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Clinical characteristics and mortality risk factors in COVID-19 patients with pulmonary embolism

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ABSTRACT

Aims: To evaluate the clinical characteristics, radiological findings, and mortality-related factors in patients with COVID-19-associated pulmonary embolism (PE).

Methods: This multicenter retrospective cohort study analyzed data from 13 tertiary centers and included adult patients with molecularly confirmed SARS-CoV-2 infection and radiologically verified PE.

Results: A total of 112 patients were included (mean age: 59.9±14.1 years), of whom 50% had severe pneumonia. PE and COVID-19 were diagnosed simultaneously in 29.5% of cases. The median interval between COVID-19 diagnosis and PE development was 6 days. Despite standard or intermediate-dose thromboprophylaxis, PE occurred in 42.9% of patients. Computed tomography pulmonary angiography demonstrated predominantly peripheral embolic involvement (58.0%). According to early mortality risk stratification, 5.4% of patients were classified as high risk and 19.6% as intermediate-high risk. The in-hospital and 30-day mortality rates were 7.1% and 12.5%, respectively. Mortality was significantly associated with advanced age, comorbidities, severe pneumonia, thrombocytopenia, elevated lactate dehydrogenase and ferritin levels, high/intermediate-high risk classification, intensive care unit admission, and invasive mechanical ventilation. Multivariate logistic regression identified thrombocytopenia as an independent predictor of 30-day mortality (OR 10.11, 95% CI 1.49-68.92; p=0.01).

Conclusion: PE commonly develops during the early phase of COVID-19 and may occur despite thromboprophylaxis. Early recognition and individualized, risk-adapted anticoagulation strategies are essential.

Keywords: COVID-19, pulmonary embolism, biomarkers, thrombosis, mortality

INTRODUCTION

The emergence of Coronavirus Disease 2019 (COVID-19) in early 2020 precipitated an unprecedented global health crisis marked by rapid transmissibility and considerable mortality worldwide.[1] Beyond its primary respiratory manifestations, COVID-19 has been increasingly recognized as a multisystem disorder associated with significant thromboinflammatory complications. In particular, critically ill patients demonstrate a markedly increased predisposition to venous thromboembolism (VTE). Growing clinical evidence has consistently shown that disease severity is strongly associated with an elevated risk of acute thrombotic events, including pulmonary embolism (PE) and deep vein thrombosis.[2-4]

The pathophysiological mechanisms underlying VTE in COVID-19 are complex and multifactorial, encompassing

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all major components of Virchow's triad: endothelial injury, hypercoagulability, and circulatory stasis. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects vascular endothelial cells, leading to diffuse endothelial dysfunction and promoting both localized and systemic thrombotic responses.[5] The accompanying inflammatory and procoagulant state is characterized by elevated levels of fibrinogen, fibrin degradation products, fibrin, and D-dimer. In addition, direct viral cytopathic injury together with an exaggerated cytokine-mediated inflammatory response is believed to trigger pathological platelet activation, further amplifying the underlying coagulopathic process.[6,7] Prolonged immobilization, particularly among critically ill and intensive care unit patients, contributes to venous stasis and further increases thrombotic risk, thereby completing the classical prothrombotic framework described by Virchow's triad.

Histopathological examinations and autopsy studies of patients who died from COVID-19 have consistently demonstrated a high prevalence of diffuse pulmonary microthrombi.[8] These pathological findings have led to the growing recognition that the development of acute respiratory distress syndrome (ARDS), the most severe and life-threatening manifestation of COVID-19, is closely linked to profound pulmonary endothelial injury and dysregulated intravascular coagulation. Accordingly, the pulmonary vascular pathology observed in severe COVID-19 is increasingly considered distinct from classical ARDS and has been described as pulmonary intravascular coagulopathy (PIC) or localized pulmonary thrombosis.[9,10]

This concept is further supported by clinical evidence demonstrating that the incidence of PE in patients with COVID-19 exceeds that of concomitant deep vein thrombosis (DVT).[11] This epidemiological pattern suggests that thrombotic events associated with COVID-19 may differ from the traditional thromboembolic pathway of systemic VTE and instead reflect a process of in situ pulmonary immunothrombosis. Collectively, these findings contribute to a better understanding of the distinct pathophysiology underlying COVID-19-associated ARDS and may guide the development of targeted therapeutic strategies aimed at mitigating the localized thromboinflammatory response.

Clinical studies evaluating COVID-19 patients with thromboembolic complications have consistently demonstrated a strong association between PE and increased mortality.[12] These findings suggest that thrombotic events contribute substantially to disease progression and adverse clinical outcomes, highlighting the critical importance of early recognition and appropriate anticoagulation strategies in high-risk patients. Consequently, several national and international guidelines recommend routine pharmacological VTE prophylaxis for hospitalized patients with COVID-19, particularly in those with severe disease or additional thrombotic risk factors.[13] These recommendations are supported by accumulating evidence indicating that thrombotic risk increases in parallel with the severity of respiratory failure, emphasizing the central role of optimized antithrombotic management in reducing VTE-related morbidity and improving survival.

Nevertheless, despite the widespread adoption of standardized thromboprophylaxis protocols, acute PE remains a frequent, severe, and potentially fatal complication of COVID-19. Although existing studies have associated PE with increased mortality, detailed evidence delineating the specific demographic, biochemical, and clinical profiles that predispose patients to thromboembolic deterioration remains limited. Moreover, there is a relative paucity of data specifically addressing multivariable predictors of mortality among patients with both COVID-19 and PE.

To address this gap, the present study was designed to provide a comprehensive, multidimensional assessment of the clinical characteristics of patients with COVID-19 pneumonia complicated by radiologically confirmed PE. The primary aim was to identify independent determinants of adverse outcomes through systematic evaluation of baseline demographic features, laboratory parameters, and indicators of disease severity. This approach seeks to enhance current understanding of the prognostic significance of PE in COVID-19 and to inform more precise, risk-adapted therapeutic strategies aimed at improving survival.

METHODS

This study was conducted with the approval of the Non-interventional Ethics Committee of Sakarya University (Date: 29.01.2021, Decision No: E-71522473-050.01.04-6095). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This multicenter retrospective cohort study pooled data from 13 tertiary medical centers following approval by the national Ministry of Health and the administrative boards of all participating institutions. The study included adult patients with real-time polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection who developed acute PE either at initial presentation or within 45 days of COVID-19 diagnosis, between April 1, 2020, and February 1, 2021. Pediatric patients (<18 years), pregnant individuals, and those with a prior history of thromboembolic disease were excluded from the analysis. The 45-day interval was selected as a predefined inclusion window to capture PE events occurring during the acute and early post-acute phases of COVID-19. The requirement for written informed consent was waived by the Institutional Review Board due to the retrospective nature of the study. A diagnosis of COVID-19 was established based on positive real-time polymerase chain reaction (RT-PCR) results obtained from oro-nasopharyngeal swab samples, in conjunction with compatible clinical manifestations and characteristic radiological findings consistent with viral pneumonia. The definitive diagnosis of pulmonary thromboembolism (PE) was confirmed exclusively by computed tomography pulmonary angiography (CTPA). This imaging modality was performed in patients presenting with clinical suspicion of thromboembolic disease at hospital admission or in those who developed unexplained acute cardiopulmonary deterioration during hospitalization. Electronic medical records and paper-based files were systematically reviewed to collect data on demographic characteristics, clinical features, laboratory parameters, radiological findings, therapeutic interventions, and survival outcomes.

In accordance with national COVID-19 management guidelines issued by the Ministry of Health, pharmacological thromboprophylaxis in patients with severe disease consisted of low-molecular-weight heparin (LMWH; enoxaparin 40 mg subcutaneously twice daily) or unfractionated heparin (UFH; 7,500 U subcutaneously twice daily). In patients with non-severe disease, standard prophylaxis was administered as enoxaparin 40 mg subcutaneously once daily.[13]

Risk stratification for PE severity and assessment of early mortality risk (defined as in-hospital or 30-day all-cause mortality) were performed in accordance with the 2019 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and management of acute PE. The primary outcome was 30-day all-cause mortality, defined as death from any cause within 30 days of PE diagnosis, with the date of diagnosis serving as the starting point for follow-up. Clinical severity of COVID-19 pneumonia was classified according to national protocols; severe disease was defined as the presence of any one of the following criteria: peripheral oxygen saturation (SpO_2) ≤90% on room air, respiratory rate >30 breaths per minute, or radiological evidence of bilateral diffuse pulmonary infiltrates.[14] Secondary macrophage activation syndrome (MAS) was diagnosed after exclusion of bacterial superinfection, based on a characteristic clinical and laboratory constellation including persistent fever, markedly elevated C-reactive protein (CRP), serum ferritin levels exceeding 700 µg/L, increased D-dimer concentrations, absolute lymphopenia, thrombocytopenia, relative neutrophilia, and progressive hepatic dysfunction. Baseline laboratory parameters were obtained from the measurements recorded at the time of PE diagnosis. For baseline laboratory definitions, absolute lymphopenia was defined as a lymphocyte count <800/µL, while thrombocytopenia was defined as a platelet count <150×10^9/L. Pathological elevations in lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin, blood urea nitrogen, and creatinine were defined as values exceeding the upper limits of normal according to the reference ranges of the local laboratory.

Statistical Analysis

Data management and statistical analyses were performed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the study variables. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were presented as mean±standard deviation (SD) or median, as appropriate. Comparisons of categorical variables between groups were conducted using the Chi-square test. The normality of continuous variables was assessed using the Shapiro-Wilk test. For non-normally distributed variables, between-group comparisons were performed using the Mann-Whitney U test. Variables that demonstrated statistical significance in univariate analyses were subsequently entered into multivariate regression models to identify independent predictors of mortality. Multivariable logistic regression analysis was performed to evaluate factors associated with 30-day all-cause mortality. The model included six variables: age, comorbidity status, lymphopenia, thrombocytopenia, ferritin, and LDH. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Given the limited number of mortality events (n=14) relative to the number of variables included, the regression findings were interpreted cautiously because of the potential risk of overfitting. A two-tailed p-value <0.05 was considered statistically significant. This analytical approach provided a robust framework for evaluating prognostic determinants of survival in the study population.

RESULTS

During the study period, acute PE was radiologically confirmed in 112 patients with COVID-19. Of these, 74 (66%) were male and 38 (34%) were female, with a mean age of 59.9±14 years. A severe pneumonia phenotype was present in 56 patients (50%), while secondary MAS was identified in 18 patients (16.1%). Detailed baseline demographic, clinical, and biochemical characteristics are presented in **Table 1**.

The mean interval between COVID-19 diagnosis and PE detection was 8.8±9.4 days, with a median of 6 days. Synchronous presentation of COVID-19 pneumonia and PE at admission was observed in 33 patients (29.5%). Notably, PE developed despite standard thromboprophylaxis in 48 patients (42.9%). CTPA revealed predominantly peripheral embolic involvement (segmental or subsegmental, unilateral

Table 1. Clinical features of patients with COVID-19 pneumonia complicated by pulmonary embolism

	Total (n= 112)	No mortality (n=98)	Mortality (n=14)	p
Age (n, years)	59.9 (±14.1)	58.9 (±14.1)	67.3 (±12.0)	0.039*
Male gender (n,%)	74 (66%)	64 (65.3%)	10 (71.4%)	0.769
Time from COVID-19 diagnosis to PE, days (mean±SD)	8.8 (±9.4)	9.0 (±9.8)	7.14 (±5.9)	0.986
Concurrent embolism diagnosis with COVID-19 (n,%)	33 (29.4%)	31 (31.6%)	2 (14.3%)	0.226
Comorbidity (n,%)	68 (60.7%)	56 (57.1%)	12 (85.7%)	0.041*
Presence of severe pneumonia (n,%)	56 (50%)	44 (44.9%)	12 (85.7%)	0.004*
Multifocal pneumonia on CT (n,%)	94 (83.9%)	81 (82.7%)	13 (92.9%)	0.461
MAS diagnosis (n,%)	18 (16%)	14 (14.3%)	4 (28.6%)	0.236
Steroid use (n,%)	51 (45.5%)	42 (42.9%)	9 (64.3%)	0.132
High and intermediate-high risk of early mortality from pulmonary embolism (n,%)	28 (25%)	17 (17.3%)	11 (78.6%)	0.000*
Thrombolytic use (n,%)	7 (6.3%)	3 (3%)	4 (28.6%)	0.004*
Intensive care unit admission (n,%)	26 (23.2%)	17 (17.3%)	9 (64.3%)	0.01*
Intubation requirement (n,%)	11 (9.8%)	2 (2%)	9 (64.3%)	0.000*

*p<0.05. SD: Standard deviation, CT: Computed Tomography, MAS: Macrophage activation syndrome

or bilateral) in 65 patients (58%). According to early mortality risk stratification, 6 patients (5.4%) were classified as high risk, 22 (19.6%) as intermediate-high risk, 24 (21.4%) as intermediate-low risk, and 60 (53.6%) as low risk. Anticoagulation therapy included low-molecular-weight heparin in 88 patients (78.6%), unfractionated heparin in 16 (14.3%), and direct oral anticoagulants in 8 (7.1%). Systemic thrombolysis was administered to 7 patients. Minor bleeding occurred in one patient, while major bleeding was observed in two, including one case following thrombolysis. Intensive care unit admission was required in 26 patients, and 11 patients underwent invasive mechanical ventilation. In-hospital mortality was 7.1% (n=8), while 30-day all-cause mortality was 12.5% (n=14). Exploratory analyses identified advanced age, comorbidities, severe pneumonia, thrombocytopenia, elevated LDH and ferritin levels, higher early mortality risk class, thrombolysis, ICU admission, and mechanical ventilation as significant correlates of 30-day mortality. Although D-dimer levels were higher in non-survivors, the difference was not statistically significant (p=0.33). Similarly, CRP levels, acute renal dysfunction, and hepatic impairment were not significantly associated with mortality (**Table 2**).

The multivariable logistic regression model included age, comorbidity status, lymphopenia, thrombocytopenia, ferritin, and LDH. Thrombocytopenia was significantly associated with 30-day mortality (OR 10.11, 95% CI 1.485-68.916; p=0.01). In contrast, age (p=0.14), comorbidity status (p=0.99), lymphopenia (p=0.72), ferritin (p=0.82), and LDH (p=0.29) were not significantly associated with mortality in the multivariable model.

DISCUSSION

The present investigation focused on the clinical trajectories of patients with COVID-19 pneumonia who concurrently manifested acute PE, demonstrating an in-hospital mortality rate of 7.1% and an overall 30-day mortality rate of 12.5%. Mortality in this cohort was significantly associated with advanced age, preexisting comorbidities, severe pneumonia, thrombocytopenia, and elevated serum LDH and ferritin levels. Additionally, adverse outcomes closely correlated with high or intermediate-high early mortality risk classifications, the administration of systemic thrombolysis, intensive care unit escalation, and the requirement for endotracheal intubation.

When contextualized within the regional literature, a large-scale study examining 1,500 hospitalized COVID-19 patients in Turkiye documented a baseline in-hospital mortality rate of 4.5%.[15] In contrast, specific evaluations restricted to COVID-19 pneumonia populations complicated by PE reported a higher in-hospital mortality rate of 8.7%, while a broad meta-analysis estimated pooled mortality figures as high as 45.1% among patients with both COVID-19 and PE.[16,17] The mortality in our cohort lies between these values; the recorded mortality was expectedly higher than that traditionally observed in isolated COVID-19 pneumonia lacking embolic complications, yet it remained notably lower than the fatality rates frequently described in historical datasets for COVID-19 patients suffering from concurrent PE.

In 33 patients (29.5%), PE was diagnosed at the initial presentation of COVID-19. The temporal analysis showed that the mean interval spanning from the initial molecular detection of COVID-19 to the objective confirmation of PE was 8.8 days, with a median onset occurring at the 6-day mark. PE occurred in 42.9% of patients despite standard- or intermediate-dose LMWH prophylaxis.

Although national and international guidelines recommend pharmacological thromboprophylaxis for hospitalized patients with COVID-19 pneumonia to reduce VTE-related morbidity, thromboembolic events remain a major clinical challenge.[13,18-22] This vulnerability is especially pronounced among critically ill individuals, in whom an intense systemic inflammatory response and secondary hypercoagulability frequently override conventional prophylactic measures.[21] Supporting this observation, a comprehensive meta-analysis focusing on PE epidemiology during the pandemic documented a pooled prevalence of 18.6% among patients managed with standard thromboprophylaxis, compared with 17.3% in cohorts receiving mixed-dose prophylactic strategies.[12]

Although escalating to intermediate-dose antithrombotic regimens succeeds in lowering overall VTE incidence, it also increases the risk of bleeding. This trade-off was highlighted in another meta-analysis that reported a 3.9% incidence of major bleeding events, noting that both moderate- and full-intensity therapeutic dosing schemes were independently tied to escalated bleeding risks.[22] These competing risks complicate the management of COVID-19-associated coagulopathy. Refining

Table 2. Laboratory parameters in COVID-19 pneumonia patients with pulmonary embolism

	Total		No mortality		Mortality		p
	n		n		n		
D-dimer at PE diagnosis (µg/L)	101	4408.2(±5443)	89	4027.5(±4950)	12	7231.6(±7967)	0.337
CRP level (n/ mg/L)	109	82.2(±71.3)	95	80.1(±72.9)	14	96.8(±59.2)	0.182
Lymphopenia (n,%)	106	24 (22.6%)	92	20 (21.7%)	14	4 (28.6%)	0.516
Thrombocytopenia (n,%)	112	17 (15.2%)	98	12 (12.2%)	14	5 (35.7%)	0.038*
High ferritin level (n,%)	101	51 (50.5%)	87	40 (46%)	14	11 (78.6%)	0.024*
High LDH level (n,%)	93	66 (71%)	82	57 (69.5%)	11	11 (100%)	0.033*
Liver dysfunction (n,%)	111	29 (26.1%)	93	24 (25.8%)	14	5 (35.7%)	0.521
Kidney dysfunction (n,%)	112	18 (16%)	98	14 (14.3%)	14	4 (28.6%)	0.236

*p<0.05. D-dimer: Fibrin degradation product, CRP: C-reactive protein, Lymphopenia: Decreased lymphocyte count, Thrombocytopenia: Decreased platelet count, Ferritin: Iron-storage protein, LDH: Lactate dehydrogenase

preventative antithrombotic frameworks thus demands a highly individualized approach that carefully balances a patient's baseline thrombotic predisposition against their specific hemorrhagic risks, factoring in acute physiological severity and emerging clinical trial data. Consequently, prospective investigations remain vital to establishing optimized prophylactic dosing strategies capable of suppressing embolic breakthroughs without inducing excessive bleeding.

The development of severe pneumonia and subsequent hypoxemic respiratory failure are strongly associated with increased mortality in the context of COVID-19.[23] Consistent with this pathophysiological link, Jevnikar and colleagues[24] identified a heightened frequency of acute PE episodes specifically among individuals presenting with severe hypoxemia. Consistent with this, our data show that patients suffering from severe pneumonia experienced significantly higher mortality rates, whereas the radiological extent of involvement was not associated with survival.

Biochemical monitoring within our complete cohort revealed an overall mean D-dimer concentration of 4,408 µg/L, which escalated to a mean of 7,231 µg/L among the deceased subset. For context, historical datasets have reported distinct D-dimer profiles, showcasing means of 3,519 µg/L in patients with confirmed PE compared to 1,371 µg/L in those free of embolic complications.[16] The clinical utility of elevated D-dimer levels as a primary predictor of elevated VTE risk during COVID-19 is well-established; notably, Cui et al.[3] determined that a biomarker threshold of 1,500 µg/L yielded a sensitivity of 85% and a specificity of 88.5% when forecasting VTE among critically ill individuals in intensive care units. Furthermore, from the inception of the pandemic, marked D-dimer elevations have served as an adverse prognostic signature, with circulating concentrations exceeding 1.0 mg/L independently tied to an 18-fold increase in individual mortality risk.[1,25] Within our current investigation, although the nonsurvivors exhibited substantially higher absolute D-dimer values than survivors, this difference was not statistically significant.

Regarding the anatomical distribution of the vascular occlusions, peripheral emboli were documented in 58% of our study population. A systematic review and meta-analysis of 26 studies involving 4,382 hospitalized patients with COVID-19 reported pooled incidences of peripheral and central pulmonary embolism of 12.3% and 6.8%, respectively.[12]

Few studies have examined the multivariable determinants of mortality in COVID-19 patients with acute PE. In our study, thrombocytopenia was significantly associated with 30-day mortality in the original multivariable logistic regression analysis. However, the limited number of mortality events (n=14) raises concerns regarding potential overfitting and the stability of this estimate. Thrombocytopenia may reflect the severity of the underlying COVID-19 infection rather than represent an independent prognostic factor specifically associated with pulmonary embolism. Previous evidence has demonstrated a significant association between thrombocytopenia and severe COVID-19, supporting this interpretation.[26] Larger prospective studies are needed to clarify its potential role in mortality risk assessment among patients with COVID-19-associated pulmonary embolism.

Nevertheless, previous studies examining unselected COVID-19 cohorts have identified advanced age, comorbidities, profound hypoxemia, thrombocytopenia, and elevated D-dimer and LDH concentrations as independent predictors of mortality.[27,28] Parallel to this, classical epidemiological research focusing on PE-related mortality outside the context of SARS-CoV-2 infection has consistently demonstrated a strong survival deficit linked to male gender, advanced age, underlying chronic illnesses, elevated D-dimer levels, acute renal impairment, and high early mortality risk stratifications.[29-31]

Collectively, these overlapping risk factors show that mortality in this population is multifactorial. These insights strongly emphasize the critical necessity for heightened clinical vigilance, close biomarker monitoring, and highly individualized, survival-directed therapeutic strategies designed to optimize patient outcomes.

Limitations

The present study has several limitations that should be acknowledged. Owing to its retrospective cohort design, the analysis is inherently subject to missing or incomplete clinical and laboratory data within electronic medical records, which may limit the granularity and completeness of the findings. In addition, the substantial overlap in clinical manifestations between severe COVID-19 pneumonia and acute PE may have introduced diagnostic challenges, potentially leading to under-recognition of embolic events, particularly in less severely ill patients who did not undergo routine or systematic imaging evaluation. Because our study included only patients with confirmed COVID-19-associated pulmonary embolism, the incidence or prevalence of PE in the overall COVID-19 population could not be determined. Furthermore, the absence of a comparison group without PE precluded assessment of the independent impact of PE on mortality.

To address these limitations, future prospective studies are warranted. Ideally, such investigations should include well-defined, parallel cohorts of COVID-19 patients with and without confirmed thromboembolic disease to more accurately quantify the independent impact of PE on survival. Furthermore, prospective designs would facilitate a more detailed characterization of the underlying pathophysiological mechanisms driving adverse outcomes in this high-risk population.

CONCLUSION

The majority of acute PE events in this cohort occurred early in the course of COVID-19. This temporal clustering underscores the need for a high index of clinical suspicion and vigilant monitoring for even subtle signs of thromboembolic disease during this critical period. Importantly, the occurrence of PE despite ongoing thromboprophylaxis in a substantial proportion of patients indicates that standard prophylactic regimens may be insufficient to fully counteract the intense prothrombotic milieu associated with SARS-CoV-2 infection. This highlights the limitations of a uniform anticoagulation strategy in this population.

Given the complex interplay between thrombotic risk and bleeding potential in COVID-19 pneumonia, a more

individualized, risk-adapted antithrombotic approach appears warranted. Such strategies may include selective escalation to intermediate or therapeutic-intensity anticoagulation in patients with high-risk clinical and laboratory profiles. Ultimately, close clinical surveillance and dynamic adjustment of anticoagulant therapy are essential to optimize survival while minimizing bleeding complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Non-interventional Ethics Committee of Sakarya University (Date: 29.01.2021, Decision No: E-71522473-050.01.04-6095).

Informed Consent

The requirement for written informed consent was waived by the ethics committee because of the retrospective design and the use of anonymized data. No additional intervention was performed, and there was no direct patient contact.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: AŞ; Design: AŞ, YA, NO; Supervision: AŞ; Resources: AŞ, YA, DÖ, PAK, YS, HB, MOT, EA, FB, PYG, CS, SA, MAD, NF, AÇ, PM, ÜAA; Materials: AŞ, YA; Data Collection and/or Processing: AŞ, YA, DÖ, PAK, YS, HB, MOT, EA, FB, PYG, CS, SA, MAD, NF, AÇ, PM, ÜAA; Analysis and/or Interpretation: AŞ, YA; Literature Review: AŞ, NO; Article Writing: AŞ, NO; Critical Review: AŞ, YA, NO.

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Editor Note

Nalan Ogan is a member of the Editorial Board of this journal. She was not involved in the editor assignment, reviewer selection, peer review process, or editorial decision for this manuscript. The peer review process was managed independently by another editor.

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