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Pre-treatment pan-immune-inflammation value (PIV) and pile prognostic score in patients treated with immunotherapy

Polat Olgun, Omer Diker

Near East University, Faculty of Medicine, Department of Medical Oncology, Nicosia, Cyprus.

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Abstract

Investigating predictive markers for inflammatory events in cancer, there was a trend observed in the diversity of prognostic scores obtained from blood counts. This study aimed to assess the pan-immune-inflammation value (PIV), encompassing lymphocyte, monocyte, neutrophil and platelet levels along with the PILE score (a composite profile obtained from PIV, Eastern Cooperative Oncology Group Performance Score (ECOG PS) and serum lactate dehydrogenase (LDH)) in patients with diverse tumour types undergoing treatment with immune checkpoint inhibitors (ICIs). A retrospective study was carried out on a cohort of 105 patients with assessed pre-treatment PIV and PILE scores. Only stage III–IV patients were recruited. PIV was determined using absolute values from peripheral blood cell counts (neutrophil x platelet xmonocyte/lymphocytes) integrated at the time of diagnosis. The PILE scoring system further integrated LDH levels (<245 vs. ≥245) and ECOG-PS (0-1 vs. ≥ 2) along with the incorporated PIV values. Elevated PIV levels were significantly associated with a high response rate (RR) compared to those with lower PIV levels (HR:2.63, 95% CI:1.06–6.54; p=0.037). In this study, a PILE score of 3 emerged as a potential surrogate marker for progression-free survival (PFS) (HR=3.393, 95% CI: [0.822–13.996]; p=0,091). Further, an ECOG PS ≥2 was related to an elevated risk of both progression (HR=1.862, 95% CI: [1.030–3.364]; p=0.040) and overall survival (OS) (HR=2.399, 95% CI: [1.286–4.474]; p=0.006), alongside a reduced RR (HR=3.352, 95% CI: [1.397–8.043]; p=0.007). The impact of monocyte levels on PFS was statistically significant (HR=2.291, 95% CI: [0.999–5.251]; p=0.050). The study demonstrated an association between PIV and PILE scores and RR, PFS and OS in ICI-treated patients.

Keywords: Pan-immune-inflammation value, PILE,eastern cooperative oncology group performance

Introduction

The main point of death and poor outcomes in cancer is recurrence and metastases. Thus, it is important to find predictors to determine the prognosis in cancer patients. Nutritional and immune status are known to be closely related to tumour progression and prognosis [1].Targeted therapies and immunotherapy treatment protocols have contributed to improvements in survival rates gains over the last two decades. In one study conducted in 2011–2017, the five-year survival rate for all types of cancer increased from 49% to 68% [2].

Inflammation is important in tumour formation and affect all stages of tumour growth. It can trigger the genetic or epigenetic mechanisms, leading to tumour angiogenesis and metastasis [3]. Prolonged inflammation is the cornerstone of cancer evolution [4]. Immune checkpoint inhibitors (ICIs) based therapy has been offered to improve inflammation [5]. Further, ICIs target cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death protein 1-ligand1 (PD-1/PD-L1). These monoclonal antibodies activate the antitumour function of T cells, helping the immune system to fight against tumours [6].

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Corresponding Author: Polat Olgun, Near East University, Faculty of Medicine, Department of Medical Oncology, Nicosia, Cyprus.
Email: olgunpolat100@gmail.com

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PD-L1 expression has been explored as a predictive marker to immune check point regulators in many studies. However, most PD-L1-positive tumours may be unresponsiveness to ICIs, and some patients with PD-L1-negative tumours exhibited a better response [7,8]. Consequently, there is a pressing need for robust biomarkers that not only determine treatment outcomes (prognostic markers) but also exhibit treatment efficacy (predictive markers), especially given the occurrence of ICI-related adverse events and the associated high costs [9]. Immune prognostic scores, derived from plasma biomarkers like the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), lymphocyte–monocyte ratio (LMR), systemic immune-inflammation index (SII), and prognostic nutrition index (PNI) have been defined as a prognostic value in many types of malignancies [10-15].

This study aimed to calculate the PILE score by adding PIV (neutrophil, lymphocyte, platelet, monocyte count) and Eastern Cooperative Oncology Group performance score (ECOG PS) and serum lactate dehydrogenase (LDH) levels. The primary objective was to determine the prognostic significance of individual or combined inflammatory biomarkers.

Material and Methods

This retrospective study evaluated patients with various cancer subtypes who underwent at least one cycle of ICI treatment at Burhan Nalbantoğlu Government Hospital and Near East University Hospital between 03/2017 and 06/2022. For all patients, baseline ECOG PS, tumour histology, ICI treatment line step, metastatic tumour presence, neutrophil levels, lymphocyte levels, monocyte levels, thrombocyte levels, LDH levels as well as PIV and PILE scores were recorded before the first dose of ICI treatment. Patients under 18 years of age and those with secondary malignancies, comorbidities or conditions linked to inflammation, such as steroid replacement or active infection, were excluded.

The PIV was calculated as follows: [monocyte count (10^3/mL)×platelet count (10^3/mL)×neutrophil count (10^3/mL)/ lymphocyte count (10^3/mL)]. The PILE score was determined by assessing PIV (<median=0, ≥median=1), ECOG PS (<2=0, ≥2=1), LDH (≤ULN(245 IU/L)=0, >ULN(245 IU/L)=1) using a scoring system. These three parameters were classified into two risk groups: low PILE score (0–1) and high PILE score(2–3) groups [16].

All procedures involving human participants were performed by the committee in accordance with the institutional and/or national research ethics policies and with 1964 Declaration of Helsinki and its comparable ethical standards. All participants signed written informed consent for the available medical information to be used for in hospital data storage and research purposes. This study was approved by the ethics committee of Burhan Nalbantoğlu Government Hospital (approval number: 21/21).

Demographic characteristics were described using frequencies and percentages for categorical variables and medians and ranges for continuous variables. Progression- free survival (PFS) was calculated as the time between the first ICIs treatment and progression or death and censored at the date of the last followup for patient contact. Overall survival (OS) was calculated as the time between the first ICIs treatment and death or censored at the date of the last follow up survivors. The objective response rate (ORR) was calculated as the percentage of patients whom achieved partial or complete response among all treated patients. The OS and PFS were defined using the Kaplan–Meier curves and compared using the log-rank test. Univariate and multivariate analyses were performed with using a Cox proportional hazards model to identify independent predictive and prognostic factors. Analyses were performed using the SPSS 22 software package(IBM Corp. USA), $p<0.05$ was considered statistically significant.

Results

This study reviewed of 105 patients undergoing ICI treatment (77.1% men, 22.9% women). Table 1 presents their demographic characteristics. The median age of the whole treated cohort was 64 years (range 21–86), and 51.4% had an ECOG PS of 2 or higher. Of the patients, 18.3% patients had renal cell carcinoma, 15.1% had head and neck squamous cell carcinoma, 12.9% had malignant melanoma, 12.9% had small-cell lung cancer, 10.8% had microsatellite instability high (MSI-h) with gastrointestinal tumours, 8.6% had urinary bladder cancer, 7.5% had hepatocellular carcinoma, 5.4% had cervical cancer and 8.8% had other types of cancer. In terms of treatment sequence, 41.4% of patients were receiving first-line treatment, 41.4% were receiving second-line treatment and 17.2% had undergone additional-line ICI or combination therapy. Notably, 15.3% of patients experienced immune-adverse side effects. Further, lung metastasis was detected in 37.8% of patients, liver metastasis in 28.8%, and bone metastasis in 23.4% of patients in the evaluation according to the location of metastasis.

Based on the PIV values, a higher RR (HR: 0.38, 95% CI: [0.17–0.84]; p=0.017), significantly better PFS (HR: 1.69, 95% CI: [1.12–2.53]; p=0.011) and longer OS (HR:1.89,95% CI:1.23–2.89 p=0,003) was detected (Tables 1 and 2).In multivariate analyses, PIV levels had not a significant association with PFS (HR=0.888, 95% CI: [0.46–1.69]; p=0.719) and OS (HR=1.337, 95% CI: [0.70–2.53]; p=0.370). The results based on PIV levels and RRs were consistent (HR: 2.63, 95% CI: [1.06–6.54]; p=0.037). We performed receiver operating characteristic (ROC) analysis for the PIV score to find a cut-off value for predicting the responses. The AUC was 0.637 (95% CI: 0.534-0.741). PIV score cut-off value 550.23 predicted responses with 61.2% sensitivity and 63.6% specificity (Figure 1).

Another aspect of this study examined the importance of PILE value on RR, PFS and OS in cancer patients treated with ICI.

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PILE scores were classified as low (0–1 point) and high risk (2–3 points). PFS was significantly associated with a PILE score of 2 points (HR=3.619, 95% CI: [1.522–8.606]; p=0.004) and a PILE score of 3 points (HR=7.571, 95% CI: [2.950–19.431]; p<0.001), while OS was significantly correlated with a PILE score of 2 points (HR=2.842, 95% CI: [1.191–6.779]; p=0.019) and a PILE score of 3 points (HR=8.251, 95% CI: [3.193–21.232]; p<0.001). Further, a PILE score of 3 points at baseline, although not statistically significant, exhibited potential as a surrogate marker of PFS (HR=3.393, 95% CI: [0.822–13.996]; p=0.091) in the multivariate analysis.

Considering the dynamic nature of ECOG status, we further analysed the relationship between PFS, OS and RR. ECOG PS showed substantial associations with PFS (HR=2.872, 95% CI: [1.894–4.357]; p<0.001), OS (HR=3.322, 95% CI: [2.138–5.164]; p<0.001) and RR (HR=0.260, 95% CI: [0.116–5.584]; p=0.010). Multivariate analyses further revealed that an ECOG PS ≥2 was linked to an elevated risk of progression (HR=1.862, 95% CI: [1.030–3.364]; p=0.040), poorer survival (HR=2.399, 95% CI: [1.286–4.474]; p=0.006) and a reduced RR (HR=3.352, 95% CI: [1.397–8.043]; p=0.007) (Tables 2 and 3).

The univariate analysis (Tables 2 and 3) revealed a negative impact of monocyte levels on PFS (HR=2.900, 95% CI: [1.402–5.999]; p=0,004), OS (HR=3.492, 95% CI: [1.591–7.664]; p=0.002) and RR (HR=0.200, 95% CI: [0.044–0.912]; p=0,038) outcomes. Notably, monocyte PFS (HR=2.291, 95% CI: [0.999–5.251]; p=0.050) and OS (HR=1.780, 95% CI: [0.743–4.264]; p=0.196) were independently significant in the multivariate analysis (Table 2).

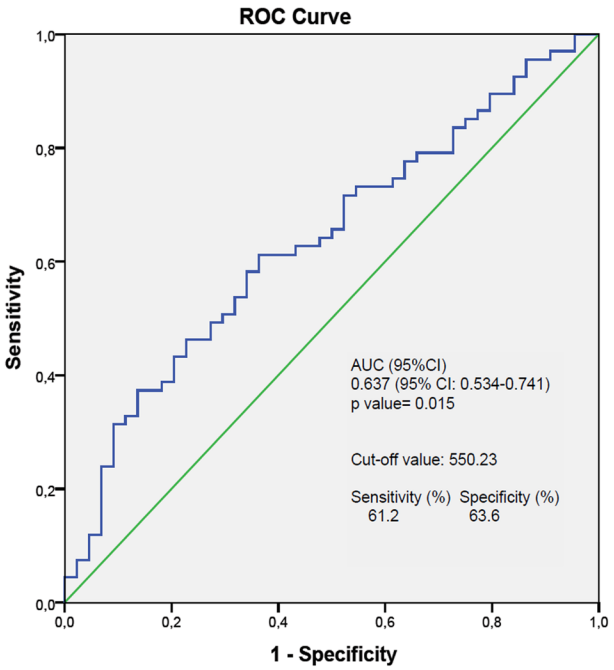

Figure 1. The results of a receiver opearting characteristic (ROC) curve analysis of the PIV score to find a cut-off value for predicting the response. AUC: Area under curve

Table 1. Characteristics of all cancer types excluding non small cell lung cancer patients

Age at start (years), Median		64 (21–86)
Sex n (%)	**Male**	81 (77.1)
	Female	24 (22.9)
ECOG performance status score n (%)	**0-1**	54 (48.6)
	2-4	57 (51.4)
Tumour histology (%)	**Renal cell carcinoma**	17 (18.3)
	Head neck squamous cell carcinoma	14 (15.1)
	Malign melanoma	12 (12.9)
	Small cell lung cancer	12 (12.9)
	MSI-H gastrointestinal tumour	10 (10.8)
	Urinary bladder cancer	8 (8.6)
	Hepatocellular carcinoma	7 (7.5)
	Cervix carcinoma	5 (5.4)
	Stomach cancer	2 (2.2)
	Malign mesothelioma	2 (2.2)
	Thymic squamous cancer	2 (1.1)
	Oesophageal squamous cell cancer	1 (1.1)
	Adrenocortical cancer	1 (1.1)
	Nasopharynx cancer	1 (1.1)
Immunotherapy line n (%)	**1st line**	46 (41.4)
	2nd line	46 (41.4)
	3rd line	5 (4.5)
	4th line	11 (9.9)
	5th line	3 (2.7)
Tumour site of metastasis (%)	**Lung**	42 (37.8)
	Brain	11 (9.9)
	Liver	32 (28.8)
	Bone	26 (23.4)
	Mediastinum	22 (19.8)
	Pleural	5 (4.5)
	Cervical	11 (9.9)
	Adrenal	9 (8.1)
Statistics median (range)	**Neutrophil (10^3/mL)**	4850 (1380–14900)
	Lymphocyte (10^3/mL)	1520 (117–7680)
	Monocyte (10^3/mL)	690 (42–1620)
	Thrombocytes (10^3/mL)	266000 (70000–913000)
		3.5 (2.3–4.9)
Pre-treatment PIV ratio n, Median		592.85 (47.63–14866.9)
Pre-treatment neutrophil ratio n, Median		4.85 (1.38–14.90)
Pre-treatment lymphocyte ratio n, Median		1.52 (0.12–7.68)
Posttreatment monocyte ratio n, Median		0.69 (0.10–1.62)
Pre-treatment platelet ratio n, Median		266.00 (70.00–913.00)
Pre-treatment Lactate dehydrogenase level	**Median**	1.00 (0–1.00)
	<245 (IU/L)	40 (36.0)
	>245 (IU/L)	69 (62.2)

n: number, ECOG: European Colleaque Oncology Group, ml: milliliter, IU/L: international units per litre

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Table 2. Univariable and multivariable analyses of overall survival and progression-free survival with Cox regression analysis (N=111)

Variables	Progression-free survival		Overall survival	
	Unadjusted HR (95% CI), P-value	Adjusted HR (95% CI), P-value	Unadjusted HR (95% CI), P-value	Adjusted HR (95% CI), P-value
ECOG PS≥2	2.872 (1.894–4.357) .000	1.862 (1.030–3.364) .040	3.322 (2.138–5.164) .000	2.399 (1.286–4.474) .006
Age	1.080 (0.721–1.617) .708		1.177 (0.772–1.795) .450	
Sex	0.927 (0.564–1.524) .765		0.842 (0.494–1.436) .528	
Presence of lung metastasis	1.260 (0.836–1.899) .269	-	1.2990.(0.850–1.986) .226	
Presence of liver metastasis	1.199 (0.773–1.858) .418	-	1.277 (0.816–1.999) .285	
Presence of bone metastasis	2.063 (1.298–3.276) .002	1.314 (0.785–2.201) .299	1.994 (1.243–3.200) .004	1.364 (0.819–2.272) .232
Immunotherapy line	1.295 (0.856–1.960) .221		1.534 (0.994–2.368) .053	
Lymphocyte	0.910 (0.752–1.100) .330		0.824 (0.665–1.022) .078	
Neutrophil	1.084 (1.006–1.169) .035	1.103 (1.006–1.210) .037	1.073 (0.991–1.162) .081	
Monocyte	2.900 (1.402–5.999) .004	2.291 (0.999–5.251) .050	3.492 (1.591–7.664) .002	1.780 (0.743–4.264) .196
Thrombocyte	1.001 (1.000–1.003) .142		1.001 (0.999–1.003) .205	
LDH	1.502 (0.978–2.308) .063		1.224 (0.789–1.898) .367	
PIV	1.691 (1.126–2.539) .011	0.888 (0.465–1.696) .719	1.890 (1.235–2.895) .003	1.337 (0.705–2.534) .374
PILE	**N/A .000**	**N/A .224**	**N/A .000**	**N/A .317**
1	1.463 (0.608–3.522) .396	1.320 (0.515–3.380) .563	1.208 (0.495–2.949) .679	0.860 (0.335–2.207) .754
2	3.619 (1.522–8.606) .004	2.400 (0.791–7.288) .122	2.842 (1.191–6.779) .019	1.190 (0.389–3.644) .761
3	7.571 (2.950–19.431) .000	3.393 (0.822–13.996) .091	8.251 (3.193–21.232) .000	2.089 (0.504–8.661) .310

HR: hazard ratio, CI: confidence interval, ECOG: European Colleaque Oncology Group, LDH: lactate dehidrogenase, PIV: panimmune-inflammation value, PILE: score composite from PIV, LDH and ECOG PS, N/A: not applicable

Table 3. Odds ratios for occurrence of second primary malignancies derived from the logistic regression models (N = 111). Univariate and multivariate analyses of clinicopathologic factors and immune-inflammation-nutritional parameters

Variables	OR for response	
	Unadjusted OR (95% CI), P-value	Adjusted OR (95% CI), P-value
ECOG PS ≥2	0.260 (0.11–0.584) .0.01	3.352 (1.397–8.043) .007
Age	1.030 (0.482–2.205) .939	
Sex	0.987 (0.386–2.525) .978	
Presence of lung metastasis	1.240 (0.568–2.710) .589	
Presence of liver metastasis	0.821 (0.354–1.904) .646	
Presence of bone metastasis	0.478 (0.182–1.257) .135	
Immunotherapy line	0.347 (0.158–0.764) .009	0.313 (0.130–0.751) .009
Lymphocyte	1.268 (0.904–1.780) .169	
Neutrophil	0.916 (0.782–1.073) .279	
Monocyte	0.200 (0.044–0.912) .038	0.597 (0.111–3.221) .549
Thrombocyte	0.998 (0.995–1.002) .324	
LDH	0.977 (0.443–2.156) .954	
PIV	0.386(0.176–0.845) .017	2.635 (1.061–6544) .037
PILE	**N/A .000**	
1	3.250 (0.771–13.693) .108	
2	0.455 (0.107–1.937) .286	
3	0.375 (0.070–1.999) .251	

OR: odds ratio, CI: confidence interval, ECOG: European Colleaque Oncology Group , LDH: lactate dehidrogenase, PIV: panimmune-inflammation value, PILE: score composite from PIV, LDH and ECOG PS, N/A: Not applicable

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Discussion

Patients with an ECOG PS>1 are typically excluded from clinical trials. However, in our study, 51.4% of patients with an ECOG PS>1 were included and received ICI treatment, aligning with real-world practice. This decision was influenced by considerations of tolerability and side-effect profiles, reflecting a pragmatic approach.Our study showed an overall worse outcome in patients with an ECOG PS>1 in terms of OS, PFS and ORR. The diminished OS, PFS and RR resulted in patients with an ECOG>1 who underwent ICI treatment could be due, at least in part, to a compromised immune response. One of the key features of aging is an increase in proinflammatory blood and a decreased ability to generate effective inflammatory responses to immunogenic stimulation. Cancer cachexia is the main result of this chronic systemic inflammation, which affects the prognosis of cancer [17]. Another potential factor to consider is the extended time required for ICI efficacy, which present a challenge for frail patients and increase the risk of early mortality. In one meta-analysis involving 3600 receiving ICI treatment in various lines for lung cancer. The authors found that an ECOG PS of 2 or higher was linked with poorer RR, PFS and OS [18]. Similarly, Bagley et al., focusing on stage 4 melanoma patients treated with ICI, identified an ECOG PS of 2 as a predictor of worsened prognosis [19]. These results were similar in almost all cancer subgroups.

In last decades, studies on the intricate association between malignant tumour tissues and the complex spectrum of inflammation, in which monocytes play a crucial role, have gained considerable importance for predicting tumour prognosis [20]. Monocytes accumulate in the tumour microenvironment and differentiate into tumour-associated macrophages (TAMs). These TAMs are polarised towards M2 macrophages, contributing to poor antigen presentation and cytokine-induced inhibition of T helper 1 adaptive immunity. TAMS derived from monocytes within tumour tissues can infiltrate the extracellular matrix, driving angiogenesis through proangiogenic factors and facilitating metastasis [21].

Although the full relationship between peripheral blood and TAMs remains unclear, various studies have demonstrated that elevated monocyte counts are correlated with increased TAM infiltration and poorer OS [22]. High monocyte counts may serve as an indicator of anti-tumour immunity and increased tumour burden, ultimately leading to a decrease in the LMR, which is associated with poorer survival [23]. Our study corroborates these findings, monocytes were an independent factor influencing PFS. Further, monocytes exhibited better survival and RR outcomes in the univariate analysis.

PIV is an innovative composite serum biomarker that draws from distinct subpopulations of absolute counts of peripheral blood cells. This individual markers independently reflect the systemic inflammation and immunity status of cancer patients [24]. Uncontrolled inflammation in the tumour microenvironment (TME) induces carcinogenesis. Neutrophils and platelets secrete pro-tumourigenic cytokines, contributing to tumour progression. In contrast, lymphocytes and monocytes bolster anti-tumour effects by provacating the immune response against cancer cells [25,26]. Platelets also play a key role in the TME, triggering thrombus formation with circulating tumour cells (CTCs), thereby allowing tumour cells to evade the immune system and facilitating tumour growth, invasion and metastasis formation [27]. Neutrophils also release pre-tumour cytokines, chemokines and reactive oxygen species, thereby regulating the TME and promoting tumour growth [28]. Tumour infiltration by CD4 (suppressor) and CD8 (cytotoxic) T-lymphocytes derived from lymphocytes contributes to the anti-tumour immune response [29]. An elevated baseline PIV is an important indicator of an adverse prognosis in patients with different types of cancer, containing breast cancer, malign melanoma and glioblastome multiforme(GBM). For example, a study on melanoma demonstrated that higher PIV scores were linked with immunotherapy resistance in candidates for first-line ICI treatment [30-32].

As mentioned above, studies have shown that high baseline PIV scores are associated with a poor prognosis. This study introduced a more robust prognostic score, named PILE, which was developed by integrating the PIV score with established predictive and prognostic parameters, including ECOG PS and LDH parameters.

Previous sections have highlighted the prognostic significance of neutrophils, platelets, monocytes and ECOG PS. LDH, an essential coenzyme in anaerobic glycolysis, is often elevated due to increased glycolytic fragments within the tumour and hypoxia-induced tumour necrosis, particularly in cases with a high tumour burden [33]. High baseline PILE scores have been correlated with poor clinical outcomes in all types lung cancer patients treated with ICI combined with chemotherapy [34,35]. Another study showed a decrease in OS for patients with higher PILE scores treated with ICIs [36]. In our study, like the PIV score, the PILE scoring system demonstrated decreased PFS and worse survival in the univariate analysis. With these results, it has become one of the largest-scale studies emphasizing the relationship between pile score and immunotherapy.

Limitations

Our study had several limitations. First, our study is retrospective nature design and reliance on data from only two centres limit the generalisability of the findings. Second, the diminished number of patient participation and the heterogeneity of tumour types may have affected the robustness of the results. In this context, disease specific multicentre prospective studies needs at exploring and establishing optimal scoring systems.

Conclusion

The combination of complete blood count data, serum biochemistry and simply clinical evaluation has the potential to create a scoring system for patients undergoing immunotherapy.

To achieve improved treatment outcomes, it is imperative to employ multiple scales assessing a range of factors in addition to ECOG PS. Randomised trials are also needed to support better treatment outcomes.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
All procedures involving human participants were performed by the committee in accordance with the institutional and/or national research ethics policies and with 1964 Declaration of Helsinki and its comparable ethical standards. All participants signed written informed consent for the available medical information to be used for in-hospital data storage and research purposes. This study was approved by the ethics committee of Burhan Nalbantoğlu Government Hospital (approval number: 21/21).

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