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ORIGINAL RESEARCH

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Angiographic Findings, Heart Score, Laboratory Parameters, and Mortality in Patients Presenting to the Emergency Department with Chest Pain

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Abstract

Objective: Ischemic heart disease is the leading cause of global mortality, with chest pain being its most common symptom. Given its high prevalence and associated mortality, a comprehensive evaluation of cardiac function, angiographic findings, HEART Score, laboratory parameters, and mortality risk is essential for improving patient outcomes. This study aimed to examine the relationship between cardiac function, angiography reports, HEART Score, laboratory parameters, and mortality in patients presenting to the emergency department with chest pain.

Materials and Methods: This single-center, retrospective study included 644 patients presenting with chest pain to the Gaziantep City Hospital Emergency Department between January and June 2024. Gaziantep City Hospital is a tertiary-care referral center with an annual emergency department census exceeding approximately 1.2 million visits, including a high volume of cardiovascular emergency admissions. Data on age, gender, laboratory findings, echocardiography, electrocardiography (ECG) changes, HEART Score, angiography reports, and hospital discharge outcomes were analyzed.

Results: Among the 644 patients, 32.8% had myocardial wall motion abnormalities, which were significantly associated with early mortality (p=0.026). Two-vessel disease was present in 23.1% of patients, and three-vessel disease was present in 16.1%. Left anterior descending artery (LAD) stenosis ≥80% was associated with mortality (p=0.04) and multivessel disease (p<0.001). Although 47.8% of patients had ischemia-compatible ECG findings, these findings and troponin levels were not significantly associated with mortality. The neutrophil/lymphocyte ratio (AUC=0.641, p=0.004) and C-reactive protein (CRP) level (AUC=0.617, p=0.01) were significant predictors of mortality.

Conclusion: Myocardial wall motion abnormalities and LAD stenosis ≥80% were independent risk factors for mortality. The neutrophil/lymphocyte ratio and CRP level were also useful for predicting mortality. These findings may improve risk stratification and clinical decision-making for patients presenting to the emergency department with chest pain.

Keywords: Acute coronary syndrome, chest pain, HEART score, percutaneous coronary angiography

Introduction

According to data published by the World Health Organization (WHO) in 2019, ischemic heart disease ranks first among the top 10 causes of death [1] Based on WHO's cardiovascular disease (CVD) reports, an estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. CVDs encompass a range of disorders affecting the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism.

A commonly used term, acute coronary syndrome (ACS), describes a sudden condition in patients with coronary artery disease that can lead to myocardial ischemia. Heart attacks and strokes develop acutely and require urgent intervention. The American Heart Association (AHA) states that chest pain is the leading reason for hospital visits related to coronary artery disease

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(CAD) [2]. Patients diagnosed with CAD frequently present to the emergency department with chest pain felt in the middle of the sternum, which may radiate to the left shoulder, arms, elbows, and sometimes the jaw or back, causing discomfort. To reduce the global incidence of CVD and acute coronary syndrome (ACS), it is crucial to establish a universal diagnostic approach and rapid treatment strategy.

Despite advances in diagnostic strategies for chest pain, the relationship between angiographic severity, echocardiographic findings, hematological inflammatory markers, and mortality remains incompletely understood. Identifying predictors of short-term mortality may improve early risk stratification and clinical decision-making in the emergency department.

Therefore, this study aimed to evaluate the association between coronary angiographic findings, echocardiographic parameters, HEART score, and laboratory biomarkers with 30-day mortality in patients presenting to the emergency department with chest pain.

Although previous studies have examined angiographic severity, clinical risk scores, or inflammatory markers individually, few studies have evaluated the combined relationship between coronary angiographic findings, echocardiographic parameters, inflammatory biomarkers, and clinical outcomes in patients presenting to the emergency department with chest pain. In particular, the prognostic value of integrating anatomical findings from coronary angiography with inflammatory biomarkers and echocardiographic abnormalities remains insufficiently explored in emergency department populations. Therefore, the present study aimed to investigate the relationship between coronary angiographic findings, echocardiographic parameters, HEART score, inflammatory biomarkers, and mortality in patients presenting to the emergency department with chest pain.

Materials and Methods

This single-center, retrospective, observational study was conducted in the Emergency Department of Gaziantep City Hospital. The medical records of adult patients who presented with chest pain between January 1, 2024, and June 30, 2024, were retrospectively reviewed. Ethical approval was obtained from the Gaziantep Islam Science and Technology University Ethics Committee before data collection. (Approval Date: 28/12/2023; Decision No: 496.41.16) The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective design and use of anonymized data, the requirement for informed consent was waived by the ethics committee.

The inclusion criteria were as follows: patients whose first admission was to our emergency department, with chest pain as the primary complaint; patients aged 18 years or older who were suspected of ACS and underwent diagnostic tests; patients who received a specialist consultation; patients who underwent percutaneous coronary intervention (PCI) as treatment; and patients who provided informed consent. The exclusion criteria were as follows: patients whose first admission was not to the emergency department; patients whose records were incomplete during the archive search; patients who did not receive a specialist consultation; and patients who left the hospital voluntarily before completing treatment.

After applying the inclusion and exclusion criteria, a total of 644 patients were included. Both physical and digital hospital records were reviewed to extract patients' age, gender, laboratory parameters (creatine kinase-MB [CK-MB], troponin, neutrophil, lymphocyte, and RDW), echocardiography findings, ECG changes (STEMI and non-STEMI), HEART score, angiographic findings (including the left main coronary artery, left anterior descending artery, right coronary artery, and circumflex artery), and discharge status.

Electrocardiographic findings were independently evaluated by two cardiology specialists blinded to patient outcomes. Discrepancies were resolved by consensus to ensure standardized interpretation. Echocardiography was performed during hospitalization using standard transthoracic echocardiography protocols. Left ventricular ejection fraction (EF) and the presence of regional wall motion abnormalities were recorded. Echocardiographic examinations were performed and interpreted by experienced cardiologists according to standard clinical practice.

HEART Score Assessment

The HEART score was calculated for all patients at the time of emergency department admission. The score consists of five components: history, electrocardiography (ECG), age, cardiovascular risk factors, and troponin level, each graded from 0 to 2 points, resulting in a total score ranging from 0 to 10.

Patient history was categorized as slightly suspicious (0 points), moderately suspicious (1 point), or highly suspicious (2 points) for acute coronary syndrome. ECG findings were classified as normal (0 points), nonspecific repolarization disturbance (1 point), or significant ST-segment deviation (2 points). Age was scored as <45 years (0 points), 45–65 years (1 point), and >65 years (2 points). Cardiovascular risk factors included hypertension, diabetes mellitus, hyperlipidemia, smoking, obesity, and a family history of coronary artery disease. Patients with no risk factors received 0

points, those with 1–2 risk factors received 1 point, and those with ≥3 risk factors or a history of atherosclerotic disease received 2 points. Troponin levels were scored as normal (0 points), 1–3× the normal limit (1 point), or >3× the normal limit (2 points).

Based on the total HEART score, patients were categorized into low-risk (0–3), moderate-risk (4–6), and high-risk (7–10) groups.

Age Stratification

For subgroup analyses, patients were categorized into two age groups: younger than 45 years (<45 years) and 45 years or older (≥45 years). This threshold was selected based on previous literature evaluating premature coronary artery disease. The relationship between age groups and coronary angiographic findings, multivessel disease, and mortality was analyzed.

A sample size calculation was performed using G*Power 3.1 software, considering 30-day mortality as the primary endpoint. With 80% power, a 0.05 type I error rate, and an effect size of 0.30, the minimum required sample size was determined to be 98 patients. However, a total of 644 patients were included to ensure higher statistical power.

Statistical Analysis

Study data were analyzed using SPSS (Statistical Package for the Social Sciences) version 27.0 and MedCalc version 22.007 software. Numerical data were expressed as mean±standard deviation and median (interquartile range [IQR]), while categorical data were presented as percentages. The chi-square test was used to compare categorical variables. The Kolmogorov-Smirnov test was used to evaluate the normality of distribution. The independent samples t-test was used for normally distributed continuous variables. Receiver operating characteristic (ROC) analysis was used to calculate the area under the curve (AUC) values of biomarkers. Sensitivity, specificity, and cut-off values for biomarkers were determined using the Youden index J.

All hypotheses were tested using a two-tailed approach, and a p-value of <0.05 was considered statistically significant.

Results

During the study period, a total of 1192 patients presented to the emergency department with chest pain and were screened for eligibility. After applying the inclusion and exclusion criteria, 644 patients were included in the final analysis. The patient selection process is illustrated in Figure 1.

The demographic data of the patients are shown in Table 1. The median age of the study patients was 61.49 years (range, 18–97 years). In total, 63.2% of the patients were male. When the patients' HEART scores were categorized according to risk groups, 79.2% of the patients were found to be at moderate risk.

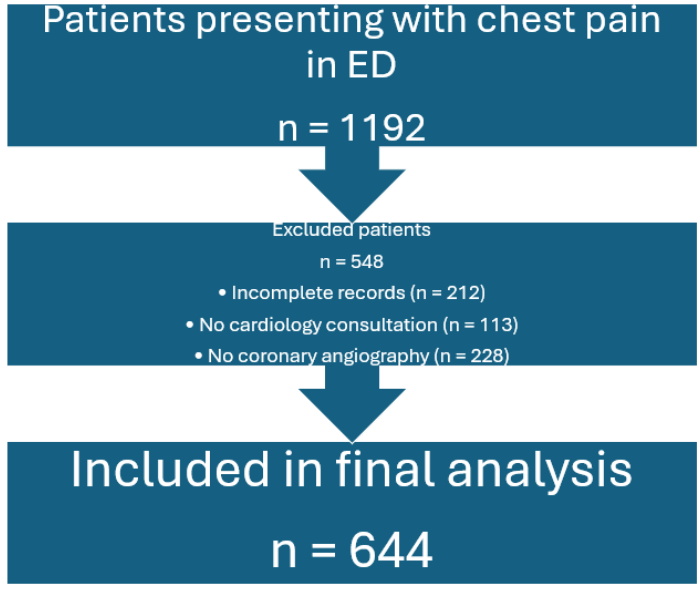

Figure 1. Patient selection process flow diagram

In our study, as shown in Table 2, analysis of ejection fraction (EF) values revealed that 36.3% of patients had EF >60%, 46% had EF between 40% and 60%, and 17.7% had EF <40%. Additionally, the overall mortality rate was found to be 5.9%. The number of patients with wall motion abnormality detected on echocardiography (ECHO) was 211 (32.8%). When echocardiographic findings were compared with early mortality, mortality was found to be significantly higher in patients with wall motion abnormality (p=0.026). Furthermore, the presence of LAD stenosis >80% on coronary angiography (p=0.04) and echocardiographic wall motion abnormality (p=0.026) were both associated with increased

Table 1. Demographic characteristics of study patients and HEART score

Presentiable	Mean ± SD; n (%)
Age (Years)	61.49 (18–97)
Gender	
Male	408 (63.2)
Female	236 (36.8)
HEART score	
Low risk (0–3)	72 (11.2)
Moderate risk (4–6)	510 (79.2)
High risk (>7)	62 (9.6)

SD: standard deviation, n: number

Table 2. Echocardiographic and coronary angiography results of patients

Presentiable	n (%)
EF values (%)	
>60	234 (36.3%)
40-60	296 (46.0%)
<40	114 (17.7%)
Echocardiographic wall motion abnormality	
Present	211 (32.8%)
Absent	433 (67.2%)
ECG findings (Ischemia-Consistent)	
Present	308 (47.8%)
Absent	336 (52.2%)
LAD critical stenosis	
Present	318 (49.4%)
Absent	326 (50.6%)
RCA critical stenosis	
Present	231 (35.9%)
Absent	413 (64.1%)
LMCA critical stenosis	
Present	28 (4.3%)
Absent	616 (95.7%)
CX critical stenosis	
Present	250 (38.8%)
Absent	394 (61.2%)
Two-Vessel disease	
Present	149 (23.1%)
Absent	495 (76.9%)
Three-Vessel disease	
Present	104 (16.1%)
Absent	549 (83.9%)
LAD >80% stenosis	
Present	276 (42.9%)
Absent	368 (57.1%)
Mortality	
Present	38 (5.9%)
Absent	606 (94.1%)

N: number, EF: Ejection fraction, ECG: Electrocardiogram, LAD: Left anterior descending artery, RCA: Right coronary artery, LMCA: Left main coronary artery, Cx: Circumflex artery

mortality. A total of 644 patients underwent echocardiography in our hospital. Among them, 36.3% had an ejection fraction (EF) >60%. Additionally, 32.8% of patients showed myocardial wall motion abnormality on echocardiography. At the time of emergency department admission, 47.8% of patients exhibited electrocardiographic (ECG) findings consistent with ischemia. Analysis of their reports showed that 23.1% had critical stenosis in two vessels and 16.1% had critical stenosis in three vessels. When 30-day mortality was evaluated, the overall mortality rate was calculated as 5.9% (Fig. 2).

The study categorized patients' EF values according to the heart failure classification. A significant association was found between low EF values and myocardial wall motion abnormality (Table 3, Fig. 1).

The relationship between laboratory test results at emergency department admission and mortality was analyzed, as shown in Table 4. CRP level (p=0.04), white blood cell (WBC) count (p<0.001), and neutrophil/lymphocyte ratio (p<0.001) showed significant differences between the two groups. No significant relationship was found between troponin levels and mortality.

Patients' HEART scores calculated in the emergency department were categorized into low-, moderate-, and high-risk groups, and their relationship with mortality was analyzed, as shown in Table 5. No significant association was found between HEART score risk groups and mortality (p=0.11).

In patients with LAD stenosis >80% following the CAG procedure, the relationship with concomitant stenosis in other vessels was

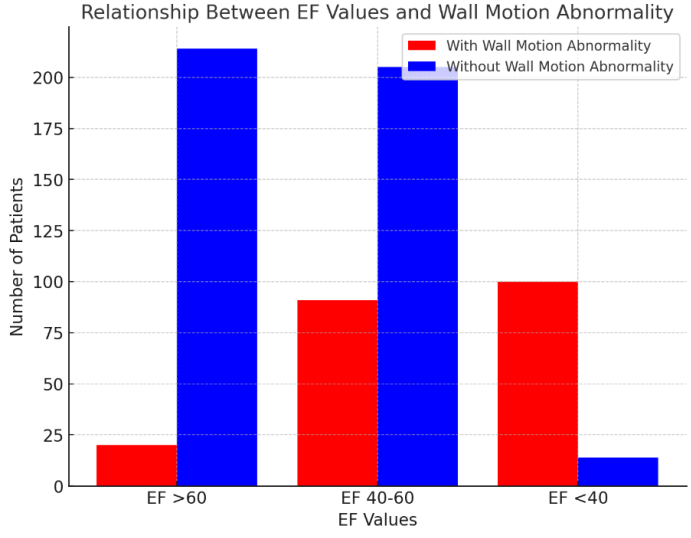

Figure 2. The relationship between EF values calculated during echocardiography and myocardial wall motion abnormality in study patients

Table 3. Relationship between EF values and wall motion abnormality in echocardiography

Parameters	EF values				
	EF >60	EF <60 -EF>40	EF<40	Total	p*
Echocardiographic wall motility Abnormalitiy					
Present	20	91	100	211	<0.001
Absent	214	205	14	433	

* Chi-square test was used. EF: Ejection Fraction

Table 4. Relationship between laboratory results and mortality

Parameters	30-Day Mortality Mean ± *SD*		
	Absent	Present	p*
Troponin değeri (ng/L)	7456.36 ±2366.7	8507.73±2149.29	0.089
CRP (mg/L)	31.67±28.2	50.9± 17.05	0.04*
Neutrophil count (x10^9/L)	8.09±4.9	10.35±6.00	0.006
Lymphocyte count (x10^9/L)	2.2±1.25	1.68±1.13	0.594
CKMB (U/L)	39.05±27.78	24.71±14.8	0.890
WBC (x10^9/L)	10.93±3.78	12.35±5.6	<0.001*
Neutrophil/Lymphocyte Ratio	5.48 ±4.3	11.02±14.6	<0.001*

*Independent Samples T-Test was used. A p-value <0.05 was considered statistically significant. SD: Standard deviation, CRP: C-Reactive protein, CKMB: Creatinine kinase-MB, WBC: White blood cell count

Table 5. Relationship between HEART score and mortality

Mortality	HEART score			
	Low risk	Moderate risk	High risk	p*
Present	1	31	6	0.11
Absent	71	479	56	

* Chi-square test was used

examined, and LAD stenosis >80% was found to be significantly associated with multivessel disease (p<0.001) (Table 6).

The relationship between LAD stenosis >80% and critical stenosis in the circumflex artery (CX), right coronary artery (RCA), and left main coronary artery (LMCA) was analyzed.

- CX stenosis was significantly associated with LAD stenosis >80% (p<0.001). Among patients with CX stenosis, 141 (56.4%) also had LAD stenosis >80%, while 109 (43.6%) did not.
- RCA stenosis showed a significant relationship with LAD stenosis >80% (p<0.001). Among patients with RCA stenosis, 125 (54.1%) had LAD stenosis >80%, while 106 (45.9%) did not.
- LMCA stenosis was also significantly associated with LAD stenosis >80% (p<0.001). Among patients with LMCA stenosis, 21 (75%) had LAD stenosis >80%, while 7 (25%) did not.

These results indicate that critical stenosis in the CX, RCA, and LMCA is strongly associated with LAD stenosis >80%.

In our study, patients were grouped as older or younger than 45 years, and the relationship with CAG results was examined. Being older than 45 years was found to be associated with multivessel disease (p<0.001). When patients were grouped by age, no significant relationship was observed between mortality and LAD stenosis >80% (Table 7).

Table 6. Relationship between LAD >80 stenosis and multivessel disease

Parameters	LAD> 80 Stenosis n (%)			
	Present	Absent	Total	p*
Two-vessel disease present	98	31	129	<0.001
Absent	178	317	595	
Three-vessel disaese present	87	17	104	<0.001
Absent	189	351	540	

* Chi-square test was used. LAD: Left anterior descending artery, N: number

Table 7. Relationship between multivessel disease, LAD >80% stenosis, and mortality in patients grouped by age (<45 and ≥45 years)

Parameters	Age			
	<45	>45	Total	p*
Two-vessel disaese present	9	140	149	0.017
Absent	65	430	495	
Three-Vessel disaese present	4	100	104	0.008
Absent	70	470	540	
LAD >80 stenosis present	26	250	276	0.154
Absent	48	320	368	
Mortality present	2	36	38	0.215
Absent	72	534	606	

LAD: Left anterior descending artery

The association between coronary angiography (CAG) findings, echocardiography (ECHO) findings, and mortality was evaluated. The presence of LAD stenosis >80% was significantly associated with 30-day mortality (p=0.04). Additionally, echocardiographic wall motion abnormalities were found to be significantly related to mortality (p=0.026). Other coronary findings, including two-vessel disease (p=0.203), three-vessel disease (p=0.302), RCA critical stenosis (p=0.89), LMCA critical stenosis (p=0.237), and CX critical stenosis (p=0.345), were not significantly associated with mortality. Similarly, ischemic ECG findings (p=0.34) and elevated troponin levels above the cut-off value (p=0.349) were not statistically significant in predicting 30-day mortality.

When laboratory results were evaluated for mortality prediction using ROC analysis, the neutrophil/lymphocyte ratio (NLR) was found to be a significant predictor, with an AUC of 0.641 (p<0.004). CRP levels ranked second, with an AUC of 0.617 (p=0.01). However, troponin levels were not statistically significant for mortality prediction (p=0.23) (Fig. 3).

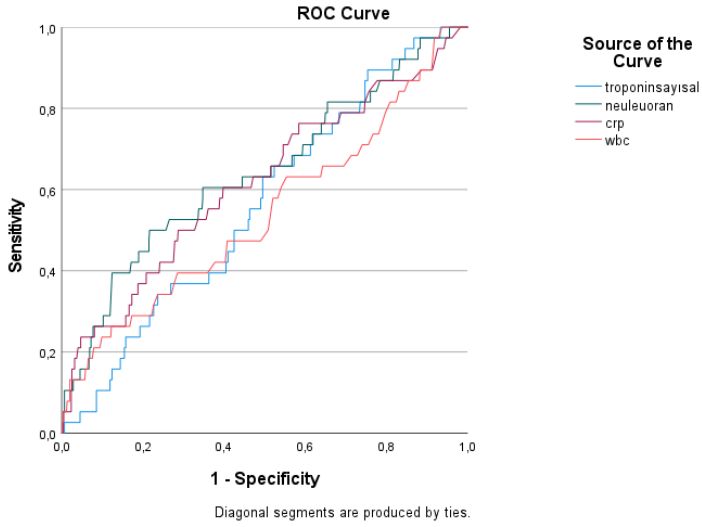

Figure 3. ROC analysis of hematologic parameters for mortality prediction

Discussion

This study evaluated the relationship between coronary angiographic findings, echocardiographic parameters, inflammatory biomarkers, and mortality in patients presenting to the emergency department with chest pain. The main findings of this study were that severe LAD stenosis was associated with mortality, echocardiographic wall motion abnormalities were predictive of adverse outcomes, inflammatory markers such as neutrophil-to-lymphocyte ratio and C-reactive protein demonstrated prognostic value, and the HEART score was not significantly associated with mortality. The HEART score was originally developed to predict major adverse cardiac events rather than mortality alone. Therefore, the lack of association between HEART score categories and mortality in our study should be interpreted cautiously and does not necessarily indicate that the HEART score is ineffective for risk stratification in patients presenting with chest pain.

The most prominent symptom of ischemic heart disease is chest pain, which may radiate to the left shoulder, arm, elbow, jaw, or back and often indicates coronary artery disease-related chest pain [3]. Chest pain is also one of the most common reasons for emergency department visits [1]. However, not all admissions for chest pain are related to coronary artery disease, as only a portion of these cases represent true cardiac pathology [3]. The 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain introduced updated approaches emphasizing cost-effective diagnostic strategies and shared decision-making in the management of patients presenting with suspected cardiac chest pain [4].

Our findings suggest that severe stenosis of the left anterior descending artery may be associated with an increased mortality risk. The LAD artery supplies a large portion of the left ventricular myocardium, and critical stenosis in this vessel can result in extensive myocardial ischemia and impaired ventricular function. Previous studies examining hemodynamically significant LAD disease have similarly demonstrated its association with adverse clinical outcomes [5]. In addition, inflammatory biomarkers, including CRP, WBC count, and neutrophil-to-lymphocyte ratio, were associated with mortality, whereas troponin levels did not demonstrate a similar relationship. These findings suggest that while troponin is essential for the diagnosis of acute coronary syndrome, it may be less useful as an isolated predictor of mortality in patients presenting with chest pain.

Various risk stratification models have been developed for the evaluation of coronary artery disease. The HEART score, which incorporates history, ECG, age, risk factors, and troponin levels, is one of the most widely used clinical risk classification systems for patients presenting with chest pain. Its primary aim is to predict major adverse cardiac events rather than mortality alone. In our study, the HEART score did not show a significant association with mortality, which is consistent with previous studies reporting that clinical risk scores may be more effective in predicting composite cardiac events rather than mortality specifically [6–8].

In a study by Daniel Nour et al. [9], angiographic determinants of coronary hemodynamics were evaluated in patients undergoing coronary angiography, demonstrating frequent involvement of the LAD artery in patients with coronary artery disease. In our study, we also observed a substantial prevalence of LAD involvement and

a strong association between LAD lesions and multivessel disease. This relationship may partly explain the prognostic significance of severe LAD stenosis observed in our cohort.

Hematological parameters are routinely measured in patients presenting to the emergency department and may provide additional prognostic information. In our analysis, inflammatory markers such as CRP, WBC count, and neutrophil-to-lymphocyte ratio were associated with mortality. Increasing evidence suggests that systemic inflammation plays an important role in the development and progression of atherosclerosis. Previous studies have also reported that the neutrophil-to-lymphocyte ratio may serve as a simple and inexpensive marker reflecting the inflammatory status of patients with cardiovascular disease [10]. In addition, other hematological ratios, including monocyte-to-lymphocyte ratio and monocyte-to-HDL ratio, have been reported to correlate with disease severity in coronary artery disease [11].

Age-related differences in coronary artery disease have been reported in several studies. Younger patients tend to demonstrate less extensive coronary involvement, whereas older patients more frequently exhibit multivessel disease and higher mortality rates. Studies comparing younger and older populations with coronary artery disease have similarly reported that multivessel involvement and more complex coronary lesions are more common among older patients [12]. A large meta-analysis conducted in South Africa also reported variability in mortality rates among young patients with coronary artery disease [13].

Endothelial dysfunction and inflammatory activation are known to contribute to the pathogenesis of coronary artery disease. [13,14] CRP is one of the most widely used inflammatory markers in clinical practice and has been investigated extensively in relation to coronary artery disease. Several studies have demonstrated a relationship between elevated CRP levels and the presence or severity of coronary artery disease [15–18]. For example, Zhu et al. [15] reported a positive correlation between high-sensitivity CRP and coronary artery disease, while a meta-analysis by Qureshi et al. [16] also demonstrated a relationship between CRP levels and cardiovascular risk. However, other studies have reported conflicting findings regarding the association between CRP and coronary artery disease [17]. These inconsistencies highlight the complexity of inflammatory pathways involved in atherosclerosis.

Chest pain remains one of the leading causes of emergency department visits worldwide. Although not all cases are related to cardiac disease, a subset of patients may have significant coronary pathology requiring urgent evaluation. Coronary angiography remains the gold standard for diagnosing coronary artery disease; however, assessment of cardiac function is also important in determining patient prognosis. Echocardiography is widely used in clinical practice because it is noninvasive, readily available, and provides rapid information regarding cardiac structure and function [19]. Previous studies evaluating revascularization strategies in patients with reduced left ventricular function have demonstrated differences in long-term outcomes between percutaneous coronary intervention and coronary artery bypass grafting [20]. The presence of echocardiographic wall motion abnormalities in our study supports the importance of functional cardiac assessment in patients with suspected coronary disease.

This study has several strengths. The relatively large sample size enhances the statistical power and reliability of the findings. In addition, the study provides a comprehensive evaluation of coronary angiographic findings, inflammatory laboratory markers, and echocardiographic parameters, allowing a multidimensional assessment of patients presenting with chest pain in the emergency department.

However, several limitations should be considered. First, this was a single-center study, which may limit the generalizability of the findings. Second, only patients who underwent coronary angiography were included, which may introduce selection bias. Third, the study focused on routinely available laboratory markers and did not evaluate additional biomarkers that may provide further prognostic information. Finally, long-term outcomes beyond the early follow-up period were not assessed.

Our findings highlight the potential importance of combining anatomical, functional, and inflammatory markers when evaluating patients presenting with chest pain. Identification of severe LAD stenosis, echocardiographic abnormalities, and elevated inflammatory markers may assist clinicians in identifying patients at increased risk of adverse outcomes. Future research should focus on multicenter prospective studies to further evaluate the prognostic value of these markers and to explore strategies for improving risk stratification and management in patients with suspected coronary artery disease.

Study Limitations

This study has several limitations. First, it was retrospective and single-center, which may limit the generalizability of the results. Second, only patients who underwent coronary angiography in our hospital were included; therefore, patients managed with alternative strategies, such as CABG or optimal medical therapy, were not evaluated. Third, the analysis was limited to routinely available laboratory markers (NLR, CRP, and WBC), and other potential prognostic biomarkers were not assessed. Finally, long-term outcomes beyond 30-day mortality were not collected, restricting conclusions to short-term prognosis.

Conclusion

Our study highlights that LAD stenosis >80% is significantly associated with mortality, reinforcing its importance as a critical determinant of adverse outcomes. Hematological markers, particularly NLR and CRP, were valuable predictors of mortality, whereas troponin was not significantly associated with early mortality.

These findings suggest that incorporating inflammatory markers into CAD risk assessment may improve the early identification of high-risk patients. Further research is needed to refine risk stratification tools and individualized treatment strategies.

Ethics Committee Approval: This study was approved by the Gaziantep Islam Science and Technology University Ethics Committee before data collection (Approval Date: 28/12/2023; Decision No: 496.41.16).

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ORIGINAL RESEARCH

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Retrospective Study on the Impact of Neurovascular Calcifications on Increasing Intracranial Hemorrhage Risk in Acute Ischemic Stroke Patients Treated With Thrombolytic Therapy in the Emergency Department

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Abstract

Objective: Intravenous thrombolysis with alteplase (IV tPA) is an established treatment for acute ischemic stroke, but hemorrhagic transformation remains an important complication. Although numerous parameters have been evaluated to minimize the risk of hemorrhagic transformation, no definitive predictor has yet been identified. This study primarily evaluated the association between CTA-detected neurovascular calcifications and hemorrhagic transformation in patients with acute ischemic stroke treated with intravenous alteplase and secondarily assessed their association with functional outcomes at discharge.

Materials and Methods: We retrospectively analyzed 243 patients with acute ischemic stroke who were treated with IV tPA and underwent computed tomography angiography (CTA) between 2018 and 2022. Intracranial internal carotid/carotid siphon calcifications were assessed on CTA by blinded radiologic review using the Kockelkoren calcification scoring system. The primary outcome was hemorrhagic transformation on follow-up CT, and the secondary outcome was poor functional outcome at discharge, defined as a modified Rankin Scale (mRS) score of 3–6.

Results: Calcifications were more common in older patients, those with hypertension, and those with higher red cell distribution width values. Calcification presence or pattern was not significantly associated with hemorrhagic transformation on follow-up CT. Contralateral calcification was independently associated with poor functional outcome at discharge (aOR 2.95, 95% CI 1.09–7.98). In subgroup analyses based on the CTA calcification score, non-intimal calcification was associated with poor functional outcome at discharge on both the ipsilateral and contralateral sides (p=0.03 and p=0.01, respectively). Because symptomatic hemorrhagic transformation occurred in only a small number of patients, hemorrhagic findings should be interpreted cautiously.

Conclusion: In this cohort of patients with acute ischemic stroke treated with intravenous alteplase, the overall presence of intracranial carotid calcification on CTA was not significantly associated with hemorrhagic transformation on follow-up CT. However, a pattern-specific exploratory analysis suggested an inverse association between ipsilateral non-intimal calcification and hemorrhagic transformation, which should be interpreted cautiously given the low number of hemorrhagic events. In contrast, contralateral calcification, particularly a non-intimal pattern, was associated with worse functional outcome at discharge, suggesting possible short-term prognostic value. These findings do not support withholding thrombolytic therapy on the basis of calcification alone, but they indicate that calcification pattern and laterality may merit further investigation in larger studies with 90-day outcomes. Intracranial ICA/carotid siphon calcifications on CTA should not be used in isolation to defer intravenous thrombolysis. In this cohort, calcification patterns appeared more relevant to short-term discharge outcomes than to hemorrhagic transformation risk. These findings are hypothesis-generating and require confirmation in larger multicenter studies.

Keywords: Acute ischemic stroke, alteplase, hemorrhagic transformation, intracranial arterial calcification, intravenous thrombolysis

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Introduction

Intravenous thrombolysis with alteplase (IV tPA) improves neurological outcomes in patients with ischemic stroke. However, intracranial hemorrhage occurs in 2–7% of patients treated with IV tPA. Although various scoring systems based on risk factors predictive of hemorrhagic transformation have been developed, these have not altered treatment protocols [1].

Intracranial arterial calcifications are established imaging markers of atherosclerotic burden and vascular remodeling. The biological significance of these calcifications may differ according to their dominant layer within the arterial wall, and computed tomography angiography (CTA)-based methods have been proposed to distinguish predominantly intimal patterns from predominantly medial/adventitial patterns [2,3]. This distinction may be relevant because plaque-related instability, arterial stiffness, impaired vasoreactivity, and reduced collateral capacity could influence both hemorrhagic transformation and post-stroke recovery [4–8].

The published literature remains inconsistent. Gocmen et al. [9] reported that non-intimal intracranial carotid calcifications were more common in patients with acute hemorrhagic complications after IV thrombolysis. Tábuas-Pereira et al. [10] and Yu et al. [11] also suggested that intracranial carotid calcification burden may be related to hemorrhagic transformation and prognosis after thrombolysis, although these studies differed in scoring strategy and patient selection. Kauw et al. [12] further suggested that the effect of intravenous thrombolysis may vary according to the calcification pattern. In contrast, other studies have not found a clear association between calcification scores and prognosis after IV thrombolysis [13,14]. These discrepancies likely reflect heterogeneity in calcification classification, the inclusion of endovascularly treated patients, stroke subtype selection, and outcome definition.

Accordingly, the present study evaluated whether intracranial carotid siphon calcifications and their CTA-based patterns, as classified using the Kockelkoren scoring system, are associated with hemorrhagic transformation after IV tPA and with short-term functional outcomes at hospital discharge in a CTA-selected acute ischemic stroke cohort [3].

Materials and Methods

The study protocol was approved by the Dokuz Eylul University Institutional Non-Interventional Clinical Research Ethics Committee of Blinded for peer review (Decision No: 2023/23-12; Date: 19.07.2023). The study was performed in compliance with the ethical principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design of the study.

This retrospective observational cohort study was conducted using data from patients admitted to the emergency department of a tertiary university hospital, which serves as a stroke center, between January 1, 2018, and December 30, 2022. Eligible patients were those with acute ischemic stroke who were treated with IV tPA and evaluated with neurovascular CTA. The exclusion criteria were alternative final diagnoses, unavailable follow-up data, clear contraindications to thrombolysis identified during the treatment process, and incomplete vascular imaging due to technical limitations.

A total of 314 patients diagnosed with acute ischemic stroke on admission, treated with IV tPA, and evaluated with neurovascular CTA initially met the screening criteria. Thirteen patients were excluded because advanced evaluation revealed alternative diagnoses, 29 because outcome data were unavailable after transfer or treatment abandonment, 12 because clinically relevant hemorrhagic transformation risk factors were identified during or after IV thrombolysis, and 16 because carotid siphon thrombosis precluded complete evaluation of the vascular wall. Of the remaining 244 patients, one was excluded from the final statistical analysis because of incomplete data. Therefore, the final study cohort consisted of 243 patients (Fig. 1).

Clinical Management and Outcome Definitions

Admission National Institutes of Health Stroke Scale (NIHSS) scores, demographic characteristics, vascular risk factors, and laboratory

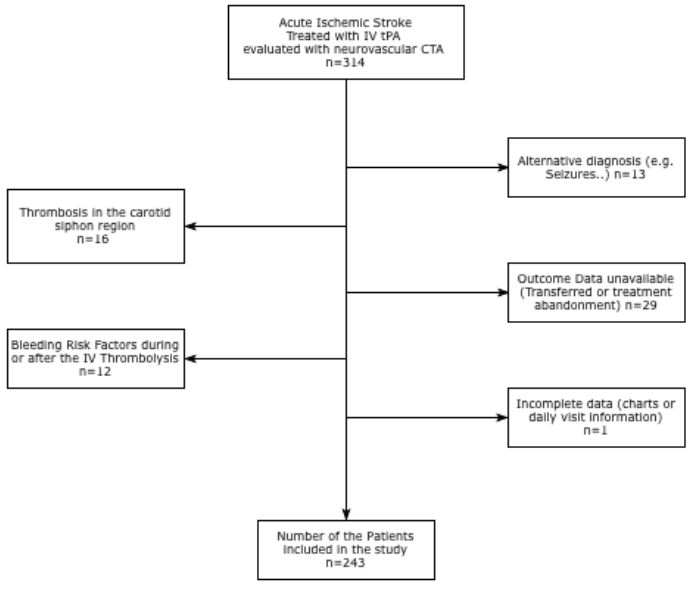

Figure 1. Flowchart of the study

data were recorded. Imaging was re-evaluated by a radiologist from the study team who was blinded to clinical information, prior reports, and outcomes. Discharge modified Rankin Scale (mRS) scores were derived from dependency information documented in the medical records.

All patients with suspected stroke underwent non-contrast head computed tomography (CT) on arrival. CTA was performed in patients considered likely to benefit from mechanical thrombectomy without waiting for creatinine results; in the remaining patients, CTA was obtained after creatinine results became available and before transfer from the emergency department to the stroke unit. IV tPA (Actilyse, Boehringer Ingelheim, Germany) was administered at 0.9 mg/kg in eligible patients after review of clinical findings and non-contrast CT.

Neurological examinations and vital signs were reassessed every 15 minutes during treatment. Although additional brain CT scans were performed in some patients because of clinical deterioration, hemorrhagic outcomes in this study were classified according to the routine 24-hour follow-up brain CT in all patients. Earlier CT scans, when available, were reviewed for clinical purposes but were not used for statistical outcome assessment; the routine 24-hour follow-up CT served as the reference scan in all patients.

Any hemorrhagic transformation on follow-up CT was treated as the primary radiological outcome. Symptomatic hemorrhagic transformation was defined as hemorrhage on follow-up CT accompanied by a ≥2-point worsening in NIHSS without another clear cause. Hemorrhagic transformations without corresponding NIHSS worsening were classified as asymptomatic hemorrhagic transformations. Poor short-term functional outcome was defined as a discharge mRS score ≥3; a discharge mRS score ≤2 was considered a good outcome.

CTA Acquisition and Calcification Assessment

All patient images were acquired using a commercially available 160-slice multidetector CT scanner (Aquilion Prime, Canon Medical Systems, Otawara, Japan) located in the emergency department. A tube voltage of 120 kVp was used for all scans. A total of 100 cc of contrast agent was injected via an antecubital vein using an auto-injector. Sequential regions of interest (ROIs) placed in the aortic arch triggered axial-plane imaging once the contrast threshold was reached, followed by the creation of angiographic reformatted images in three planes.

CTA examinations were reviewed for calcifications in the intracranial internal carotid artery and carotid siphon. Calcifications were categorized as ipsilateral or contralateral according to the clinically affected hemisphere and, when available, MRI lesion laterality. Calcium scoring followed the method of Kockelkoren et al. [3] circularity was scored as 0 for no calcification, 1 for punctate calcification, 2 for calcification spanning <90 degrees, 3 for 90–270 degrees, and 4 for >270 degrees. Thickness ≥1.5 mm received 1 point, and thickness <1.5 mm received 3 points. Morphology was scored as 0 for indistinct, 1 for irregular, and 4 for regular and continuous calcification. Total scores <7 were classified as dominant intimal calcification, and scores ≥7 were classified as non-intimal (medial/adventitial) calcification.

Statistical Analysis

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Numerical variables were assessed for normality using the Kolmogorov–Smirnov test and are presented as mean ± standard deviation or median (interquartile range [IQR]) according to distribution. Comparisons of numerical variables were performed using Student's t-test, the Mann–Whitney U test, or the Kruskal–Wallis test, as appropriate.

Binary logistic regression was used to evaluate factors associated with any hemorrhagic transformation on follow-up CT and with poor functional outcome at discharge. Variables with $p<0.20$ in univariable analyses were considered eligible for multivariable modeling, and clinically relevant covariates were additionally retained based on guideline recommendations and prior literature. To limit overfitting, separate multivariable models were constructed for any hemorrhagic transformation (43 events) and poor functional outcome at discharge, whereas symptomatic hemorrhagic transformation (9 events) was analyzed descriptively and not modeled separately.

Each multivariable model included the calcification variable of interest together with age, sex, hypertension, diabetes mellitus, atrial fibrillation, infarction on admission CT, admission NIHSS score, dense artery sign, and mechanical thrombectomy status; poor-outcome models also included any hemorrhagic transformation on follow-up CT. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are reported for multivariable models. A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

Results

The cohort consisted of 243 patients who received IV tPA and underwent neurovascular CTA. Calcifications were more frequent in older patients and in patients with hypertension, and patients with calcifications had higher red cell distribution width values at admission. No significant sex-based difference was observed in calcification presence or pattern (Table 1).

Table 1. Baseline characteristics according to calcification status and pattern

Panel A. Any calcification

Characteristic	Absent (n=32)	Present (n=211)	*p*
Age, years	59.1±14.7	72.6±10.7	<0.001
Sex, female, n (%)	14 (43.7%)	88 (41.7%)	0.827
Diabetes mellitus, n (%)	6 (18.8%)	72 (32.1%)	0.083
Hypertension, n (%)	16 (50.0%)	144 (68.2%)	0.043
Atrial fibrillation, n (%)	2 (6.3%)	20 (9.5%)	0.423*
Large-vessel occlusion, n (%)	11 (34.4%)	59 (28.0%)	0.455
Infarction on admission CT, n (%)	3 (9.4%)	34 (16.1%)	0.242*
Mechanical thrombectomy, n (%)	5 (15.6%)	24 (11.4%)	0.328*
Any hemorrhagic transformation on follow-up CT, n (%)	7 (21.9%)	36 (17.1%)	0.506
Symptomatic hemorrhagic transformation, n (%)	0 (0.0%)	9 (4.3%)	0.274*
Poor functional outcome at discharge (mRS ≥ 3), n (%)	9 (28.1%)	100 (47.4%)	0.041
RDW, median (IQR)	13.6 (13.1–14.2)	14.6 (13.7–15.9)	<0.001

Panel B. Ipsilateral calcification pattern

Characteristic	No calcification (n=39)	Intimal (n=87)	Non-intimal (n=117)	*p*
Age, years	59.9±14.6	69.9±9.99	75.1±10.2	<0.001
Sex, female, n (%)	14 (35.8%)	30 (34.4%)	58 (49.5%)	0.068
Diabetes mellitus, n (%)	9 (23.1%)	26 (29.9%)	43 (36.8%)	0.245
Hypertension, n (%)	21 (53.8%)	50 (57.5%)	89 (76.1%)	0.005
Atrial fibrillation, n (%)	2 (5.1%)	8 (9.2%)	12 (10.3%)	0.626
Large-vessel occlusion, n (%)	13 (33.3%)	27 (31.0%)	30 (25.6%)	0.557
Infarction on admission CT, n (%)	6 (15.4%)	11 (12.6%)	20 (17.1%)	0.682
Mechanical thrombectomy, n (%)	6 (15.4%)	12 (13.8%)	11 (9.4%)	0.486
Any hemorrhagic transformation on follow-up CT, n (%)	10 (25.6%)	15 (17.2%)	18 (15.4%)	0.344
Symptomatic hemorrhagic transformation, n (%)	0 (0.0%)	5 (5.7%)	4 (3.4%)	0.280
Poor functional outcome at discharge (mRS ≥ 3), n (%)	12 (30.8%)	35 (40.2%)	62 (53.0%)	0.030
RDW, median (IQR)	13.7 (13.1–14.2)	14.6 (13.6–15.5)	14.6 (13.8–16.1)	<0.001

Panel C. Contralateral calcification pattern

Characteristic	No calcification (n=43)	Intimal (n=88)	Non-intimal (n=112)	*p*
Age, years	60.3±13.6	70.8±10.3	74.8±10.4	<0.001
Sex, female, n (%)	20 (46.5%)	30 (34.0%)	52 (46.4%)	0.172
Diabetes mellitus, n (%)	8 (18.6%)	29 (33.0%)	41 (36.6%)	0.097
Hypertension, n (%)	18 (41.9%)	60 (68.2%)	82 (73.2%)	<0.001
Atrial fibrillation, n (%)	2 (4.7%)	8 (9.1%)	12 (10.7%)	0.500
Large-vessel occlusion, n (%)	14 (32.6%)	31 (35.2%)	25 (22.3%)	0.113
Infarction on admission CT, n (%)	4 (9.3%)	14 (15.9%)	19 (17.0%)	0.481
Mechanical thrombectomy, n (%)	7 (16.3%)	13 (14.8%)	9 (8.0%)	0.216
Any hemorrhagic transformation on follow-up CT, n (%)	8 (18.6%)	17 (19.3%)	18 (16.1%)	0.824
Symptomatic hemorrhagic transformation, n (%)	1 (2.3%)	5 (5.7%)	3 (2.7%)	0.467
Poor functional outcome at discharge (mRS ≥ 3), n (%)	11 (25.6%)	39 (44.3%)	59 (52.7%)	0.010
RDW, median (IQR)	13.8 (13.2–14.7)	14.6 (13.6–15.5)	14.5 (13.7–16.1)	0.011

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. For binary variables, only the presence of the characteristic is reported; percentages were calculated within columns. P values were calculated using the Pearson chi-square test or Fisher's exact test for categorical variables and the Student t test or Mann–Whitney U test for continuous variables, as appropriate. An asterisk (*) indicates Fisher's exact test. CT: Computed tomography; IQR: Interquartile range; mRS: modified Rankin Scale; RDW: Red cell distribution width; SD: Standard deviation.

Poor functional outcome at discharge was more frequent among patients with calcification than among those without calcification (47% vs. 28%, p=0.041). When calcification laterality and pattern were considered, poor functional outcome at discharge was more common in patients with ipsilateral non-intimal calcification and in those with contralateral non-intimal calcification. In contrast, discharge NIHSS differed significantly only across ipsilateral Kockelkoren categories, with the highest median NIHSS observed in the non-intimal group (Tables 2 and 3).

Any hemorrhagic transformation was detected in 43 patients (17.7%), whereas symptomatic hemorrhagic transformation occurred in only 9 patients (3.7%). Baseline infarction on admission CT, large-vessel occlusion, and mechanical thrombectomy were associated with any hemorrhagic transformation on follow-up imaging. Because symptomatic hemorrhagic transformation was infrequent, symptomatic hemorrhagic transformation results are presented descriptively and should be interpreted as exploratory (Table 4).

In multivariable analysis, contralateral calcification presence was associated with poor functional outcome at discharge (aOR 2.95, 95% CI 1.09–7.98; p=0.033), and contralateral non-intimal calcification was also associated with poor functional outcome at discharge (aOR 3.32, 95% CI 1.16–9.49; p=0.025). Calcification presence was not consistently associated with hemorrhagic transformation. However, ipsilateral non-intimal calcification showed an inverse association with any hemorrhagic transformation (aOR 0.31, 95% CI 0.10–0.95; p=0.040). Given the limited number of hemorrhagic transformation events across subgroups and the number of related comparisons, this apparently protective association should be interpreted cautiously rather than as definitive evidence of a biologically protective effect (Table 5).

Table 2. Distribution of calcification status according to functional outcome at discharge and discharge NIHSS score

Calcification category	Good outcome (mRS ≤2; n=134)	Poor outcome (mRS ≥3; n=109)	*p*	Discharge NIHSS median (IQR)	*p*
No calcification	23 (17.2%)	9 (8.3%)	0.041	4 (2–7)	0.307
Any calcification	111 (82.8%)	100 (91.7%)		5 (3–9)	
No ipsilateral calcification	27 (20.1%)	12 (11.0%)	0.054	4 (2–7)	0.181
Any ipsilateral calcification	107 (79.9%)	97 (89.0%)		5 (3–9)	
No contralateral calcification	32 (23.9%)	11 (10.1%)	0.005	4 (2–7)	0.166
Any contralateral calcification	102 (76.1%)	98 (89.9%)		5 (3–9)	

Data are presented as n (%) unless otherwise stated. Percentages were calculated within outcome columns and should not be interpreted as event rates within calcification categories. Discharge NIHSS scores are presented as median (IQR). P values for categorical variables were calculated using the Pearson chi-square test, and discharge NIHSS scores were compared using the Mann-Whitney U test. IQR: Interquartile range; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 3. Distribution of Kockelkoren calcification categories according to discharge functional outcome and discharge NIHSS score

Kockelkoren category	Good outcome (mRS ≤2; n=134)	Poor outcome (mRS ≥3; n=109)	*p*	Discharge NIHSS median (IQR)	*p*
Panel A. Ipsilateral calcification pattern					
No calcification	27 (20.1%)	12 (11.0%)	0.030	4 (2–7)	0.033
Intimal calcification	52 (38.8%)	35 (32.1%)		4 (2–7)	
Non-intimal calcification	55 (41.0%)	62 (56.9%)		5.5 (3–9.75)	
Panel B. Contralateral calcification pattern					
No calcification	32 (23.9%)	11 (10.1%)	0.010	4 (2–7)	0.312
Intimal calcification	49 (36.6%)	39 (35.8%)		5 (2–10)	
Non-intimal calcification	53 (39.6%)	59 (54.1%)		5 (3–9)	

Data are presented as n (%) unless otherwise stated. Percentages were calculated within outcome columns and should not be interpreted as event rates within calcification categories. Discharge NIHSS scores are presented as median (IQR). P values for categorical variables were calculated using the Pearson chi-square test, and discharge NIHSS scores were compared using the Kruskal-Wallis test. No post hoc pairwise comparisons were performed. IQR: Interquartile range; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 4. Characteristics according to hemorrhagic transformation on follow-up CT

Panel A. Any hemorrhagic transformation on follow-up CT

Characteristic	Absent (n=200)	Present (n=43)	*P*
Age, years, mean±SD	70.4±12.2	72.3±12.0	0.234
Sex, female, n (%)	87 (43.5%)	15 (34.8%)	0.299
Diabetes mellitus, n (%)	66 (33.0%)	12 (27.9%)	0.516
Hypertension, n (%)	133 (66.5%)	27 (62.8%)	0.642
Atrial fibrillation, n (%)	19 (9.5%)	3 (7.0%)	0.430*
Large-vessel occlusion, n (%)	49 (24.5%)	21 (48.8%)	<0.001
Infarction on admission CT, n (%)	23 (11.5%)	14 (32.6%)	<0.001
Time to IV tPA, min, mean±SD	163±57	164±52	0.963
Mechanical thrombectomy, n (%)	17 (8.5%)	12 (27.9%)	<0.001
Any calcification, n (%)	175 (87.5%)	36 (83.7%)	0.506
Ipsilateral calcification, n (%)	171 (85.5%)	33 (76.7%)	0.156
Contralateral calcification, n (%)	165 (82.5%)	35 (81.4%)	0.863
Ipsilateral calcification pattern			
No calcification, n (%)	29 (14.5%)	10 (23.3%)	0.185
Intimal calcification, n (%)	72 (36.0%)	15 (34.9%)	
Non-intimal calcification, n (%)	99 (49.5%)	18 (41.9%)	
Contralateral calcification pattern			
No calcification, n (%)	35 (17.5%)	8 (18.6%)	0.824
Intimal calcification, n (%)	71 (35.5%)	17 (39.5%)	
Non-intimal calcification, n (%)	94 (47.0%)	18 (41.9%)	

CT: Computed tomography.

Panel B. Symptomatic hemorrhagic transformation on follow-up CT

Characteristic	Absent (n=234)	Present (n=9)	*P*
Age, years, mean±SD	70.6±12.2	75.9±9.7	0.169
Sex, female, n (%)	99 (42.3%)	3 (33.3%)	0.432*
Diabetes mellitus, n (%)	75 (32.1%)	3 (33.3%)	0.595*
Hypertension, n (%)	157 (67.1%)	3 (33.3%)	0.045*
Atrial fibrillation, n (%)	21 (9.0%)	1 (11.1%)	0.581*
Large-vessel occlusion, n (%)	66 (28.2%)	4 (44.4%)	0.240*
Infarction on admission CT, n (%)	36 (15.4%)	1 (11.1%)	0.590*
Time to IV tPA, min, mean±SD	162±56	180±55	0.353
Mechanical thrombectomy, n (%)	27 (11.5%)	2 (22.2%)	0.292*
Any calcification, n (%)	202 (86.3%)	9 (100.0%)	0.274*
Ipsilateral calcification, n (%)	195 (83.3%)	9 (100.0%)	0.201*
Contralateral calcification, n (%)	192 (82.1%)	8 (88.9%)	0.506*
Ipsilateral calcification pattern			
No calcification, n (%)	39 (16.7%)	0 (0.0%)	0.280
Intimal calcification, n (%)	82 (35.0%)	5 (55.6%)	
Non-intimal calcification, n (%)	113 (48.3%)	4 (44.4%)	

Table 4. Continue

Panel B. Symptomatic hemorrhagic transformation on follow-up CT			
Characteristic	**Absent (n=234)**	**Present (n=9)**	***P***
Contralateral calcification pattern			
No calcification, n (%)	42 (17.9%)	1 (11.1%)	0.467
Intimal calcification, n (%)	83 (35.5%)	5 (55.6%)	
Non-intimal calcification, n (%)	109 (46.6%)	3 (33.3%)	

Data are presented as mean ± SD or n (%), as appropriate. Percentages were calculated within columns. P values for categorical variables were calculated using the Pearson chi-square test, except where indicated by an asterisk (*), for which Fisher's exact test was used. Continuous variables were compared using the independent-samples t-test. CT: Computed tomography; IV tPA: intravenous tissue plasminogen activator.

Table 5. Multivariable associations of calcification parameters with hemorrhagic transformation on follow-up CT and poor functional outcome at discharge

Panel A. Any hemorrhagic transformation on follow-up CT				
Calcification parameter	**aOR**	***P***	**95% CI**	
			CI Lower	**CI Upper**
Any calcification	0.45	0.160	0.144	1.38
Ipsilateral calcification	0.37	0.055	0.136	1.02
Contralateral calcification	0.59	0.330	0.205	1.69
Ipsilateral intimal calcification	0.44	0.130	0.15	1.28
Ipsilateral non-intimal calcification	0.31	0.040	0.102	0.95
Contralateral intimal calcification	0.63	0.420	0.208	1.92
Contralateral non-intimal calcification	0.54	0.290	0.17	1.71
Panel B. Poor functional outcome at discharge (mRS ≥3)				
Any calcification	2.31	0.130	0.78	6.79
Ipsilateral calcification	2.31	0.110	0.82	6.44
Contralateral calcification	2.95	0.033	1.09	7.98
Ipsilateral intimal calcification	1.88	0.253	0.64	5.55
Ipsilateral non-intimal calcification	2.84	0.060	0.96	8.38
Contralateral intimal calcification	2.59	0.080	0.89	7.47
Contralateral non-intimal calcification	3.32	0.025	1.16	9.49

Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were derived from multivariable binary logistic regression analyses using the enter method. Each calcification parameter shown in the table was entered into a separate model adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, presence of infarction on admission CT, admission NIHSS score, dense artery sign, and mechanical thrombectomy status. Because of the low number of hemorrhagic transformation events, estimates for hemorrhagic transformation should be interpreted cautiously. aOR: Adjusted odds ratio; CI: Confidence interval; CT: Computed tomography; NIHSS: National Institutes of Health Stroke Scale.

Discussion

This study evaluated whether intracranial carotid siphon calcifications on CTA were associated with hemorrhagic transformation after IV tPA and with short-term functional outcome at hospital discharge. The main findings were that calcification presence and pattern were not consistently related to post-thrombolytic hemorrhagic transformation, whereas contralateral calcification, particularly contralateral non-intimal calcification, was associated with poorer discharge status. Because only nine patients experienced symptomatic hemorrhagic transformation, all hemorrhagic transformation results should be regarded as exploratory.

Interest in intracranial arterial calcifications in ischemic stroke has increased in recent years. Prior studies have shown that

intracranial arterial calcifications are common in patients with cerebrovascular disease and may reflect different forms of vascular injury depending on their morphology and distribution [15–17]. In addition, CTA-based morphologic classification systems have provided a structured framework for distinguishing predominantly intimal from predominantly medial/adventitial calcification patterns in the intracranial internal carotid artery [3].

In our cohort, calcifications were more common in older patients and in patients with hypertension, which is consistent with the broader vascular literature and supports the interpretation that intracranial arterial calcification is better understood as a marker of chronic vascular burden than as an isolated imaging phenomenon [17,18]. Whether intracranial carotid calcification is associated with hemorrhagic transformation after intravenous alteplase remains uncertain. From a biological perspective, different calcification patterns may plausibly correspond to different vascular properties. Intimal calcification is generally discussed in relation to atherosclerotic plaque burden and plaque-related instability, whereas medial or non-intimal calcification has been associated with arterial stiffening, impaired vasomotor function, and reduced vascular compliance [2,4,6–8]. Based on these concepts, it is reasonable to examine whether the calcification pattern may be related to reperfusion-related hemorrhagic transformation in ischemic tissue. However, the available clinical literature has been inconsistent, and our results add to that heterogeneous body of evidence rather than resolving it.

Several previous studies suggested that intracranial carotid calcification burden or pattern may be associated with hemorrhagic transformation or post-thrombolysis prognosis. A higher frequency of acute hemorrhagic complications in patients with non-intimal calcifications was reported in one thrombolysis cohort [9]. Other studies also suggested that calcification burden or calcification pattern may carry prognostic information in patients with ischemic stroke treated with IV tPA [10–12]. In contrast, other reports did not identify a clear and consistent association between intracranial carotid artery calcification scores and post-thrombolysis prognosis [13,14]. Taken together, the prior literature is better characterized as heterogeneous than directional, which was also the rationale for the present study. This framing is important because it clarifies that the current work was not designed to confirm a universally established effect, but rather to examine a question that remains unresolved across different cohorts and methodologies.

In the present cohort, neither overall calcification presence nor most calcification subcategories showed a stable association with hemorrhagic transformation. Although ipsilateral non-intimal calcification showed an inverse association with any hemorrhagic transformation in one adjusted model, this isolated finding should not be overinterpreted. It was not supported by a broader pattern of consistently lower hemorrhagic transformation risk across calcification variables, and symptomatic hemorrhagic transformation was too infrequent for a robust separate regression analysis. For this reason, this result is better viewed as an exploratory signal than as evidence of a biologically protective relationship.

The discrepancy across published studies likely reflects genuine methodological heterogeneity rather than a simple contradiction. Calcification assessment is not standardized across the literature. Some studies relied on burden-based or semiquantitative scores, whereas others used morphologic classifications designed to distinguish intimal from non-intimal calcification [3,14]. Study populations also differ substantially. Some cohorts excluded patients undergoing thrombectomy, some focused on selected stroke subtypes such as non-cardioembolic stroke, and some did not evaluate all patients with CTA [11,12]. Endpoints also vary, ranging from any hemorrhagic transformation to symptomatic hemorrhage, discharge status, and later functional outcome. These differences complicate direct comparison and may explain why one study identifies an apparent association while another does not.

In our study, the inclusion of only patients who underwent CTA improved the reliability of calcification morphology assessment and reduced the risk of mistaking adjacent calcified structures for true arterial wall calcification. At the same time, this requirement may have preferentially selected patients with more severe stroke, suspected large-vessel occlusion, or possible thrombectomy candidacy, thereby limiting generalizability to the broader population of intravenous alteplase-treated stroke patients.

Another notable finding in our cohort was the association between calcification presence and higher RDW values. RDW has traditionally been used in the evaluation of anemia, but it is increasingly discussed as a nonspecific biomarker linked to inflammation, oxidative stress, and adverse cardiovascular profiles [19,20]. In addition, potential links between RDW, vascular calcification, and stroke prognosis have been suggested in previous studies [21–23]. Within this context, the higher RDW values observed in patients with intracranial calcifications in our cohort may indicate that these imaging findings coexist with a broader systemic vascular or inflammatory profile. This interpretation remains tentative, but it is clinically interesting because RDW is inexpensive, routinely measured, and rapidly available in emergency settings.

The association between contralateral calcification and poor functional outcome at discharge also deserves careful interpretation. The biological basis of this association is not straightforward, and our data do not allow causal inference. One possibility is that contralateral calcification functions as a marker of diffuse intracranial vascular disease rather than a lesion-specific characteristic. This interpretation is compatible with prior work suggesting that arterial calcification may accompany chronic vascular damage, altered hemodynamics, and downstream embolic or prognostic burden [24,25]. In that framework, contralateral non-intimal calcification may identify patients with an adverse cerebrovascular profile, reduced vascular reserve, or more extensive systemic vascular disease. However, this interpretation should remain hypothesis-generating. The current data do not show that contralateral calcification itself causes poor functional outcome; rather, they suggest that calcification may serve as an imaging marker of an adverse vascular profile.

The laterality finding should also be interpreted conservatively. A simple lesion-centered assumption would be that ipsilateral calcification should be more relevant to tissue-level events in the affected hemisphere, whereas contralateral calcification might be less informative. Our results did not follow that simple pattern. Instead, contralateral calcification showed the more consistent association with poor functional outcome at discharge. This may indicate that laterality in this setting reflects asymmetry in overall intracranial vascular burden, collateral pathways, or chronic arterial remodeling rather than purely local plaque behavior. Because collateral imaging, perfusion parameters, and long-term follow-up were not available in the present study, this interpretation should be regarded as hypothesis-generating rather than definitive.

These findings may also have practical implications for the interpretation of imaging findings in patients with acute ischemic stroke treated with IV tPA. Based on the present results, intracranial carotid calcifications on CTA should not be used in isolation to infer a high risk of post-thrombolytic hemorrhagic transformation or to discourage otherwise guideline-concordant alteplase treatment. At the same time, the observed association between contralateral calcification, especially contralateral non-intimal calcification, and poor functional outcome at discharge raises the possibility that calcification pattern and laterality may contribute to early short-term risk stratification. At present, however, this possible prognostic role should be viewed as preliminary and should not be considered practice-changing.

Conclusion

In this CTA-selected cohort of patients with acute ischemic stroke treated with IV tPA, intracranial arterial calcifications were not consistently associated with post-thrombolytic hemorrhagic transformation. Some calcification patterns, particularly contralateral and contralateral non-intimal calcifications, were associated with poor short-term functional outcome at discharge. These findings should be interpreted cautiously because symptomatic hemorrhagic transformation was uncommon, and functional outcome was assessed only at discharge.

Limitations

This retrospective single-center study is subject to residual confounding and limited external validity.

The cohort included only patients who underwent CTA, which may have selected for more severe stroke and limited the generalizability of the findings to all patients treated with IV thrombolysis.

Symptomatic hemorrhagic transformation occurred in only 9 patients, which limited statistical power and precluded a reliable separate multivariable model for symptomatic hemorrhagic transformation.

Functional outcome was measured at discharge rather than at 90 days, so the reported associations apply only to short-term hospital outcomes.

Ethics

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylul University Institutional Non-Interventional Clinical Research Ethics Committee of Blinded for peer review (Decision No: 2023/23-12; Date: 19.07.2023).

Informed Consent: The requirement for informed consent was waived because of the retrospective design of the study.

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ORIGINALRESEARCH

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Prognosis Assessment in Spontaneous (non-traumatic) Intracerebral Hemorrhage with Artificial Intelligence-Assisted Hemorrhage Volume Analysis

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Abstract

Objective: Spontaneous (non-traumatic) intracerebral hemorrhage (sICH) is associated with high mortality and morbidity rates. With the increasing incidence of sICH, hemorrhage volume and hemorrhage location on brain computed tomography (CT) are important in determining prognosis. CT scans obtained from patients with sICH are reported using artificial intelligence (AI)-assisted programs. These programs provide data on the type, volume, and location of bleeding. In this study, we aimed to investigate the reliability of AI-assisted hemorrhage volume measurement, the effect of measured volume on QTc, and the contribution of these parameters to predicting mortality in patients with sICH.

Materials and Methods: The study was designed as a retrospective, single-center cohort study. Hemorrhage volumes on CT images were calculated using AI algorithms from Hevi AI. QTc values were calculated using the Bazett formula, and statistical analyses were conducted by grouping patients according to 1-week and 1-month mortality.

Results: Eighty-five patients diagnosed with sICH were included in the study. The mean age of the patients was 62.9±14.6 years. No significant association was observed between age and 1-month mortality (p=0.890). Large hemorrhage volume, low Glasgow Coma Scale (GCS) score, and prolonged QTc duration were significantly associated with 1-week mortality (p<0.001). Hemorrhage volume showed a moderate-to-high significant negative correlation with GCS (r=-0.755, p<0.001) and a moderately significant positive correlation with QTc (r=0.477, p<0.001). In the Cox regression analysis performed to determine the effect of risk factors on mortality, large hemorrhage volume and low GCS level increased the probability of 1-week mortality (p=0.001, hazard ratio=1.018, confidence interval [CI]=1.008–1.029; and p=0.020, HR=0.852, CI=0.745–0.975, respectively).

Conclusion: AI-assisted measurement of large hemorrhage volume and low GCS appear to be important prognostic indicators, particularly regarding 1-week mortality.

Keywords: Artificial intelligence; hemorrhage volume; mortality; QTc interval; spontaneous (non-traumatic) intracerebral hemorrhage

Introduction

Spontaneous (non-traumatic) intracerebral hemorrhage (sICH) is defined as non-traumatic intracranial hemorrhage and is associated with high mortality and morbidity rates [1]. ICH is the second most common subtype of stroke and is associated with high mortality and morbidity worldwide [1,2]. Risk factors for sICH include advanced age, smoking, alcohol use, chronic hypertension, diabetes mellitus, medication use (anticoagulation, narcotics, stimulants), and etiological factors such as amyloid angiopathy, primary or metastatic tumors, and vascular malformations [3]. The primary parameters affecting the clinical course of sICH include hemorrhage volume, location, and low GCS. Furthermore, QTc prolongation due to sICH not only exacerbates the clinical picture but also stands out as a prognostic indicator [4].

Due to sICH, there is a direct interaction between the central nervous system and the cardiac system. This interaction is associated with an imbalance in the autonomic nervous system and can cause various ECG changes. One of these changes is

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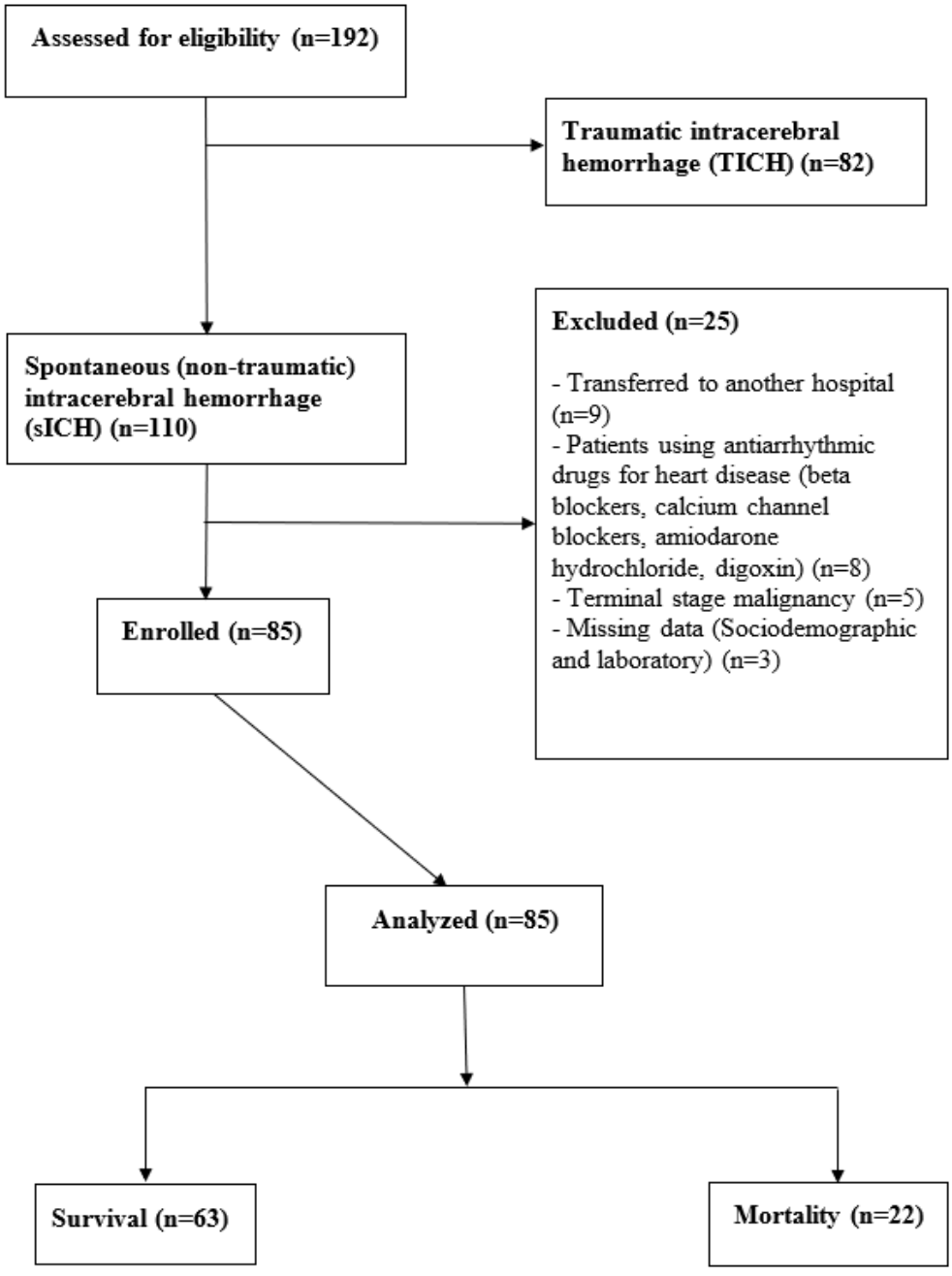
the QTc interval. As a parameter that affects heart rhythm and reflects ventricular repolarization on ECG, the QTc interval plays an important role in determining clinical prognosis. All these parameters are critical determinants of mortality risk and are particularly crucial for predicting prognosis in the early stages [5].

The 2022 American Heart Association/American Stroke Association guidelines for the management of patients with sICH recommend that CT evaluation within the first hours after onset is reasonable to identify patients at risk for subsequent hemorrhage expansion [6]. The volume, shape, location, and density of the hemorrhage detected on CT are clinically relevant. Manual volume assessment on CT can typically be accomplished by measuring the hemorrhage area on consecutive images using area measurement tools and multiplying the total area by the slice thickness. However, such manual segmentation is time-consuming and therefore impractical for use in emergency departments [4]. In recent years, artificial intelligence (AI) technologies have gained significant ground in medical imaging and clinical data analysis.

Study Flow Diagram



AI-assisted hemorrhage volume analysis provides clinicians with rapid and reliable data in the management of patients with sICH, enabling early intervention. With AI-assisted programs that have diagnostic accuracy, sensitivity, and specificity close to those of gold standard methods, these segmentation times can be calculated in seconds. This allows emergency department clinicians to obtain quantitative data about hemorrhage volume quickly and practically, enabling them to be proactive in patient management.

The pathophysiology underlying QTc prolongation in sICH is complex, with many factors implicated. In sICH, excessive sympathetic activation, particularly affecting the right insula or thalamus, leads to catecholamine-mediated myocardial damage, myocardial stunning, and repolarization abnormalities. Factors such as hemorrhage location, medications used, and fluid and electrolyte balance contribute to QTc prolongation. However, studies investigating the relationship between hemorrhage volume and QTc prolongation are limited [7].

In this study, the primary objective was to examine the effects of AI-assisted hemorrhage volume detection on early mortality in sICH. Second, we aimed to investigate the relationship between hemorrhage volume and QTc prolongation, as well as the predictive power of QTc.

Materials and Methods

The study was a retrospective, single-center cohort study. The study was approved by the University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital Health Application and Research Center Clinical Research Ethics Committee, dated June 17, 2025, and numbered 4922. Patients were selected from those over the age of 18 who presented to Department of Emergency Medicine, Şişli Hamidiye Etfal Training and Research Hospital between May 1, 2024, and May 1, 2025.

Study Inclusion Criteria

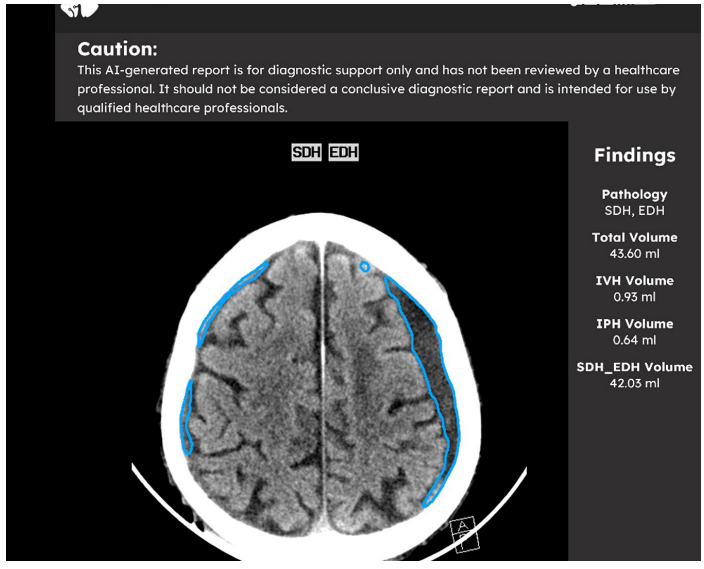
Patients who presented to the emergency department with non-traumatic neurological symptoms, had intracranial hemorrhage detected by cranial CT, and had hemorrhage volume determined by artificial intelligence were included in the study.

Data Collection

Patient demographics, clinical features, and cranial CT images were retrieved from the hospital automation system. Non-contrast cranial CT scans were obtained using a SOMATOM Definition Edge 128-slice multidetector computed tomography device (Siemens Healthineers, Forchheim, Germany), and the images were reconstructed with a 5-mm slice thickness. For manual measurement of hemorrhage volume, a simplified version of the formula used for the volume of an ellipsoid (4/3π×[A/2]×[B/2]×[C/2]) was used. Here, A, B, and C are the three diameters of the ellipsoid, as previously defined. Since π (pi) was taken as approximately 3, the formula was simplified to ABC/2 [8].

Hevi AI [9] is a program that uses a novel deep learning (DL) architecture consisting of convolutional neural networks (CNNs) and recurrent neural networks (RNNs), a common type of DL method with an attention mechanism, to detect and subcategorize ICH in non-contrast head CT scans. It utilizes state-of-the-art deep learning technology. It distinguishes between various intracranial hemorrhage subtypes and provides automatic hemorrhage volume measurements for rapid assessment. Accuracy, sensitivity, and specificity on the validation set were 99.41%, 99.70%, and 98.91%, respectively, with an average prediction time of 45±8 seconds for head CT scans. It is an artificial intelligence program integrated into the hospital PACS system (Figure 1. Hemorrhage volume detected with Hevi AI). No bias or statistically significant differences were found between the two methods (manual measurement and Hevi AI) (p=0.296, confidence interval=-2.52 to 2.25, Bland–Altman analysis).

At the time of admission to the emergency department, the first available and technically satisfactory routine 12-lead ECG (25 mm/s paper speed, 10 mm/mV amplitude, and 500 Hz sampling rate; Nihon Kohden, Tokyo, Japan) was obtained from our digital ECG system. The duration of the QRS complex was defined as the time to the end of the T wave, and this time was used to measure QTc. After evaluating the QT interval in multiple leads, the highest reported QT interval in any given lead was used. Five consecutive



Picture 1. Hemorrhage volume detected with Hevi AI

heartbeats in lead II were used to evaluate QTc duration and RR intervals by two clinicians specializing in arrhythmias, who were blinded to other independent variables. The measurement was performed using a combination of automated technology and manual procedures. Interobserver agreement was assessed. Data were included if two observers agreed manually and the other observer agreed automatically on all measurements. When there was a discrepancy, the average of the two values was calculated. To ensure that the QTc interval remained constant regardless of heart rate, heart rates ranging from 60 to 100 beats/minute were used. After adjusting for heart rate, the QTc interval was determined. QT correction: QTc (ms) was calculated as follows using RR (s) and HR (bpm) values [10]. The most commonly used formula for determining the QTc interval is the Bazett formula.

Bazett formula: $QTcB=QT/RR^{1}/^{2}$

The normal duration of a QTc interval is 360 ms or longer; a duration longer than 450 ms in men and 460 ms in women is considered prolonged [11,12].

Statistical Analysis

We performed the power analysis of our study using G*Power software (version 3.1.9.7). The calculations were made using the following parameters: Cox regression for time-dependent mortality was calculated using hazard ratio (HR)=2, power (1–β)=0.80, alpha level=0.05, confidence interval=95%, and 30% mortality criteria, and it was determined that at least 80 patients should be included in the study. Mean, standard deviation, median (25–75), highest frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was assessed using the Kolmogorov–Smirnov test. The independent samples t-test was used to analyze normally distributed continuous independent variables. The Mann–Whitney U test was used in the analysis of quantitative independent data. The chi-square test was used to analyze qualitative independent data. Cox regression analysis was used to assess the probability of risk factors for 1-week and 1-month mortality. Correlations between continuous variables were examined using the Pearson correlation test for normally distributed data. Receiver operating characteristic (ROC) analysis was performed to determine the predictive value of independent variables for 1-week and 1-month mortality. A value of $p<0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS software (version 28.0, IBM Corp., Armonk, NY, USA).

Results

A total of 85 patients with sICH were included in the study. The number of male patients (n=51) was higher than the number of female patients (n=34). The mean age of all patients was 62.9±14.6 years. The mean age of female patients (67.5±15.3 years) was significantly higher than that of male patients (59.9±13.5 years) (p=0.018) (not shown in the table). During the 1-month follow-up of all patients, we found that 22 (25.9%) patients died. There were no differences between the survival and mortality groups in terms of sociodemographic characteristics, laboratory findings, and chronic diseases during the 1-month period. The three most frequently diagnosed chronic diseases among the groups were hypertension (HT), diabetes mellitus (DM), and coronary artery disease (CAD). Although the rate of surgical treatment after hemorrhage was higher in the survival group, there was no difference between the groups (Table 1).

However, no significant association was observed between age and 1-week or 1-month mortality (p=0.665, p=0.890). A significant association was found between mortality and hemorrhage volume. A larger hemorrhage volume (119.29±51.9) was significantly associated with higher mortality ($p<0.001$), and hemorrhage size appeared to be associated with a poorer prognosis. Low GCS and prolonged QTc duration were significantly associated with increased mortality ($p<0.001$). Low GCS is a strong indicator of poor prognosis, while prolonged QTc duration increases the risk of mortality (Table 2).

The most common hemorrhage type was intraparenchymal hemorrhage (IPH) (68.2%), concentrated in the parietal and frontal lobes. Overall mortality was increased in right hemisphere hemorrhages, but these findings did not reach statistical significance. In 28 (32.9%) patients, hemorrhage occurred within the ventricle (Table 3).

Hemorrhage volume showed a moderately to highly significant negative correlation with GCS ($r=-0.755$, $p<0.001$) and a moderately significant positive correlation with QTc ($r=0.477$, $p<0.001$). No significant relationship was found between age and hemorrhage volume (Table 4).

ROC analysis of the predictive value of hemorrhage volume and QTc for 1-week mortality revealed that both parameters were predictive and highly sensitive and specific (AUC=0.975, $p<0.001$ and AUC=0.857, $p<0.001$, respectively; Figure 1. ROC analysis of hemorrhage volume and QTc for 1-week mortality) (Table 5).

ROC analysis of the predictive value of hemorrhage volume and QTc for 1-month mortality revealed that both parameters were predictive and moderately sensitive and specific (AUC=0.886, $p<0.001$ and AUC=0.729, p=0.001, respectively; Figure 2. ROC analysis of hemorrhage volume and QTc for 1-month mortality) (Table 6).

In a Cox regression analysis performed to determine the probability

Table 1. Analysis of sociodemographic, laboratory, and chronic diseases among survival and mortality groups in all patients during a 1-month follow-up

		Survival (n=63)	Mortality (n=22)	
		mean±SD median (25-75)	mean±SD median (25-75)	p
Age	year	62.6±12.6	63.1±15.4	0.890[t]
Gender	male	35 (55.6%)	16 (72.7%)	0.245[x2]
	female	28 (44.5%)	6 (27.3%)	
Chronic diseases:				
HT (n%)	+	33 (52.4%)	16 (72.7%)	0.096[x2]
DM (n%)	+	33 (52.4%)	12 (54.5%)	0.861[x2]
CAD (n%)	+	22 (34.9%)	9 (40.9%)	0.615[x2]
Hematological parameters:				
Hemoglobin	g/dl	12.5±2.1	12.9±1.5	0.257[t]
Platelet	10^9/L	258±87	237±96	0.343[t]
aPTT	second	25 (24-28)	28 (24-30)	0.272[m]
PT	second	12.5±1.7	12.1±1.5	0.342[t]
INR	-	1.06 (0.98-1.14)	1.13 (1.05-1.95)	0.057[m]
Glucose	mg/dL	148 (116-201)	198 (138-224)	0.055[m]
Sodium	mEq/L	138 (136-140)	139 (136-140)	0.468[m]
Potassium	mEq/L	4.5±0.6	4.4±0.6	0.675[t]
Calcium	mg/dL	8.7±0.4	8.8±0.5	0.792[t]
Using antiaggregant (n%)	+	13 (20.6%)	7 (31.8%)	0.287[x2]
Using anticoagulant (n%)	+	9 (14.3%)	6 (27.3%)	0.169[x2]
Surgical treatment after hemorrhage (n%)	+	42 (66.7%)	14 (63.6%)	0.796[x2]

HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; aPTT: Activated partial thromboplastin time; PT: Prothrombin time; [m]Mann Whitney U; [x2]Chi-Square test; [t]T-test; SD: Standard deviation

of independent variables on 1-week and 1-month mortality, the probability of mortality increased with large hemorrhage volume and low GCS level. Advanced age and QTc duration were not found to be significant. These results suggest that hemorrhage

Table 2. Baseline characteristics of patients with intracerebral hemorrhage according to gender and mortality status

	Mortality (1-week)			Mortality (1-month)		
	Yes (n=15)	No (n=70)	p	Yes (n=22)	No (n=63)	p
	mean±SD median (25-75)	mean±SD median (25-75)		mean±SD median (25-75)	mean±SD median (25-75)	
Age, year	61.46±13.4	63.28±14.9	0.665[t]	62.6±12.6	63.1±15.4	0.890[t]
Volume, mL	119.29±51.9	28.04±24.9	<0.001[t]	94.1±57.8	26.7±25.1	<0.001[t]
GCS	6 (4-7)	15 (12-15)	<0.001[m]	7 (5-10)	15 (13-15)	<0.001[m]
QTc, ms	491.6±33.5	446.3±26.4	<0.001[t]	475.5±40.5	446.9±25.6	0.005[t]
Gender male n%	10 (66.7%)	41 (58.6%)	0.772[x2]	16 (72.7%)	35 (55.6%)	0.245[x2]

SD: Standard deviation; GCS: Glasgow Coma score; QTc: Corrected QT interval, p: Statistical significance (<0.05), [m]Mann Whitney U, [x2]Chi-Square test, [t]T-test

Table 3. Hemispheres and areas where bleeding occurs

Area and frequency of the lesion n (%)		Right hemisphere n (%)		Left hemisphere n (%)
Intraparenchymal hemorrhage (IPH)	58 (68.2)	19 (22.4)	Frontal	19 (22.4)
Subdural hemorrhage (SDH)	23 (27.1)	28 (32.9)	Parietal	24 (28.2)
Epidural hemorrhage (EDH)	10 (11.8)	14 (16.5)	Temporal	15 (17.6)
Subarachnoid hemorrhage (SAH)	37 (43.5)	1 (1.2)	Occipital	4 (4.7)
Intraventricular hemorrhage (IVH)	28 (32.9)	7 (8.2)	Lateral Ventricle	4 (4.7)
		8 (9.4)	Third-Ventricle	4 (4.9)
		5 (5.9)	Fourth-Ventricle	4 (4.9)
		6 (7.1)	Thalamus	3 (3.5)
		0	Pons	(1.2)

* A patient may experience hemorrhage in more than one area

Table 4. Correlation analysis of hematoma volume with age, QTc and GCS

Pearson correlation		Age, year	GCS	QTc, ms
Volume, mL	r	-0.008	-0.755	0.477
	p	0.939	<0.001	<0.001
	n	85	85	85

GCS: Glasgow Coma score; QTc: Corrected QT interval; r: correlation coefficient

volume and GCS are predictive factors for 1-week and 1-month mortality (Table 7).

Discussion

In our study, we found that large hemorrhage volume, low GCS score, and prolonged QTc were variables that showed significant differences in 1-week and 1-month mortality. We found a moderate-to-high inverse relationship between large hemorrhage volume and GCS level and a positive, weak-to-moderate correlation between hemorrhage volume and QTc. In the analysis conducted to determine the probability of risk factors for mortality, it was found that large hemorrhage volume and low GCS level increased the probability of 1-week mortality. The probability of 1-month mortality was found to increase only with large hemorrhage volume.

Hemorrhage volume in patients with sICH shows a strong correlation with mortality, and this correlation is a frequently emphasized prognostic factor in the literature. Our study demonstrates that AI-assisted hemorrhage volume analysis provides rapid and reliable results in sICH management, making an important contribution to guiding clinical decisions. The importance of parameters such as hemorrhage volume, GCS, and QTc interval in prognostic assessments has been supported by previous studies. Broderick et al. [13] reported that mortality was significantly increased when hemorrhage volume exceeded 30 mL. This finding supports the conclusion in our study that large hemorrhage volume is associated with mortality. The GCS score

Table 5. Receiver Operating Characteristic (ROC) Curve analysis with variables for mortality (1-week)

Mortality	Sensitivity (%)	Specificity (%)	AUC	95% CI	Cut off	p
Volume, mL	100	87.1	0.975	0.947-1.000	62.2	<0.001
QTc, ms	80.0	98.6	0.857	0.709-1.000	486	<0.001

AUC: Area Under the Curve; %95 CI: Confidence Interval; p: Statistical significance (<0.05); QTc: Corrected QT interval

Table 6. Receiver Operating Characteristic (ROC) Curve analysis with variables for mortality (1-month)

Mortality	Sensitivity (%)	Specificity (%)	AUC	95% CI	Cut off	p
Volume, mL	77.3	87.3	0.886	0.808-0.964	56.6	<0.001
QTc, ms	54.5	98.4	0.729	0.583-0.876	486	0.001

AUC: Area Under the Curve; %95 CI: Confidence Interval; p: Statistical significance (<0.05); QTc: Corrected QT interval

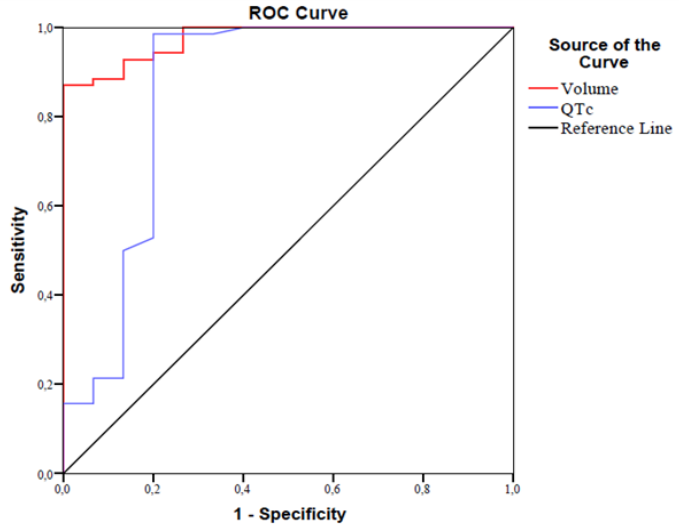


Figure 1. ROC analysis of hemorrhage volume and QTc for 1-week mortality

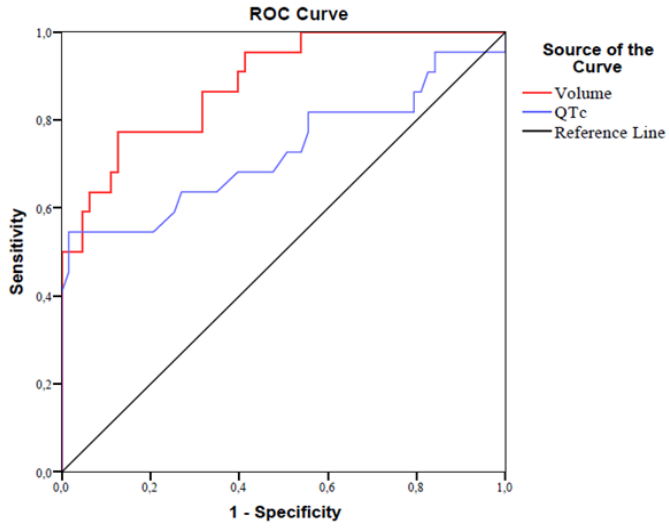


Figure 2. ROC analysis of hemorrhage volume and QTc for 1-month mortality

is widely used as an indicator of neurological status in patients with sICH, and a low GCS score is considered a strong predictor of mortality. A study by Jungin Han et al. [14] in patients with stroke emphasized the strong relationship between low GCS scores and increased mortality rates. Similarly, in our study, it was determined that a low GCS score showed a negative correlation with mortality and was one of the important indicators in predicting short-term mortality risk. This finding indicates that the GCS score should continue to be used as an important determinant of clinical prognosis.

In the literature, QTc prolongation in sICH has been accepted as an electrocardiographic finding associated with intracranial hemorrhage and has been identified as a predictive parameter that may contribute to mortality. In a study on sICH cases by Osama Amin et al., [5] it was reported that QTc prolongation increased complications and mortality after intracranial hemorrhage. Our study concluded that QTc interval prolongation is associated with mortality. However, the absence of a risk factor increasing the probability of mortality in the sample group and its weak-to-moderate correlation with hemorrhage volume can be explained by the location of the hemorrhage. Another reason is that the QTc interval included in the study was measured at the time of admission; indeed, studies have shown that other ECG changes, such as QTc prolongation, appear hours later in sICH. These findings indicate that the QTc interval should be evaluated

Table 7. Cox regression analysis of one-week and one-month in-hospital mortality of cases with variables

Mortality	1-week			1-month		
	HR	95% CI	*p*	HR	95% CI	*p*
Age, year	0.984	0.941-1.028	0.467	0.990	0.958-1.023	0.546
Volume, mL	1.018	1.004-1.031	0.009	1.018	1.007-1.029	0.001
GCS, point	0.726	0.556-0.948	0.019	0.862	0.740-0.1003	0.054
QTc, ms	1.020	0.993-1.047	0.141	1.013	0.994-1.032	0.183
IPH	3.229	0.129-80.736	0.475	0.535	0.053-5.415	0.596
SDH	0.321	0.018-5.587	0.436	1.143	0.125-10.442	0.906
EDH	6.034	0.136-268.165	0.353	0.445	0.017-11.316	0.624
SAH	2.274	0.394-13.129	0.358	1.242	0.319-4.838	0.755
IVH	0.367	0.055-2.41	0.300	0.672	0.176-2.570	0.561

HR: Hazard Ratio; %95 CI: Confidence Interval; GCS: Glasgow Coma Score; QTc: Corrected QT interval; IPH: Intraparenchymal hemorrhage; SDH: Subdural hemorrhage; EDH: Epidural hemorrhage; SAH: Subarachnoid hemorrhage; IVH: Intraventricular hemorrhage, p: Statistical significance (<0.05), (1-week and 1-month Cox regression Omnibus Tests of Model Coefficients p<0.001, No significant multicollinearity was detected among variables included in the Cox regression model (VIF range: 1.116–2.601)

more carefully as a risk factor in intracranial hemorrhages. The QTc interval should be examined in more detail in future studies as a parameter that may reflect the interaction between the cardiac and neurological systems.

AI-based analyses are increasingly used in sICH prognosis. In recent years, numerous studies have reported that AI algorithms successfully predict mortality risk by accurately determining hemorrhage volume in cerebral hemorrhage cases. The study by Kai Gong et al. [15] reported that AI algorithms improved clinical decisions by rapidly and accurately detecting hemorrhage volume. Our study supports this finding and shows that AI-assisted analyses provide clinically significant benefits in rapidly classifying patients, creating treatment plans, and predicting prognosis. In our study, the prognostic value of hemorrhage volume detected by the AI-assisted program was investigated, as the diagnostic values of the AI-assisted program were similar to those of the manual method. Previous studies have shown the importance of this diagnostic method in terms of high accuracy, sensitivity, and specificity, as well as its ability to provide quantitative data within seconds and demonstrate prognosis for mortality. This result strengthens the applicability of AI-based systems in emergency medicine practice and neurology.

Our study found that certain demographic factors, such as age and gender, did not have a significant effect on mortality. This finding is consistent with the study by Justin T. Hsieh et al. [16] and suggests that demographic factors such as age may be of secondary importance in sICH prognosis. The limited effect of age on mortality indicates that more specific neurological and cardiac parameters should be prioritized, particularly in clinical practice. However, advanced studies suggest that artificial intelligence could further refine prognosis predictions by integrating other demographic and clinical data more comprehensively. However, the small number of patients in the study and the advanced average age of the groups are parameters that may explain these nonsignificant results for age, which is a nonmodifiable risk factor for mortality.

The strongest predictors of 30-day mortality and functional outcome in patients with sICH are baseline hemorrhage volume and subsequent hemorrhage expansion [17]. However, precise hemorrhage measurement is rare in routine clinical practice, primarily due to the lack of available tools that are fast, effective, and reliable for volumetric assessment. The hemorrhage volume determined using our AI-assisted algorithm, which provides a rapid and highly sensitive diagnostic method, was found to be associated with early (1-week) and 1-month mortality risk. Large hemorrhage volume measured at presentation is a prognostic factor consistent with the literature, and awareness of the need for aggressive treatment is warranted.

Questions regarding the optimal medical and surgical management of sICH remain [18]. However, the primary procedures to be performed in emergency departments include initial medical stabilization; rapid and accurate neuroimaging to establish the diagnosis and explain the etiology; standardized neurological assessment to determine baseline severity; prevention of hemorrhage expansion through blood pressure management and reversal of coagulopathy; and prevention of secondary brain injury. In the acute phase, timely and aggressive management can mitigate secondary brain injury. In this regard, the rapid and easy detection of prognostic factors, such as bleeding volume, using AI-assisted programs may readily guide patient management.

Limitations of Our Study and Future Research

Our study has some limitations. The small number of cases is a significant limitation. In particular, the retrospective design may have led to the omission of some potential variables. Future studies using prospective designs will be important to validate these findings and compare the effectiveness of different AI algorithms. Furthermore, large-scale studies conducted in different hospitals and centers could improve the generalizability of AI-assisted prognostic models. The relationship between hemorrhage localization and QTc interval was not investigated. Additionally, the fact that QTc was calculated from the initial ECG and that 24–48-hour ECG monitoring with Holter or a monitor was not performed may have obscured the prognostic value of this risk factor. Another limitation is that only patients whose measurements could be obtained by the AI system were included in the study.

Conclusion

In conclusion, large bleeding volume and low GCS score emerge as critical factors in determining short-term (1-week) mortality risk in patients with sICH. It was concluded that AI-assisted hemorrhage volume analysis can be used as a powerful tool in predicting the prognosis of sICH and has the potential to improve clinical management. Future research should focus on the combined assessment of these parameters and the investigation of the integration of AI-based systems into broader clinical practice.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (Date: June 17, 2025; Approval No: 4922).

Informed Consent: The requirement for informed consent was waived due to the retrospective design.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: Not declared.

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Authorship Contributions: Concept: D.O., B.E., E.A.; Design: A.M., S.C.; Data Collection and/or Processing: S.C., A.A.; Analysis and/or Interpretation: A.M., B.E., E.A.; Literature Search: D.O., A.M., B.E., E.A.; Writing: D.O., A.M., E.A.

Peer-review: Externally peer-reviewed.

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Clinical Characteristics and Short-Term Outcomes of Adult Patients Presenting to the Emergency Department with Hemoptysis: A Retrospective Cohort Study

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Abstract

Objective: This study aimed to characterize the clinical profile of adults presenting with hemoptysis to the emergency department (ED), describe short-term clinical outcomes and their distribution across predefined FLHASc risk strata, and explore patterns of healthcare resource utilization within this cohort.

Materials and Methods: This retrospective cohort study included consecutive adults presenting with hemoptysis to the ED of (blinded for review), Türkiye, between June 1, 2019, and December 31, 2024. Patients were categorized as low risk (FLHASc=0) or moderate-to-high risk (FLHASc≥1). Primary outcomes were 28-day mortality, intensive care unit (ICU) admission, and invasive mechanical ventilation (IMV).

Results: Of 322 screened patients, 258 were analyzed (mean age 62.1±17.8 years; 74% male): 63 (24.4%) were low risk and 195 (75.6%) were moderate-to-high risk. Pure bright-red hemoptysis and active malignancy occurred only in the higher-risk group (62.6% vs. 0%; 23.6% vs. 0%; both p<0.001). Lobar consolidation predominated in low-risk patients (52.4% vs. 25.1%; p<0.001). Overall 28-day all-cause mortality was 9.3%, with a numerically higher rate in the moderate-to-high-risk group (11.3% vs. 3.2%; p=0.094). ICU admission (11.3% vs. 9.5%) and IMV (13.3% vs. 7.9%) rates were numerically higher in the moderate-to-high-risk group without reaching statistical significance.

Conclusion: In this retrospective cohort, predefined FLHASc risk categories were associated with differences in clinical presentation, imaging findings, and short-term outcome distribution. These findings provide descriptive insight into risk patterns within a mixed-etiology emergency department population. Prospective multicenter studies are required before conclusions can be drawn regarding predictive performance or clinical implementation.

Keywords: Computed tomography; emergency department; hemoptysis; mortality; risk stratification

Introduction

Hemoptysis is a time-critical cardiorespiratory emergency in which the immediate threat to life is hypoxemic asphyxiation from airway flooding rather than exsanguination. This pathophysiology places a premium on early risk stratification at emergency department (ED) arrival to avert decompensation and prioritize definitive hemostasis [1,2]. Current management combines rapid stabilization with contrast-enhanced computed tomography (CT) for localization, reserving bronchoscopy for persistent bleeding or tissue sampling when CT is nondiagnostic [3,4].

In Türkiye, lung cancer, pneumonia, bronchiectasis, and tuberculosis are the leading causes, reflecting both malignant and infectious contributors to the national burden [2]. Etiological patterns vary, with lung cancer, bronchiectasis, and tuberculosis being common causes, resulting in wide variation in resource utilization. This highlights the need for standardized early risk tools to guide imaging, intervention, and disposition [5,6].

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Although several risk tools have been proposed, their application across diverse epidemiological settings remains variable [4]. The Florence Hemoptysis Score (FLHASc) stratifies short-term risk but lacks validation in mixed etiologies, and its links to practical outcomes remain limited [7]. This study aimed to describe the clinical characteristics, etiological spectrum, and short-term outcomes of adult patients presenting to a tertiary ED with hemoptysis. Additionally, we explored how predefined FLHASc risk categories were distributed within this cohort and how these categories were associated with clinical outcomes and resource utilization.

Therefore, the primary aim of this study was to characterize the demographic, clinical, and etiological features of adults presenting with hemoptysis to a tertiary ED. A secondary objective was to describe short-term outcomes and explore their distribution across predefined FLHASc risk categories.

Materials and Methods

Study Design and Setting

We conducted a retrospective observational cohort study of consecutive adult patients presenting with hemoptysis to the ED of a tertiary care center (blinded for review). The study period extended from June 1, 2019, to December 31, 2024. Ethical approval was obtained from the Muğla Sıtkı Kocman University Institutional Review Board (Approval No.: 250104/141; Approval Date: 16/07/2025), and informed consent was waived due to the retrospective design. The study complied with the Declaration of Helsinki and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The index time was the first ED assessment, and 28-day outcomes were determined from hospital records and national death registries. The study flow diagram is presented in Figure 1 in accordance with STROBE recommendations.

Study Population

The study included all patients aged 18 years or older whose primary ED admission diagnosis was hemoptysis, identified using the International Classification of Diseases, Tenth Revision (ICD-10) code R04.2. Hemoptysis was defined as the expectoration of blood originating from the lower respiratory tract. We excluded patients with trauma-related airway bleeding, pseudohemoptysis (e.g., from epistaxis or hematemesis), those under 18 years of age, and encounters with insufficient data in the electronic health record (EHR) to confirm the diagnosis or calculate the FLHASc score. Pseudohemoptysis exclusions were confirmed independently by two reviewers using clinical notes, thoracic imaging, and available endoscopy; discordances were adjudicated by a senior emergency physician.

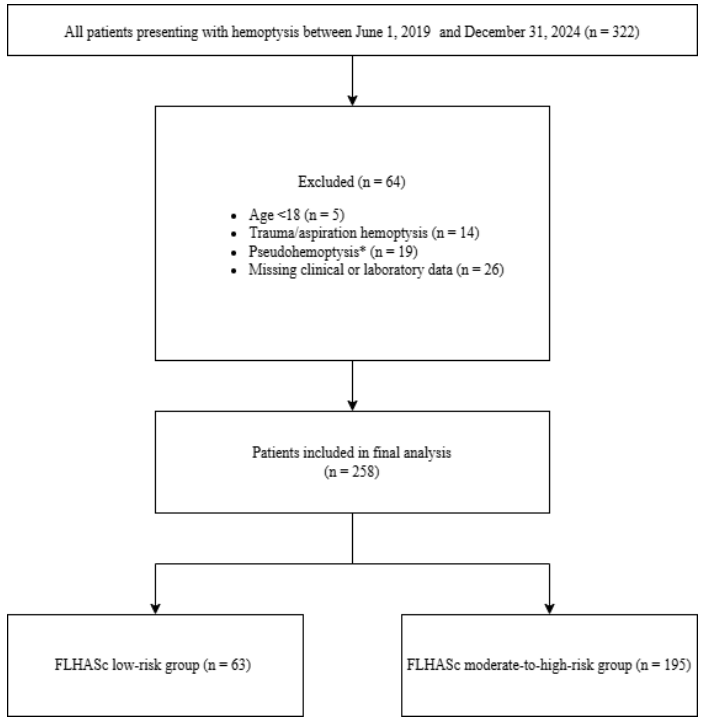

Figure 1. Flowchart of patient selection and FLHASc-based risk stratification *Pseudohemoptysis refers to bleeding from extrapulmonary sources such as epistaxis or hematemesis. Abbreviations: FLHASc: Florence Hemoptysis Score

Data Sources and Collection

Data were retrospectively extracted from the hospital's electronic health records using a standardized form. Two investigators independently collected and verified all data; discrepancies were resolved by a senior reviewer. Variables included demographics, smoking status, comorbidities (malignancy, bronchiectasis, tuberculosis, chronic obstructive pulmonary disease [COPD]), and prior oncologic therapies. Clinical data included vital signs and Glasgow Coma Scale scores. Laboratory results included hematologic, coagulation, renal, hepatic, inflammatory, and cardiac markers. Imaging findings from chest radiography and CT were categorized as normal or abnormal, and bronchoscopy findings were incorporated to determine final etiologies.

Risk Stratification and Variables

Patients were risk-stratified using the FLHASc, calculated from data available at the initial ED presentation. The FLHASc assigns points as follows: systolic blood pressure <100 mmHg (3 points), pure-blood hemoptysis (1 point), history of pulmonary malignancy (1 point), and ≥2 hemoptysis episodes within 24 hours (1 point), yielding a total score from 0 to 6 [7]. For standardization, "pure-blood hemoptysis" was defined as the expectoration of undiluted blood without visible sputum admixture at the index visit, as reported by the patient and documented in clinician notes,

and "≥2 hemoptysis episodes within 24 hours" was defined as at least two discrete expectorations in the preceding 24 hours, confirmed by patient history and corroborated by nursing or physician documentation. Consistent with its derivation study, we dichotomized the score for analysis: low risk (score=0) and moderate-to-high risk (score≥1). [7] Patients with any missing component required for FLHASc calculation were excluded from the primary analysis.

Outcomes

The primary outcomes were 28-day all-cause mortality, need for invasive mechanical ventilation (IMV), and ICU admission. Secondary outcomes included hospital admission, transfusion of blood products, and performance of definitive hemostatic procedures. Resource utilization was assessed during the index ED encounter and ensuing hospitalization, including thoracic CT and bronchoscopy. All outcome data were obtained from the hospital EHR and verified through national death registry records where applicable.

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test. Group comparisons between the low-risk and moderate-to-high-risk strata were performed using the independent samples t-test or Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Fisher's exact test was used when expected cell counts were <5. Continuous variables compared using the Mann–Whitney U test are presented as median (minimum–maximum), and those compared using the independent samples t-test are presented as mean±standard deviation. Categorical variables were summarized as counts and percentages. All statistical tests were two-tailed, with a p-value<0.05 considered statistically significant. Analyses were conducted using IBM SPSS Statistics Version 27.0 (IBM Corp., Armonk, NY, USA) and RStudio Version 2024.12.0 (RStudio, PBC, Boston, MA, USA). No formal sample size calculation was performed; all eligible patients during the study period were included in the analysis. Patients with missing key variables were excluded, and no imputation or sensitivity analyses were performed.

Results

During the five-and-a-half-year study period, 322 consecutive patients presented to the ED with hemoptysis; after exclusions, 258 comprised the analytic cohort (Fig. 1), with 63 (24.4%) classified as FLHASc low risk and 195 (75.6%) as moderate-to-high risk. The cohort had a mean age of 62.1±17.8 years and was predominantly male (74.0%). Baseline characteristics by risk stratum are summarized in Table 1.

The analysis revealed significant disparities in comorbidities that reflected the underlying structure of the FLHASc. The moderate-to-high-risk group had markedly higher rates of both extrapulmonary malignancy (10.3% vs. 0%; p=0.005) and primary lung cancer (23.6% vs. 0%; p<0.001), whereas chronic kidney failure was more prevalent in the low-risk stratum (9.5% vs. 2.6%; p=0.028). This pattern extended to anticancer therapies, with ongoing chemotherapy (27.7% vs. 0%; p<0.001) and radiotherapy (20.0% vs. 0%; p<0.001) documented exclusively in the higher-risk group, whereas antiplatelet/anticoagulant use and smoking history distribution remained comparable between groups.

Beyond comorbidities, the presentation characteristics of hemoptysis itself further distinguished the risk strata. Pure bright-red hemoptysis occurred exclusively in the moderate-to-high-risk group (62.6% vs. 0%; p<0.001), accompanied by significantly higher bleeding volumes and more frequent recurrent episodes. The moderate-to-high-risk group demonstrated not only a greater proportion of patients with recurrent bleeding (23.1% vs. 9.5%; p=0.030) but also a wider distribution in episode frequency despite identical medians (2 [1–6] vs. 2 [1–2]; p<0.001).

Laboratory parameters, including hematologic, biochemical, and blood gas analyses, showed no significant differences between FLHASc risk groups. However, imaging findings closely reflected risk stratification: pulmonary masses (30.8% vs. 12.7%; p=0.008), atelectasis, and pulmonary embolism (6.2% vs. 0%; p=0.043) were more frequent in higher-risk patients, whereas consolidation predominated in low-risk cases (52.4% vs. 25.1%; p<0.001). Bronchoscopic findings showed no intergroup differences; complete radiological and bronchoscopic results are detailed in Table 2.

The etiological distribution, derived from this comprehensive diagnostic workup, revealed distinct and expected patterns across risk strata. Infectious etiologies, particularly bacterial pneumonia, were common in both groups but represented a greater proportion of causes in the low-risk stratum. Malignancy-related hemoptysis predominated in the moderate-to-high-risk group, whereas cardiogenic causes, such as congestive heart failure, were more frequent in low-risk patients, and pulmonary embolism occurred exclusively in the higher-risk stratum (p=0.026). The complete etiological spectrum is presented in Table 3, and its distribution by sex and risk category is illustrated in Figure 2, which highlights the predominance of malignancy among high-risk males and infectious or cardiovascular causes among low-risk females.

With respect to clinical management and outcomes, tranexamic acid was administered to over 85% of patients in both groups.

Table 1. Comparison of Demographic, Clinical, and Hemoptysis Characteristics Between Low and Moderate to High-Risk Patients Based on the FLHASc

Characteristics		Low risk (n=63)	Moderate to high risk (n=195)	X^2 / Z / t	p
Age, years		63.9±17.2	61.54±17.9	-0.845	0.398
Sex, n (Men/Women)		44/19	147/48	0.500	0.479
Physiological parameters on admission					
SBP (mm Hg)		129 (103-210)	130 (65-208)	-0.424	0.672
DBP (mm Hg)		79 (45-135)	80 (30-126)	0.882	0.378
HR (beats/min)		100 (58-141)	100 (62-155)	-0.124	0.901
RR (breaths/min)		14 (10-25)	13 (10-36)	-2.988	0.003
Oxygen saturation (SaO2%)		94(74-100)	94 (73-100)	-0.326	0.744
Temperature (°C)		36.9 (35.9-39.2)	36.5 (35.3-39.8)	-1.552	0.121
GCS Score		15 (6-15)	15 (3-15)	-0.018	0.985
Previous medical history, n (%)					
Extrapulmonary malignancy	No	63 (100)	175 (89.7)	0.005	0.005
	Yes	0 (0)	20 (10.3)		
Coronary artery disease	No	43 (68.3)	153 (78.5)	2.187	0.139
	Yes	20 (31.7)	42 (21.5)		
Diabetes mellitus	No	52 (82.5)	158 (81)	0.007	0.934
	Yes	11 (17.5)	37 (19)		
Hypertension	No	46 (73)	152 (77.9)	0.402	0.526
	Yes	17 (27)	43 (22.1)		
Chronic Kidney Failure	No	57 (90.5)	190 (97.4)	0.028	0.028
	Yes	6 (9.5)	5 (2.6)		
Cerebrovascular disease	No	62 (98.4)	187 (95.9)	0.693	0.693
	Yes	1 (1.6)	8 (4.1)		
Pulmonary comorbidities, n (%)					
Primary lung cancer	No	63 (100)	149 (76.4)	16.512	< 0.001
	Yes	0 (0)	46 (23.6)		
Lung metastases	No	63 (100)	186 (95.4)	0.118	0.118
	Yes	0 (0)	9 (4.6)		
COPD	No	48 (76.2)	170 (87.2)	3.591	0.058
	Yes	15 (23.8)	25 (12.8)		
Asthma	No	60 (95.2)	185 (94.9)	1.000	>0.999
	Yes	3 (4.8)	10 (5.1)		
Tuberculosis	No	61 (96.8)	192 (98.5)	0.598	0.598
	Yes	2 (3.2)	3 (1.5)		
Pulmonary hypertension	No	62 (98.4)	192 (98.5)	1.000	>0.999
	Yes	1 (1.6)	3 (1.5)		
Aspergilloma	No	62 (98.4)	193 (99)	0.570	0.570
	Yes	1 (1.6)	2 (1)		

Table 1. Continue

Characteristics		Low risk (n=63)	Moderate to high risk (n=195)	X^2 / Z / t	p
Current medication use, n (%)					
Antiplatelet	No	39 (61.9)	136 (69.7)	1.006	0.316
	Yes	24 (38.1)	59 (30.3)		
Anticoagulant	No	55 (87.3)	166 (85.1)	0.049	0.825
	Yes	8 (12.7)	29 (14.9)		
Others	No	43 (68.3)	118 (60.5)	0.909	0.340
	Yes	20 (31.7)	77 (39.5)		
Ongoing chemotherapy, n (%)	No	63 (100)	141 (72.3)	22.064	< 0.001
	Yes	0 (0)	54 (27.7)		
Ongoing radiotherapy, n (%)	No	63 (100)	156 (80)	13.326	< 0.001
	Yes	0 (0)	39 (20)		
Smoking history, n (%)					
Current smoker		15 (23.8)	44 (22.6)	1.208	0.547
Former smoker		25 (39.7)	92 (47.2)		
Never smoker		23 (36.5)	59 (30.3)		
Characteristics of hemoptysis, n (%)					
Type of expectoration	Pure bright blood	0 (0)	122 (62.6)	74.773	< 0.001
	Blood-streaked sputum	63 (100)	73 (37.4)		
Amount of expectoration	More than a glass of water (>200 ml)	2 (3.2)	33 (16.9)	18.778	< 0.001
	A glass of water (200 ml)	6 (9.5)	47 (24.1)		
	Half a tea glass (100 ml)	20 (31.7)	52 (26.7)		
	A tablespoon (15 ml)	21 (33.3)	38 (19.5)		
	A teaspoon (5 ml)	14 (22.2)	25 (12.8)		
Type of presentation	First episode of hemoptysis	57 (90.5)	150 (76.9)	4.693	0.030
	Recurrent hemoptysis	6 (9.5)	45 (23.1)		
Number of episodes		2 (1-2)	2 (1-6)	-4.347	< 0.001

Data were presented as median (minimum-maximum), mean±standard deviation or n (%). Statistically significant p values are in bold. Z, t, are the test statistics for Mann Whitney U, independent samples-t and Chi-Square test; respectively. Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; DBP: Diastolic Blood Pressure; FLHASc: Florence Hemoptysis Score; GCS: Glasgow Coma Scale; HR: Heart Rate (beats/min); RR: Respiratory Rate (breaths/min); SBP: Systolic Blood Pressure

No significant differences were observed in rates of IMV (13.3% vs. 7.9%; p=0.356) or blood transfusion (9.2% vs. 11.1%; p=0.846). The overall 28-day all-cause mortality rate was 9.3% (n=24), with a numerically higher rate in the moderate-to-high-risk group (11.3% vs. 3.2%; p=0.094), representing a greater than threefold difference. The moderate-to-high-risk group accounted for all four ED deaths and had higher ICU admission rates (11.3% vs. 9.5%). Comprehensive management and outcome data are summarized in Table 4. No additional subgroup or sensitivity analyses were performed beyond the predefined FLHASc risk stratification.

Discussion

In this single-center cohort of ED patients with hemoptysis, predefined FLHASc risk categories were associated with distinct clinical and radiological patterns. Patients in the moderate-to-high-risk group more frequently demonstrated features such as pure bright-red hemoptysis, recurrent bleeding episodes, and malignancy-related findings, whereas infectious patterns and lobar consolidation were more common among low-risk patients. These differences likely reflect the structural components of the FLHASc within this cohort rather than independent predictive

Table 2. Comparison of Laboratory, Radiological, and Bronchoscopic Findings Between FLHASc Risk Groups					
Characteristics		**Low risk (n=63)**	**Moderate to high risk (n=195)**	**X^2 / Z / t**	**p**
Laboratory findings					
Hemoglobin (g/dL)		12.7±2.9	12.2±2.41	-1.036	0.300
Hematocrit (%)		39.4±8.8	37.7±6.8	-0.669	0.503
White blood cell count (x10^3/µL)		9.23±4.2	8.77±6	-0.810	0.418
Platelet count (x10^3/µL)		243±106	254±95.2	-0.729	0.467
PT (s)		12.6 (9.2-35.1)	12.8 (8.9-262.1)	-1.216	0.224
aPTT (s)		26.3 (18.3-65)	25.7(18.2-129.3)	-0.793	0.428
INR		1.12 (0.9-3.11)	1.13 (0.8-23.72)	-0.997	0.319
Troponin T (pg/mL)		8.1 (2.32-1657)	7.6 (2-238)	-0.078	0.938
D-dimer (ng/mL)		531 (20-7189)	711 (10-9782)	-1.064	0.287
Urea (mg/dL)		32.7±40.3	31±18.3	-1.019	0.308
Creatinine (mg/dL)		0.88±0.2	0.84±0.55	-1.630	0.103
Sodium (mEq/L)		137±3.6	137±3.7	-0.734	0.463
Potassium (mEq/L)		4.35±0.53	4.24±0.47	-1.309	0.191
Calcium (mg/dL)		8.83±0.88	8.98±0.62	-0.729	0.144
Aspartate transaminase (IU/L)		18±31.8	16±30.3	-0.720	0.471
Alanine transaminase (IU/L)		14±12.7	13±30.7	-0.619	0.536
Total bilirubin (mg/dL)		0.36±0.35	0.39±0.12	-0.146	0.884
Direct bilirubin (mg/dL)		0.14±0.14	0.16±1.03	-0.787	0.431
Indirect bilirubin (mg/dL)		0.19±0.17	0.23±0.19	-0.116	0.908
C-reactive protein (mg/L)		13.7 (0.39-324)	20.3 (0.42-270)	-0.033	0.974
pH		7.40±0.05	7.41±0.06	-1.204	0.229
pCO_2 (mmHg)		42±7.1	42±8.4	-0.479	0.632
pO_2 (mmHg)		34±24.8	37±19.6	-0.145	0.885
HCO_3^- (mmol/L)		25.3±4.3	25.6±3.7	-0.309	0.757
Lactate (mmol/L)		1.4±0.9	1.4±1.6	-1.147	0.251
sO_2 (%)		65±21.8	67.6±25.2	-0.031	0.975
Chest X-ray findings, n (%)					
Chest X-ray performed	No	1 (1.6)	15 (7.7)	0.129	0.129
	Yes	62 (98.4)	180 (92.3)		
Chest X-ray results, n (%)	No abnormal findings	26 (41.3)	107 (54.9)	27.757	<0.001
	Tumor	4 (6.3)	36 (13.3)		
	Pleural effusion	4 (6.3)	8 (4.1)		
	Atelectasis	1 (1.6)	24 (12.3)		
	Consolidation	28 (44.4)	30 (15.4)		

Table 2. Continue

Characteristics		Low risk (n=63)	Moderate to high risk (n=195)	X^2 / Z / t	p
Chest CT findings, n (%)					
Chest CT performed	No	4 (6.3)	10 (5.1)	0.751	0.751
	Yes	59 (93.7)	185 (94.9)		
Cavitation	No	61 (96.8)	187 (95.9)	1.000	>0.999
	Yes	2 (3.2)	8 (4.1)		
Bronchiectasis	No	60 (95.2)	187 (95.9)	0.733	0.733
	Yes	3 (4.8)	8 (4.1)		
Segmental or lobar consolidation	No	30 (47.6)	146 (74.9)	16.311	<0.001
	Yes	33 (52.4)	49 (25.1)		
Ground-glass opacity	No	59 (93.7)	166 (85.1)	2.384	0.123
	Yes	4 (6.3)	29 (14.9)		
Pleural effusion	No	55 (87.3)	160 (82.1)	0.605	0.437
	Yes	8 (12.7)	35 (17.9)		
Solid pulmonary mass	No	55 (87.3)	135 (69.2)	7.107	0.008
	Yes	8 (12.7)	60 (30.8)		
Thoracic aortic rupture	No	63 (100)	194 (99.5)	1.000	>0.999
	Yes	0 (0)	1 (0.5)		
PTE	No	63 (100)	183 (93.8)	0.043	0.043
	Yes	0 (0)	12 (6.2)		
Bronchoscopic findings, n (%)					
Bronchoscopy performed	No	46 (73)	136 (69.7)	0.113	0.737
	Yes	17 (27)	59 (30.3)		
Bronchoscopy results, n (%)	Hemorrhage	7 (11.1)	27 (13.8)	2.853	0.848
	Endobronchial tumor	6 (9.5)	20 (10.3)		
	Tuberculosis	1 (1.6)	8 (4.1)		
	Vasculitis	0 (0)	4 (2.1)		
	Pneumonia	1 (1.6)	2 (1)		
	Aspergilloma	0 (0)	1 (0.5)		
	No abnormal findings	48 (76.2)	133 (68.2)		

Data were presented as median (minimum-maximum), mean±standard deviation or n (%). Statistically significant p values are in bold. Z, t, are the test statistics for Mann Whitney U, independent samples-t and Chi-Square test; respectively. Abbreviations: aPTT: Activated Partial Thromboplastin Time; HCO_3^-: Bicarbonate; CT: Computed Tomography; FLHASc: Florence Hemoptysis Score; INR: International Normalized Ratio; pCO_2: Partial Pressure of Carbon Dioxide (mmHg); pH: Potential of Hydrogen; pO_2: Partial Pressure of Oxygen (mmHg); PT: Prothrombin Time (seconds); PTE: Pulmonary Thromboembolism; SD: Standard Deviation; sO_2: Oxygen Saturation (%).

effects. Although numerically higher rates of short-term adverse outcomes and greater resource utilization were observed in the moderate-to-high-risk group, this study was not designed to evaluate predictive performance. Therefore, these findings should be interpreted as descriptive and hypothesis-generating rather than confirmatory.

This phenotypic separation should be interpreted cautiously, as part of the observed differences across FLHASc risk strata arises from the score's inherent structure. Key variables, such as pure-blood hemoptysis and pulmonary malignancy, are integral components of the score rather than independent outcomes; therefore, the higher prevalence of malignancy-related etiologies and mass lesions in higher-risk groups likely reflects score-driven

Table 3. Etiological distribution of hemoptysis according to FLHASc risk groups

Characteristics		Low risk (n=63)	Moderate to high risk (n=195)	X^2	p
Etiological causes of hemoptysis, n (%)					
Infectious causes	Bacterial Pneumonia	32 (91.4)	48 (81.4)	1.984	0.347
	Fungal Infection	1 (2.9)	2 (3.4)		
	Tuberculosis	2 (5.7)	9 (15.3)		
Malignancy	Primary lung cancer	10 (100)	49 (81.7)	0.980	0.642
	Endobronchial metastasis	0 (0)	5 (8.3)		
	Parenchymal metastasis	0 (0)	6 (10)		
Pulmonary	Bronchiectasis	4 (44.4)	5 (20.8)	2.722	0.445
	Diffuse alveolar hemorrhage	3 (33.3)	7 (29.2)		
	Chronic bronchitis	2 (22.2)	8 (33.3)		
	Autoimmune disease	0 (0)	4 (16.7)		
Cardiovascular	Congestive heart failure	6 (100)	9 (40.9)	6.669	0.026
	Pulmonary embolism	0 (0)	12 (54.5)		
	Ruptured thoracic aortic aneurysm	0 (0)	1 (4.5)		
Unknown		3 (9.1)	30 (90.9)	—	—

Data were reported as number (%) as appropriate. is the Chi-Square test statistic. Abbreviations: FLHASc: Florence Hemoptysis Score

enrichment rather than true independent prediction. Accordingly, the FLHASc should be interpreted primarily as a clinical triage tool, not a diagnostic classifier [7].

The phenotypic separation reflects core hemoptysis mechanisms, with high-risk cases characterized by pure bleeding, recurrence, and malignancy linked to vascular invasion and thromboembolism [8,9]. The low-risk pattern with consolidation reflects the slower course of inflammatory or infectious causes. This distinction emphasizes that, in ED hemoptysis, airway flooding and hypoxemia, rather than blood loss, pose the main threat, requiring early localization and airway protection [10,11]. This mechanistic interpretation provides the physiological basis for our observed clinical stratification and supports the risk-based differentiation embedded within the FLHASc.

Our cohort's etiological spectrum, featuring substantial burdens of infection, bronchiectasis, and malignancy, reflects the transitional epidemiology of Türkiye and similar regions [2,12]. This contrasts sharply with malignancy-predominant Western cohorts and has important implications for risk tool application [8,13]. Prognostic scores derived from malignancy-weighted populations may demonstrate spectrum bias when applied to mixed-etiology settings [7]. Our findings suggest that FLHASc-based categorization reflects observable clinical differences within this mixed-etiology cohort.

The lack of laboratory differences suggests that hemoptysis risk stratification depends mainly on clinical and radiological findings, as routine laboratory tests offer limited prognostic value for early assessment [14]. Similarly, a tertiary university hospital-based cohort including 391 patients reported no significant laboratory differences except for hemoglobin, supporting the

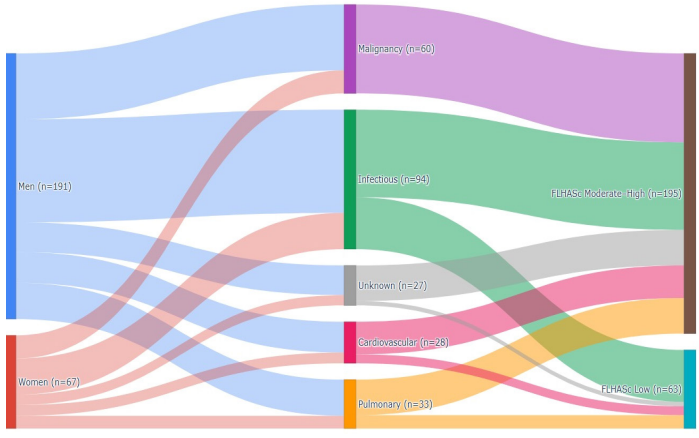

Figure 2. Sankey diagram showing the relationships among sex, etiologic category, and FLHASc risk strata in an emergency department hemoptysis cohort Flow thickness represents patient volume; malignancy and infectious etiologies predominate in moderate-to-high-risk cases, whereas pulmonary and cardiovascular causes are predominant in low-risk groups. Abbreviations: FLHASc: Florence Hemoptysis Score

Table 4. In-Hospital Management, Clinical Outcomes, and Disposition of Patients According to FLHASc Risk Groups

Characteristics		Low risk (n=63)	Moderate to high risk (n=195)	X^2 / Z	p
In-hospital management and interventions, n (%)					
Tranexamic acid treatment	No	8 (12.7)	26 (13.3)	1.000	>0.999
	Yes	55 (87.3)	169 (86.7)		
Mechanical ventilation	No	58 (92.1)	169 (86.7)	0.851	0.356
	Yes	5 (7.9)	26 (13.3)		
Blood transfusion	No	56 (88.9)	177 (90.8)	0.038	0.846
	Yes	7 (11.1)	18 (9.2)		
Blood transfusion products	No	56 (88.9)	177 (90.8)	3.451	0.285
	Packed red blood cells	7 (11.1)	11 (5.6)		
	Fresh frozen plasma	0 (0)	5 (2.6)		
	Platelet concentrate	0 (0)	2 (1)		
Clinical outcomes and disposition					
Emergency department disposition	Discharged	16 (25.4)	35 (17.9)	2.278	0.501
	Hospitalized (ward)	41 (65.1)	134 (68.7)		
	Transferred to ICU	6 (9.5)	22 (11.3)		
	Exitus in ED	0 (0)	4 (2.1)		
Short-term outcomes (28-day mortality) (Time to Death/Median days)		2.5 (2-3)	4 (1-24)	-0.798	0.464
Overall mortality	Survived	61 (96.8)	173 (88.7)	2.811	0.094
	Death	2 (3.2)	22 (11.3)		

Data were presented as median (minimum-maximum) or n (%). Statistically significant p values are in bold. Z, are the test statistics for Mann Whitney U and Chi-Square test; respectively. Abbreviations: ED: Emergency Department; FLHASc: Florence Hemoptysis Score; ICU: Intensive Care Unit.

concordance of our findings with previous evidence [15]. This consistency across cohorts reinforces the robustness of the clinical-radiological framework as the primary determinant of early risk differentiation.

Our imaging findings were consistent with current evidence-based practice, as higher-risk patients more frequently underwent CT angiography in routine clinical care [16,17]. The concordance between risk strata and imaging patterns observed in routine clinical practice aligns with current evidence-based imaging strategies and illustrates how predefined risk categories may correspond to differences in diagnostic resource utilization.

Although this study was not designed to establish management algorithms, the observed differences across FLHASc risk categories may offer preliminary insights for future research exploring structured care pathways. In our cohort, low-risk patients were more frequently associated with infectious patterns and lower intervention rates, whereas moderate-to-high-risk patients more commonly underwent advanced imaging and specialist evaluation. These findings describe current practice patterns rather than prescriptive recommendations and should be interpreted within the descriptive scope of the study.

Although differences in 28-day mortality, ICU admission, and invasive mechanical ventilation did not reach statistical significance, the consistent direction and magnitude of effects across outcomes suggest a clinically meaningful risk gradient. The lack of significance likely reflects limited event numbers rather than the absence of a true association, rendering these findings hypothesis-generating and supportive of further adequately powered prospective studies.

Future studies may explore the integration of risk-based tools into electronic health systems and assess their potential impact in prospective multicenter settings. Multicenter prospective validation using decision-curve analysis is essential to quantify clinical benefits. Further studies should refine score thresholds,

assess treatment–risk interactions, and include equity measures to ensure broader applicability in emergency care.

This study did not assess FLHASc discrimination via ROC analyses but evaluated the score in its intended real-world role as a first-line clinical stratification tool. Accordingly, emphasis was placed on outcome distribution and resource utilization across predefined risk strata rather than on predictive modeling or threshold optimization.

Limitations Study

This study has several limitations that should be considered when interpreting the findings. The single-center retrospective design limits generalizability and precludes causal inference. The FLHASc's dependency on historical elements introduces potential information bias, whereas the exclusion of patients with missing data may have created selection bias. Our inability to analyze time-to-intervention metrics prevented the assessment of care delays, and our dichotomized approach leaves ordinal threshold analysis for future investigation. Recognizing these limitations provides context for interpretation and defines clear directions for methodological improvement in subsequent studies. As this was a descriptive observational study, no formal predictive modeling or discrimination analysis was performed.

Conclusion

In this consecutive emergency department cohort, predefined FLHASc risk categories were associated with differences in clinical presentation and short-term outcomes. Although these findings provide descriptive insight into risk distribution in a mixed-etiology population, further prospective and multicenter studies are required before definitive conclusions can be drawn regarding predictive performance or implementation in routine practice.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Muğla Sıtkı Kocman University Institutional Review Board (Approval No.: 250104/141; Approval Date: 16/07/2025). The study complied with the Declaration of Helsinki and adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Informed Consent: Informed consent was not obtained as this is a retrospective study.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept: H.E.K., D.O.K., Y.G., F.C.T., Design: H.E.K., D.O.K., Y.G., Data Collection or Processing: H.E.K., Y.G., Analysis or Interpretation: F.C.T., H.E.K., Literature Search: H.E.K., D.O.K., Y.G., Writing: H.E.K., D.O.K.

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ORIGINALRESEARCH

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Investigation of the Effectiveness of BAR, Shock Index and Early Warning Scores in the Prognosis of Patients with Diabetic Foot

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Abstract

Objective: Diabetic foot infections are severe complications of diabetes mellitus and are associated with substantial morbidity and mortality. This study aimed to evaluate the prognostic performance of commonly used early warning scores, the shock index (SI), and the blood urea nitrogen-to-albumin ratio (BAR) in predicting clinical outcomes among patients with diabetic foot infections presenting to the emergency department (ED).

Materials and Methods: This prospective study included adult patients presenting to the ED with diabetic foot infections. The predictive value of qSOFA, MEWS, NEWS2, REMS, TREWS, SI, and BAR was assessed for 28-, 90-, and 180-day mortality and amputation outcomes using receiver operating characteristic (ROC) curve analysis.

Results: A total of 92 patients were included. BAR demonstrated the highest prognostic accuracy for mortality at all time points (AUC: 0.802 at 28 days, 0.774 at 90 days, and 0.787 at 180 days). SI was the only parameter significantly associated with 28-day amputation risk (AUC: 0.636). None of the evaluated scores showed adequate predictive performance for 90- or 180-day amputation.

Conclusion: BAR appears to be a reliable marker of short- and medium-term mortality risk in patients with diabetic foot infections presenting to the ED, whereas SI may assist in the early identification of patients at increased risk for early amputation. These findings highlight the complementary roles of systemic and hemodynamic markers in the emergency risk stratification of diabetic foot infections.

Keywords: Amputation, diabetic foot, emergency department, mortality, shock index

Introduction

Diabetic foot infections are severe complications of diabetes mellitus (DM), significantly increasing both morbidity and mortality rates. Patients presenting to emergency departments (EDs) with diabetic foot infections are often in advanced stages with complicated infection patterns, posing significant challenges in determining appropriate treatment strategies [1,2]. Approximately 18.6 million people globally have diabetic foot ulcers, which are associated with reduced physical capacity, lower quality of life, and greater demands on healthcare services. Without appropriate treatment, these ulcers can progress to severe soft tissue infections, gangrene, and potentially limb loss [3,4].

Blood urea nitrogen (BUN), a byproduct of protein metabolism in the human body, is primarily eliminated through the kidneys. BUN concentration is a crucial determinant of renal function, metabolic status, and nutritional state [5]. Albumin, a negative acute-phase reactant, has demonstrated prognostic significance in various critical illnesses, often indicating adverse outcomes [6,7]. The blood urea nitrogen-to-albumin ratio (BAR) has recently been identified as a predictive factor associated with the prognosis of multiple diseases. It has been reported as an independent risk factor in determining the prognosis of critical conditions such as aspiration pneumonia, sepsis, and gastrointestinal bleeding [5,8-10].

The shock index (SI), defined as the ratio of heart rate to systolic blood pressure, serves as a reliable, easily obtainable, and noninvasive measure of hemodynamic stability. It integrates two vital signs into a single, comprehensive physiological variable [11].

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It is recommended for grading hypovolemic shock and assessing transfusion requirements [12].

Early identification of critically ill patients at risk for adverse outcomes is crucial. The development of early warning scores can aid clinicians in expediting treatment, potentially leading to improved outcomes. Several scoring systems, including the Rapid Emergency Medicine Score (REMS) [13], Quick Sequential Organ Failure Assessment (qSOFA) [14], Modified Early Warning Score (MEWS) [15], National Early Warning Score (NEWS2) [16], and Emergency Department Triage Early Warning Score (TREWS) [17], are widely used in EDs as primary early warning tools.

This study aimed to investigate the relationship between early warning scores derived from vital signs, laboratory parameters, and clinical outcomes in patients diagnosed with diabetic foot who presented to the ED. Specifically, we sought to evaluate the potential utility of SI and BAR in addition to routinely used early warning scores. The findings of this study may contribute to the development of new strategies for the early diagnosis, treatment, and follow-up of diabetic foot infections.

Materials and Methods

Study Design

This single-center, prospective study was conducted under protocol number 2011-KAEK-25-2022/06-08 and approved by the Clinical Research Ethics Committee of Bursa Yuksek Ihtisas Training and Research Hospital (Date: 29.06.2022, Decision no: 2011-KAEK-25-2022/06-08). Patients diagnosed with diabetic foot and presenting to a tertiary ED between July 1, 2022, and December 31, 2023, were enrolled in the study. The sample size was determined by the number of consecutive eligible patients presenting to the ED during the predefined study period.

Inclusion and Exclusion Criteria

Patients aged ≥18 years with a confirmed diagnosis of diabetes mellitus who provided informed consent were included. Patients were excluded if they were <18 years old, declined consent, were pregnant, had a history of lower extremity amputation, had chronic kidney disease, had chronic hepatic failure, or presented with a repeat visit for the same condition.

Data Collection

A standardized data collection form was meticulously developed to ensure the systematic and comprehensive documentation of patient information throughout the study. The collected data included demographic variables (age, sex, educational status), detailed medical history (including comorbidities, current medications, and type of diabetes), as well as key clinical parameters such as wound characteristics, laboratory results, and vital signs. ED outcomes were also recorded.

To facilitate objective assessment and risk stratification, several prognostic scoring systems were calculated for each patient, including BAR, SI, TREWS, MEWS, NEWS2, REMS, and qSOFA.

Longitudinal follow-up data regarding major outcomes, specifically amputation and mortality, were collected at 28, 90, and 180 days after admission through a review of hospital records and/or structured telephone interviews conducted with patients or their designated relatives.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA; 2012 release). Numerical data were summarized using mean±standard deviation (SD), median with range, or interquartile range (IQR), whereas categorical variables were expressed as counts and percentages. Normality of distribution was evaluated using the Kolmogorov-Smirnov test, and homogeneity of variances was assessed using Levene's test. To evaluate the ability of BAR, SI, and early warning scores to predict mortality and amputation, receiver operating characteristic (ROC) curve analyses were performed. Logistic regression was used to determine factors independently associated with mortality. A two-sided p-value of <0.05 was considered statistically significant, and results are presented with 95% confidence intervals (CIs).

Results

Patient Characteristics and Clinical Findings

A total of 92 patients meeting the inclusion criteria were enrolled in the study. The mean age of the patients was 62.40±11.53 years, and 65 patients (70.7%) were male. Comorbid conditions were present in 76 patients (82.6%), with hypertension (64.1%) and coronary artery disease (CAD) (34.8%) being the most common. The majority of patients were diagnosed with type 2 diabetes mellitus (95.7%), and 10 patients (10.9%) were not receiving any antidiabetic treatment at the time of admission. Diabetic ketoacidosis was identified in 2 patients (2.2%) at ED presentation. Local wound characteristics demonstrated a high burden of advanced infection. Wound discharge was observed in 66 patients (71.7%), wound necrosis in 62 patients (67.4%), and ulceration in 52 patients (56.5%) (Table 1). Although a formal guideline-based infection severity classification such as IWGDF could not be systematically applied because of the lack of complete systemic infection parameters, these findings indicate that the study

Table 1. Baseline clinical and demographic characteristics of the study population

Demographic characteristics		
Age (year) *		62.40±11.53
Age Range#	<65 year	55 (59.8)
	≥65 year	37 (40.2)
Gender#	Male	65 (70.7)
	Female	27 (29.3)
Comorbidities		
Comorbidity#		76 (82.6)
Hypertension#		59 (64.1)
Coronary Artery Disease#		32 (34.8)
Asthma/COPD#		4 (4.3)
Cerebrovascular Disease#		2 (2.2)
Congestive Heart Failure#		17 (18.5)
Peripheral Vascular Disease#		24 (26.1)
Malignancy#		0
Other#		8 (8.7)
Smoking#		30 (32.6)
Diabetes-Related Characteristics		
Regular use of medication for diabetes#	Does Not Use Medication	10 (10.9)
	İnsulin	56 (60.9)
	Oral Antidiabetic agent	20 (21.7)
	İnsulin+ Oral Antidiabetic agent	6 (6.5)
Type of diabetes #	Type 1	4 (4.3)
	Type 2	88 (95.7)
Diabetic Ketoacidosis#		2 (2.2)
Diabetic Ketosis#		1 (1.1)
Wound Characteristics and Care		
Antibiotic use for diabetic foot#		29 (31.5)
Wound ulceration#		52 (56.5)
Wound necrosis#		62 (67.4)
Wound discharge#		66 (71.7)
Emergency Department Outcomes		
Admission to the service#		55 (59.8)
Admission to intensive care unit#		3 (3.3)
Transfer to another hospital#		1 (1.1)
Discharged#		33 (35.9)

Table 1. Baseline clinical and demographic characteristics of the study population

Demographic characteristics	
Clinical Outcomes	
Mortality within 28 days#	14 (15.2)
Amputation within 28 days#	37 (40.2)
Mortality within 90 days#	17 (18.5)
Amputation within 90 days#	47 (51.1)
Mortality within 180 days#	20 (21.7)
Amputation within 180 days#	49 (53.3)
Total#	92 (100)

n (%), * mean ± standard deviation, COPD: Chronic Obstructive Pulmonary Disease

population predominantly consisted of patients with advanced local diabetic foot infection at the time of ED presentation.

Mortality and Amputation Outcomes

During the 180-day follow-up period, 20 patients (21.7%) died, and 49 patients (53.7%) underwent amputation. Mortality and amputation rates increased progressively over time, with clinically meaningful events occurring at 28, 90, and 180 days.

Scoring Systems

The median values of the prognostic scores were as follows: SI, 0.7 (IQR, 0.6–0.8); qSOFA, 0 (IQR, 0–0); MEWS, 1 (IQR, 0–1); NEWS2, 1 (IQR, 0–2); REMS, 3 (IQR, 3–6); TREWS, 4 (IQR, 3–5); and BAR, 7.70 (IQR, 4.92–13.09) (Table 2).

Mortality Prediction

Receiver operating characteristic (ROC) curve analyses were performed to evaluate the ability of BAR, SI, and early warning scores to predict mortality. For 28-day mortality, BAR demonstrated the highest discriminative ability, with an AUC of 0.802 (95% CI: 0.685–0.918; p<0.001), followed by REMS (AUC: 0.749; p=0.003). Similar findings were observed for 90-day mortality, for which BAR remained the strongest predictor (AUC: 0.774; p<0.001), and for 180-day mortality, for which BAR again showed superior performance (AUC: 0.787; p<0.001) (Table 3, Figure 1).

Optimal cut-off values were determined using the Youden index. A BAR threshold of 9.84 consistently demonstrated favorable sensitivity and specificity for predicting mortality across all time points.

Amputation Prediction

In ROC analyses evaluating amputation outcomes, SI showed modest predictive value for 28-day amputation (AUC: 0.636; p<0.05).

Table 2. Baseline Clinical and Laboratory Characteristics of the Study Cohort

Variables	Value
DM time (year), Median IQR (25-75)	10 (10-20)
Time of onset of wounds(day) IQR (25-75)	30 (14-60)
Clinical Scores	
qSOFA Score Median IQR (25-75)	0 (0-0)
MEWS Score Median IQR (25-75)	1 (0-1)
NEWS2 Score Median IQR (25-75)	1 (0-2)
REMS Score Median IQR (25-75)	3 (3-6)
TREWS Score Median IQR (25-75)	4 (3-5)
Shock Index Median IQR (25-75)	0.7 (0.6-0.8)
BAR Median IQR (25-75)	7.70 (4.92-13.09)
Vital Signs	
Temperature, C^0 Mean ± SD	36.36 ±0.25
Heart rate, /min Median IQR (25-75)	88.5 (83-95.75)
SBP, mm/Hg Median IQR (25-75)	122 (110-139.75)
DBP, mm/Hg Median IQR (25-75)	70 (64-80)
MAP, mm/Hg Median IQR (25-75)	89.5 (83-95.75)
Oxygen Saturation, Median IQR (25-75)	97 (95.25-99)
Respiratory Rate, /min Median IQR (25-75)	15 (14-16)
GCS, Median IQR (25-75)	15 (15-15)
Laboratory Parameters	
Glucose, mg/dL Median IQR (25-75)	222.50 (175.75-319.25)
BUN, mg/dL Median IQR (25-75)	24 (16-39.25)
Lactate, Median IQR (25-75)	1.4 (0.9-2.07)
Base Deficit Median IQR (25-75)	1.1 (-2.17-3.1)
Creatinine, mg/dL Median IQR (25-75)	1.07 (0.82-1.65)
Albumin, g/dL Mean ± SD	3.14±0.7
Leukocyte Count, Median IQR (25-75)	14315 (10335-20145)
Platelet Count, Mean ± SD	376000.01±145000.36
CRP,mg/L Mean ± SD	144.42 ±106.70

DM: Diabetes Mellitus, BAR; BUN/Albumin Rate, qSOFA: Quick Score of Sepsis, MEWS: Modified Early Warning Score, NEWS2: National Early Warning Score, REMS: Rapid Emergency Medicine Score, TREWS: Triage in Emergency Department Early Warning Score, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, GCS: Glasgow Coma Scale, MAP: Mean Arterial Pressure, CRP: C-Reactive protein

However, none of the evaluated scores, including BAR and early warning scores, demonstrated statistically significant predictive performance for amputation at 90 or 180 days (Figure 2).

Multivariate Analysis

Additionally, multivariate logistic regression analysis was conducted to identify independent predictors of 180-day mortality. The analysis revealed that congestive heart failure was significantly associated with increased mortality risk at 180 days [odds ratio (OR): 3.338; 95% confidence interval (CI): 1.072–10.396; p=0.038], as was coronary artery disease (CAD) [OR: 4.134; 95% CI: 1.396–12.242; p=0.010] (Table 4).

Discussion

In this prospective study, we evaluated the prognostic performance of BAR, SI, and commonly used early warning scores in predicting mortality and amputation outcomes in patients presenting to the ED with diabetic foot. The principal finding of this study is that BAR consistently outperformed all other evaluated scores in predicting 28-, 90-, and 180-day mortality, whereas none of the scoring systems demonstrated adequate performance in predicting long-term amputation outcomes.

Diabetic foot infections are associated with substantial morbidity and mortality, particularly in advanced stages of disease. Reported rates of amputation and mortality vary widely in the literature, reflecting differences in patient populations, comorbidity burden, access to healthcare services, and disease severity at presentation [18-23]. In our cohort, the 180-day amputation rate (53.7%) and mortality rate (21.7%) were relatively high. These outcomes should be interpreted in the context of advanced local infection at ED presentation, as more than two-thirds of patients exhibited wound necrosis and discharge, clinical features commonly associated with moderate-to-severe diabetic foot infections according to IWGDF definitions [2].

Early warning scores such as qSOFA, MEWS, NEWS2, REMS, and TREWS are widely used for risk stratification in ED patients with suspected infection or sepsis [13-17,24]. Although these tools have demonstrated variable prognostic performance in general sepsis populations [25-30], evidence specific to diabetic foot patients remains limited. In the present study, several scores showed statistically significant associations with short- and medium-term mortality; however, their overall discriminative ability in diabetic foot patients was inferior to that of BAR.

SI has been proposed as a simple and noninvasive indicator of hemodynamic instability and has demonstrated prognostic value in sepsis and critical illness [12,31-33]. In our cohort, SI did not

Table 3. 28, 90 and 180-Day Mortality Performance Table of Scores According to ROC Analysis

	AUC (95% CI)	p	Scores	Cut-off value	Sensitivity %	Specificity %	Youden index
28-Day mortality	0.802 (0.685-0.918)	<0.001	BAR	9.8≤	71.4	67.9	0.393
	0.666 (0.522-0.809)	<0.05	MEWS	1≤	85.7	43.6	0.293
	0.749 (0.608-0.890)	0.003	REMS	6≤	64.3	79.6	0.439
	0.742 (0.601-0.883)	=0.004	TREWS	5≤	57.1	78.2	0.353
90-Day mortality	0.774 (0.645-0.902)	<0.001	BAR	9.8≤	70.6	69.3	0.399
	0.689 (0.559-0.818)	<0.05	MEWS	1≤	88.2	45.3	0.335
	0.689 (0.542-0.837)	<0.05	NEWS2	1≤	76.5	50.7	0.272
	0.691 (0.536-0.845)	<0.05	REMS	5≤	70.6	58.7	0.293
	0.702 (0.556-0.849)	0.009	TREWS	5≤	52.9	78.7	0.316
180-Day mortality	0.787 (0.674-0.900)	<0.001	BAR	9.8≤	75.5	72.2	0.399
	0.685 (0.566-0.804)	<0.05	MEWS	1≤	90.0	47.2	0.335
	0.651 (0.507-0.796)	<0.05	NEWS2	1≤	70.0	50.0	0.272
	0.649 (0.497-0.801)	<0.05	TREWS	4≤	70.0	45.8	0.293

AUC: Area Under The Curve, CI: Confidence Interval, BAR: BUN/Albümin Rate, MEWS: Modified Early Warning Score, NEWS2: National Early Warning Score, REMS: Rapid Emergency Medicine Score, TREWS: Triage in Emergency Department Early Warning Score

predict mortality but showed modest predictive performance for early (28-day) amputation. A high SI reflects early hemodynamic compromise driven by systemic inflammatory response and relative hypovolemia, which are hallmark features of sepsis. In the setting of diabetic foot infection, this systemic deterioration may exacerbate microvascular dysfunction and tissue hypoperfusion in the affected limb, accelerating ischemia, necrosis, and failure of limb-salvage strategies. Consequently, patients presenting with elevated SI may require more urgent and aggressive surgical interventions, including early amputation, to achieve source control and prevent further systemic deterioration. However, SI failed to predict amputation outcomes at later time points, suggesting limited utility beyond the acute phase.

BAR integrates information on renal function, nutritional status, and systemic inflammatory burden into a single composite marker. Previous studies have demonstrated its prognostic value in conditions such as sepsis, aspiration pneumonia, gastrointestinal bleeding, and critical illness [5,8-10,34]. Mechanistically, an elevated BAR may reflect renal hypoperfusion, increased protein catabolism, and hypoalbuminemia secondary to inflammation and vascular permeability. Experimental and clinical studies

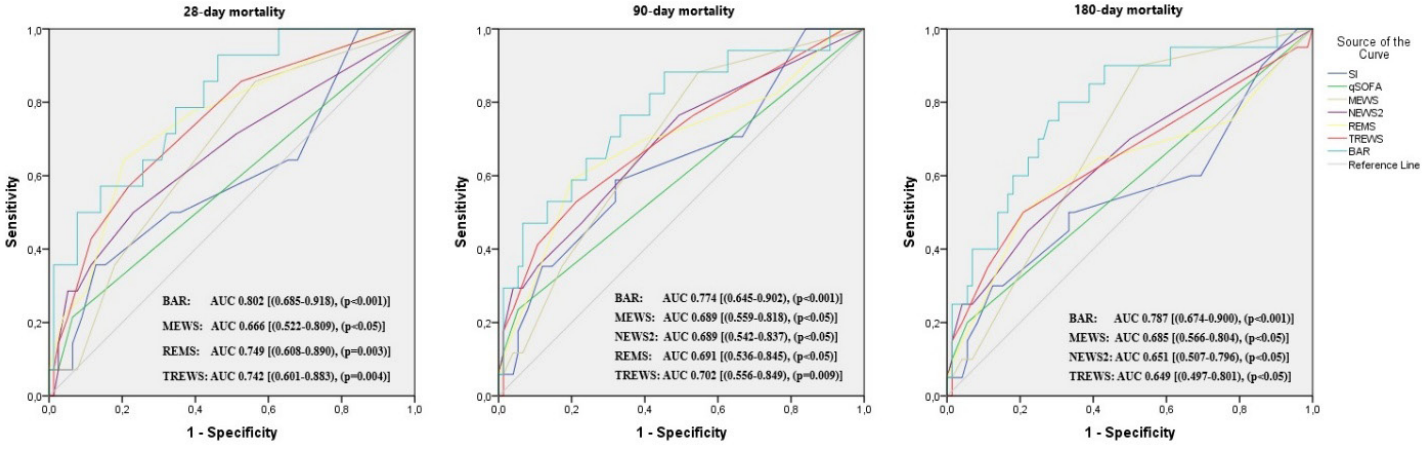

Figure 1. Receiver-operating characteristic curves of the BAR, MEWS, NEWS2, REMS and TREWS for the prediction mortality at 28, 90, and 180 days. AUC: Area Under the Curve, BAR: BUN/Albumin Rate, MEWS: Modified Early Warning Score, NEWS2: National Early Warning Score, REMS: Rapid Emergency Medicine Score, TREWS: Triage in Emergency Department Early Warning Score

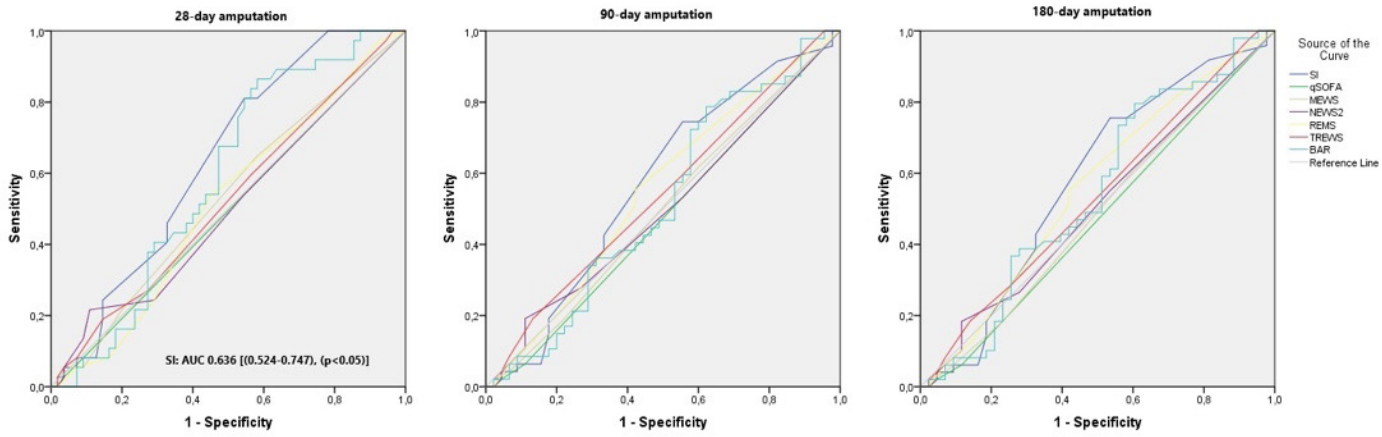

Figure 2. Receiver-operating characteristic curves of the SI for the prediction amputation within 28, 90, and 180 days. AUC; Area Under the Curve; SI: Shock Index

Table 4. Logistic Regression Analysis Table of Variables with 180-Day Mortality

Variables	OR	95 % CI	p
Peripheral Vascular Disease	0.809	0.245-2.672	0.728
Smoking	0.857	0.293-2.510	0.779
GCS	0.221	0.038-1.277	0.092
Congestive Heart Failure	3.338	1.072-10.396	0.038
Coronary Artery Disease	4.134	1.396-12.242	0.010
Hypertension	2.698	0.819-8.890	0.103
Age	1.016	0.948-1.089	0.656

GCS: Glasgow Coma Scale. CI: Confidence interval

have emphasized the role of inflammatory modulation, renal injury, and autophagy-related pathways in systemic infections and diabetic complications [35,36]. Our findings extend this literature by demonstrating that BAR is a robust and consistent predictor of mortality in patients with diabetic foot, a population characterized by chronic inflammation, metabolic dysregulation, and heightened susceptibility to systemic infection.

Although BAR and other systemic scores demonstrated predictive value for mortality, none of the evaluated scores reliably predicted amputation outcomes. This finding is not unexpected, as amputation decisions in diabetic foot disease are primarily driven by local factors such as the extent of tissue necrosis, infection severity at the limb level, vascular status, and feasibility of limb salvage, rather than systemic inflammatory or hemodynamic parameters alone. Therefore, although BAR and SI may reflect overall physiological stress and risk of death, they may have limited ability to capture the complex, multidisciplinary, and locally determined nature of amputation decision-making [37].

Limitations

This study has several limitations. First, its single-center design may limit the generalizability of the findings to other healthcare settings. Second, the relatively small sample size may have reduced the statistical power for certain subgroup analyses. Third, although detailed wound characteristics were available, complete systemic infection parameters were lacking, precluding systematic guideline-based infection severity classification according to the IWGDF criteria. Fourth, follow-up was limited to 180 days, preventing assessment of longer-term outcomes. Finally, residual confounding related to unmeasured clinical or treatment-related factors cannot be excluded. Future multicenter studies with larger cohorts and standardized severity classification are warranted to validate and extend these findings.

Conclusions

In conclusion, this study demonstrates that BAR is a strong and consistent predictor of short- and medium-term mortality in patients presenting to the ED with diabetic foot. Although BAR did not predict amputation outcomes, SI showed modest predictive value for early amputation, suggesting complementary roles for these parameters in risk stratification. Given its simplicity, availability, and prognostic performance, BAR may serve as a useful tool for identifying high-risk diabetic foot patients in the emergency setting. Future studies should explore the integration of BAR into multimodal prognostic models and evaluate its role in guiding clinical decision-making and resource allocation.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Ethical committee during the study planning phase (Date: 29.06.2022, Decision no: 2011-KAEK-25-2022/06-08).

Informed Consent: Written informed consent was obtained.

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ORIGINAL RESEARCH

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A New Diagnostic Tool for Acute Appendicitis: Clearmine Score

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Abstract

Objective: This study aimed to evaluate the diagnostic value of clinical, physical examination, and laboratory findings for acute appendicitis, to create a novel scale using the most meaningful parameters, and to compare it with current diagnostic scores.

Materials and Methods: This was a single-center, retrospective, observational study. Between July 2011 and January 2015, 172 patients aged ≥18 years who visited the emergency department and underwent surgery with a diagnosis of acute appendicitis were included in the study. Patients were divided into two groups, acute appendicitis and negative appendectomy, according to the histopathology reports. ROC analyses of age, sex, clinical characteristics, physical examination results, and laboratory findings were performed, and the areas under the curves were obtained according to the diagnostic groups. Clearmine (CRP, leukocyte, anorexia, rebound tenderness, migration of pain, neutrophil) scores and other scales were compared in terms of diagnostic value for acute appendicitis.

Results: A total of 110 patients were male. The mean age was 34.2±15.8 years. The negative appendectomy rate was 16.3%. Among the clinical presentations, migration of pain (AUC:0.78) and anorexia (AUC:0.75) had the highest diagnostic value. The parameters with the highest diagnostic value were rebound tenderness (AUC:0.68) among physical examination findings and neutrophil count (AUC:0.71), leukocyte count (AUC:0.70), and CRP (AUC:0.68) among laboratory findings. The Clearmine score reached the highest diagnostic value for acute appendicitis when the cutoff was ≥6 points (AUC:0.92). Other scales, including Alvarado, Andersson, Ohmann, and Tzanakis, had lower AUCs.

Conclusion: Compared with other acute appendicitis diagnostic scales currently used in the literature, the Clearmine score has greater diagnostic value; it is practical and useful for use in the emergency department.

Keywords: Acute appendicitis, Clearmine score, emergency medicine, missed appendicitis, negative appendectomy

Introduction

Approximately 10% of emergency department admissions are due to abdominal pain, and acute appendicitis remains the most common surgical cause [1-3]. Since the first appendectomy was performed, mortality rates have decreased dramatically from 67% to less than 1%, largely due to advances in surgical techniques, particularly laparoscopic surgery [4-7]. Despite improvements in treatment, diagnostic challenges persist. The clinical presentation of acute appendicitis can vary widely, and the decision to perform appendectomy is often finalized intraoperatively, contributing to reported negative appendectomy rates of up to 30% [2,8,9].

The diagnosis of acute appendicitis relies on a combination of clinical history, physical examination, laboratory findings, and imaging modalities. To integrate these components, several diagnostic scoring systems have been developed, including the Alvarado, Ohmann, Tzanakis, and Andersson scores [10-13]. Although advances in imaging have improved diagnostic accuracy, clinical scoring systems remain valuable, particularly in emergency

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departments and resource-limited settings. Previous studies have shown that these scores can reduce negative appendectomy and complication rates; however, their overall diagnostic performance remains variable and sometimes limited [10-15].

On the other hand, although new approaches derived from commonly used inflammation markers, such as the neutrophil/lymphocyte ratio, are popular in this regard, studies have also shown their limited diagnostic accuracy [16].

Imaging methods are not always accessible everywhere, laboratory data alone cannot provide sufficient diagnostic power, and clinical scales continue to be valuable. However, the existing scoring systems in the literature led us to develop a new scale that could offer a more successful, practical, and rapid diagnostic evaluation for the emergency department. This is because some of them contain complex parameters that make practical application difficult, some include imaging parameters that may not always be accessible, and some have limited diagnostic success. In our study, we aimed to develop a new clinical scale that could solve all these problems and compare this scale with existing scales in terms of diagnostic value.

Materials and Methods

Study Settings and Design

This was a single-center, retrospective, observational study. The patients' clinical data were obtained by reviewing emergency department files, operative notes, epicrises, and the hospital information processing system database. We included patients aged 18 years and older who underwent appendectomy for acute appendicitis in the emergency department between July 2011 and January 2015. Pediatric patients, pregnant patients, and patients with incomplete clinical information were excluded from the study. There were 217 patients who were diagnosed with acute appendicitis and underwent appendectomy in the emergency department. Among these patients, 45 were excluded from the study because of missing information. A total of 172 patients who met the inclusion criteria were included in the study. Clinical findings, physical examination characteristics, laboratory data, and imaging results were recorded. Patients were divided into two groups according to the histopathological analysis of the excised appendix tissue. Patients with a confirmed diagnosis of acute appendicitis were classified into the "Acute Appendicitis (AA) Group," and patients with histopathological results incompatible with acute appendicitis were classified into the "Negative Appendectomy (NA) Group" (Figure 1).

The diagnostic value of a new scoring system that could be formed from clinical and physical examination findings and laboratory findings with the highest diagnostic value was investigated. ROC analyses were used to compare the scoring systems. In addition, false-positive (negative appendectomy) and false-negative (missed appendicitis) rates were compared.

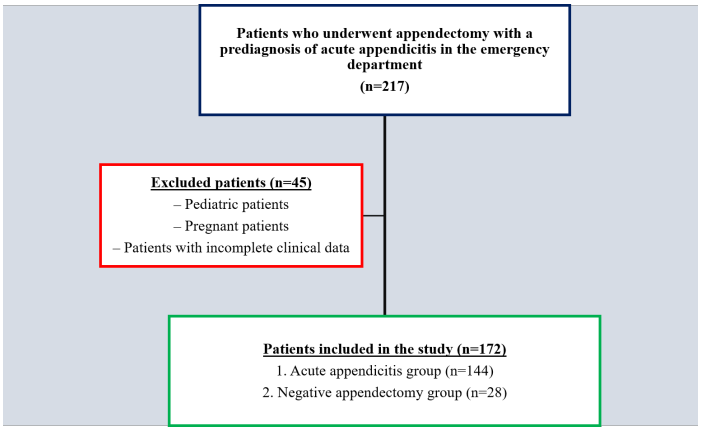

Figure 1. Flow chart of patient selection and study design.

Ethical Statement

The study was conducted with the approval of the Ethics Committee Presidency of Trakya University Faculty of Medicine (Protocol code: TUTF-GOBAEK 2015/112; May 27, 2015). The Declaration of Helsinki was fully complied with, and the data required to protect patient privacy were obtained from clinical records without any clinical intervention.

Examination of Laboratory Results

The diagnostic value of leukocyte count (WBC), neutrophil count (NEU#), neutrophil percentage (NEU%), and C-reactive protein (CRP) level for acute appendicitis was analyzed. The "Sysmex® pocH-100i Automated Hematology Analyzer, SN:F6797, Sysmex Corp., Kobe, Japan" was used for hemogram examination. The "Architect® c 16000 Clinical Chemistry and Immunoassay Test Analyzer, SN:C1600280, Abbott Laboratories, Illinois, USA" was used for CRP analysis.

Radiodiagnostic Examination

Diagnostic evaluation of the patients with USG was performed by radiologists at our hospital who had sufficient experience in the field; 3.5–7.5 MHz linear and convex probes of the "Mindray® UMT-150 (SN:PTA35003299, Shenzhen Biomedical Electronics Co. Ltd., Hamburg, Germany)" device were used.

Appendicitis Scoring Systems and Development of the Clearmine Score

For comparison, established appendicitis scoring systems were calculated for each patient according to their original definitions. The Alvarado score includes migration of pain to

the right lower quadrant, anorexia, nausea/vomiting, right lower quadrant tenderness, rebound tenderness, elevated body temperature, leukocytosis, and neutrophil left shift. The Andersson score consists of right lower quadrant pain, rebound tenderness or muscular defense, body temperature, leukocyte count, proportion of neutrophils, and C-reactive protein level. The Tzanakis score incorporates right lower quadrant tenderness, rebound tenderness, leukocytosis, and ultrasonographic findings. The Ohmann score includes right lower quadrant pain, rebound tenderness, abdominal rigidity, coughing pain, leukocyte count, and age- and sex-related variables. In addition, the Clearmine score developed in this study comprises the degree of pain migrating to the right lower quadrant, anorexia, rebound tenderness, leukocyte count, neutrophil count, and C-reactive protein level. All scoring systems were calculated retrospectively from recorded clinical, physical examination, laboratory, and imaging data.

A new diagnostic score, the Clearmine score, was developed using clinical and physical examination findings and laboratory parameters, which demonstrated the highest diagnostic performance on the basis of ROC curve analysis. Parameters were selected according to their AUC values and clinical applicability. Ultrasonography, despite its diagnostic value, was excluded to preserve simplicity and feasibility in emergency settings. Highly correlated variables were evaluated, and among correlated parameters, the one with the highest diagnostic performance was retained to avoid redundancy. Score weighting was assigned according to defined AUC categories to reflect the relative diagnostic contribution of each parameter. The cutoff values used for continuous variables, including WBC, neutrophil percentage, and CRP, were predefined on the basis of receiver operating characteristic (ROC) curve analysis and are presented in Table 2. The overall score was calculated by summing individual parameter points, and its diagnostic performance and optimal cutoff value were evaluated using ROC analysis. The detailed point allocation and diagnostic performance of the individual parameters are presented in the Results section.

Primary and Secondary Outcomes of the Study

The primary outcome of the study was the diagnostic accuracy of the Clearmine score for acute appendicitis, with histopathological findings used as the reference standard. The secondary outcomes included comparisons of the diagnostic performance of the Clearmine score with that of established appendicitis scoring systems and determination of the optimal cutoff value for clinical use.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 20.0 for Windows®, license no: 10240642, IBM Inc., Chicago, IL, USA. The distribution of continuous data was checked using the Kolmogorov–Smirnov test. Independent sample t-tests were used to compare the mean ages of the groups since they were normally distributed. The Pearson chi-square test was used to compare categorical data. Descriptive data are presented as means±standard deviations or numbers (percentages), as appropriate. While evaluating the diagnostic value of age, sex, clinical characteristics, physical examination and laboratory findings, imaging results, and clinical scales, receiver operating characteristic (ROC) curves were drawn, and areas under the curve (AUCs) were calculated. Additionally, cutoff values, sensitivity, and specificity ratios were calculated. Clearmine scores were analyzed using the DeLong test and compared with other important diagnostic parameters using receiver operating characteristic (ROC) curves.

For all statistical analyses, $p<0.05$ was chosen as the significance limit.

Results

Among the 172 patients included in the study, 83.7% (n=144) were in the acute appendicitis group, and 16.3% (n=28) were in the negative appendectomy group. A total of 64% (n=110) of all patients were male, 66.7% (n=96) were in the acute appendicitis group, and 50% (n=14) were in the negative appendectomy group. In the acute appendicitis group, there was no significant difference in sex rates compared with those in the general patient population (p=0.09); however, in the negative appendectomy group, the female rate was significantly greater (p<0.001). In addition, the rate of negative appendectomy was 22.6% in females and 12.7% in males, and there was a significant difference between the sex groups (p=0.01). The mean age of all patients was 34.2±15.8 years: 35.4±16.4 years in the acute appendicitis group and 27.8±10.2 years in the negative appendectomy group. This difference between the groups was statistically significant (p<0.001). A total of 55.8% (n=96) of the patients were under 30 years of age.

In the acute appendicitis group (n=144), according to histopathologic examinations, 31.9% (n=46) of the patients were reported as having simple inflammation, 18.8% (n=27) as having suppurative appendicitis, 16% (n=23) as having phlegmonous appendicitis, 1.4% (n=2) as having gangrenous appendicitis, 17.4% (n=25) as having perforated appendicitis, and 14.6% (n=21) as having plastron appendicitis. In the reports of the same group, only 47.9% (n=69) of patients had a known cause of luminal obstruction. Fecalith was the most common cause, with a rate of 73.9% (n=51). In 39.3% (n=11) of the patients in the negative appendectomy group, no histopathological findings were

detected, and cases were recorded as nonspecific abdominal pain. Descriptive data and histopathological results are given in detail in Table 1.

Receiver operating characteristic (ROC) analyses were performed to investigate the diagnostic value of clinical, physical, laboratory, and imaging data and acute appendicitis clinical scale scores in the detection of acute appendicitis. The areas under the curve in the ROC curves were compared. Sex, age, anorexia, nausea and vomiting, migration of pain to the right lower quadrant, absence of urinary complications, Rovsing's sign, persistence of abdominal pain, rebound tenderness, right lower quadrant pain, rigidity, pain intensity, leukocyte count, neutrophil count, neutrophil percentage, CRP, USG findings compatible with appendicitis, fever, and diagnostic scores of Alvarado, Ohmann, Andersson, Tzanakis, and Clearmine, a new scale created in our study, were evaluated (Figure 2).

Table 1. Descriptives and histopathological results

		Total (n=172)	Acute appendicitis (n=144)	Negative appendectomy (n=28)	p
Age (years)		34.2±15.8	35.4±16.4	27.8±10.2	<0.001*
Sex	Male	110 (64)	96 (66.7)	14 (50)	c) 0.01#c
	Female	62 (36)	48 (33.3)	14 (50)	
	p	-	0.09#a	b) <0.001#b	-
Causes that obstruct the lumen					
Cause			Total n (%)	Perforated appendicitis n (%)	Nonperforated appendicitis n (%)
No causative factor			75 (52.1)	7 (4.9)	68 (47.2)
Fecalith			51 (35.4)	12 (8.3)	39 (27.1)
Calculus			10 (6.9)	6 (4.2)	4 (2.8)
Carcinoid tumor			3 (2.1)	0 (0.0)	3 (2.1)
Appendiceal neuroma			2 (1.4)	0 (0.0)	2 (1.4)
Cecum tumor			2 (1.4)	0 (0.0)	2 (1.4)
Tubular adenoma			1 (0.7)	0 (0.0)	1 (0.7)
Total			144 (100)	25 (17.4)	119 (82.6)
Confirmed diagnosis in negative appendectomies					
Diagnosis			Total n (%)	Female n (%)	Male n (%)
Nonspecific abdominal pain			11(39.3)	4 (28.6)	7 (50.0)
Meseneteric lymphadenopathy			8 (28.6)	2 (14.3)	6 (42.9)
Ovarian cyst rupture			2 (7.1)	2 (14.3)	-
Typhlitis			1 (3.6)	1 (7.1)	0 (0.0)
Appendagitis			1 (3.6)	1 (7.1)	0 (0.0)
Pelvic inflammatory disease			1 (3.6)	1 (7.1)	-
Ileal perforation			1 (3.6)	0 (0.0)	1 (7.1)
Ectopic pregnancy			1 (3.6)	1 (7.1)	-
GALT lymphoma			1 (3.6)	1 (7.1)	0 (0.0)
Ileal ischemia			1 (3.6)	1 (7.1)	0 (0.0)
Total			28 (100)	14 (100)	14 (100)

GALT: gut-associated lymphoid tissue; *: independent sample t test; #: chi-square test; a: comparison of Acute Appendicitis group vs total; b: comparison of Negative Appendectomy group vs total; c: comparison of female vs male within Negative Appendectomy group. Note: Data in the table are expressed as means ± standard deviations or n(%) as applicable.

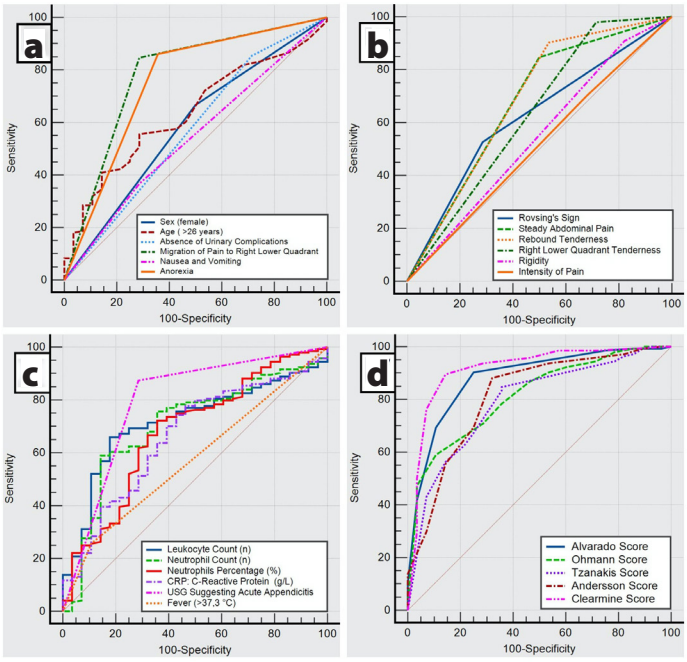

Figure 2. ROC analyses evaluating the predictive value of clinical and physical examinations, laboratory parameters and diagnostic scales for acute appendicitis. a: Comparison of anamnesis variables, b: Comparison of physical examination findings, c: Comparison of laboratory and vital measurements, d: Comparison of Clearmine and other scales.

The presence of pain in the right lower quadrant had the highest diagnostic value for acute appendicitis (AUC=0.78). Anorexia was the second highest complaint (AUC=0.75). Among the laboratory findings, leukocyte count and neutrophil count were found to have the highest diagnostic value (AUC=0.70 and AUC=0.71, respectively). Abdominal USG was also found to have a very high diagnostic value (AUC=0.79) (Table 2) .

Creation of the Clearmine score

On the basis of the data obtained, a new diagnostic scale was created from the parameters with the highest AUC values. Migration of pain to the right lower quadrant (AUC=0.78), anorexia (AUC=0.75), neutrophil count (AUC=0.71), leukocyte count (AUC=0.70), rebound tenderness (AUC=0.68), and CRP (AUC=0.68) were included in the scale. The acronym "CLeARMiNe," meaning "clear mine," was created using the first or first two letters of the parameters. Despite having high diagnostic value, the USG parameter was not included in the scale because it would require additional personnel, time, and experience for practical use of the scale. Neutrophil percentage also had high diagnostic value, but since it was highly correlated with neutrophil count, we included only neutrophil count, which had a relatively high AUC value. Thus, we tried to maintain the simplicity of the scale. The point coefficient was assigned according to the AUC values of the parameters in the scale. CRP, rebound tenderness, and leukocyte count, with AUC values between 0.65 and 0.70, were assigned 1 point; neutrophil count and anorexia, with AUC values between 0.70 and 0.75, were assigned 2 points; and pain migration to the right lower quadrant, with an AUC value above 0.75, was assigned 3 points. The diagnostic evaluation of the patients was performed on a total of 10 points. ROC analysis revealed that the cutoff value for the Clearmine score was 6 points and above. A score of 6 or above was found to have greater diagnostic value than other acute appendicitis diagnostic scales (AUC=0.92; sensitivity=91%; specificity=85.7%) (Table 2) .

According to the Clearmine score, 1.4% of acute appendicitis patients scored between 0 and 2 points, 7.9% scored between 3 and 5 points, and 90.6% scored 6 or above. Among negative appendectomy patients, 85.7% scored between 0 and 5. In negative appendectomy patients who scored 6 points or more, the prominent diagnoses were ovarian cyst rupture, nonspecific abdominal pain, mesenteric lymphadenopathy, and pelvic inflammatory disease. Among the scales used in the present study, the Clearmine score had the lowest rates of misdiagnosis, that is, the lowest rates of negative appendectomy diagnosis and missed appendicitis (Table 3) .

Discussion

Acute appendicitis is the most common cause of surgery in patients who present to the emergency department with abdominal pain. According to previous studies, acute appendicitis, which can occur in all age groups, is frequently observed between the first and third decades of life [2,17]. In our study, we found that most patients in the acute appendicitis group were younger than 30 years (55.8%). Additionally, in the literature, the frequency of acute appendicitis decreases with increasing age [18]. In our study, a similar change was observed in the patient group with increasing age.

Despite advances in diagnostic methods, false-positive diagnoses leading to negative appendectomy results remain an important problem in the management of suspected acute appendicitis. Contemporary evidence indicates that negative appendectomy rates remain clinically relevant, with recent systematic reviews reporting pooled rates of approximately 10–15%, despite the widespread use of imaging and laparoscopic surgery. Moreover, several recent studies have consistently demonstrated that negative appendectomy rates are significantly higher in females than in males. This difference has been largely attributed to the overlap between gynecologic conditions and appendicitis-like clinical presentations, which continues to complicate accurate diagnosis [9,19]. In line with these findings, the negative

Table 2. ROC analysis of important parameters for acute appendicitis diagnosis

Parameters	p*	AUC	CI 95%	Cutoff value	Sen (%)	Spe (%)	DeLong p values vs *Clearmine score*
Sex	0.16	0.58	0.47-0.70	-	33	50	-
Age (years)	0.02	0.64	0.54-0.74	≥27	56	71	<0.001
Absence of urinary symptoms	0.24	0.57	0.45-0.69	-	86	29	-
Migration of pain to the RLQ	<0.001	0.78	0.68-0.89	-	85	71	0.001
Nausea and vomiting	0.49	0.54	0.43-0.66	-	63	29	-
Intensity of pain	0.85	0.51	0.39-0.63	-	70	32	-
Anorexia	<0.001	0.75	0.64-0.86	-	86	64	<0.001
Fever	0.21	0.58	0.47-0.68	-	26	89	-
Steady abdominal pain	0.003	0.67	0.56-0.80	-	85	50	<0.001
Rovsing's sign	0.04	0.62	0.51-0.73	-	53	71	<0.001
Rebound tenderness	0.002	0.68	0.56-0.81	-	90	46	<0.001
Right lower quadrant tenderness	0.11	0.60	0.47-0.72	-	97	27	-
Rigidity	0.46	0.54	0.42-0.67	-	19	82	-
Leukocyte count (n)	0.001	0.70	0.60-0.80	>12500	66	82	<0.001
Neutrophils percentage (%)	0.002	0.69	0.57-0.80	76	71	64	<0.001
Neutrophil count (n)	0.001	0.71	0.61-0.82	>10000	59	86	<0.001
CRP	0.003	0.68	0.57-0.79	0.35	74	57	<0.001
USG suggesting acute appendicitis	<0.001	0.79	0.68-0.90	-	88	70	
Alvarado score	<0.001	0.88	0.81-0.95	≥7	90	75	0.04
Ohmann score	<0.001	0.81	0.73-0.89	≥12	81	61	0.01
Tzanakis score	<0.001	0.80	0.71-0.89	≥8	86	64	0.01
Anderson score	<0.001	0.82	0.73-0.91	≥9	89	68	0.01
Clearmine score	<0.001	0.92	0.85-0.98	≥6	91	86	-

RLQ: Right lower quadrant; *: ROC analysis; Sen: Sensitivity; Spe: Specificity; AUC: Area under the curve; CI: Confidence interval. Note: AUC values were compared using the DeLong method. Clearmine score was used as the reference model for ROC curve comparisons.

appendectomy rate in our study was 16.3%, and female patients had higher rates than male patients.

Recent evidence suggests that, among the clinical features of acute appendicitis, pain that initially arises periumbilically and subsequently migrates to the right lower quadrant remains one of the most valuable diagnostic indicators [20,21]. In our study, we similarly found that pain migration had the highest diagnostic value. On the basis of these results and the current literature, migration of pain to the right lower quadrant should be considered a typical finding of acute appendicitis and should be included in diagnostic algorithms.

Anorexia has been reported as an important presenting symptom in acute appendicitis and is included among the classic clinical features of the disease in contemporary literature. Recent systematic reviews and clinical overviews describe anorexia, often accompanying nausea and vomiting, among the characteristic symptoms that increase the likelihood of an appendicitis diagnosis when present [20]. Alvarado [10] reported that anorexia had a high diagnostic value for acute appendicitis and added it to the scale in his study, in which he defined the MANTRELS score. Similarly, anorexia was the symptom with the highest diagnostic value after pain migration for acute appendicitis and was included in our diagnostic scale.

Rebound tenderness has long been recognized as a key physical examination finding suggestive of peritoneal irritation and is frequently evaluated in suspected acute appendicitis [22]. We also determined the sensitivity of rebound tenderness as the

Table 3. Misdiagnosis rates of scales

Scales	Negative appendectomy (False positive) (%)	Missed appendicitis (False negative) (%)
Alvarado score	4.1	8.1
Ohmann score	6.4	15.7
Tzanakis score	6.0	12.0
Andersson score	5.4	9.0
Clearmine score	2.3	7.8

physical examination finding with the highest diagnostic value, at 90%, and thus decided to include rebound tenderness in the diagnostic scale.

Inflammatory parameters in routine laboratory tests remain essential for the diagnosis of acute appendicitis. Contemporary evidence shows that basic complete blood count parameters, particularly total leukocyte count, neutrophil count, and neutrophil percentage, are significantly elevated in patients with histopathologically confirmed acute appendicitis [10,23,24]. In addition to leukocyte count, neutrophil count was the laboratory parameter with the highest diagnostic value in our study. Neutrophil percentage ranked third after these two parameters. Thus, we decided to include leukocyte count and neutrophil count parameters in the Clearmine score that we created for acute appendicitis.

C-reactive protein (CRP) is a well-established acute-phase reactant whose level increases in response to inflammation, including in acute appendicitis. Recent clinical evidence indicates that CRP has moderate diagnostic value for suspected acute appendicitis [25,26]. In our study, the cutoff value of CRP was 0.35 mg/dL, and we included it in our scale. In this way, the high sensitivity of CRP can be utilized, and its low specificity can be compensated for when it is used in combination with other parameters.

Today, the diagnosis of acute appendicitis has become much easier with abdominal USG and abdominal CT/magnetic resonance imaging, but the need for extra devices/personnel or exposure to radiation/contrast material is a concern [17,27,28]. Therefore, diagnostic scales that are suitable for practical use are still important, especially in emergency departments. There are many scales, such as the Andersson, Tzanakis, Ohmann, and Alvarado scales, in the literature [10-13]. Despite many alternatives, some patients are still misdiagnosed or not clearly diagnosed with these scales. When we compared the diagnostic values, both the highest AUC value and the lowest rates of negative appendectomy or missed appendicitis were associated with the Clearmine score. On the basis of these results, we believe that our scale is suitable for use in the diagnosis of acute appendicitis and will minimize misdiagnosis.

Study Limitations

Our study is a single-center study with a relatively limited sample size. When multicenter studies with larger samples are conducted, the value of the Clearmine score for acute appendicitis will be more clearly understood. This study included only patients who underwent appendectomy and had a confirmed histopathological diagnosis. The exclusion of cases of suspected appendicitis that were managed conservatively or did not undergo surgery may have created a higher-risk cohort and led to an overestimation of diagnostic performance. The Clearmine score was developed and tested within the same dataset without external validation, which may introduce overfitting and optimistic performance estimates and limit generalizability.

Conclusion

The rate of negative appendectomy is higher in females, and gynecologic pathologies are the most common causes. Acute appendicitis is mostly observed in the 20–25-year age group. Simple inflammatory appendicitis is the most common form. The Clearmine score is a simple and rapidly applicable scale with high predictive value for the diagnosis of acute appendicitis, particularly in emergency departments. The Clearmine score was more effective than other scales that are currently in use for acute appendicitis. When these results are supported by multicenter studies with larger samples, the Clearmine score may become a preferred tool in routine diagnostic evaluation for acute appendicitis.

Ethics Committee Approval: The study was conducted with the approval of the Ethical Committee Presidency of Trakya University Faculty of Medicine (Protocol code: TUTF-GOBAEK 2015/112; May 27, 2015). The Declaration of Helsinki was fully complied with, and data required to protect patient privacy were obtained from clinical records without any clinical intervention.

Informed Consent: Informed consent was not required by the ethics committee in this study.

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ORIGINAL RESEARCH

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Predictors of In-Hospital Mortality Among Older Adults Presenting to the Emergency Department with Hip Fracture

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Abstract

Objective: This study aimed to identify predictors of in-hospital mortality among geriatric patients presenting with acute hip fracture.

Materials and Methods: This retrospective cohort study included consecutive patients aged ≥65 years with radiologically confirmed proximal femoral fractures who presented to a tertiary emergency department between January 2020 and January 2025. Demographic characteristics, comorbidities, functional status, laboratory parameters, trauma characteristics, fracture patterns, and in-hospital complications were recorded. Univariable and multivariable logistic regression analyses were performed to identify independent predictors.

Results: A total of 833 patients were included (mean age 83.6±7.1 years; 64.9% male). The in-hospital mortality rate was 9.1%. Compared with survivors, non-survivors had poorer baseline function (ADL 3 vs. 4; IADL 4 vs. 5), a higher comorbidity burden (CCI 9 vs. 7), and greater physiological instability (NEWS2 4 vs. 3). Laboratory differences were notable, with significantly lower serum sodium levels (134 vs. 138 mmol/L) and higher creatinine levels (1.4 vs. 0.9 mg/dL) among non-survivors. High-energy trauma was more frequent among patients who died (14.5% vs. 6.2%). In the multivariable model, higher BMI (aOR 1.11; 95% CI 1.03–1.20), an increased Charlson Comorbidity Index (aOR 1.22; 95% CI 1.05–1.40), higher NEWS2 scores (aOR 1.51; 95% CI 1.33–1.73), and lower serum sodium levels (aOR 0.76; 95% CI 0.70–0.82) were independently associated with increased mortality, whereas DVT/PE showed a strong but statistically non-significant trend toward higher risk.

Conclusion: Early mortality in geriatric patients with hip fracture presenting to the emergency department is primarily driven by comorbidity burden, physiological derangement, and electrolyte abnormalities. Simple parameters available in the emergency department may facilitate rapid risk stratification and guide early management.

Keywords: Aged, emergency service, hospital, hip fractures, mortality, risk factors

Introduction

Traumatic musculoskeletal injuries are a common reason for emergency department (ED) visits worldwide. In Türkiye alone, there were more than 129 million ED visits in 2021. Nearly 900,000 of these required urgent surgery, and approximately 170,000 were due to fractures or dislocations of the extremities [1,2]. Among these injuries, hip fractures are among the most serious conditions affecting older adults and are associated with long-term disability, loss of independence, and increased mortality.

Despite advances in perioperative and geriatric care, mortality after hip fracture remains high. Studies report that 5–10% of patients die within 30 days, while 90-day mortality may reach 10–20% [3,4]. Unplanned readmissions are also common and are often related to postoperative complications, frailty, multimorbidity, and inadequate post-discharge support [5,6]. These outcomes place a substantial burden on both patients and healthcare systems.

Several factors associated with poor outcomes after hip fracture have been identified, including advanced age, frailty, multimorbidity, impaired functional status, cognitive decline, and early in-hospital complications [7–9]. However, most previous studies were conducted in inpatient wards or orthopedic units. Prognostic assessment in the ED differs from inpatient evaluation

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because emergency physicians must make early management decisions before definitive surgical treatment, often with limited clinical information and under conditions of acute physiological instability. Unlike inpatient studies, which mainly focus on postoperative outcomes, ED-based assessment may support triage decisions, ICU admission, monitoring intensity, and disposition planning using variables available at presentation [10,11]. Early identification of high-risk patients in the ED may therefore improve initial management and facilitate timely intervention.

Although ED-based care for older trauma patients is becoming increasingly important, real-world data from middle-income countries remain limited. In addition, predictors identifiable at ED presentation that independently influence in-hospital mortality are not fully understood. Therefore, this study aimed to identify predictors of in-hospital mortality in adults aged 65 years and older presenting to the emergency department with acute hip fracture.

Materials and Methods

Study Design and Setting

This single-center, retrospective observational cohort study was conducted in the Emergency Medicine Department of a tertiary academic referral hospital in Türkiye. The ED provides 24/7 care, has an annual census of approximately 400,000 visits, and serves a diverse urban population. The study covered the period from January 1, 2020, to January 1, 2025. The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 23.07.2025, Decision no: 2025-13-28) and was conducted in accordance with the Declaration of Helsinki. All patient data were de-identified prior to analysis to ensure confidentiality.

Study Population

All consecutive adults aged ≥65 years who presented to the ED with a diagnosis of acute proximal femoral (hip) fracture were screened. Potential cases were identified through the hospital information management system using ICD-10 codes S72.0–S72.9.

Inclusion Criteria

- Age ≥65 years
- Radiologically confirmed acute proximal femoral fracture (X-ray or CT)
- Available demographic, clinical, and radiologic data

Exclusion Criteria

- Age <65 years
- Periprosthetic, pathological, or metastatic fractures
- History of ipsilateral hip surgery (arthroplasty or internal fixation)
- Incomplete or unverifiable medical records

A STROBE-compliant patient flowchart illustrating the screening, inclusion, and exclusion process is presented in Figure 1.

Data Collection

Electronic health records (EHRs) were independently reviewed by two trained investigators using a standardized protocol. Fracture presence, laterality, and morphology were confirmed through radiology reports and Picture Archiving and Communication System (PACS) imaging, including plain radiographs and computed tomography (CT), when available. Discrepancies were resolved by consensus or, when required, adjudicated by a senior emergency physician.

All variables were extracted into a predefined electronic case report form (eCRF) incorporating internal validation rules. Demographic and baseline characteristics included age, sex, and body mass index (BMI). Pre-fracture functional status was assessed using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales, ambulation level, and fall history within the preceding year. Frailty was evaluated using the Clinical Frailty Scale (CFS), while cognitive status—including documented dementia type and severity—and sensory impairment, including vision status, were recorded. Comorbidity burden was quantified using the Charlson Comorbidity Index (CCI). Medication exposure before admission included psychoactive agents, antihypertensive drugs, anticoagulant and antiplatelet therapies, and osteoporosis treatments. Admission laboratory parameters, including hemoglobin, sodium, creatinine,

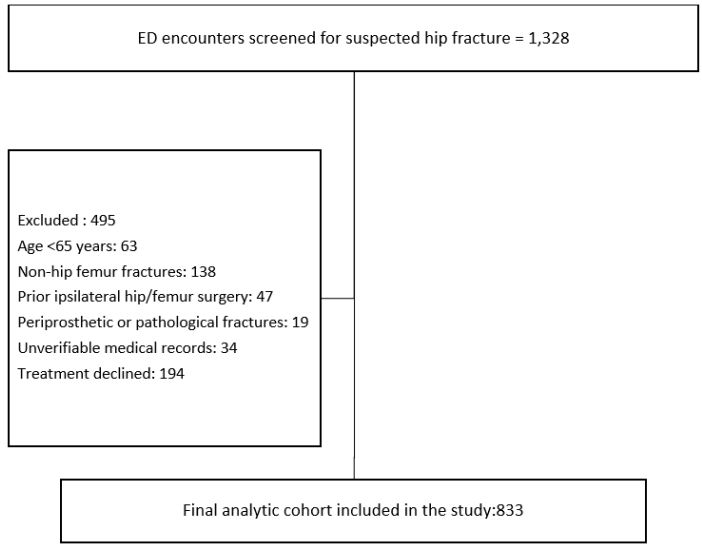

Figure 1. Flow chart of the study

albumin, and C-reactive protein (CRP), were obtained from initial ED testing. Injury-related characteristics included trauma mechanism, location (indoor vs. outdoor), laterality, fracture type (femoral neck, intertrochanteric, or subtrochanteric), AO/OTA 31 classification, displacement, and comminution.

In-hospital complications were defined according to standard diagnostic criteria and included pneumonia, deep vein thrombosis or pulmonary embolism (DVT/PE), myocardial infarction (MI), stroke confirmed by neuroimaging, surgical site infection (SSI), pressure ulcer, reoperation, and delirium. Details of ED disposition and ward or intensive care unit (ICU) admission were documented.

Outcomes

The primary outcome of this study was all-cause in-hospital mortality following the index hip fracture presentation. Secondary outcomes included the development of in-hospital complications and the need for ward or ICU admission.

Statistical Analysis

All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Normality was assessed using the Kolmogorov–Smirnov test, together with histogram and Q–Q plot inspection. Continuous variables are presented as mean±standard deviation (SD) or median with interquartile range (IQR), as appropriate, while categorical variables are summarized as frequencies and percentages.

Univariable analyses were performed using Pearson's chi-square test or Fisher's exact test for categorical variables and Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate. Variables with clinical relevance or a univariable p value <0.10 were entered into multivariable logistic regression analysis to identify independent predictors of in-hospital mortality. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided p value <0.05 was considered statistically significant. To reduce overfitting, the events-per-variable (EPV) ratio was calculated; the final model yielded an EPV of 8, which was considered acceptable for logistic regression modeling. Multicollinearity was evaluated using the variance inflation factor (VIF), tolerance statistics, condition indices, and variance decomposition proportions. No evidence of severe multicollinearity was identified, with all VIF values ranging from 1.006 to 1.652. Creatinine was excluded from the final multivariable model because of potential conceptual overlap with age, comorbidity burden, and physiological severity indicators. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, while discriminative performance was evaluated using the C-statistic/area under the receiver operating characteristic curve (AUC).

Results

Of the 1,328 patients assessed for eligibility, 833 consecutive individuals who fulfilled the predefined inclusion and exclusion criteria were enrolled and constituted the final analytic cohort (Fig. 1).

Triage categories were distributed as follows: 15 patients (1.8%) were Emergency Severity Index (ESI) level 1, 133 (16.0%) were level 2, and 685 (82.2%) were level 3. A total of 819 patients (98.3%) arrived at the ED via Emergency Medical Services (EMS). Overall, 53.7% of patients presented during daytime and 46.3% during nighttime. Seasonal variation demonstrated a predominance of presentations in spring (n=299, 35.9%), followed by winter (n=200, 24.0%), summer (n=184, 22.1%), and autumn (n=150, 18.0%). Of the patients included in the study, 91.6% (n=763) were admitted to the hospital from the ED, whereas 8.4% (n=70) were discharged directly from the ED. Among hospitalized patients, 160 (19.2%) required intensive care unit (ICU) admission. Among survivors who were discharged following the index hospitalization, 115 (14.8%) were readmitted within 30 days and 317 (40.9%) within 90 days. The in-hospital mortality rate was 9.1% (n=76).

In-hospital non-survivors were more likely to be male (47.4% vs. 33.8%, p=0.018) and had a higher mean BMI (25.3±4.2 vs. 23.9±3.9 kg/m^2, p=0.009). Age distribution was similar between groups (median 85 vs. 84 years, p=0.671). Pre-fracture functional assessments revealed significantly greater impairment among non-survivors. Median ADL (3 vs. 4, p=0.006) and IADL scores (4 vs. 5, p=0.003) were lower in those who died, indicating reduced baseline independence. Non-survivors had a substantially higher comorbidity burden, reflected in elevated CCI scores (median 9 vs. 7, p<0.001). Physiological severity at presentation was also greater, with higher NEWS2 scores (4 vs. 3, p=0.041). No significant differences were observed in residential status, fall history, visual impairment, smoking, or alcohol use between groups. Similarly, most medication classes, including psychoactive agents, antihypertensives, diuretics, anticoagulants, and antiplatelets, showed no association with mortality. The only exception was osteoporosis treatment, which was more prevalent among non-survivors (67.1% vs. 54.4%, p=0.034). Baseline characteristics of the study cohort are summarized in Table 1.

Non-survivors presented with markedly higher creatinine levels (median 1.4 mg/dL [IQR 1.2–1.7] vs. 0.9 mg/dL [0.6–1.2]) and significantly lower serum sodium levels (median 134 mmol/L [130–136] vs. 138 mmol/L [135–140]) compared with survivors (both p<0.001), while hemoglobin and CRP values remained

Table 1. Baseline Characteristics of Patients Stratified by In-Hospital Mortality

Variable	Level	Survivor, n (%)	Non-survivor, n (%)	p
Gender, n (%)	Male	256 (33.8)	36 (47.4)	0.018*
	Female	501 (66.2)	40 (52.6)	
Age (years), median (IQR)	—	84 (78–90)	85 (77–91)	0.671†
BMI (kg/m^2), mean ± SD	—	23.9±3.9	25.3±4.2	0.009&
Residential status, n (%)	Home	674 (89.0)	71 (93.4)	0.492*
	Nursing home	47 (6.2)	3 (3.9)	
	Assisted living	36 (4.8)	2 (2.6)	
Pre-fracture mobility, n (%)	Independent	364 (48.1)	32 (42.1)	0.631*
	With aid	276 (36.5)	29 (38.2)	
	Wheelchair	86 (11.4)	12 (15.8)	
	Bedbound	31 (4.1)	3 (3.9)	
Fall history, n (%)	None	512 (67.6)	54 (9.5)	0.726*
	1 fall	159 (21.0)	13 (17.1)	
	≥2 falls	86 (11.4)	9 (11.8)	
Visual impairment, n (%)	None	172 (22.7)	17 (22.4)	0.492*
	Mild	260 (34.3)	23 (30.3)	
	Moderate	229 (30.3)	29 (38.2)	
	Severe	96 (12.7)	7 (9.2)	
Smoking status	Never	320 (42.3)	27 (35.5)	0.303*
	Former	409 (54.0)	44 (57.9)	
	Current	28 (3.7)	5 (6.6)	
Alcohol use, n (%)	None	714 (94.3)	71 (93.4)	0.749*
	Yes	43 (5.7)	5 (6.6)	
Functional status, median (IQR)	ADL score	4 (2–5)	3 (1–4)	0.006ᵘ
	IADL score	5 (3–6)	4 (2–5)	0.003ᵘ
	Frailty (CFS)	6 (5–7)	7 (6–8)	0.109ᵘ
Comorbidity, median (IQR)	CCI	7 (5–8)	9 (7–10)	<0.001ᵘ
Physiology, median (IQR)	NEWS2	3 (2–4)	4 (3–6)	0.041ᵘ
Medication Profile, n (%)	Psychoactive medication	302 (39.9)	28 (36.8)	0.604*
	Antihypertensive	519 (68.6)	58 (76.3)	0.205*
	Diuretic	233 (30.8)	24 (31.6)	0.989*
	Anticoagulant	259 (34.2)	32 (42.1)	0.169*
	Antiplatelet	314 (41.5)	34 (44.7)	0.583*
	Osteoporosis Treatment	412 (54.4)	51 (67.1)	0.034*

ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; CFS: Clinical Frailty Scale; CCI: Charlson Comorbidity Index; NEWS2: National Early Warning Score 2. * Pearson's chi-square test; † Mann–Whitney U test; # Fisher's exact test; & independent samples t-test were used.

similar between groups. Trauma patterns differed substantially by mortality status. High-energy trauma was more common among non-survivors (14.5%, n=11 vs. 6.2%, n=47; p=0.007), and motor vehicle–related injuries demonstrated more than a threefold increase in the mortality group (13.2%, n=10 vs. 3.4%, n=26; p<0.001). In contrast, ground-level falls predominated among survivors (84.1%, n=637 vs. 67.1%, n=51; p<0.001). Among in-hospital complications, non-survivors experienced substantially higher rates of DVT/PE (7.9%, n=6 vs. 2.6%, n=20; p=0.025), surgical site infection (11.8%, n=9 vs. 3.2%, n=24; p<0.001), and pressure ulcers (21.1%, n=16 vs. 10.6%, n=80; p=0.006) (Table 2).

In univariable analyses, higher BMI, higher CCI, elevated NEWS2 scores, and lower serum sodium levels were significantly associated with in-hospital mortality. In multivariable analysis, BMI

Table 2. Laboratory findings, trauma characteristics, and in-hospital complications according to in-hospital mortality

Variable	Level	Survivor	Non-survivor	p
Laboratory, median (IQR)	Hemoglobin	11.6 (11.4-12.8)	11.3 (10.5–13.2)	0.702†
	Creatinine	0.9 (0.6–1.2)	1.4 (1.2–1.7)	<0.001†
	Sodium	138 (135–140)	134 (130–136)	<0.001†
	CRP	29 (21–39)	33 (24–44)	0.316†
Trauma mechanism, n (%)	Ground-Level Fall	637 (84.1)	51 (67.1)	<0.001*
	High-energy trauma	47 (6.2)	11 (14.5)	0.007*
	MVA	26 (3.4)	10 (13.2)	<0.001*
	Other	47 (6.2)	4 (5.3)	0.743*
Place Of Injury, n (%)	Indoor	531 (70.1)	57 (75.0)	0.376*
	Outdoor	226 (29.9)	19 (25.0)	
Fracture Laterality, n (%)	Left	395 (52.2)	34 (44.7)	0.216*
	Right	356 (47.0)	40 (52.6)	0.351*
	Bilateral	6 (0.8)	2 (2.7)	0.113#
Fracture Location, n (%)	Femoral Neck	378 (49.9)	37 (48.7)	0.670*
	Intertrochanteric	336 (44.4)	37 (48.7)	0.360*
	Subtrochanteric	43 (5.7)	2 (2.6)	0.419#
Fracture Type, n (%)	Closed	752 (99.3)	74 (97.4)	0.128#
	Open	5 (0.7)	2 (2.6)	
Displacement, n (%)		609 (80.4)	64 (84.2)	0.427*
Comminution, n (%)		293 (38.7)	31 (40.8)	0.772*
Complication, n (%)	Pneumonia	161 (21.3)	20 (26.3)	0.309*
	DVT/PE	20 (2.6)	6 (7.9)	0.025#
	MI	41 (5.4)	8 (10.5)	0.076#
	Stroke	15 (2.0)	4 (5.3)	0.086#
	Surgical Site Infection	24 (3.2)	9 (11.8)	<0.001#
	Pressure Ulcer	80 (10.6)	16 (21.1)	0.006*
	Reoperation	27 (3.6)	5 (6.6)	0.203#
	Delirium in Hospital	228 (30.1)	29 (38.2)	0.148*

High-energy trauma includes falls from height and direct high-impact injuries; MVA refers to motor vehicle–related trauma. DVT/PE: deep vein thrombosis or pulmonary embolism; MI: myocardial infarction. * Pearson's chi-square test; † Mann–Whitney U test; # Fisher's exact test; & independent samples t-test were used.

(aOR 1.11; 95% CI 1.03–1.20), CCI (aOR 1.22; 95% CI 1.05–1.40), and NEWS2 score (aOR 1.51; 95% CI 1.33–1.73) remained independent predictors of mortality, whereas higher serum sodium levels were protective (aOR 0.76; 95% CI 0.70–0.82). DVT/PE showed a trend toward increased mortality but did not reach statistical significance (aOR 3.31; p=0.077) (Table 3).

The final multivariable model demonstrated acceptable calibration based on the Hosmer–Lemeshow goodness-of-fit test (χ^2=5.842, df=8, p=0.665). Discriminative performance was excellent, with a C-statistic (AUC) of 0.937 (95% CI 0.912–0.962).

Discussion

In this ED-based cohort of older adults with hip fractures, several clinical, physiological, and biochemical factors independently predicted in-hospital mortality. These findings likely reflect the combined effects of baseline vulnerability, acute physiological deterioration, and early in-hospital complications.

Non-survivors had poorer functional status and greater frailty. However, these measures were not independently significant after multivariable adjustment. This finding is consistent with previous studies showing that frailty-associated functional measures often lose prognostic significance once illness severity and comorbidity burden are included in predictive models [12–14]. Frailty-related parameters, such as ADL, IADL, and the Clinical Frailty Scale, reflect reduced physiological reserve and vulnerability to stressors. In contrast, NEWS2 may capture the acute clinical manifestation of this vulnerability at ED presentation [15,16]. Therefore, the prognostic effects of frailty-related measures may be attenuated because of shared variance with acute physiological instability and multimorbidity. BMI, CCI, and NEWS2 emerged as robust independent predictors. This finding supports previous evidence suggesting that multimorbidity and acute physiological instability may outweigh chronological age in determining short-term prognosis after hip fracture [17,18]. Hyponatremia also showed a strong association with mortality, consistent with studies

Table 3. Univariable and multivariable logistic regression for in-hospital mortality

Variable	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Sex (Male)	1.76 (1.10-2.83)	0.018	1.29 (0.67-2.50)	0.444
Age (per year)	1.00 (0.98–1.03)	0.735	0.98 (0.94–1.02)	0.369
BMI (kg/m^2)	1.08 (1.02–1.15)	0.007	1.11 (1.03–1.20)	0.004
Pre-fracture mobility	1.15 (0.87–1.51)	0.309	1.08 (0.76–1.51)	0.674
ADL score	0.99 (0.87–1.13)	0.824	—	—
IADL score	1.03 (0.93–1.15)	0.584	—	—
Frailty score	0.95 (0.79–1.13)	0.546	—	—
Charlson Comorbidity Index	1.19 (1.07–1.33)	0.001	1.22 (1.05–1.40)	0.007
NEWS2 score	1.60 (1.42–1.81)	<0.001	1.51 (1.33–1.73)	<0.001
Creatinine	1.00 (0.59–1.63)	0.998	—	—
Sodium (mmol/L)	0.75 (0.70–0.80)	<0.001	0.76 (0.70–0.82)	<0.001
Osteoporosis treatment	1.71 (1.05–2.86)	0.036	1.44 (0.79–2.64)	0.236
Ground-Level Fall	1.27 (0.68–2.60)	0.480	—	—
High-energy trauma	1.16 (0.43–2.60)	0.738	—	—
Motor Vehicle Accident	0.90 (0.21–2.59)	0.866	—	—
DVT/PE complication	2.47 (0.80–6.27)	0.078	3.31 (0.81–11.77)	0.077
Myocardial infarction	1.14 (0.39–2.72)	0.787	—	—
Stroke complication	1.18 (0.18–4.21)	0.830	—	—
Surgical site infection	0.63 (0.10–2.15)	0.536	—	—
Pressure ulcer	0.89 (0.39–1.82)	0.775	—	—
Delirium in hospital	1.26 (0.76–2.05)	0.356	—	—

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; NEWS2, National Early Warning Score 2; DVT/PE, deep vein thrombosis/pulmonary embolism.

linking sodium imbalance to frailty, malnutrition, and impaired physiological reserve [19,20]. Although creatinine was significant in univariable analysis, it was excluded from the final model because of conceptual overlap with comorbidity burden and physiological derangement. This approach is consistent with parsimonious modeling principles and TRIPOD recommendations [21].

High-energy trauma mechanisms were more common among non-survivors, but their effects diminished after adjustment. This suggests that the physiological consequences of injury may be more important than the trauma mechanism itself in determining mortality risk. Similarly, complications such as DVT/PE, surgical site infection, and pressure ulcers were more frequent among non-survivors, supporting previous evidence on the prognostic importance of early in-hospital complications [22,23]. However, the wide confidence intervals observed for some complications likely reflect limited event numbers and possible rare-event bias [24].

Overall, our findings suggest that simple ED-based parameters, including comorbidity burden, physiological instability, and electrolyte abnormalities, may help identify older hip fracture patients at high risk of in-hospital mortality. Because these variables are readily available at ED presentation, they may support early orthogeriatric involvement, closer monitoring, ICU triage decisions, and timely perioperative optimization. Our results also provide real-world evidence from a high-volume, middle-income ED setting and support further multicenter validation of ED-based prognostic strategies.

This study has several limitations. First, the single-center retrospective design may limit generalizability to other healthcare settings and populations. Second, despite standardized electronic data extraction, some information may have been incomplete or inaccurately documented, particularly regarding pre-fracture functional status and medication history. Therefore, residual misclassification bias may exist. Third, important perioperative variables, such as time to surgery, operative versus conservative management, anesthesia type, and perioperative care factors, were not consistently available and could not be included in the analyses. The absence of these variables may have influenced mortality outcomes and limited interpretation of the independent prognostic associations identified. Fourth, in-hospital mortality was used as the primary outcome, and post-discharge mortality events could not be assessed. Finally, some complications, including DVT/PE and surgical site infection, were relatively infrequent, resulting in wide confidence intervals and reduced precision of effect estimates.

Conclusion

In this ED-based cohort of older adults with hip fractures, mortality was primarily associated with underlying medical vulnerability rather than fracture characteristics. Comorbidity burden, physiological instability at presentation, and serum sodium levels were the strongest indicators of in-hospital mortality. These findings highlight the importance of early medical risk stratification in the ED and support early multidisciplinary and perioperative management strategies. Larger multicenter studies are needed to further validate these findings.

Ethics

Ethics Committee Approval: This study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 23.07.2025, Decision no: 2025-13-28).

Informed Consent: Written informed consent was obtained.

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LETTER TO THE EDITOR

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Reintegrating Frontline Physicians into Global Academia: Insights from Icon-EM Türkiye 2022

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To the Editor,

Armed conflicts disrupt health systems and often result in the scientific isolation of frontline physicians—those providing emergency and essential medical care in conflict-affected or resource-limited settings. In Syria, more than a decade of conflict has devastated infrastructure and fragmented healthcare delivery, leaving internally displaced persons (IDPs) and communities in tented settlements highly dependent on emergency services as their first point of access to care [1]. In this context, supporting the professional capacity of physicians working in northern Syria remains a global health priority. Since 2012, Türkiye has played a central role in providing humanitarian health services in Syria, establishing hospitals, field clinics, and referral networks that have reached millions of displaced civilians [2]. In parallel, a large number of Syrian healthcare professionals living in Syria have been trained through Türkiye and WHO-supported programs and integrated into humanitarian aid projects, thereby contributing to the resilience of local health systems [3]. Within this framework, the 2nd International Congress on Emergency Medicine (Icon-EM), held in Belek/Antalya on 10–13 November 2022, offered a rare opportunity to bridge the academic gap for physicians from northern Syria. Supported logistically by the World Health Organization (WHO), 28 Syrian physicians attended the congress through comprehensive arrangements covering cross-border travel, accommodation, and full scientific registration [4]. A dedicated session entitled "Holistic Management of Emergency Cases in Northern Syria" facilitated academic dialogue between Syrian frontline physicians and Turkish emergency medicine experts. While this session served as a key platform for direct interaction, the educational and professional gains reported by participants reflected not only this specific session but also their broader engagement with the congress program as a whole, which included plenary lectures, workshops, and networking events. Syrian participants shared their experiences in managing trauma, obstetric emergencies, and critical conditions in resource-limited settings, while Turkish academics contributed evidence-based approaches. This exchange culminated in a synthesis of context-appropriate strategies for emergency care in conflict zones. To evaluate the initiative, structured post-congress surveys were administered to the 28 Syrian physicians who attended the congress, of whom 16 (57.1%) completed the questionnaire. Descriptive statistics, including frequencies and means, were used to analyze the responses. The results highlighted four key themes:

Scientific benefits: Fifteen of the 16 respondents (93.8%) agreed or strongly agreed that the congress was scientifically beneficial (mean score: 4.25/5), reporting improved knowledge and an updated understanding of emergency case management.

Academic motivation: Fourteen participants (87.5%) indicated that the congress encouraged them to conduct academic research (mean: 3.88/5), and 13 participants (81.3%) felt more motivated to give academic presentations in the future (mean: 3.94/5).

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Networking opportunities: Thirteen participants (81.3%) stated that the event helped them build new academic relationships (mean: 4.00/5), fostering a sense of recognition and inclusion within the international medical community.

Future engagement: Fifteen participants (93.8%) expressed their willingness to attend or contribute to similar initiatives in the future (mean: 4.13/5).

These findings confirm that the initiative not only enhanced participants' scientific competence but also strengthened their academic engagement and motivation for ongoing collaboration.

In this regard, they align with prior literature emphasizing that capacity-building initiatives in humanitarian contexts not only enhance individual competencies but also contribute to system-level resilience [5]. What distinguishes the Türkiye–WHO initiative is its integration of academic capacity building within an already established humanitarian health framework. By connecting frontline physicians to international academic platforms, this model addressed both immediate training needs and the long-term consequences of scientific isolation.

In conclusion, the Icon-EM Türkiye 2022 experience demonstrates that, with targeted support, physicians in northern Syria can be effectively reintegrated into the global academic community. Sustaining such initiatives is essential to strengthening emergency care systems, improving outcomes for displaced populations, and promoting equity in global health.

Ethics

Ethics Committee Approval: Ethical approval was not required because this letter reports a post-congress educational feedback survey using anonymized aggregate data; no identifiable personal or clinical data were collected. Participation in the survey was voluntary.

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