocito; PCR: proteína C reactiva; PCT: procalcitonina.*

Tabla 2. Área bajo la curva ROC y precisión de cada uno de los marcadores inflamatorios estudiados como predictores de absceso abdominal tras apendicectomía

Biomarcador	AUC-ROC	Punto de corte	S	E	VPP	VPN	OR	p
PCR (mg/l)	0.741	21.9	72%	67%	67%	72%	5.25	< 0.0001
PCT (ng/ml)	0.761	0.37	74%	75%	74%	76%	8.6	< 0.0001
INL	0.724	7.77	73%	63%	65%	71%	4.5	< 0.0001
IPL	0.731	191.8	73%	73%	72%	74%	7.2	< 0.0001

AUC-ROC: área bajo la curva característica operativa del receptor; E: especificidad; INL: índice neutrófilo-linfocito; IPL: índice plaqueta-linfocito; OR: *odds ratio*; PCR: proteína C reactiva; PCT: procalcitonina; S: sensibilidad; VPN: valor predictivo negativo; VPP: valor predictivo positivo.

inflamatorios[13,14]. En este estudio se buscó determinar y comparar la precisión de la PCR, la PCT, el INL y el IPL como predictores de APA en pediatría. Este es el primer estudio que determina y compara estos parámetros con el objetivo de analizar su valor pronóstico en la aparición de APA. Se comprobó que los valores de PCR, PCT, INL e IPL en el momento de la admisión fueron significativamente mayores en los pacientes con APA frente a aquellos sin esta complicación, mostrando todos una precisión aceptable. No obstante, la PCT fue el biomarcador que demostró mayor rendimiento.

La incidencia de APA en nuestra cohorte fue del 5%, inferior a la reportada en series similares en las que alcanza hasta el 18%[15]. En cuanto a las variables clínicas pronósticas, aunque el sobrepeso se ha descrito como un factor de riesgo para el desarrollo de APA debido a que el tejido adiposo intraperitoneal puede inhibir la respuesta inflamatoria frente a la contaminación de la cavidad abdominal[15], en nuestra población los pacientes con APA tenían un peso

menor que aquellos sin colección posoperatoria (35.8 ± 14.9 kg vs. 41.4 ± 17.1 kg; p = 0.021). Sin embargo, este hallazgo podría tener sesgos porque no se registró la talla de todos los pacientes y, por lo tanto, desconocemos el índice de masa corporal. Asimismo, se ha demostrado que la perforación del apéndice cecal es un factor de riesgo para el desarrollo de APA[16], y aunque en este trabajo no se estudió directamente esta asociación, nuestros resultados sugieren lo mismo, ya que hubo más pacientes con perforación apendicular (18.6% vs. 6.6%) y peritonitis (64% vs. 11%) entre los pacientes con APA frente al grupo NAPA. Por otra parte, en este trabajo no se han encontrado diferencias estadísticamente significativas entre los diferentes abordajes quirúrgicos y su asociación con la aparición de APA, y tampoco en la antibioterapia utilizada, ya que, de acuerdo con el protocolo del servicio, todos los pacientes recibieron el mismo esquema de antibióticos antes y después de la intervención quirúrgica.

Delgado et al.[17] reportaron valores significativamente mayores de PCR en pacientes con APA en comparación con aquellos sin complicaciones (81.8 vs. 33.1 mg/l, respectivamente), con un AUC-ROC de 0.73, aunque con una baja sensibilidad para el diagnóstico del absceso (65%) y una especificidad discretamente superior, del 72%. Estos resultados son similares a los encontrados en nuestro estudio, en el que la PCR demostró un VPP del 67% para la aparición de colección posoperatoria. Sin embargo, en la experiencia de otros autores, la PCR no mostró diferencias entre pacientes con y sin APA (8.20 vs. 5.36 mg/l; p = 0.06), y se concluyó que los análisis de laboratorio en el posoperatorio tienen una utilidad clínica limitada para evaluar el desarrollo de absceso peritoneal[18]. Estas diferencias podrían explicarse porque los investigadores del estudio en mención evaluaron el valor de la PCR durante el posoperatorio, mientras que en nuestro estudio se analizaron los parámetros inflamatorios en el momento de la admisión en el servicio de urgencias. Respecto a la PCT, Gavela et al.[19] evaluaron su uso como predictor de la gravedad de la apendicitis y demostraron que estaba significativamente más elevada en los pacientes con apendicitis perforada y peritonitis (4.95 ng/ml) que en aquellos con apendicitis simple (0.15 ng/ml), con una especificidad y un VPP similares a los nuestros, pero con una sensibilidad y un VPN mucho mayores, del 97% y el 89%, respectivamente, en comparación con el presente estudio, en el que la sensibilidad fue del 74% y el VPN fue del 76%[19]. Es posible que estas diferencias se deban a discrepancias en las características sociodemográficas de cada población y al objetivo primario de cada estudio, lo que hace que los resultados no sean por completo comparables.

Lodwick et al.[20] describieron la linfocitopenia como un predictor efectivo de colección posapendicectomía, lo cual sugiere indirectamente que el INL podría ser un parámetro inflamatorio útil. Otros autores han confirmado esta hipótesis, reportando que el INL tiene un AUC-ROC de 0.85 y un punto de corte de 10.5 con una sensibilidad del 85% y una especificidad del 75% para predecir la aparición de APA[17]. Este poder predictivo del INL es superior al documentado en nuestro estudio (AUC-ROC 0.724, sensibilidad 73% y especificidad 63%) al establecer el punto de corte en 7.7; probablemente esta disparidad en los resultados se explique porque en dicho estudio se utilizó un punto de corte mayor que en el nuestro, lo cual aumenta la sensibilidad de la prueba, pero puede incrementar el número de falsos negativos. En ese mismo trabajo, el INL demostró el mejor rendimiento como predictor de APA, en comparación con el número absoluto de leucocitos, neutrófilos, fibrinógeno y PCR[17]; sin embargo, un posible sesgo es que se excluyó a la población menor de 5 años. Tener en cuenta el grupo etario de los pacientes resulta de gran importancia clínica; de hecho, Aydoğdu et al.[21] evaluaron diferentes índices celulares en el diagnóstico de la apendicitis pediátrica y llegaron a la conclusión de que, en la infancia, los valores de referencia de INL, IPL e índice linfocito-monocito varían según la edad y el sexo, por lo que debe tenerse en cuenta al evaluar los resultados de las pruebas sanguíneas.

Durante el proceso inflamatorio de la apendicitis aguda se desencadena una reacción inmunitaria que también involucra a las plaquetas. Por ello, se han estudiado los cambios plaquetarios para determinar la utilidad del IPL en el diagnóstico y el pronóstico de la apendicitis[22]. Nuestro análisis documentó un valor de IPL significativamente mayor en los pacientes con APA (260.8) que en aquellos sin esta complicación (153.1), lo cual se asoció con un aumento de hasta 7.2 veces en la probabilidad de desarrollar APA (OR: 7.2; intervalo de confianza del 95%: 3.7-14). Estos hallazgos son concordantes con lo descrito en la literatura, documentándose que los pacientes con valores más altos de IPL tenían mayor probabilidad de presentar apendicitis complicadas y complicaciones posoperatorias[8].

Este estudio describe la utilidad de la PCT como predictor de APA en pacientes pediátricos intervenidos por apendicitis aguda, con mejor rendimiento

diagnóstico que la PCR, el INL y el IPL. Debido a su amplia disponibilidad, el personal sanitario debe conocer su potencial papel en la prevención, el diagnóstico y el tratamiento oportuno del APA, con el objetivo de disminuir la morbimortalidad asociada a esta complicación. En los pacientes con una sospecha clínica razonable de APA, con síntomas como fiebre e intolerancia a la vía oral durante el posoperatorio, los valores elevados de PCT en el preoperatorio apoyan la realización de una prueba de imagen de manera urgente.

Este estudio presenta las limitaciones propias de un estudio retrospectivo en un único centro hospitalario, además de la heterogeneidad fisiológica en los recuentos celulares del hemograma en la población pediátrica. Hasta donde tenemos conocimiento, es el primer trabajo que compara estos cuatro marcadores inflamatorios como predictores de APA, por lo que se requieren estudios prospectivos con mayor número de pacientes para contrastar nuestros resultados y buscar estrategias de prevención en el desarrollo de APA, como ajustar el protocolo perioperatorio de fluidoterapia y antibióticos en los pacientes con alto riesgo de colección peritoneal.

Conclusiones

La PCT es un buen biomarcador como predictor de APA en la población pediátrica. La evaluación de los valores de PCT antes de la intervención quirúrgica permitiría optimizar el manejo perioperatorio y la antibioticoterapia en el posoperatorio, convirtiéndose en una herramienta valiosa para prevenir esta complicación.

Financiamiento

Los autores declaran no haber recibido financiamiento para este estudio.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución. Los autores han obtenido la aprobación del Comité de Ética para el análisis de datos clínicos obtenidos de forma rutinaria y anonimizados, por lo que no fue necesario el consentimiento informado. Este trabajo fue aprobado por el Comité Ético de Investigación Clínica (No. Registro 3318-0000200) y ha seguido las recomendaciones de la guía STARD *(Standards for Reporting Diagnostic accuracy studies).*

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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ORIGINAL ARTICLE

Effects of ropivacaine alone or in combination with dexmedetomidine on cesarean section: a systematic review and meta-analysis

Efectos de la ropivacaína sola o en combinación con dexmedetomidina en la cesárea: revisión sistemática y metaanálisis

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Abstract

Objective: *Different from physiological pain, post-operative pain is caused by surgical trauma. We aimed to systematically assess the effects of ropivacaine alone or in combination with dexmedetomidine on cesarean section and to conduct a meta-analysis.* **Methods:** *According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and Cochrane intervention system review manual, retrieval software and data analysis tools were used for literature retrieval, screening, exclusion and inclusion, data extraction, analysis and statistics, and risk assessment. A total of 37 literatures were retrieved, and 11 literatures were left after 26 duplicates were excluded.* **Results:** *A total of 37 literatures were retrieved in all databases, of which 11 literatures were left and finally 7 all published in English were obtained. They were seven randomized controlled trials on ropivacaine alone or in combination with dexmedetomidine applied in 502 parturients receiving cesarean section. The results of meta-analysis on main outcome indices showed that the number of parturients in need of rescue (χ^2 = 28.62, p < 0.001, I^2 = 93%), incidence rate of adverse reactions (χ^2 = 28.66, p = 0.007, I^2 = 55%), satisfaction (χ^2 = 7.97, p = 0.05, I^2 = 62.3%), visceral respiratory response (χ^2 = 19.26, p < 0.001, I^2 = 89.6%), satisfaction with muscle relaxation (χ^2 = 6.92, p = 0.03, I^2 = 71.1%), and spinal anesthesia grade (χ^2 = 25.89, p < 0.01, I^2 = 92.3%).* **Conclusions:** *Ropivacaine combined with dexmedetomidine has a better prognostic effect on cesarean section and causes fewer adverse reactions.*

Keywords: *Ropivacaine. Dexmedetomidine. Cesarean section. Meta-analysis.*

Resumen

Objetivo: *A diferencia del dolor fisiológico, el dolor posoperatorio está ocasionado por un trauma quirúrgico. El objetivo es evaluar sistemáticamente los efectos de la ropivacaína sola o en combinación con dexmedetomidina en la cesárea y realizar un metaanálisis.* **Métodos:** *De acuerdo con la declaración PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement) y el Cochrane Intervention System Review Manual, se utilizaron software y herramientas de análisis de datos para la recuperación de la literatura, los exámenes de detección, la exclusión y la inclusión, la extracción de datos, el análisis y las estadísticas, y la evaluación del riesgo. Se obtuvieron 37 estudios, de los cuales quedaron 11 después de excluir 26 duplicados* **Resultados:** *De las bases de datos se obtuvieron 37 estudios, de los cuales se seleccionaron 11 y finalmente se obtuvieron 7, todos publicados en inglés. Correspondieron a 7 ensayos controlados aleatorizados sobre ropivacaína sola o en combinación con dexmedetomidina en 502 parturientas sometidas a cesárea. Los resultados del metaanálisis*

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sobre los principales índices de resultados mostraron que el número de parturientas con necesidad de rescate (χ^2 = 28.62; p < 0.001; I^2 = 93%), la tasa de incidencia de reacciones adversas (χ^2 = 28.66; p = 0.007; I^2 = 55%), la satisfacción (χ^2 = 7.97; p = 0.05; I^2 = 62.3%), la respuesta respiratoria visceral (χ^2 = 19.26; p < 0.001; I^2 = 89.6%), la satisfacción con la relajación muscular (χ^2 = 6.92; p = 0.03; I^2 = 71.1%), el grado de anestesia espinal (χ^2 = 25.89,; p < 0.01; I^2 = 92.3%). **Conclusiones:** *La ropivacaína combinada con dexmedetomidina tiene un mejor efecto pronóstico en la cesárea y provoca menos reacciones adversas.*

Palabras clave: *Ropivacaína. Dexmedetomidina. Cesárea. Metaanálisis.*

Introduction

Different from physiological pain, post-operative pain is caused by surgical trauma. After tissue injury at the surgical incision, inflammatory mediators are released under stress, and then the sensory nerves feel the conduction of stimulus of inflammatory mediators to the center. The pain sensitivity of patients also changes postoperatively, thereby producing an unpleasant emotional expression in the cerebral cortex, which is the protective response of the body to harmful stimuli[1]. Post-operative pain is one of the most common problems faced by patients, which is not conducive to the rapid post-operative recovery of patients, and the severer the pain is, the greater the patient's physiological and psychological fluctuation will be[2]. In general, the pain is the severest within 2 days after surgery, and it mostly lasts for < 1 week. If not controlled well, post-operative pain may transform into chronic pain or persistent pain, and even neuropathic pain in severe cases.

With the opening of the two-child policy in China, the cesarean section rate has been increasing. After cesarean section, incision pain and uterine contraction pain are serious problems faced by parturients[3]. Postpartum pain is an important factor causing anxiety, depression and insomnia in parturients, seriously affecting the post-operative rehabilitation and lactation, and also affecting parturients' care for newborns. Therefore, multi-modal analgesia is adopted after cesarean section. Post-operative analgesia methods commonly used in clinic include patient-controlled epidural analgesia (PCEA), patient-controlled intravenous analgesia (PCIA), oral administration or intramuscular injection and even intravenous infusion of opioids or antipyretic analgesics, and ultrasound-guided plane block of transverse abdominal muscle (TAP) popular in recent years[4,5]. Nowadays when minimally-invasive surgery is strongly advocated, cesarean section is considered as a cruel operation, after which parturients often suffer from highly severe pain. At present, PCEA and PCIA are mainly adopted by anesthesiologists for post-operative analgesia. However, these two analgesia methods lead to serious complications such as nausea and vomiting, pruritus, respiratory depression, epidural hematoma, hemodynamic instability, and even unsatisfactory analgesia[6]. Besides, systemic administration has limitations of drugs and short duration of action, causes severe gastrointestinal discomfort, nausea, vomiting, increased urinary retention, hepatic and renal dysfunction, and increased frequency of administration, and affects the rest and sleep quality of parturients.

At present, the local anesthetics used in TAP include lidocaine, bupivacaine, and ropivacaine. Among them, ropivacaine characterized by long duration of action, low toxicity, and good sensorimotor block separation has become a preferred local anesthetic in field block for anesthesiologists[7]. Despite a good analgesic effect in clinic, ropivacaine has short duration of block and fails to meet the demand for post-operative analgesia with one-time administration[8]. Therefore, local anesthetics with longer duration of action are needed, or local anesthetic adjuvants need to be rationally used to prolong the duration of action of local anesthetics, without causing any unnecessary complications to increase the duration of sensory block. Dexmedetomidine, a research hotspot in the field of anesthesia and analgesia, is often applied. As a highly-selective α-adrenergic receptor agonist, dexmedetomidine is characterized by sedation, anti-anxiety, analgesia, stabilization of hemodynamics, inhibition on sympathetic nerve activity, and mild respiratory depression[9]. At present, dexmedetomidine has been widely used in intensive care unit sedation, non-invasive endoscopic examination, pre-operative medication, adjuvant medication during anesthesia, and post-operative analgesia[10]. Dexmedetomidine has been combined with bupivacaine to markedly prolong the sensory and motor block duration and to improve intraoperative and post-operative analgesia for women undergoing

cesarean section, without any significant complications for the mothers or infants[11]. However, there are few reports on the combination of dexmedetomidine and ropivacaine for analgesia in cesarean section. The present study aims to observe the analgesic effect of dexmedetomidine combined with ropivacaine on cesarean section and related adverse reactions, so as to provide a new idea for multi-modal analgesia.

Methods

Literature retrieval method

The retrieval strategy was developed according to Cochrane international standards and the PRISMA flowchart, and the English databases included PubMed, Web of Science, and EMbase.

– English retrieval words
  Dexmedetomidine, ropivacaine, cesarean delivery or cesarean section, and randomized controlled trial.
– Retrieval time period
  The retrieval was restricted to human randomized controlled trials in the above databases from the establishment to April 30, 2021.

Data extraction

The basic information included the research title, first author, publication time, control group and observation group, intervention measures, and indices.

Literature quality assessment

The quality of included literatures was assessed using the Cochrane risk of bias assessment tool, criteria for judging risk of bias in the risk of bias assessment tool, and possible approach for summary assessments of the risk of bias for each important outcome within and across studies designated by Cochrane.

Statistical analysis

Meta-analysis was conducted for indices enrolled using RevMan5.4 provided by Cochrane, and the forest plot made by RevMan software was used to assess the publication bias.

Random effects model (REM) was used in the case of $I^2 > 50\%$ in heterogeneity test, while fixed effects model (FEM) was used in the case of $I^2 \leq 50\%$. The effect scale indices included two-category data and continuous data.

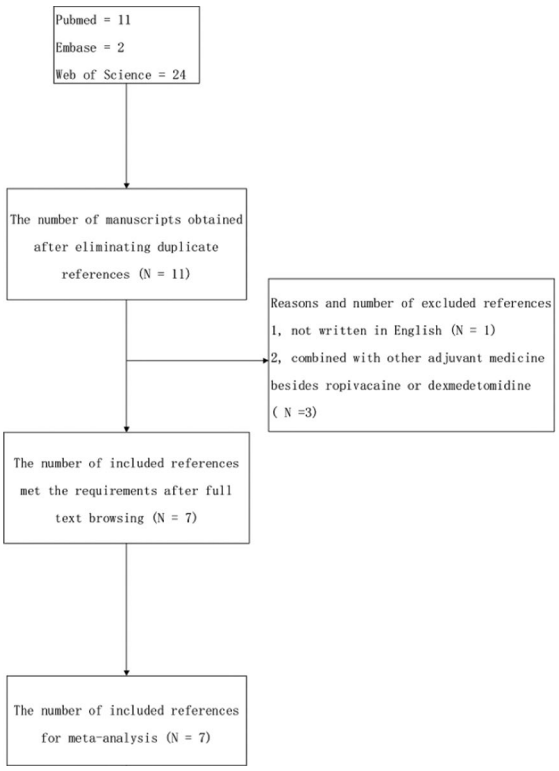

Figure 1. Preferred reporting Items for systematic reviews and meta-analysis flowchart.

Results

Literature retrieval results

A total of 37 literatures were retrieved in all databases, and 11 literatures were left after 26 duplicates were excluded. Then, one literature was excluded according to the inclusion and exclusion criteria, and three literatures were excluded after reading the full text. Finally, seven literatures all published in English were obtained (Fig. 1).

Basic characteristics of included studies

The indices, that is, the number of parturients in need of rescue, adverse reactions, satisfaction, incidence rate of transient neurological syndrome (TNS), visceral respiratory response, satisfaction with muscle relaxation, spinal anesthesia grade, mean time for rescue analgesia, visual analog scale (VAS) score, 24 h mean cumulative dose for rescue analgesia, pain-free

Table 1. Basic characteristics of included studies

First author	Published year	Treatment/control group	Treatment method	Outcome index
Bi[12]	2020	25/25	Ropivacaine/ropivacaine + dexmedetomidine	1, 5, 6, 7
Qian[13]	2020	35/35	Ropivacaine/ropivacaine + dexmedetomidine	1,9, 11, 12
Bhardwaj[14]	2017	30/30	Ropivacaine/ropivacaine + dexmedetomidine	1, 2, 3, 8, 9, 10
Kong[15]	2018	51/51	Ropivacaine/ropivacaine + dexmedetomidine	2, 4, 9, 13, 14
Mo and Qiu[16]	2017	40/40	Ropivacaine/ropivacaine + dexmedetomidine	2, 9, 13
Tang[17]	2020	30/30	Ropivacaine/ropivacaine + dexmedetomidine	2
Zhao[18]	2017	40/40	Ropivacaine/ropivacaine + dexmedetomidine	9

1: number of parturients in need of rescue; 2: adverse reactions; 3: satisfaction; 4: incidence rate of TNS; 5: visceral respiratory response; 6: satisfaction with muscle relaxation; 7: spinal anesthesia grade; 8: mean time for rescue analgesia; 9: VAS score; 10: 24 h mean cumulative dose for rescue analgesia; 11: pain-free duration; 12: time to first analgesia required; 13: Ramsay sedation score; 14: MMSE score.

duration, time to first analgesia required, Ramsay sedation score, and mini-mental state examination (MMSE) score, were covered in three studies, five studies, one study, one study, one study, one study, one study, one study, five studies, one study, one study, one study, two studies, and one study, respectively (Table 1).

Quality assessment of included studies

The randomization method was known in all of the seven included studies. The allocation concealment was known in two studies and unknown in the remaining five studies. The blind method for subjects was unknown in three studies, and the blind method for result assessment was unknown in two studies. The outcome indices were incomplete in one study, and the selective reporting was high risk in one study and also unknown in one study (Fig. 2).

Meta-analysis and publication bias

Number of parturients in need of rescue

As shown in figure 3, the number of parturients in need of rescue was reported in three studies, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results showed that the number of parturients in need of rescue in ropivacaine + dexmedetomidine group was significantly smaller than that in ropivacaine control group, and the difference was statistically significant ($\chi^2 = 28.62$, $p < 0.001$, $I^2 = 93\%$), indicating that ropivacaine combined with dexmedetomidine can significantly improve the prognosis of parturients receiving cesarean section.

Incidence rate of adverse reactions

As shown in figure 4, the incidence rate of adverse reactions was reported in five studies, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results showed that the incidence rate of adverse reactions in ropivacaine + dexmedetomidine group was significantly lower than that in ropivacaine control group, and the difference was statistically significant ($\chi^2 = 28.66$, $p = 0.007$, $I^2 = 55\%$), indicating that ropivacaine combined with dexmedetomidine can significantly reduce the incidence rate of clinical adverse reactions in parturients receiving cesarean section.

Satisfaction of parturients

As shown in figure 5, the satisfaction of parturients was reported in one study, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results showed that the number of parturients with excellent satisfaction in ropivacaine + dexmedetomidine group was significantly larger than that in ropivacaine control group, and the difference was statistically significant ($\chi^2 = 7.97$, $p = 0.05$, $I^2 = 62.3\%$), indicating that ropivacaine combined with dexmedetomidine can significantly enhance the satisfaction of parturients receiving cesarean section.

Incidence rate of TNS

As exhibited in figure 6, the incidence rate of TNS was reported in 1 study, the results belonged to two-category data and FEM was used ($I^2 < 50\%$). The results revealed that the incidence rate of TNS in ropivacaine +

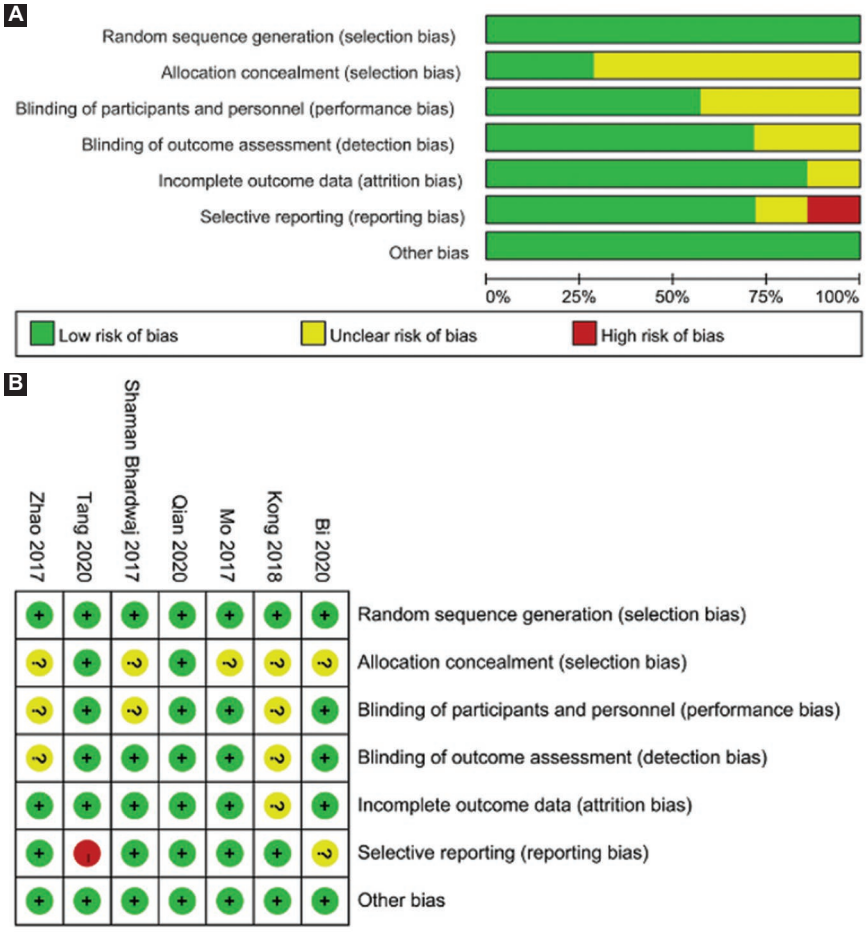

Figure 2. A and **B:** *Risk of bias of included literatures.*

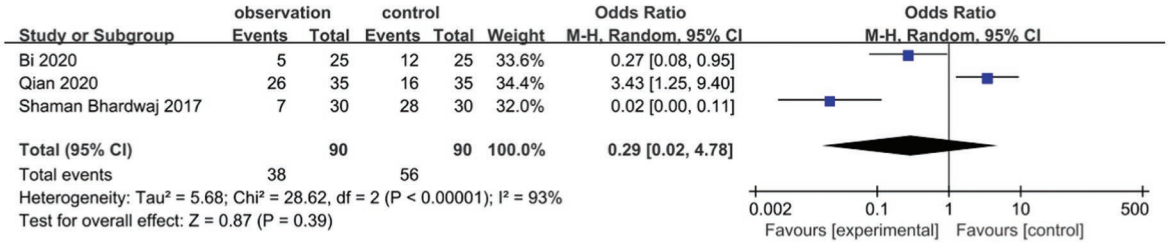

Figure 3. Forest plot of meta-analysis on the number of parturients in need of rescue in the two groups.

dexmedetomidine group was significantly lower than that in ropivacaine control group, and there was no statistically significant difference ($\chi^2 = 0.16$, $p = 0.93$, $I^2 = 0\%$).

Visceral respiratory response

As presented in supplementary data figure S1, the visceral respiratory response of parturients was reported in one study, the results belonged to two-category data, and REM was used ($I^2 > 50\%$). The results revealed that the number of parturients with visceral respiratory response in grade 2 and 3 in ropivacaine + dexmedetomidine group was significantly smaller than that in ropivacaine control group, and there was a statistically significant difference ($\chi^2 = 19.26$, $p < 0.001$, $I^2 = 89.6\%$), suggesting that ropivacaine combined with dexmedetomidine can improve the visceral respiratory response of parturients receiving cesarean section.

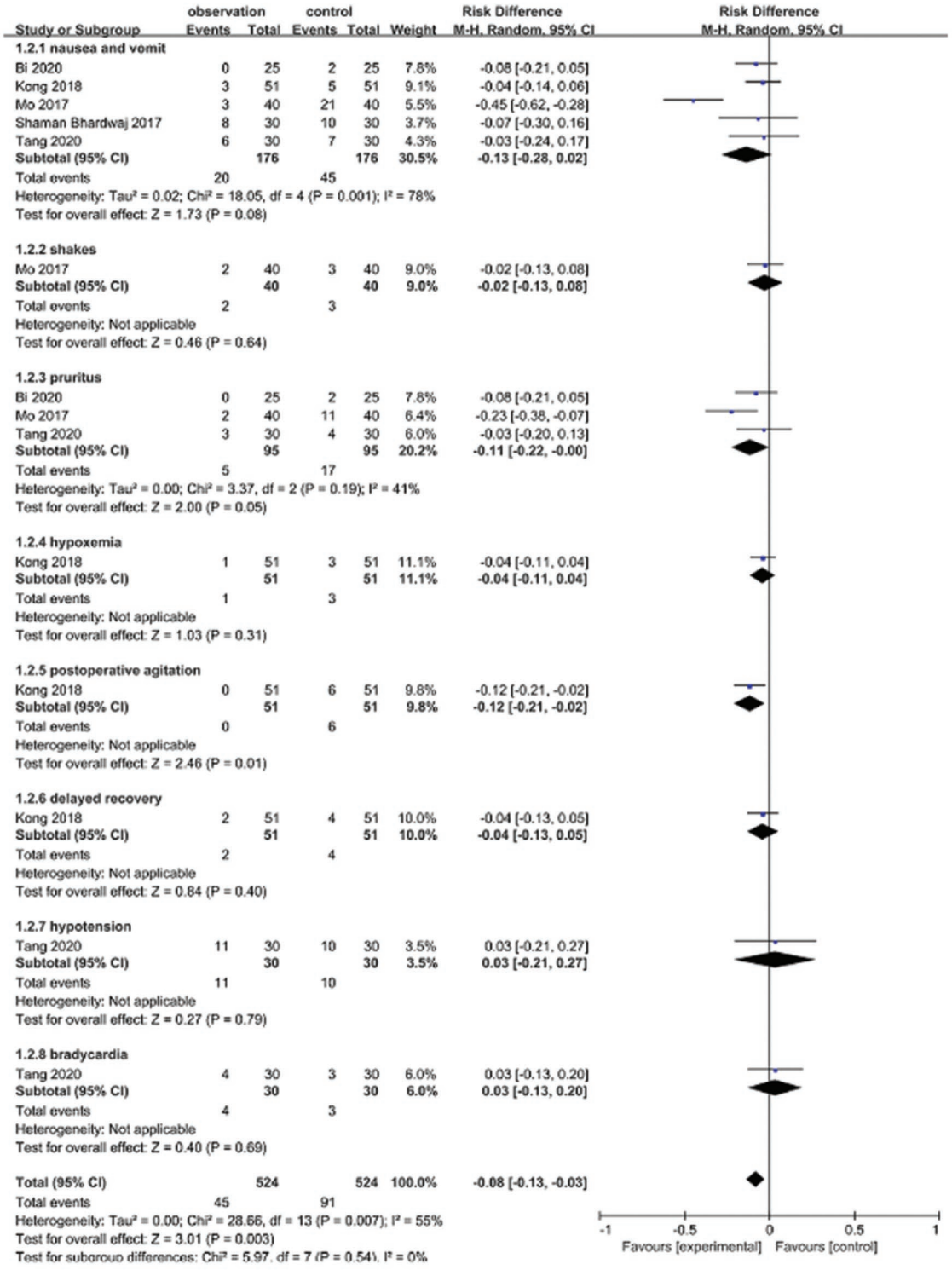

Figure 4. Forest plot of meta-analysis on the incidence rate of adverse reactions in the two groups.

Satisfaction with muscle relaxation

As displayed in supplementary data figure S2, the satisfaction of parturients with muscle relaxation was reported in one study, the results belonged to two-category data and REM was used (I^2 > 50%). The results revealed that the satisfaction of parturients with muscle relaxation in ropivacaine + dexmedetomidine

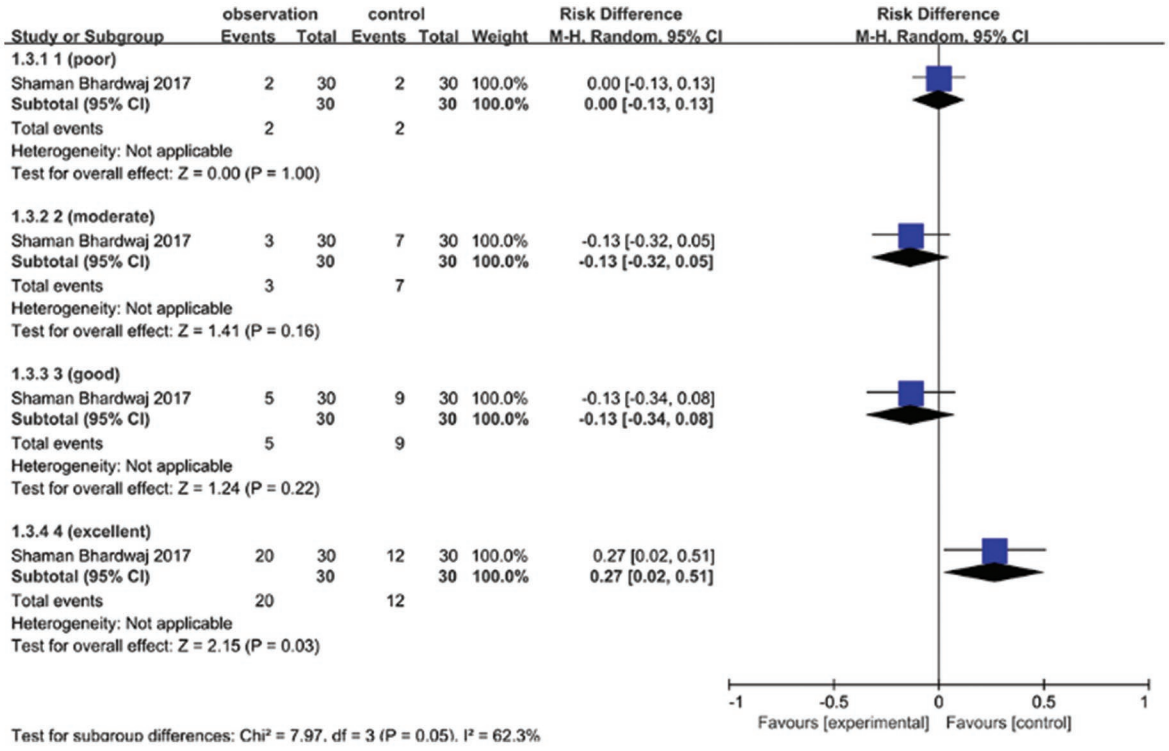

Figure 5. Forest plot of meta-analysis on the satisfaction of parturients in the two groups.

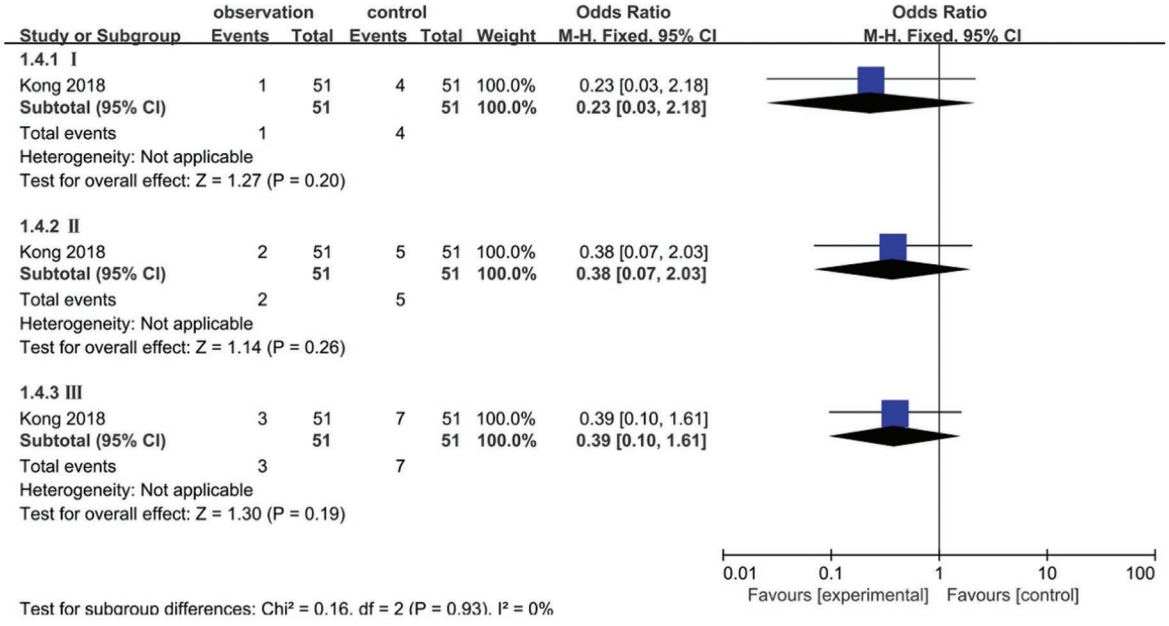

Figure 6. Forest plot of meta-analysis on the incidence rate of transient neurological syndrome in the two groups.

group was significantly higher than that in ropivacaine control group, and there was a statistically significant difference ($\chi^2 = 6.92$, $p = 0.03$, $I^2 = 71.1\%$), suggesting that ropivacaine combined with dexmedetomidine can raise the satisfaction of parturients receiving cesarean section with muscle relaxation.

Spinal anesthesia grade

The spinal anesthesia grade of parturients was reported in 1 study, the results belonged to two-category data and REM was used (I^2 > 50%) (Supplementary data Fig. S3). The results manifested that the number of parturients receiving spinal anesthesia in grade 2 and 3 in ropivacaine + dexmedetomidine group was significantly smaller than that in ropivacaine control group, and there was a statistically significant difference (χ^2 = 25.89, p < 0.01, I^2 = 92.3%), suggesting that ropivacaine combined with dexmedetomidine can lower the spinal anesthesia grade of parturients receiving cesarean section.

Mean time for rescue analgesia

The mean time for rescue analgesia of parturients was reported in one study, the results belonged to continuous data, and REM was used (I^2 > 50%) (Supplementary data Fig. S4). The results manifested that the mean time for the 4th and 5th rescue analgesia was significantly shorter in ropivacaine + dexmedetomidine group than that in ropivacaine control group, while the mean time for the 1st to 3rd rescue analgesia was significantly longer in ropivacaine + dexmedetomidine group than that in ropivacaine control group, showing statistically significant differences (χ^2 = 15.31, p = 0.0005, I^2 = 87%). It can be seen that the mean time for rescue analgesia is decreased under ropivacaine combined with dexmedetomidine compared with that under ropivacaine.

VAS score

The VAS score of parturients was reported in five studies, the results belonged to continuous data, and REM was used (I^2 > 50%) (Supplementary data Fig. S5). The results manifested that the VAS score at T1-T4 was significantly lower in ropivacaine + dexmedetomidine group than that in ropivacaine control group, showing a statistically significant difference (χ^2 = 66.68, p < 0.001, I^2 = 96%; χ^2 = 54.85, p < 0.001, I^2 = 95%; χ^2 = 16.59, p = 0.002, I^2 = 88%; χ^2 = 11.86, p = 0.003, I^2 = 83%). It can be seen that the VAS score obviously declines under ropivacaine combined with dexmedetomidine compared with that under ropivacaine.

24 h mean cumulative dose for rescue analgesia

The 24 h mean cumulative dose for rescue analgesia of parturients was reported in one study, and the results belonged to continuous data (Supplementary data Fig. S6). It was found that the 24 h mean cumulative dose for rescue analgesia was significantly lower in ropivacaine + dexmedetomidine group than that in ropivacaine control group, displaying a statistically significant difference (p < 0.001). It can be seen that the 24 h mean cumulative dose for rescue analgesia obviously declines under ropivacaine combined with dexmedetomidine compared with that under ropivacaine.

Pain-free duration

The pain-free duration of parturients was reported in one study, and the results belonged to continuous data (Supplementary data Fig. S7). It was found that the pain-free duration was significantly longer in ropivacaine + dexmedetomidine group than that in ropivacaine control group, and the difference was statistically significant (p < 0.001). It can be seen that the pain-free duration is prolonged and the prognosis is good under ropivacaine combined with dexmedetomidine compared with those under ropivacaine.

Time to first analgesia required

The time to first analgesia required was reported in one study, and the results belonged to continuous data (Supplementary data Fig. S8). It was found that the time to first analgesia required was significantly later in ropivacaine + dexmedetomidine group than that in ropivacaine control group, and the difference was statistically significant (p < 0.001). It can be seen that the time to first analgesia required is later and parturients have milder pain under ropivacaine combined with dexmedetomidine than those under ropivacaine.

Ramsay sedation score

The Ramsay sedation score of parturients was reported in two studies, the results belonged to continuous data, and REM was used (I^2 > 50) (Supplementary data Fig. S9). It was found that the Ramsay sedation score at T1-T2 was significantly better in ropivacaine + dexmedetomidine group than that in

ropivacaine control group, and the difference was statistically significant (χ^2 = 12.36, p < 0.001, I^2 = 92%; χ^2 = 102.53, p < 0.001, I^2 = 99%), indicating that the Ramsay sedation score greatly rises and the prognosis is good under ropivacaine combined with dexmedetomidine compared with those under ropivacaine.

MMSE SCORE

The MMSE score of parturients was reported in 1 study, the results belonged to continuous data, and REM was used (I^2 > 50) (Supplementary data Fig. S10). The results showed that the MMSE score after 1 d was significantly superior in ropivacaine + dexmedetomidine group to that in ropivacaine control group, and the difference was statistically significant (χ^2 = 67.60, p < 0.001, I^2 = 99%), indicating that the MMSE score after 1 d greatly rises and the prognosis is good under ropivacaine combined with dexmedetomidine compared with those under ropivacaine.

Discussion

All the seven included studies had a small sample size (< 200 cases), so false-positive or false-negative results caused by random errors could not be excluded.

Several outcome indices were selected from the seven literatures, including the number of parturients in need of rescue, adverse reactions, satisfaction, incidence rate of TNS, visceral respiratory response, satisfaction with muscle relaxation, spinal anesthesia grade, mean time for rescue analgesia, VAS score, 24 h mean cumulative dose for rescue analgesia, pain-free duration, time to first analgesia required, Ramsay sedation score, and MMSE score[12-18]. The authenticity and reliability of the above outcome indices were assessed using the RevMan software.

The randomization method was known in all of the seven included studies. The allocation concealment was known in two studies and unknown in the remaining five studies. The blind method for subjects was unknown in three studies, and the blind method for result assessment was unknown in two studies. The outcome indices were incomplete in one study, and the selective reporting was high risk in one study and also unknown in one study.

The number of parturients in need of rescue, adverse reactions, satisfaction, incidence rate of TNS, visceral respiratory response, satisfaction with muscle relaxation, and spinal anesthesia grade were all two-category data. The results showed that ropivacaine + dexmedetomidine group had a significantly smaller number of parturients in need of rescue, those with visceral respiratory response in grade 2 and 3 and those receiving spinal anesthesia in grade 2 and 3, and significantly lower incidence rates of adverse reactions and TNS than ropivacaine control group, while ropivacaine + dexmedetomidine group had a significantly larger number of parturients with excellent satisfaction and significantly better satisfaction with muscle relaxation than ropivacaine control group. It can be seen that ropivacaine combined with dexmedetomidine can significantly improve the prognosis and satisfaction of parturients receiving cesarean section and reduce the incidence rate of clinical adverse reactions.

The mean time for rescue analgesia, VAS score, 24 h mean cumulative dose for rescue analgesia, pain-free duration, time to first analgesia required, Ramsay sedation score, and MMSE score were all continuous data. The results revealed that the mean time for the 4th and 5th rescue analgesia was significantly shorter, the VAS score at T1-T4 and 24 h mean cumulative dose for rescue analgesia were significantly lower, and the time to first analgesia required was significantly later in ropivacaine + dexmedetomidine group than those in ropivacaine control group, while the Ramsay sedation score at T1-T2 and MMSE score after 1 d were significantly superior in ropivacaine + dexmedetomidine group to those in ropivacaine control group. The above findings demonstrate that parturients in ropivacaine + dexmedetomidine group had milder pain, a better prognosis and a significantly better mental state than those in ropivacaine control group.

Nevertheless, this study is limited. The number of patients is small. In addition, the results between many studies are not compared, which may have a negative impact on the conclusion.

Conclusions

Ropivacaine combined with dexmedetomidine has a better prognostic effect and causes fewer adverse reactions in parturients receiving cesarean section under anesthesia. The meta-analysis results remain to be improved with larger-sample higher-quality studies.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols. The study does not involve patient personal data.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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Supplementary data

Supplementary data are available at DOI: 10.24875/CIRU.23000532. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Integrated pulmonary index in pediatric sedation for endoscopy: a prospective cohort study

Índice pulmonar integrado en sedación pediátrica para endoscopia: estudio de cohorte prospectivo

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Abstract

Objective: *Integrated pulmonary index (IPI™) is a device working with fuzzy logic principle that analyzes patient's end-tidal carbon dioxide ($ETCO_2$), respiratory rate (RR), peripheral oxygen saturation (SpO_2), and pulse rate and provides a number between 1 and 10. We aimed to investigate the usefulness of IPI monitor in pediatric patients.* **Methods:** *After the Investigational Review Board approval pediatric patients undergoing gastrointestinal endoscopy under sedation were recruited. Propofol (Group P) and ketamine (Group K) were used for sedation. The primary outcome measure was average periprocedural IPI values. Secondary outcome measures were recovery time, endoscopist, and anesthetist satisfactions. Correlation of IPI values with physiological parameters was examined as well.* **Results:** *Periprocedural IPI scores were comparable between the groups (6.3 [4.9-7] vs. 6.8 [5.3-7.6] in Group P and Group K, respectively, p = 0.153). Recovery time was significantly longer in Group K (p < 0.001). Endoscopist and anesthetist satisfaction scores were comparable. Low IPI scores were significantly associated with low $ETCO_2$, RR, and SpO_2 values (p < 0.001).* **Conclusions:** *IPI monitor is a valuable tool in the monitorization of the pediatric patients undergoing sedation with propofol and ketamine. Both drugs are associated with comparable IPI scores. $ETCO_2$, RR, and SpO_2 values are measured lower in patients with low IPI scores (1-3 points).*

Keywords: *Gastrointestinal. IPI. Ketamine. Non-operating room. Propofol.*

Resumen

Objetivo: *El índice pulmonar integrado (IPI™) es un dispositivo que funciona con el principio de lógica difusa para analizar el dióxido de carbono al final de la espiración ($ETCO_2$), la frecuencia respiratoria (FR), la saturación periférica de oxígeno (SpO_2) y la frecuencia cardiaca (FC), y proporciona un número entre 1 y 10. Nuestro objetivo fue investigar la utilidad del monitor IPI en pacientes pediátricos.* **Métodos:** *Tras la aprobación por la Junta de Revisión de Investigaciones, se reclutaron pacientes pediátricos sometidos a endoscopia gastrointestinal bajo sedación. Para la sedación se utilizó propofol (grupo P) o ketamina (grupo K). La medida de resultado primaria fueron los valores medios del IPI periprocedimiento. Las medidas de resultado secundarias fueron el tiempo de recuperación y la satisfacción del endoscopista y del anestesista. También se examinó la correlación de los valores del IPI con los parámetros fisiológicos.* **Resultados:** *Las puntuaciones del IPI periprocedimiento fueron comparables entre los grupos (6.3 [4.9-7] en el grupo P frente a 6.8 [5.3-7.6] en el grupo K; p = 0.153). El tiempo de recuperación fue significativamente mayor en el grupo K (p < 0.001). Las puntuaciones de satisfacción del endoscopista y del*

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anestesista fueron comparables. Unas puntuaciones bajas del IPI se asociaron significativamente con valores bajos de $ETCO_2$, FR y SpO_2 (p < 0.001). **Conclusiones:** *El monitor IPI es una herramienta valiosa para la monitorización de los pacientes pediátricos sometidos a sedación con propofol o ketamina. Ambos fármacos se asocian a puntuaciones de IPI comparables. Los valores de $ETCO_2$, FR y SpO_2 son más bajos en pacientes con puntuaciones de IPI bajas (1-3 puntos).*

Palabras clave: *Gastrointestinal. IPI. Ketamina. Sala no quirúrgica. Propofol.*

Introduction

Respiratory depression and airway obstruction are the main causes of morbidity during sedation. Although pulse oximetry is a part of routine monitoring, it has disadvantages such as delayed display of arterial deoxygenation and lack of information about ventilation[1]. Capnography was found to be superior to pulse oximetry in detecting hypoventilation and airway obstruction, and the use of capnography decreased hypoxemia and apnea episodes during sedation[2-4]. Current clinical practice guidelines suggest that capnography should be used routinely, especially in moderate and deep sedation where verbal communication with patients cannot be maintained[5-7].

The integrated pulmonary index (IPI™) is a commercially available tool developed to detect changes in respiratory status of patients during sedation. This software works with a principle using the fuzzy logic mathematical model algorithm[8]. It analyzes patients' physiological parameters such as end-tidal carbon dioxide ($ETCO_2$), respiratory rate (RR), peripheral oxygen saturation (SpO_2), and pulse rate (PR) together and displays a number between 1 and 10 on the monitor (Supplementary data table 1). Studies have shown that there is agreement between IPI values and clinical assessment of the patient's respiratory status[9]. Effects of many sedative drugs individually on IPI have still not been studied.

Propofol and ketamine are among the agents frequently used in endoscopy procedures. While propofol provides rapid recovery with its short half-life, it can cause severe hemodynamic instability and respiratory failure. On the other hand, ketamine causes less hemodynamic instability and less respiratory failure, but it may cause increased secretion, agitation on awakening, and prolonged recovery[10].

The aim of this study was to investigate the periprocedural IPI values in pediatric patients sedated with propofol and ketamine. The primary outcome measure was average periprocedural IPI values. The secondary outcome measures were recovery time, endoscopist, and anesthetist satisfactions. The hypothesis of the study was that the patients sedated with ketamine would have higher IPI values.

Methods

This study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date: May 07, 2021/No: 09.2021.511) and recorded on the public website (https://clinicaltrials.gov/, No: NCT05137574). Pediatric patients undergoing elective upper and/or lower gastrointestinal endoscopy under sedation at our hospital between May 2021 and November 2021 were included in the study. Signed written informed consent was obtained from the patients' first-degree relatives or guardians. Inclusion criteria for the study were as follows: being older than 1 month and younger than 18 years of age and having American Society of Anesthesiologists (ASA) I-III physical status. Exclusion criteria were as follows: refusal to participate in the study, having an ASA IV or higher physical status, patients unsuitable for non-operating room anesthesia, and patients with a known allergy to drugs to be used for sedation. Anaphylactic reaction that may develop due to the drugs applied; respiratory failure requiring endotracheal intubation; hemodynamic failure; and gastrointestinal perforation, bleeding, or other major complications of endoscopy were determined as exclusion criteria from the study after the enrollment.

Patients were divided into two groups where propofol was used for sedation for the first group (Group P) and ketamine for the second (Group K). Patients were blind to the study design and did not know which group they would be in. The anesthetist administering the drugs and taking the measurements was the same and was not blinded to the study. The pediatric gastroenterologist performing the endoscopy procedure was blind to the study.

Routine monitoring, including pulse oximetry (SpO_2), three-lead electrocardiography, and non-invasive blood pressure, was performed after the patient entered the procedure room. A balanced crystalloid solution was started as an intravenous infusion at a rate of 10 mL/kg/h after a peripheral vascular access was placed. Midazolam 0.05 mg/kg intravenously (IV) was administered for sedation and anxiolysis. In addition,

a special nasal cannula (Smart CapnoLine Plus; Oridion Medical, Needham, MA, USA) for IPI was applied to the patient and connected to the monitor (Capnostream 20; Oridion Medical, Needham, MA, USA). Oxygen was administered at 2 L/min through the nasal cannula of the monitor. After the preparation of the surgical team was confirmed, remifentanil 0.5 μg/kg IV was administered. The patient was placed in the left lateral decubitus position and a mouthpiece was attached to the patient's mouth if upper endoscopy was to be performed. Then, propofol 0.5 mg/kg IV for Group P and ketamine 0.5 mg/kg IV for Group K was administered. The patient with a Ramsey Sedation Scale score of 5 or 6 (poor or no response to glabellar tapping) was handed over to the endoscopy team to perform the procedure. Additional doses of remifentanil 0.5 μg/kg IV, propofol 0.5 mg/kg IV (for Group P), and ketamine 0.5 mg/kg IV (for Group K) were added at the discretion of the anesthetist when needed.

Data were collected by the anesthetist performing the sedation procedure. Demographic and anthropometric measurements of the patient, ASA physical status, amount of drugs used, procedure, and recovery times were recorded. $ETCO_2$, RR, SpO_2, and PR values were recorded at 3-min intervals starting from the anesthetic induction of the patient. Our primary outcome measure was mean IPI values. The secondary outcome measures were recovery time, endoscopist and anesthetist satisfactions. The endoscopist and anesthesiologist satisfactions were graded according to the Likert scale between 1 and 10 points. Jaw-thrust maneuvers and number of bag-valve-mask assisted ventilations applied to the patient during the procedure were also recorded. Finally, the correlation of IPI values with $ETCO_2$, RR, SpO_2, and PR was analyzed. Individual IPI values were grouped as low IPI (IPI 1-3), medium IPI (IPI 4-6), and high IPI (IPI 7-10) and $ETCO_2$, RR, SpO_2, and PR values were compared between these groups.

Jamovi software (Version 2.3, https://www.jamovi.org) was used for statistical analysis. Categorical data were defined by number and percentage. Continuous data were defined as mean and standard deviation, or median and interquartile range for normal and non-normal distributions, respectively. Shapiro-Wilk test and histogram graphs were used for normality testing. X^2 test was used for the analysis of categorical data. Student's t and Mann-Whitney U-tests were used for the analysis of continuous data with normal and non-normal distributions, respectively. In the analysis of the continuous data regarding $ETCO_2$, RR, SpO_2, and PR according to the IPI score categories of the participants, Kruskal-Wallis test was used with Dwass-Steel-Critchlow-Fligner (DSCF) test for the pairwise comparisons. The independent variables of the study were age, gender, height, body weight, duration of procedure, midazolam dose, remifentanil dose, drug group, ASA score, type of intervention, and number of bag-valve-mask maneuvers. The dependent variables were $ETCO_2$, RR, SpO_2, PR, IPI scores, and IPI score categories. G*Power program (version 3.1) was used for power analysis of our study. Regarding the IPI score, which is the primary outcome measure of the study, with the α error of 5%, the power of the study being 80%, and the effect size of 0.75 obtained from the preliminary measurements on eight patients, the sample size was calculated to be 58.

Results

A total of 66 patients were eligible for the study, of which 60 were included in the final analysis. The flow diagram of the study is presented in figure 1. Thirty-six (60%) of the patients were female and the mean age was 13 (25^{th}-75^{th} percentiles: 9-15) years. Demographic and clinical characteristics of the patients are demonstrated in table 1. There was no significant difference between the two groups in terms of age, gender, height, body weight, ASA, type of intervention, amount of midazolam, and remifentanil used. There was no significant difference between the two groups in terms of the number of jaw-thrust maneuvers ($p = 0.06$, Mann-Whitney U-test). However, when categorizing the maneuver, a significant difference was observed between the groups, where the number of the patients not requiring the jaw-thrust maneuver was 4 (13.3%) and 13 (43.3%) in the Groups K and P, respectively ($p = 0.023$, X^2 test). The IPI scores were comparable between the groups (6.3 [4.9-7] vs. 6.8 [5.3-7.6] in Group P and K, respectively, $p = 0.153$, Mann-Whitney U-test). While there was no significant difference between the two groups in terms of procedure time, recovery time was significantly longer in Group K ($p < 0.001$). There was no significant difference between the two groups in terms of endoscopist and anesthetist satisfactions as well.

Descriptive statistics of IPI values and their corresponding physiological parameters are presented in figure 2 and Supplementary data table 2. Comparison of physiological parameters such as $ETCO_2$, RR, SpO_2, and PR between low, medium, and high IPI groups is given in table 2. While there was no

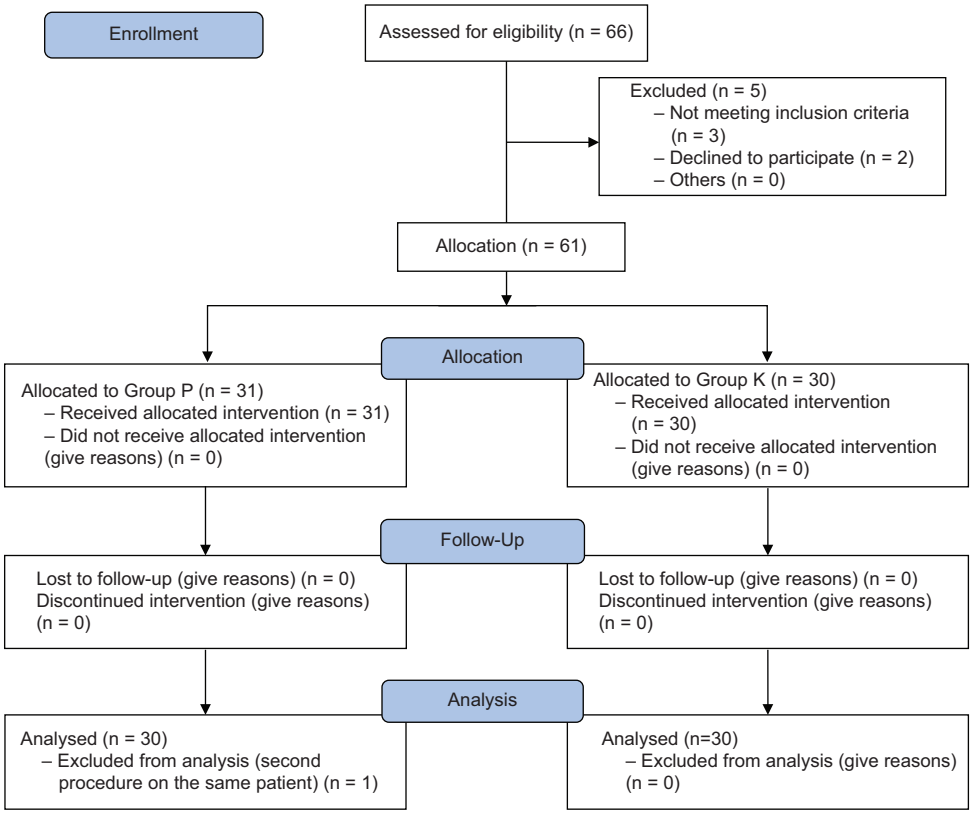

Figure 1. *Study flow diagram.*

difference between the IPI groups in terms of PR, a statistically significant difference was demonstrated between the low, medium, and high IPI groups in terms of $ETCO_2$, RR, and SpO_2 ($p < 0.001$, Kruskal-Wallis test). Pairwise comparisons between the groups revealed that $ETCO_2$ in the low IPI group was significantly lower compared to the other two ($p < 0.001$, DSCF test); SpO_2 in the high IPI group was significantly higher compared to the other two ($p < 0.001$, DSCF test); and RR values were significantly different between all the three groups ($p < 0.001$, DSCF test).

There were no complications in the patients related to the endoscopy procedure itself. Severe hypoxemia developed in two patients in Group K, in which assisted ventilation was provided with a bag-valve-mask, and the hypoxemia resolved in a short time. No bag-valve-mask ventilation was needed in Group P.

Discussion

We investigated the effectiveness of the IPI monitoring in pediatric patients sedated with propofol and ketamine and the main result of our study was that these drugs had comparable IPI scores. There was a good relationship between physiological parameters and IPI scores.

Cardiopulmonary complications continue to be important causes of morbidity and mortality in these procedures[11]. Current clinical practice guidelines recommend monitoring the hemodynamic and respiratory status of patients, as well as their state of consciousness during sedation procedures. The Association of Anesthetists recommends capnography monitoring whenever verbal communication with sedated patients is interrupted[7]. Many studies have shown that the use of capnography provides additional safety in addition to pulse oximetry[1,12,13]. Some studies have stated that derangements in respiratory pattern occurs before hypoxia develops and this can be detected by capnography[14,15]. IPI is a technology that has been introduced for more than a decade[8]. Although it has a complicated working principle like the fuzzy logic mathematical model, the value between 1 and 10 reflected on the monitor makes it extremely easy to use. In addition, grouping these values and using a three-point scale instead of a ten-point scale (low, medium, and high IPI corresponding to 1-3, 4-6, and 7-10 points, respectively) makes the use of the

Table 1. Demographic and clinical characteristics of the patients

Parameter	Group P	Group K	p
Age (years)	14.5 (10-15)	12.0 (7-13.75)	0.089
Sex			
Female	19 (52.8)	17 (47.2)	0.598
Male	11 (45.8)	13 (54.2)	
Height (cm)	153.5 (123.5-160.75)	142.5 (120-160)	0.424
Body weight (kg)	42.5 (25.75-50.75)	39.5 (19.25-52)	0.437
BMI (kg/m^2)	19 ± 5.29	18.5 ± 6.05	0.734
ASA			
I	14 (56.0)	11 (44.0)	0.715
II	13 (44.8)	16 (55.2)	
III	3 (50)	3 (50.0)	
Procedure			
Gastroscopy	21 (53.8)	18 (46.2)	0.066
Colonoscopy	8 (61.5)	5 (38.5)	
Gastroscopy + colonoscopy	1 (12.5)	7 (87.5)	
Midazolam amount (mg)	2.0 (1.5-2)	2.0 (1-2)	0.187
Remifentanil amount (μg)	40.0 (21.25-90)	30.0 (20.5-50)	0.609
Propofol/Ketamine amount (mg)	104.33 ± 50.03	72.50 ± 55.20	
IPI	6.3 (4.9-7)	6.8 (5.3-7.6)	0.153
Jaw-thrust maneuver (number)	1 (1-2) (0-6)	1 (0-2) (0-5)	0.06
0	4 (23.5)	13 (76.5)	0.023*
1	13 (68.4)	6 (31.6)	
≥ 2	13 (54.2)	11 (45.8)	
Procedure duration (min)	12.0 (10-22.5)	15.5 (10-29.5)	0.229
Recovery duration (min)	15.0 (13.5-20)	28.5 (25-30)	< 0.001*
Endoscopist satisfaction (1-10-point Likert scale)	10.0 (10-10)	10.0 (10-10)	0.190
≤ 6	1	0	
7-9	0	4	
10	29	26	
Anesthetist satisfaction (1-10-point Likert scale)	10.0 (8-10)	10.0 (10-10)	0.502
≤ 6	3	4	
7-9	6	2	
10	21	24	

*p < 0.05.
Categorical variables are given as number (percentage). Continuous variables are given as median (25th-75th percentiles) or mean ± standard deviation. For jaw-thrust maneuvers minimum-maximum values are given as well.
Group P: propofol used group; Group K: ketamine used group; BMI: body mass index; ASA: American Society of Anesthesiologist physical status; IPI: integrated pulmonary index.

Table 2. Distribution of physiological parameters according to low, medium, and high IPI groups

Parameter	Low IPI (1-3)	Medium IPI (4-6)	High IPI (7-10)	p
Number of measurements	71	85	257	
$ETCO_2$ (mmHg)	12[a] (0-34.5)	44 (35-49)	42 (36-47)	< 0.001*
RR (breaths/min)	2[b] (0-10)	13[b] (10-20)	19[b] (14-23)	< 0.001*
SpO_2 (%)	96 (86.5-100)	99 (97-100)	100[c] (99-100)	< 0.001*
PR (beats/min)	104 (85.5-125)	103 (82-128)	105 (90-116)	0.886

*p < 0.05.
[a]Significant difference compared to the medium and high IPI groups (p < 0.001, Dwass-Steel-Critchlow-Fligner (DSCF) test).
[b]Significant difference between all the IPI groups (p < 0.001, DSCF test).
[c]Significant difference compared to the low and medium IPI groups (p < 0.001, DSCF test).
Variables are given as median (25th-75th percentiles).
$ETCO_2$: end-tidal carbon dioxide; RR: respiratory rate; SpO_2: peripheral oxygen saturation; PR: pulse rate.

monitor even more practical. The use of the monitor in this way is more advantageous in cases where sedation is performed by the endoscopist or a nurse[11,16].

In our study, the mean IPI values were 6.3 in the propofol group and 6.8 in the ketamine group. Garah et al.[11] demonstrated that factors such as young age, use of propofol alone, high midazolam dose, and presence of an anesthesiologist were associated with low IPI values. In our study, we initially administered a standard dose of midazolam to the patients to benefit from its anxiolytic and amnestic properties. At the beginning of the procedure, we provided "balanced sedation" by applying remifentanil and the appointed intravenous anesthetic agent. The IPI values we obtained were consistent with the values in the propofol + midazolam or propofol + midazolam + fentanyl groups in the study of Garah et al.[11] In their study, the threshold value for the low midazolam dose was 0.08 mg/kg. In our study, we used midazolam at a dose of 0.05 mg/kg as a standard, and our IPI values were consistent with the low midazolam group in that study.

The presence of an anesthetist during the endoscopy procedure is a comfort for the endoscopy team. Evaluating the patient separately and creating a personalized anesthetic protocol not only increases the safety of the patient but also ensures the endoscopy team to focus on the endoscopy procedure itself. The American Society for Gastrointestinal Endoscopy recommends that endoscopists apply propofol-based sedation if it will increase patient safety, comfort, or the effectiveness of the procedure. According to the American Gastroenterological Association and Canadian Association of Gastroenterology guidelines, there is no increased risk associated with propofol administration by non-anesthetists[17,18]. Nevertheless, more than 20 European national anesthesia societies, including the Italian Society of Digestive Endoscopy and the Spanish Society of Anesthesia, have recommended the administration of propofol to be limited only to those trained in general anesthesia practice[19-21]. When deciding whether to provide the sedation by the endoscopy team, either by nurses or physicians, or by the anesthesia team, factors such as the patient's

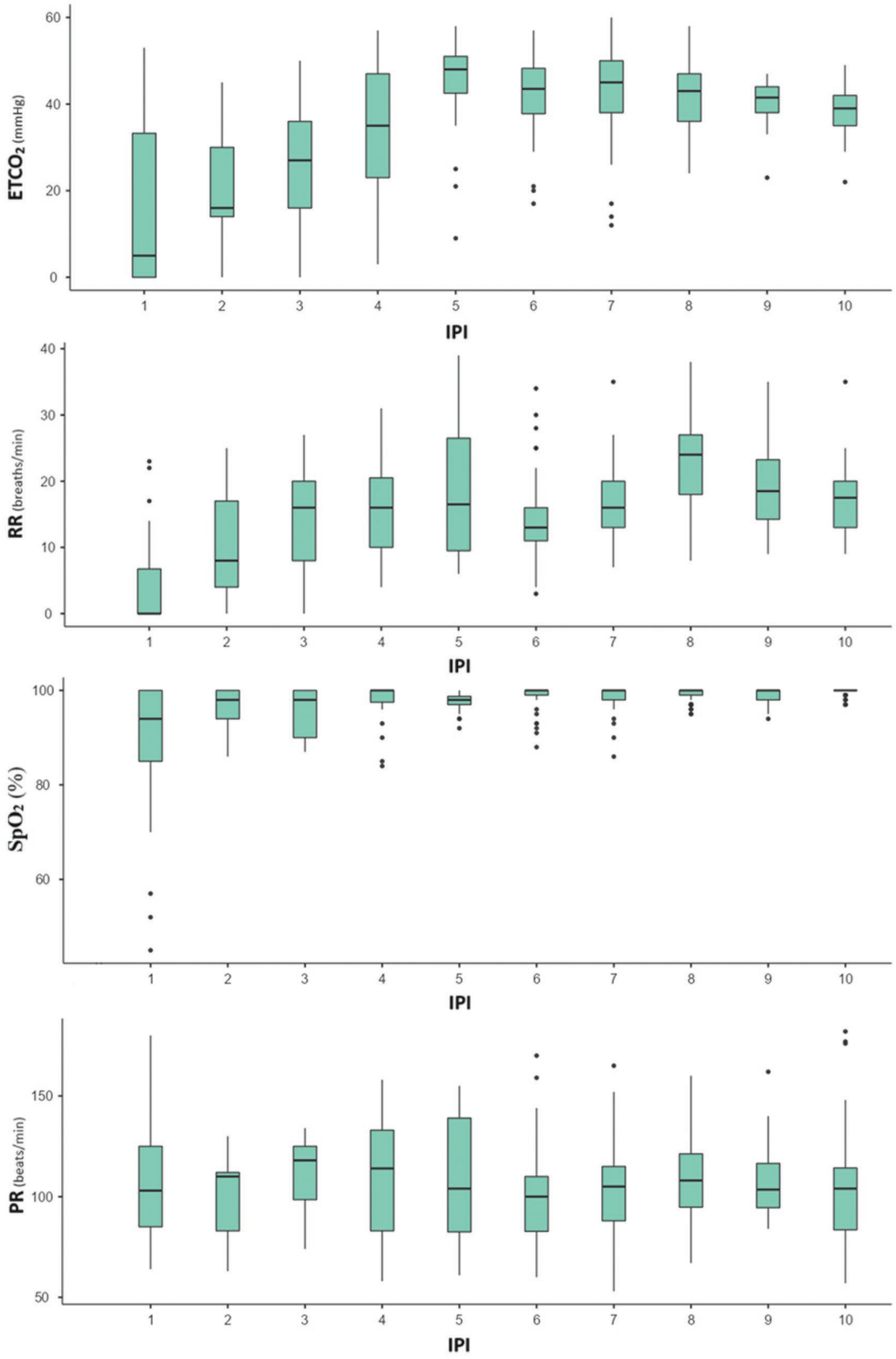

Figure 2. *Distribution of physiological variables with different IPI values. $ETCO_2$: end-tidal carbon dioxide; RR: respiratory rate; SpO_2: peripheral oxygen saturation; PR: pulse rate. Please note that IPI is determined by the combination of all the four parameters using the fuzzy logic principle.*

ASA physical status, comorbidities, the possibility of difficult airway or intubation, the types of drugs used, and probably less important factors such as the cost of the procedure should be considered altogether[22]. In our clinic pediatric endoscopy, procedures are routinely performed under sedation provided by the anesthesia team. We think that the endoscopist satisfaction scores in our study also reflect this practice.

In case of hypoxemia during the procedure nasal oxygen was increased, jaw-thrust maneuver was performed, and ventilation with bag-valve-mask was used if needed. No endotracheal intubation was needed in our study. The fact that the patient has an anesthesia team that only deals with sedation and the implementation of a protocol in accordance with the concept of balanced anesthesia played an important role here. While only two patients in the ketamine group were ventilated with a bag-valve-mask due to deep hypoxia, none of the patients in the propofol group required bag-valve-mask ventilation. In our study, the jaw-thrust maneuver was less in the ketamine group. Propofol, ketamine, dexmedetomidine, etomidate, midazolam, pentobarbital, and various combinations of these drugs are used for pediatric gastrointestinal endoscopy procedures. Each drug has its own advantages and disadvantages, and this should be considered. Propofol, especially when given as a bolus, may cause respiratory depression, apnea, and hemodynamic instability[23,24]. In a large review that examined the safety profile of propofol and included 17,066 patients, 9.3% of patients had desaturation, 1.9% had apnea, and 1.4% needed assisted ventilation[25]. Ketamine has advantages such as having analgesic effect, less respiratory depression, and not causing hemodynamic instability. Disadvantages include nausea, unpleasant recovery reactions, and rarely apnea or laryngospasm. Hallucinations usually occur in children over the age of 15. Apnea and laryngospasm occur in < 1% of patients[26,27]. Although ketamine generally preserves airway muscle tone and protective reflexes and does not suppress spontaneous breathing, desaturation is sometimes inevitable in the case of laryngospasm. Our findings were consistent with the literature.

Satisfaction scores of the team providing the sedation were also measured. The evaluation was made on parameters such as the patient's immobility, maintenance of spontaneous breathing, analgesia, no need for jaw-thrust, or assisted ventilation. There was no significant difference between the two groups in terms of anesthetist satisfaction. Even though ketamine, considering the above-mentioned characteristics, seems to be more advantageous, it is not surprising that the anesthetist who knows the pros and cons of both drugs achieves similar satisfaction scores with both drugs.

In our study, a statistically significant difference was found between low, medium, and high IPI groups in terms of $ETCO_2$, RR, and SpO_2. In the low IPI group, $ETCO_2$, RR, and SpO_2 values were below the physiological limits. This was an expected result when we consider the principle of the IPI's fuzzy logic model methodology. The expected effect of propofol is that the RR and subsequently SpO_2 decrease. Ketamine can lower SpO_2 for the reasons mentioned above. Respiratory depression has various effects on $ETCO_2$. Some studies have shown that there is an increase in $ETCO_2$ values with sedation[28,29]. However, insufficient CO_2 reaching the sample line with airway obstruction and hypoventilation will be associated with a low $ETCO_2$ reading[1]. It should be kept in mind that these measured CO_2 values do not reflect arterial CO_2 values and there may be significant differences between the two[30]. Arterial blood gas analysis should be used for the latest. The low $ETCO_2$ values in the low IPI group in our study were consistent with the findings of Berkenstadt et al.[1] In addition, RR and SpO_2 values were lower in the low IPI group in our study. Although reducing the IPI score, which we evaluate over ten scales, to three scales as low-medium-high makes the interpretation easier, it may deprive us of some valuable physiological parameters. This must be done very carefully as it may compromise the patient's follow-up.

Our study had few limitations. First, the same anesthetist provided sedation to the patient and measured the IPI scores. Blinding of this part of the study would have resulted in more objective approach to the IPI monitorization with two different drugs. Second limitation of our study was that we did not measure the level of sedation objectively. We do not routinely measure the sedation-anesthesia depth for non-operating room procedures, but in such a study, sedation depth monitoring with processed electroencephalography (EEG) could have been important in terms of the group homogeneity; yet keeping in mind that the processed EEG monitor could be unreliable in pediatric patients. Thirdly, we included both upper endoscopy and colonoscopies in the study. Anesthetic implications of these are different, specifically as regard to the airway control for the upper endoscopy and more need for analgesia for the colonoscopy. Selecting only one of these procedures for the study would have been more solid in terms of

the group homogeneity. Another is the age of the patients. We had a broad range of the age, and the pattern of the respiratory complications could have been dependent on the age, so it would be prudent to have a narrower age range for the patients. And finally, we did not measure the patients' pain levels objectively. Considering that ketamine has analgesic activity unlike propofol, having an objective pain scale would be valuable. Future studies may also include the measures of depth of sedation such as Bispectral Index and/or level of analgesia such as Analgesia Nociception Index.

Conclusion

IPI monitor is a valuable tool in the monitorization of the pediatric patients undergoing sedation for endoscopic procedures with propofol and ketamine. In this study, we found that both propofol and ketamine were associated with comparable IPI scores. IPI scores had good correlation with the physiological parameter routinely monitored; and $ETCO_2$, RR, and SpO_2 values were measured lower in the patients with low IPI scores (1-3 points).

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study. IRB number: Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date: 07.05.2021/No: 09.2021.511) Clinical trial registration number: https://clinicaltrials.gov/, No: NCT05137574 (https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000BK3J&selectaction=Edit&uid=U0004KE3&ts=2&cx=-d2tci9)

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/CIRU.24000615. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ARTÍCULO ORIGINAL

Inclusión para la gestión del riesgo de desastres en hospitales del Instituto Mexicano del Seguro Social

Inclusion for disaster risk management in hospitals of the Instituto Mexicano del Seguro Social

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Resumen

Objetivo: *Determinar el nivel de inclusión para la gestión de emergencias y desastres en hospitales del Instituto Mexicano del Seguro Social.* **Métodos:** *Se adaptó la metodología de Inclusión para la Gestión de Riesgo de Desastres en Hospitales (INGRID-H) de la Organización Panamericana de la Salud para su aplicación mediante autoevaluación en 276 hospitales. Para ello, se realizaron sesiones de asesoría con expertos mediante un formato en cascada, visitas de verificación y cumplir con el tiempo de 180 días entre cada evaluación.* **Resultados:** *En la primera autoevaluación, 220 hospitales enviaron sus informes, y en la segunda lo hicieron 236. Se seleccionaron 186 hospitales que cumplieron con los criterios de inclusión para el análisis de resultados. La media obtenida para el nivel de inclusión en la primera autoevaluación fue del 36.70% y en la segunda fue del 52.03%, con una correlación de 0.410 y $p < 0.001$, con un intervalo de confianza del 95%, siendo estadísticamente significativa.* **Conclusiones:** *La adaptación de la herramienta INGRID-H basada en autoevaluaciones y tutorías con expertos permitió obtener un diagnóstico y realizar acciones con base en ajustes razonables para incrementar el nivel de inclusión para la gestión del riesgo de desastres en los hospitales.*

Palabras clave: *Gestión de riesgos. Desastres. Discapacidad. Inclusión. Hospitales.*

Abstract

Objective: *Determine the level of inclusion in hospital disaster risk management of the Mexican Social Security Institute.* **Methods:** *The methodology Disability Inclusion in Hospital Disaster Risk Management (INGRID-H) of the Pan American Health Organization was adapted for self-assessment in 276 hospitals. Expert advice sessions were conducted using a cascade format, including verification visits, and 180 days between each evaluation.* **Results:** *In the first self-assessment, 220 hospitals submitted their reports, and in the second, 236. 186 met inclusion criteria and were selected for analysis. In the first self-assessment the mean obtained for the level of inclusion was 36.70%, and in the second was 52.03%, with a correlation of 0.410 and $p < 0.001$, with a confidence interval of 95%, being statistically significant.* **Conclusions:** *The adaptation of the INGRID-H tool using self-assessments and tutorials with experts made it possible to obtain a national diagnosis and increase the level of inclusion for disaster risk management in hospitals.*

Keywords: *Risk management. Disaster. Disability. Inclusion. Hospitals.*

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Introducción

Se estima que actualmente 1300 millones de personas sufren una discapacidad importante, lo que representa aproximadamente el 16% de la población mundial. Este número está en aumento debido al crecimiento de la enfermedades no transmisibles y al incremento en la esperanza de vida de las personas[1,2]. Esta población representa uno de los grupos más excluidos y afectados de forma desproporcionada por las crisis, emergencias o desastres; incluso en circunstancias normales, las personas con discapacidad tienen más dificultades para acceder a salud, educación, empleo y participación social, y presentan de dos a cuatro veces más probabilidades de morir en desastres y emergencias que las personas sin discapacidad[3].

En México, de acuerdo con el Censo de Población y Vivienda 2020, de 126 millones de habitantes en el país, el 5.7% tienen discapacidad o algún problema o condición mental[4].

El informe de la Encuesta Global 2023 sobre Personas con Discapacidad y Desastres de la Oficina de las Naciones Unidas para la Reducción del Riesgo de Desastres[2] revela avances limitados en la inclusión de la discapacidad en los últimos 10 años. Los desastres afectan a todos, pero tienen un impacto desproporcionado en las personas con discapacidad, que siguen experimentando barreras a la participación y exclusión social, por lo que es fundamental consolidar acciones y esfuerzos a todos los niveles, y más aún desde los servicios de salud, para que en los momentos de emergencias y desastres, de acuerdo con la estrategia «Hospitales seguros frente a desastres»[5], se cumpla con la premisa de «no dejar a nadie atrás».

En este trabajo se presenta la experiencia del Instituto Mexicano del Seguro Social (IMSS) en la adaptación para la implementación de la metodología de «Inclusión para la Gestión del Riesgo de Desastres en Hospitales» (INGRID-H) de la Organización Panamericana de la Salud (OPS) y la Organización Mundial de la Salud (OMS) como parte de las acciones que se están desarrollando en el marco de la «Política Institucional para la Atención de la Salud de Grupos en Situación de Vulnerabilidad, con Enfoque de Derechos Humanos y Perspectiva de Género»[6].

La metodología INGRID-H favorece la inclusión con base en la atención a las necesidades de las personas con discapacidad que laboran en el establecimiento de salud, está dirigida a todo el personal del hospital y hace énfasis en aquel que trabaja en la gestión del riesgo de emergencias y desastres. Los aspectos que evalúa son la visibilidad de las personas con discapacidad, la participación de las personas con discapacidad, la accesibilidad universal, las capacidades desarrolladas para la respuesta a desastres, y el plan hospitalario de respuesta a emergencias y desastres. Una vez que el hospital es evaluado obtiene una calificación que lo cataloga como excluyente, probablemente inclusivo o inclusivo, y se le recomiendan acciones a implementar para incrementar el nivel de inclusión[7,8].

Métodos

Con el apoyo del Centro Colaborador de la OMS/OPS Mex-35 para servicios de salud resilientes y con la finalidad de homologar las intervenciones y las asesorías, se formó un equipo de facilitadores en la metodología INGRID-H para personal de salud con formación y experiencia en gestión de servicios de salud y acreditados como evaluadores del «Programa Hospital Seguro» de México. Estos profesionales de la salud se integraron a los equipos de tarea tanto en la difusión de la información y asesoría referente a la metodología INGRID-H como en las posteriores visitas de verificación en todo el país.

Se observó la necesidad de adaptar la metodología INGRID-H para que fuese aplicada en formato de autoevaluación y no como evaluación por los facilitadores, para así lograr el despliegue nacional y una amplia difusión de esta actividad, y contar con la información de los hospitales del IMSS en los tiempos definidos (180 días entre cada evaluación). El universo de hospitales fue de 276, que incluyen unidades de segundo y tercer nivel, y se estableció como meta un cumplimiento de envío de autoevaluaciones del 80%.

Fase de asesoría

De julio a septiembre de 2022 se llevaron a cabo cuatro talleres de capacitación presencial para cada región del país (las unidades médicas de los tres niveles de atención del IMSS están organizadas para fines prácticos en la República Mexicana en cuatro regiones geográficas: centro, sureste, occidente y norte), con la participación de un total de 230 profesionales de la salud adscritos a diferentes hospitales. Los talleres incluyeron aspectos conceptuales de

discapacidad, inclusión, metodología y uso de la herramienta INGRID-H.

Durante octubre y noviembre de 2022, mediante sesiones virtuales regionales, se capacitó a 404 directivos de los hospitales nacionales sobre cómo realizar la autoevaluación con la metodología INGRID-H, en las cuales se establecieron compromisos:

- El cuerpo de gobierno debía establecer su equipo de tarea para la autoevaluación.
- Las fechas y el método para envío de las cédulas de autoevaluación junto con evidencia gráfica.

Fase de autoevaluación

La autoevaluación inicial y la autoevaluación a los 180 días (conforme el ciclo que especifica INGRID-H) se recibieron a través de correo electrónico y se habilitó una carpeta compartida en la nube institucional para recibir las evidencias de las acciones implementadas en cada hospital, de acuerdo con el plan de acción básico de INGRID-H.

Las unidades enviaron el plan de acción básico y el informe de la evaluación con la herramienta INGRID-H en formato electrónico.

Para facilitar el seguimiento del nivel de avance y los resultados de las evaluaciones se desarrollaron un portal web de Microsoft SharePoint para comunicación interna y un tablero en Microsoft Power BI, lo que permitió elevar el grado de cumplimiento de los compromisos establecidos para el despliegue nacional.

Fase de verificación y asesoría

En el momento en que se definió por el equipo de facilitadores adaptar la metodología INGRID-H en formato de autoevaluación se consideró que podría existir un sesgo en la información, tanto por el riesgo de desconocimiento de conceptos como por subestimación o sobreestimación en la forma de autoevaluarse, y por ello se estableció la necesidad de implementar visitas de verificación y validación de la información. En estas visitas se revisaron y validaron la información de la autoevaluación, el plan hospitalario para emergencias y desastres, y las acciones implementadas en el hospital, y además se hizo un recorrido por las instalaciones y se entrevistó al personal. Como valor agregado, se programó que la sesión hospitalaria se realizara el día de la visita para que el equipo de facilitadores presentara ante el personal el tema «Por una cultura de inclusión».

Resultados

Para el despliegue nacional de INGRID-H se incluyeron en total 276 unidades médicas hospitalarias: 240 de segundo nivel de atención, 33 de tercer nivel de atención y 3 de atención ambulatoria.

En la primera autoevaluación se recibieron 220 informes, lo que representa un 80% del total de las unidades incluidas, y para la segunda autoevaluación se recibieron 236 informes, lo que representa el 86% del total de las unidades.

La primera autoevaluación se considera como diagnóstico inicial de la unidad y la segunda autoevaluación permite visualizar el seguimiento y las acciones implementadas para incrementar su nivel de inclusión. Conforme a la metodología establecida por la OPS/OMS, el ciclo debe completarse a los 180 días, pero en la realidad los tiempos para recabar la información, validación de la información, visitas de verificación, análisis de resultados y seguimiento de planes de acción hacen que los procesos tomen mayor tiempo para su conclusión, requiriendo en algunos casos periodos entre cada ciclo mayores que lo definido.

Al realizar la comparación de las autoevaluaciones y para el análisis de los resultados se excluyeron 90 unidades, ya fuera porque no enviaron alguna de las autoevaluaciones o porque estaba incompleta la información que se solicitó; por lo anterior, se realizó el análisis comparativo de resultados de 186 hospitales. La clasificación de los hospitales de acuerdo con su calificación global se muestra en la figura 1.

En la primera autoevaluación, 125 hospitales se clasificaron como excluyentes, 45 como probablemente inclusivos y 16 como inclusivos. En la segunda autoevaluación, 67 hospitales se clasificaron como excluyentes, 77 como probablemente inclusivos y 42 como inclusivos. Observamos que existe una reducción del 46% en los hospitales clasificados como excluyentes, así como un aumento del 70% en los hospitales clasificados como probablemente inclusivos y del 163% en el número de unidades clasificadas como inclusivas. La calificación mínima obtenida en la primera autoevaluación fue del 1.86% y la máxima del 93.76%, en la segunda autoevaluación la calificación mínima fue del 8.94% y la máxima fue del 98.04% (Fig. 2).

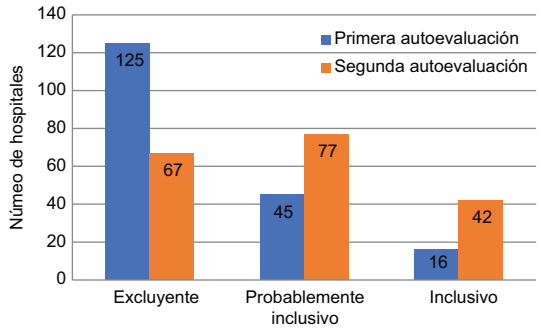

Figura 1. *Clasificación de los hospitales de acuerdo con su nivel de inclusión.*

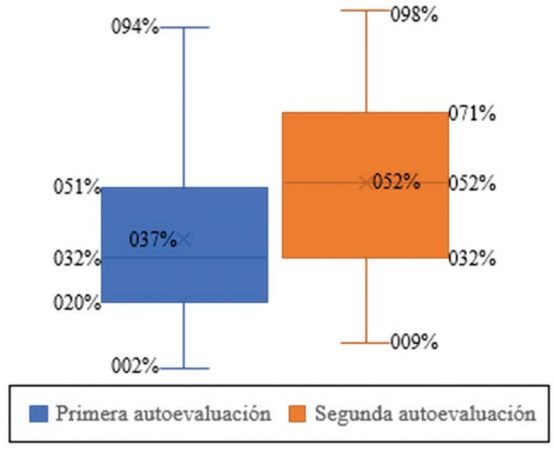

Figura 2. *Resultados globales de las dos autoevaluaciones.*

Tabla 1. Estadísticas de las muestras emparejadas

Aspecto a comparar		Media	n	Desv. desviación	Desv. error promedio
Par 1	INGRID-H 1	36.70%	186	20.98%	1.54%
	INGRID-H 2	52.03%	186	22.99%	1.69%
Par 2	Visibilidad 1	32.17%	186	31.66%	2.32%
	Visibilidad 2	52.70%	186	32.28%	2.37%
Par 3	Representación 1	17.20%	186	34.35%	2.52%
	Representación 2	39.43%	186	44.23%	3.24%
Par 4	Accesibilidad 1	47.33%	186	19.49%	1.43%
	Accesibilidad 2	55.50%	186	18.88%	1.38%
Par 5	Capacidades	36.52%	186	35.31%	2.59%
	Capacidades 2	47.99%	186	34.43%	2.52%
Par 6	Plan hospitalario	48.31%	186	32.01%	2.35%
	Plan hospitalario 2	61.83%	186	29.45%	2.16%

Tabla 2. Correlaciones de las muestras emparejadas

Aspecto a comparar		n	Correlación	p
Par 1	INGRID-H 1 e INGRID-H 2	186	0.41	0.000
Par 2	Visibilidad 1 y visibilidad 2	186	0.293	0.000
Par 3	Representación 1 y representación 2	186	0.235	0.001
Par 4	Accesibilidad 1 y accesibilidad 2	186	0.351	0.000
Par 5	Capacidades 1 y capacidades 2	186	0.306	0.000
Par 6	Plan hospitalario 1 y plan hospitalario 2	186	0.285	0.000

Por cada uno de los aspectos que evalúa INGRID-H se hizo un análisis comparativo de los resultados y se establecieron tres rangos de cumplimiento: 0% a < 44.9%, ≥ 44.9% a < 72.5% y ≥ 72.5% a 100%, conforme a la escala del índice de INGRID-H (Fig. 3).

Para el análisis estadístico se aplicó la prueba t para muestras relacionadas, utilizando el *software* SPSS versión 25.0. Se encontró que la media obtenida en la primera autoevaluación fue del 36.70% y en la segunda autoevaluación fue del 52.03%, con una correlación de 0.410 y un valor de $p < 0.001$, con un intervalo de confianza del 95%, por lo que la diferencia entre los resultados globales es estadísticamente significativa (Tablas 1 y 2).

Discusión

La revisión intermedia del Marco de Sendai[9] enfatiza la importancia de adoptar un enfoque que abarque a toda la sociedad para la implementación de la reducción del riesgo de desastres inclusiva, y subraya la urgencia de involucrar a todos los segmentos de la sociedad, incluidas las personas con discapacidad que a menudo se pasan por alto, en los esfuerzos de preparación, respuesta y recuperación ante desastres. Las personas con discapacidad no son visualizadas en el antes, el durante y el después de una emergencia, o más aún, no son integradas, consultadas ni representadas en la gestión de las emergencias, y por lo tanto tampoco conocemos cuáles son sus necesidades[10].

Los trabajos publicados sobre accesibilidad e inclusión se han enfocado en los recursos y las barreras percibidas por los usuarios y los directivos de las instalaciones de salud con un enfoque en el acceso

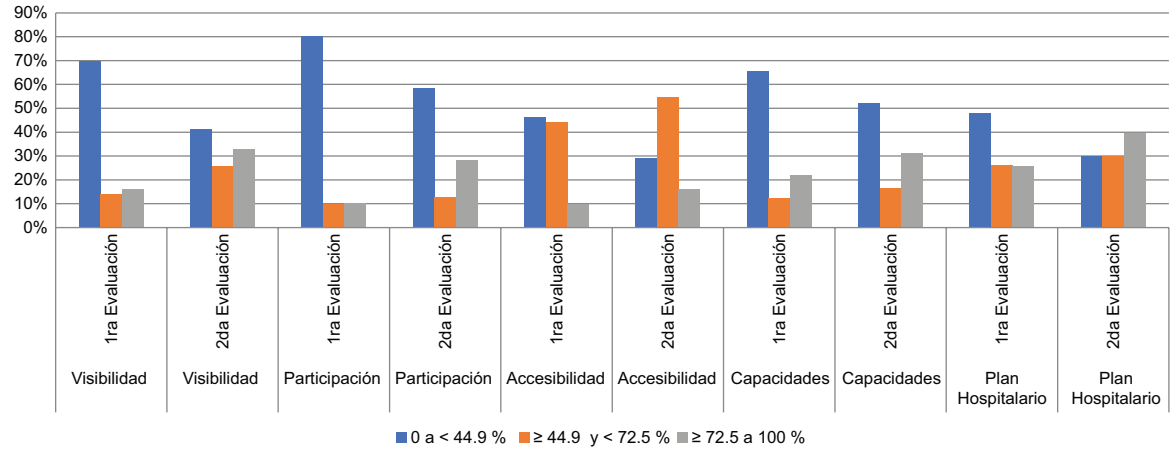

Figura 3. *Comparación de los resultados obtenidos por los hospitales en cada aspecto de INGRID-H.*

a los servicios de salud. En este sentido, Villarreal et al.[11] encontraron una accesibilidad limitada en el segundo y el primer niveles de atención en el IMSS, considerando las barreras que el usuario tiene que vencer para acceder a los servicios de salud y los recursos disponibles. Existen también extensos reportes de evaluaciones de la accesibilidad con un enfoque en las barreras físicas, la cadena de accesibilidad y la comunicación, como el publicado por la Federación Coordinadora de Personas con Discapacidad Física de Gipuzkoa[12], que sin duda contribuyen a garantizar el acceso a los servicios y representan una base sólida para la inclusión en la gestión del riesgo de desastres. Gutiérrez et al.[13] validaron una escala de evaluación de la inclusión destinada a centros y servicios para personas con discapacidad, con el fin de ayudar a las organizaciones a autoevaluar el estado en que se encuentran respecto a los valores y los procesos inclusivos, y así facilitar el desarrollo de culturas, políticas y prácticas inclusivas.

La adaptación que se realizó de la metodología INGRID-H de la OPS/OMS en un formato de autoevaluación permitió contar con un diagnóstico inicial a gran escala para conocer dónde estamos y definir, conforme al plan de acción, actividades específicas para fortalecer la inclusión. Un total de 186 unidades enviaron su información en la primera autoevaluación, lo que permitió observar que no conocemos a las personas con discapacidad y mucho menos las hacemos participar en la gestión del riesgo. Considerando que la visibilidad y la participación que enfatiza INGRID-H están con base en el personal que labora en los centros de trabajo, permitió que desde la gobernanza las unidades médicas generaran acciones para incluirlos en sus comités y planes. La Nota orientativa sobre la gestión de riesgos de discapacidad y emergencias sanitarias de la OMS refiere que en el antes de una emergencia debemos identificar las vulnerabilidades preexistentes, los recursos y las carencias de los servicios para las personas con discapacidad, así como las oportunidades para reforzar y fortalecer las capacidades. Al comparar estos rubros en la segunda autoevaluación observamos que tanto en visibilidad como en participación el porcentaje de cumplimiento incrementó en las unidades[14].

Un ejemplo de que hace falta seguir impulsando la inclusión de las personas con discapacidad está en la publicación de Qi y Hu[15], en la cual se hace referencia a que las declaratorias de emergencia por la COVID-19 en China carecieron de una perspectiva de inclusión al pasar por alto las necesidades de las personas con discapacidad, lo cual muestra que ante una grave crisis de salud pública, y ya con conocimiento de este derecho, se sigue dejándolos de lado.

La comunicación inclusiva desde los hospitales es factible, y esto lo pudimos observar desde el impulso que se brindó a acciones específicas en la accesibilidad para fortalecer la autonomía de las personas con discapacidad; ejemplo de ello fue la adecuación de la señalética en las rutas de evacuación, y en las visitas de verificación se observó que en algunas unidades el personal de salud tomó cursos de lengua de señas mexicana.

La integración de las personas con discapacidad en la gestión del riesgo de desastres permite que nos brinden la información necesaria para que en

los planes se integren sus capacidades y necesidades específicas. Un ejemplo de cómo los planes pueden ser inclusivos es el documento de la National Fire Protection Association (NFPA), Plan de evacuación de emergencia, Guía para personas con discapacidad[16], de 2022, que proporciona orientación para desarrollar un plan de evacuación de emergencia que incluya a las personas con discapacidad.

Al revisar los resultados obtenidos en las autoevaluaciones, los planes hospitalarios de respuesta, aunque consideraban a las personas con discapacidad, realmente no cumplían con lo que se revisa en INGRID-H, por lo que se realizó énfasis en cómo integrar la variable inclusión, pero sobre todo con la visión que es hacia el trabajador de la unidad médica, además de cómo fortalecer sus capacidades y la importancia de realizar ejercicios de simulación y simulacros inclusivos.

Como se mencionó, la metodología INGRID-H se basa en la gestión del riesgo de desastres desde la inclusión de las personas con discapacidad. Se requiere seguir fortaleciendo la inclusión desde una perspectiva de derechos humanos en la que se haga realidad el acceso universal a los servicios de salud, y por qué no, visualizar que mediante esta estrategia se pueden impulsar también las intervenciones para eliminar cualquier tipo de barreras culturales, educativas, económicas, políticas, etc.[17,18].

Conclusiones

La metodología de INGRID-H se centra en los trabajadores de los hospitales que tienen alguna discapacidad e impulsa que ellos participen en la gestión del riesgo de desastres. La adaptación y la implementación mediante autoevaluación de INGRID-H desde el nivel estratégico, con una metodología basada en tutorías con expertos dirigida al nivel táctico y operativo en cascada, permitió un mayor alcance en un menor tiempo y tener un diagnóstico a gran escala para enfocar los recursos y los esfuerzos con el objetivo de incrementar el nivel de inclusión en los hospitales frente a emergencias y desastres, pero sobre todo cumplir con las premisas «no dejar a nadie atrás» y «nada para nosotros sin nosotros»[19].

La inclusión en la gestión del riesgo de desastres es uno de los pilares de la resiliencia de los hospitales y del sector de la salud, y es a través de la institucionalización de estas estrategias que se puede lograr un mayor impacto. La experiencia obtenida con este proyecto da pauta para seguir avanzando en la cultura de la inclusión y el respeto a los derechos de las personas con discapacidad.

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Los autores declaran no haber recibido financiamiento para este estudio.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. El estudio no involucra datos personales de pacientes. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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LETTER TO THE EDITOR

Is it possible for end-tidal carbon dioxide analysis to replace non-invasive blood pressure measurement?

Es posible que el análisis de dióxido de carbono al final de la marea sustituya a la medición no invasiva de la presión arterial?

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To the Editor,

The number and the complexity of interventions performed in the pediatric cardiac catheterization laboratory (CCL) have been increasing in recent years. Anesthesia-related cardiac arrests have been reported as 1.2–8.7 times higher in the CCL than that for events occurring under general pediatric anesthesia[1]. Therefore, providing continuous hemodynamic monitoring is the most important issue in CCL.

Radiofrequency ablation (RF) has proven to be an effective method for the treatment of cardiac arrhythmias in pediatric patients and has been used frequently in CCL. The procedure is preceded by an electrophysiological study that performs a systematic analysis of arrhythmias in the basal state and by evaluating the patient's response to programmed electrical stimulation. RF ablation is performed on the abnormal pathway after the arrhythmia has been induced, following an electrophysiologic study and cardiac mapping, which are used to identify and locate the area responsible for the arrhythmia. Interaction between tissue and catheter is crucial for safety and success. Contact force (CF) refers to the contact between the catheter and tissue. Rapid cardiac pacing, or rapid atrial pacing (RAP), improves the stability of and helps better CF[2]. Deep hypotensive periods, which begin and end abruptly secondary to tachycardia, may be observed during periods of RAP and induced tachyarrhythmia. In addition, the type of arrhythmia and cardiac reserve may cause hemodynamic variability. There is a delayed time for detecting hypotension when only non-invasive blood pressure is monitorized for follow-up. This raises the question: is standard non-invasive monitoring sufficient for these patients? Do we need invasive arterial blood pressure monitoring for all patients?

Arterial cannulation for monitoring in children has minor complications, such as localized hematoma, or major complications such as thrombosis, acute interruption of arterial blood supply resulting in permanent ischemia and infection. Therefore, invasive arterial blood pressure monitoring is preferred in selected patients for special procedures. This raises the second question: What other monitoring method can we use to monitor hypotension in pediatric cardiac RF patients?

End-tidal carbon dioxide ($ETCO_2$) analysis and blood pressure measurement are required according to American Society of Anesthesiologists (ASA) standards for basic anesthetic monitoring[3]. Continual $ETCO_2$ analysis is a non-invasive, real-time monitoring as a cardiac-output-related parameter and also assesses the ventilation[4]. $ETCO_2$ has been found to be well correlated with hemodynamic changes. When minute volume of respiration stays stable, it may be assumed that low values of $ETCO_2$ may be attributed to changes in cardiac output. Any level of $ETCO_2$ measured during cardiopulmonary resuscitation correlates with return of spontaneous circulation or survival in adults experiencing cardiac arrest[5].

Tachyarrhythmia begins and resolves rapidly in radiofrequency ablation. This is rapidly reflected in

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$ETCO_2$, as well. Hence, continual $ETCO_2$ monitoring allows us to detect hypotension early by comparing the baseline value.

As a result, the answer stays here; $ETCO_2$ can be easily used to detect hypotension immediately without waiting for the non-invasive blood pressure measurement time, and early intervention is possible during pediatric RF ablation.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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LETTER TO THE EDITOR

Letter to the editor about the article "Association between complete blood count parameters and histologically proven acute appendicitis"

Carta al editor sobre el artículo "Asociación entre los parámetros del hemograma y la apendicitis aguda histológicamente comprobada"

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To the Editor,

We read with great interest the article by AlHarmi R., titled "Association between complete blood count parameters and histologically proven acute appendicitis." This publication highlights the importance of laboratory values in the diagnosis of acute appendicitis[1]. Acute appendicitis is the most common surgical emergency in both pediatric and adult populations. Its diagnosis relies on clinical findings, blood parameters, and imaging modalities. While the diagnostic efficacy of imaging methods currently exceeds 90%, their utilization can be restricted by various factors. In pediatric patients, challenges include patient non-compliance, concerns regarding radiation exposure from computed tomography (CT), and the inherent difficulty for pediatric patients to articulate symptoms. In adults, pregnancy and contrast-induced nephropathy are additional considerations limiting CT use. Ultrasonography offers a non-invasive and safe alternative, but its widespread applicability is hindered by the necessity for specialized operator skills, preventing its routine use by all clinicians. Particularly for physicians practicing in rural settings, blood parameters emerge as the most readily available and crucial diagnostic tool. Among laboratory assessments, the complete blood count holds a prominent position. Its rapid turnaround time, near-universal accessibility in healthcare facilities, and satisfactory diagnostic value render it a valuable diagnostic instrument. Consequently, studies investigating blood parameters in patients with acute appendicitis are of considerable significance. The authors' valuable contribution will undoubtedly enrich the existing literature. However, engaging in a discussion about this study will contribute to both the current study and future investigations. We've shared some aspects of this study that piqued our interest and offered recommendations for the article.

First, the authors indicated that the platelet-to-lymphocyte ratio (PLR) demonstrates diagnostic utility, even if at a low value. However, the diagnostic efficacy values of PLR (AUC, sensitivity, and specificity) are insufficient for its use in diagnosis or differential diagnosis. It's possible that other parameters not assessed in the study might have similar diagnostic efficacy to PLR.

Second, bilirubin has recently emerged as a significant laboratory parameter under investigation for determining acute appendicitis and predicting complicated appendicitis[2]. Notably, it serves as an important indicator for detecting perforation, particularly in pediatric patients[3]. We recommend that the authors consider incorporating bilirubin levels into their current or prospective studies, as this could yield more impactful findings.

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Third, the inclusion and exclusion criteria should be clearly defined. Many conditions, such as systemic diseases, hematological disorders, malignancies, and pregnancy, directly influence blood parameters[4]. Therefore, patients with these conditions should be excluded from the study. The article does not provide information on whether such patients were included.

Another point to consider is the negative appendectomy rate, which is reported in the literature to be between 10% and 15%, with some studies even reaching 30%[5]. However, in your study, this rate appears to be 0%. Could you please explain how this is accounted for? Or, if such cases existed, were these patients excluded from the study?

Finally, when describing the clinical characteristics of the study groups, including information such as duration of symptoms (days), length of hospital stay, and any complications that developed, would lead to a better understanding of the patient cohorts. This information could be presented in descriptive statistics of the study groups table

We congratulate the authors on their successful study and eagerly await their response to our letter.

Sincerely,

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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