Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Full-dose versus half-dose systemic thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: 30-day mortality and its determinants in a 10-year real-world cohort

Gizem Karakurt

karakurtgizemnur31@gmail.com

Turkish Republic Ministry of Health, Lüleburgaz State Hospital

Müge Meltem Tor

Zonguldak Bülent Ecevit University Faculty of Medicine

Ayşegül Tomruk Erdem

Zonguldak Bülent Ecevit University Faculty of Medicine

Bülent Altınsoy

Zonguldak Bülent Ecevit University Faculty of Medicine

Research Article

Keywords: pulmonary embolism, systemic thrombolysis, 30-day mortality, hemodynamic instability, C-reactive protein, reduced-dose thrombolysis, real-world data

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11515049/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Systemic thrombolysis is recommended for high-risk pulmonary embolism (PE) and may be considered in selected patients with intermediate-high-risk PE. However, factors associated with short-term mortality among patients receiving thrombolytic therapy and the clinical impact of reduced-dose regimens remain incompletely defined.

Methods

This retrospective single-center cohort included 115 consecutive adults with acute high-risk or intermediate-high-risk PE who received systemic thrombolytic therapy between January 2013 and December 2022. Patients were categorized as receiving full-dose thrombolysis (alteplase 100 mg or standard-dose reteplase) or half-dose thrombolysis (alteplase 50 mg). The primary outcome was 30-day all-cause mortality. Factors associated with mortality were evaluated using conventional logistic regression. Because of the limited number of outcome events and complete separation for supplemental oxygen requirement, Firth penalized logistic regression was additionally performed as a sensitivity analysis.

Results

Thirty-day mortality occurred in 29 patients (25.2%); rates were 23.3% in the full-dose group and 28.6% in the half-dose group (OR 1.31, 95% CI 0.50–3.38; p = 0.656). In the primary multivariable model, CRP (adjusted odds ratio [aOR] 1.095 per 10 mg/L, 95% CI 1.015–1.180; p = 0.019) and hemodynamic instability (aOR 4.642, 95% CI 1.397–15.423; p = 0.012) were independently associated with 30-day mortality, whereas thrombolytic treatment strategy was not (aOR 1.442, 95% CI 0.428–4.857; p = 0.555). These findings were preserved in a six-covariate Firth model. When supplemental oxygen requirement was additionally incorporated into the penalized model, hemodynamic instability remained significantly associated with mortality (aOR 3.783, 95% CI 1.208–12.487; p = 0.022), whereas the association with CRP was attenuated (aOR 1.066 per 10 mg/L, 95% CI 0.996–1.148; p = 0.067). All 30-day deaths occurred among patients requiring supplemental oxygen (Fisher's exact p < 0.001).

Conclusions

Hemodynamic instability showed the most robust association with 30-day mortality among thrombolysis-treated patients with acute high-risk and intermediate-high-risk PE. CRP demonstrated a prognostic association that was sensitive to model specification, whereas thrombolytic treatment strategy was not independently associated with mortality. These findings emphasize the prognostic

importance of acute hemodynamic and respiratory compromise and warrant validation in larger prospective multicenter cohorts.

BACKGROUND

Although advances in diagnostic imaging, anticoagulant therapy, and reperfusion strategies have substantially improved the management of acute pulmonary embolism (PE), early mortality remains unacceptably high among patients presenting with hemodynamic instability or right ventricular (RV) dysfunction. Acute PE continues to impose a substantial burden on healthcare systems worldwide, and current international guidelines emphasize early risk stratification to guide therapeutic decision-making [1–3].

Current management of acute PE relies on prompt risk stratification based on hemodynamic status, clinical severity scores, RV function, and circulating cardiac biomarkers. Under the 2019 ESC risk-stratification framework used in the present study, patients are categorized as high-, intermediate-high-, intermediate-low-, or low-risk according to their estimated risk of early mortality. This risk-adapted approach enables timely identification of patients who may benefit from reperfusion therapy while minimizing unnecessary exposure to treatment-related complications. Among available prognostic tools, the Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), RV dysfunction detected by echocardiography or computed tomography, and elevated cardiac troponin and natriuretic peptide concentrations remain widely validated predictors of adverse clinical outcomes [1].

Systemic thrombolytic therapy remains the standard reperfusion strategy for patients with high-risk PE presenting with hemodynamic instability, obstructive shock, or cardiac arrest because it rapidly reduces thrombotic burden, improves pulmonary perfusion, and restores RV function. However, these benefits are counterbalanced by an increased risk of major bleeding and intracranial hemorrhage. Consequently, while systemic thrombolysis is strongly recommended for patients with high-risk PE, its routine use in intermediate-high-risk PE remains controversial because the potential reduction in hemodynamic deterioration must be balanced against an increased risk of major bleeding [1, 4, 5].

Because bleeding remains the principal limitation of full-dose systemic thrombolysis, reduced-dose thrombolytic therapy has emerged as a potentially promising strategy to preserve therapeutic efficacy while improving safety. The MOPETT trial and subsequent observational studies suggested potential hemodynamic benefit with lower-dose thrombolysis in selected patients; conversely, available evidence remains heterogeneous with respect to patient selection, thrombolytic regimens, and outcome definitions. Recent systematic reviews continue to emphasize that high-quality dose-finding evidence is limited and that reduced-dose thrombolysis cannot yet be considered standard care across all risk groups [6, 7].

Beyond selecting the optimal reperfusion strategy, identifying reliable prognostic factors remains fundamental to improving clinical decision-making in acute PE. Previous studies and guideline-based risk models have consistently emphasized the importance of hemodynamic instability, RV dysfunction,

cardiac biomarkers, and comorbidity burden [1–3]. In addition, increasing evidence suggests that systemic inflammation may contribute to adverse outcomes in PE, and inflammatory biomarkers such as C-reactive protein (CRP) have been investigated as adjunctive prognostic markers [8–10].

Despite growing interest in reduced-dose thrombolysis in selected patients, uncertainty persists regarding patient selection, clinical effectiveness, and mortality predictors among patients receiving different thrombolytic regimens. The clinical outcomes associated with reduced-dose thrombolysis in patients with high-risk and intermediate-high-risk PE therefore remain incompletely characterized. The present study aimed to compare clinical outcomes between full-dose and half-dose systemic thrombolysis and to identify factors independently associated with 30-day mortality among patients with acute high-risk and intermediate-high-risk PE treated at a tertiary referral center.

METHODS

Study Design and Population

This retrospective single-center cohort study was conducted at a tertiary referral center and included patients evaluated for acute pulmonary embolism between January 2013 and December 2022. Hospital records were screened to identify potentially eligible patients. Risk categories were retrospectively assigned according to the 2019 ESC risk stratification criteria using clinical, laboratory, and imaging information documented during the index PE episode [1]. High-risk PE was defined by the presence of hemodynamic instability. In the absence of hemodynamic instability, patients with an elevated clinical risk score (PESI class III–V or sPESI ≥ 1), right ventricular dysfunction, and elevated cardiac troponin levels were classified as having intermediate-high-risk PE [1]. For retrospective risk classification, diagnostic CTPA images were individually reviewed, and RV dysfunction was considered present when the RV/LV diameter ratio was ≥ 1.0. Available echocardiographic findings were also considered, with pretreatment imaging findings prioritized whenever available. In patients with intermediate-high-risk PE, systemic thrombolysis was not administered routinely; treatment was individualized according to the treating physician's clinical judgment, considering overall clinical severity and the presence of cardiac biomarker elevation and/or right ventricular dysfunction.

Adult patients with acute high-risk or intermediate-high-risk PE who received systemic thrombolytic therapy were eligible for inclusion. Patients younger than 18 years, those with pre-existing chronic thromboembolic pulmonary hypertension, patients treated with catheter-directed interventions or surgical embolectomy, those receiving anticoagulation alone, and patients whose medical records were insufficient to confirm eligibility, treatment exposure, or the primary outcome were excluded. After application of the eligibility criteria, 115 patients constituted the final study cohort.

The primary outcome was 30-day all-cause mortality. Secondary outcomes included 90-day and 1-year mortality, bleeding complications, length of hospital stay, and exploratory record-based outcomes of recurrent pulmonary embolism and documented CTEPH during available follow-up. Mortality status at

30 days, 90 days, and 1 year was ascertained from hospital electronic medical records. When mortality follow-up information was unavailable or incomplete in the medical records, patients or their relatives were contacted by telephone using contact information documented in the hospital records. Vital status was successfully ascertained for all patients at the prespecified mortality time points. Recurrent pulmonary embolism and CTEPH were identified from hospital medical records. Since all deaths occurring within 30 days occurred during the index hospitalization, in-hospital mortality and 30-day mortality were identical in the study cohort.

Data Collection

Demographic characteristics, comorbidities, clinical presentation, laboratory findings, imaging results, echocardiographic parameters, treatment characteristics, and clinical outcomes were extracted from the hospital electronic medical record system.

The Charlson Comorbidity Index was calculated for each patient to quantify baseline comorbidity burden. The non-age-adjusted Charlson Comorbidity Index was used. Baseline laboratory parameters included C-reactive protein (CRP), cardiac troponin, D-dimer, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Cardiac biomarker positivity was defined according to the institutional laboratory reference thresholds used during the study period as NT-proBNP > 125 pg/mL and/or troponin > 0.03 ng/mL. These thresholds reflected local laboratory reference limits rather than guideline-derived prognostic cutoffs. Echocardiographic evaluation included right ventricular dilatation and systolic pulmonary artery pressure (sPAP). For the echocardiographic analyses, RV dilatation was defined as an RV/LV diameter ratio ≥ 1.0 on echocardiography performed within 24–48 hours of diagnosis. This variable was analyzed separately from the broader imaging-based RV dysfunction criterion used for ESC risk classification.

Hemodynamic instability was defined according to the 2019 ESC criteria as the presence of at least one of the following at presentation: (1) cardiac arrest requiring cardiopulmonary resuscitation; (2) obstructive shock, defined as systolic blood pressure < 90 mmHg or the need for vasopressors to maintain systolic blood pressure ≥ 90 mmHg despite adequate filling status, together with evidence of end-organ hypoperfusion (altered mental status, cold or clammy skin, oliguria/anuria, or elevated serum lactate); or (3) persistent hypotension, defined as systolic blood pressure < 90 mmHg or a decrease in systolic blood pressure of ≥ 40 mmHg lasting > 15 minutes and not attributable to new-onset arrhythmia, hypovolemia, or sepsis [1]. Supplemental oxygen requirement was defined as a room-air oxygen saturation (SpO_2) < 88% at presentation; all patients meeting this criterion received supplemental oxygen therapy.

Bleeding outcomes were recorded descriptively as intracranial hemorrhage, gastrointestinal bleeding, and other documented bleeding events. Other documented bleeding events included bleeding or oozing from central or peripheral vascular access sites, hematoma, postoperative surgical-site bleeding, hematuria, and hemorrhagic respiratory secretions/hemoptysis. CTEPH was considered present when a diagnosis of CTEPH was documented in the hospital medical records during available follow-up after the

index PE event. No protocolized screening program for CTEPH was applied, and diagnostic evaluation was performed according to routine clinical practice; therefore, the study did not employ a uniform protocol of ventilation/perfusion (V/Q) scanning, CTPA, or right heart catheterization for all patients.

Patients were categorized according to thrombolytic treatment strategy as receiving either full-dose or half-dose systemic thrombolysis. Full-dose alteplase was administered as 100 mg over 2 hours, whereas half-dose alteplase consisted of 50 mg. Standard-dose reteplase was administered as two 10-U intravenous bolus injections given 30 minutes apart. Of the 115 patients, 34 received full-dose alteplase (100 mg), 39 received standard-dose reteplase, and 42 received half-dose alteplase (50 mg). Thus, the full-dose treatment group comprised patients receiving either full-dose alteplase or standard-dose reteplase, whereas all patients in the half-dose group received alteplase. The choice of reduced-dose alteplase was based on the treating physician's individual risk–benefit assessment.

Statistical Analysis

Continuous variables were assessed for normality using visual inspection of histograms and Q–Q plots together with the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. Descriptive analyses were based on available observations, and the number of available observations was reported for variables with missing data.

Baseline differences between the full-dose and half-dose thrombolysis groups were summarized using absolute standardized mean differences (SMDs) rather than significance testing. For continuous variables, SMDs were calculated as the difference in group means divided by the square root of the average of the two group-specific variances, whereas for categorical variables they were calculated using proportions. Comparisons of clinical outcomes between treatment groups were performed using the independent-samples t-test or Mann–Whitney U test for continuous variables, as appropriate, and the Pearson chi-square test or Fisher's exact test for categorical variables. For binary clinical outcomes, crude odds ratios (ORs) with 95% confidence intervals (CIs) were reported together with p values. Given the observational design, non-random treatment allocation, and limited number of outcome events, comparisons between thrombolytic treatment strategies were considered exploratory and were not intended to establish therapeutic equivalence or superiority.

Candidate predictors for univariable analysis were selected based on clinical relevance, prior evidence, and data availability. These included age, Charlson Comorbidity Index, C-reactive protein (CRP), hemodynamic instability, supplemental oxygen requirement, right ventricular dilatation, cardiac biomarker positivity, and thrombolytic treatment strategy. Variables presented in Table 1 that were not included among these candidate predictors were used for descriptive characterization of the cohort and were not systematically entered into the univariable regression analyses. Univariable logistic regression analyses were performed to evaluate the association of each candidate predictor with 30-day mortality.

CRP was entered into the regression models as a continuous variable, and effect estimates are reported per 10 mg/L increase. The linearity-in-the-logit assumption for CRP was assessed using a Box–Tidwell approach by including a CRP × ln(CRP) term in the primary multivariable model.

Table 1
Baseline characteristics of patients according to thrombolytic treatment strategy

Variable	Full-dose thrombolysis (n = 73)	Half-dose thrombolysis (n = 42)	Absolute SMD
Age, years	66.0 (59.0–77.0)	71.5 (55.2–78.0)	0.006
Charlson Comorbidity Index	3.0 (2.0–5.0)	5.0 (2.0–6.0)	0.093
CRP, mg/L	57.0 (17.0–102.0), n = 69	64.0 (28.0–121.0), n = 41	0.090
Troponin, ng/mL	0.06 (0.03–0.13), n = 65	0.05 (0.03–0.18), n = 36	0.175
NT-proBNP, pg/mL	2568 (1159–6452), n = 37	2138 (728–4649), n = 22	0.238
D-dimer, µg FEU/mL	4.8 (4.2–7.4), n = 54	6.2 (3.6–9.2), n = 28	0.343
sPAP, mmHg	45 (32–59), n = 71	40 (30–55), n = 37	0.283
Female sex	35 (47.9%)	25 (59.5%)	0.234
Hemodynamic instability	21 (28.8%)	11 (26.2%)	0.058
Supplemental oxygen requirement	57 (78.1%)	34 (81.0%)	0.071
Right ventricular dilatation	50/71 (70.4%)	28/37 (75.7%)	0.119
Chronic kidney disease	2 (2.7%)	2 (4.8%)	0.107
COPD	10 (13.7%)	2 (4.8%)	0.312
Coronary artery disease	11 (15.1%)	10 (23.8%)	0.222
Heart failure	27 (37.0%)	23 (54.8%)	0.363
Diabetes mellitus	21 (28.8%)	9 (21.4%)	0.170
Active malignancy	10 (13.7%)	8 (19.0%)	0.145
Cerebrovascular disease	5 (6.8%)	6 (14.3%)	0.244

Data are presented as median (IQR) or n (%), unless otherwise indicated. For categorical variables with missing data, values are presented as n/N (%). Missing observations (full-dose/half-dose): CRP, 4/1; troponin, 8/6; NT-proBNP, 36/20; D-dimer, 19/14; sPAP, 2/5; right ventricular dilatation, 2/5. SMD, standardized mean difference; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure; COPD, chronic obstructive pulmonary disease.

The primary conventional multivariable logistic regression model included age, Charlson Comorbidity Index, CRP, hemodynamic instability, right ventricular dilatation, and thrombolytic treatment strategy, selected on the basis of their clinical relevance while considering the limited number of outcome events. Supplemental oxygen requirement was not included in the conventional multivariable model because complete separation was observed, with no deaths occurring among patients who did not require supplemental oxygen. Its unadjusted association with 30-day mortality was therefore evaluated using Fisher's exact test. Multivariable analyses were performed using complete cases for all variables included in the respective model.

Given the limited number of outcome events relative to the number of covariates included in the multivariable model, sensitivity analyses using Firth penalized logistic regression were performed to reduce small-sample bias. In the first sensitivity analysis, the same six covariates included in the conventional multivariable model were retained. In a second penalized model, supplemental oxygen requirement was additionally included to allow its association with mortality to be estimated despite complete separation and to assess its influence on the other model estimates. An additional sensitivity analysis restricted to patients treated with alteplase was performed using Firth penalized logistic regression with the same six covariates to assess the treatment-strategy association without potential confounding by thrombolytic agent. Odds ratios (ORs) and adjusted odds ratios (aORs) are reported with 95% CIs.

Performance of the conventional multivariable logistic regression model was evaluated using the Omnibus test of model coefficients, the Hosmer–Lemeshow goodness-of-fit test, and the Nagelkerke R^2 statistic. Conventional statistical analyses were performed using IBM SPSS Statistics version 18.0. Firth penalized logistic regression sensitivity analyses were performed in Python version 3.13.5 using a custom implementation of Firth's penalized likelihood with NumPy version 2.3.5 and SciPy version 1.17.0. Profile penalized-likelihood confidence intervals and penalized likelihood-ratio p values were calculated. All tests were two-sided, and a p value < 0.05 was considered statistically significant.

Use of generative AI

ChatGPT (OpenAI) was used to assist with English translation and language editing and to support the development and checking of code used for additional statistical sensitivity analyses. All analytical decisions, statistical outputs, interpretations, and manuscript revisions were reviewed and verified by the authors, who take full responsibility for the content of the manuscript.

RESULTS

Patient Characteristics

A total of 115 consecutive patients with acute high-risk or intermediate-high-risk pulmonary embolism who received systemic thrombolytic therapy were included in the study. Of these, 32 patients (27.8%)

were classified as high-risk PE and 83 (72.2%) as intermediate-high-risk PE. Thirty-day mortality occurred in 29 patients (25.2%), whereas 86 patients (74.8%) survived. As all deaths occurred during the index hospitalization, in-hospital mortality and 30-day mortality were identical in the study population.

Baseline demographic, clinical, laboratory, and echocardiographic characteristics according to thrombolytic treatment strategy are presented in Table 1. Clinical outcomes of patients receiving full-dose and half-dose thrombolytic therapy are summarized in Table 2. Selected clinical outcomes according to thrombolytic treatment strategy are also illustrated in Fig. 1.

Table 2
Clinical outcomes according to thrombolytic treatment strategy

Outcome	Full-dose thrombolysis (n = 73)	Half-dose thrombolysis (n = 42)	OR (95% CI), half-dose vs full-dose	p value
30-day mortality	17 (23.3%)	12 (28.6%)	1.31 (0.50–3.38)	0.656
90-day mortality	22 (30.1%)	13 (31.0%)	1.04 (0.41–2.54)	1.000
1-year mortality	27 (37.0%)	17 (40.5%)	1.16 (0.49–2.70)	0.842
Other documented bleeding events	7 (9.6%)	10 (23.8%)	2.92 (0.91–9.94)	0.055
Gastrointestinal bleeding	1 (1.4%)	1 (2.4%)	1.75 (0.02–139.73)	1.000
Intracranial hemorrhage	0 (0.0%)	0 (0.0%)	Not estimable	—
Recurrent pulmonary embolism	1 (1.4%)	1 (2.4%)	1.75 (0.02–139.73)	1.000
Documented CTEPH during follow-up	2 (2.7%)	1 (2.4%)	0.87 (0.01–17.13)	1.000
Length of hospital stay, days	10.0 (7.0–13.0)	10.5 (8.2–15.8)	—	0.052

Data are presented as median (IQR) or n (%). ORs compare half-dose with full-dose thrombolysis (reference). For binary outcomes, exact conditional 95% CIs and two-sided Fisher's exact test p values are reported; the OR for intracranial hemorrhage was not estimable because no events occurred. Length of hospital stay was compared using the Mann–Whitney U test. CTEPH, chronic thromboembolic pulmonary hypertension.

Univariable Logistic Regression Analysis

Univariable logistic regression analysis was performed to evaluate variables associated with 30-day mortality (Table 3). Supplemental oxygen requirement resulted in complete separation: all 29 patients who died within 30 days required supplemental oxygen, whereas no deaths occurred among the 24 patients who did not require oxygen. Accordingly, a conventional logistic regression odds ratio could not

be estimated, and Fisher's exact test demonstrated a significant association with 30-day mortality ($p < 0.001$).

Table 3
Univariable logistic regression analysis of factors evaluated for association with 30-day mortality

Variable	OR	95% CI	*p* value
Age (per year)	1.069	1.028–1.112	0.001
Charlson Comorbidity Index	1.304	1.110–1.532	0.001
CRP (per 10 mg/L)	1.134	1.063–1.210	< 0.001
Hemodynamic instability	4.349	1.766–10.709	0.001
Right ventricular dilatation	2.718	0.852–8.668	0.091
Cardiac biomarker positivity	2.373	0.497–11.331	0.279
Half-dose thrombolysis (vs full-dose)	1.318	0.557–3.119	0.530
Supplemental oxygen requirement	Not estimable†	-	< 0.001

†Odds ratio could not be estimated using conventional logistic regression because of complete separation; p value was obtained using Fisher's exact test. All 30-day deaths occurred among patients requiring supplemental oxygen.

Increasing age was associated with higher odds of 30-day mortality (OR 1.069, 95% CI 1.028–1.112; $p = 0.001$). Likewise, a higher Charlson Comorbidity Index was associated with increased mortality (OR 1.304, 95% CI 1.110–1.532; $p = 0.001$). Higher CRP levels were also associated with increased odds of 30-day mortality (OR 1.134 per 10 mg/L increase, 95% CI 1.063–1.210; $p < 0.001$).

Hemodynamic instability at presentation was associated with higher odds of 30-day mortality (OR 4.349, 95% CI 1.766–10.709; $p = 0.001$). Right ventricular dilatation was not significantly associated with 30-day mortality (OR 2.718, 95% CI 0.852–8.668; $p = 0.091$). Cardiac biomarker positivity was not significantly associated with 30-day mortality (OR 2.373, 95% CI 0.497–11.331; $p = 0.279$). Similarly, half-dose thrombolysis was not associated with 30-day mortality compared with full-dose thrombolysis (OR 1.318, 95% CI 0.557–3.119; $p = 0.530$).

Multivariable Logistic Regression Analysis

A multivariable logistic regression model was constructed including age, Charlson Comorbidity Index, CRP, hemodynamic instability, right ventricular dilatation, and thrombolytic treatment strategy. The final multivariable model included 103 patients with complete data for all included covariates, of whom 23 experienced 30-day mortality.

The conventional multivariable model was statistically significant (Omnibus χ^2=33.434, p < 0.001). The Hosmer–Lemeshow test did not indicate evidence of lack of fit (χ^2=12.858, p = 0.117), and the Nagelkerke R^2 was 0.424. There was no evidence of a significant departure from linearity in the logit for CRP (p = 0.094).

In the primary conventional multivariable model, CRP (aOR 1.095 per 10 mg/L increase, 95% CI 1.015–1.180; p = 0.019) and hemodynamic instability (aOR 4.642, 95% CI 1.397–15.423; p = 0.012) were independently associated with 30-day mortality. Age, Charlson Comorbidity Index, right ventricular dilatation, and thrombolytic treatment strategy were not independently associated with 30-day mortality (Table 4). In the first sensitivity analysis using Firth penalized logistic regression with the same six covariates, the findings were consistent with those of the conventional multivariable model. CRP (aOR 1.083 per 10 mg/L increase, 95% CI 1.012–1.166; p = 0.021) and hemodynamic instability (aOR 4.024, 95% CI 1.321–12.735; p = 0.014) remained significantly associated with 30-day mortality. When supplemental oxygen requirement was additionally incorporated into the Firth model, hemodynamic instability remained significantly associated with mortality (aOR 3.783, 95% CI 1.208–12.487; p = 0.022), whereas the association with CRP was attenuated and no longer reached conventional statistical significance (aOR 1.066 per 10 mg/L increase, 95% CI 0.996–1.148; p = 0.067). The point estimate for supplemental oxygen requirement suggested a strong association with mortality, although with substantial imprecision (aOR 7.528, 95% CI 0.836–994.523; p = 0.078). In an additional sensitivity analysis restricted to alteplase-treated patients, 74 patients with complete data were included, of whom 16 died within 30 days. Half-dose alteplase was not significantly associated with 30-day mortality compared with full-dose alteplase (aOR 2.80, 95% CI 0.61–16.03; p = 0.189). Full results of the two penalized sensitivity analyses are presented in Supplementary Table S1 (Additional file 1). The univariable and conventional multivariable effect estimates for variables included in the final conventional model are visually summarized in Fig. 2.

Table 4
Conventional multivariable logistic regression analysis of factors evaluated for association with 30-day mortality

Variable	Adjusted OR	95% CI	*p* value
Age (per year)	1.038	0.982–1.099	0.188
Charlson Comorbidity Index	1.092	0.847–1.408	0.498
CRP (per 10 mg/L)	1.095	1.015–1.180	0.019
Hemodynamic instability	4.642	1.397–15.423	0.012
Right ventricular dilatation	3.749	0.811–17.330	0.091
Half-dose thrombolysis (vs full-dose)	1.442	0.428–4.857	0.555

The multivariable analysis was based on complete cases (n = 103; 23 30-day mortality events). Binary clinical variables were coded as 0 = absent and 1 = present.

DISCUSSION

In this retrospective cohort of patients with acute high-risk and intermediate-high-risk pulmonary embolism treated with systemic thrombolysis, hemodynamic instability at presentation showed the most robust association with 30-day mortality. In the primary conventional multivariable model, both CRP and hemodynamic instability were independently associated with 30-day mortality, whereas thrombolytic treatment strategy was not. These findings were largely preserved in a Firth penalized model including the same six covariates. However, when supplemental oxygen requirement, which caused complete separation in conventional logistic regression, was additionally incorporated into the penalized model, hemodynamic instability remained significantly associated with mortality, whereas the association with CRP was attenuated and no longer reached conventional statistical significance. These sensitivity analyses suggest that the prognostic signal associated with hemodynamic instability was more robust than that of CRP.

Systemic inflammation has increasingly been recognized as a potential contributor to adverse outcomes in acute PE. Contemporary risk-stratification strategies primarily emphasize hemodynamic status, right ventricular dysfunction, cardiac biomarkers, and clinical risk scores [1–3]. Nevertheless, inflammatory and thromboinflammatory activation may provide additional prognostic information beyond these conventional parameters [8–12]. Accordingly, inflammatory biomarkers, particularly CRP, have been investigated as potential adjunctive prognostic markers in acute PE [8–12].

Previous observational studies have reported associations between elevated CRP levels or increased inflammatory burden and adverse clinical outcomes in acute PE, including right ventricular dysfunction and short-term mortality [8–12]. In the present study, CRP was associated with 30-day mortality in the conventional multivariable model and remained significant in the six-covariate Firth sensitivity analysis. However, its association weakened after supplemental oxygen requirement was incorporated into the penalized model. This attenuation is important when interpreting CRP as a prognostic marker and suggests that part of its association with mortality may overlap with other manifestations of acute disease severity, including impaired oxygenation. Therefore, our findings support CRP as a potentially useful adjunctive marker rather than establishing it as a robust independent predictor across all model specifications. Moreover, because CRP is a nonspecific inflammatory marker, it should be interpreted in conjunction with established clinical, laboratory, and imaging parameters rather than in isolation [8, 10, 12].

In contrast, the association between hemodynamic instability and 30-day mortality remained consistent across conventional and penalized regression models. Hemodynamic instability reflects severe circulatory compromise and remains the principal feature defining high-risk PE in contemporary risk-stratification systems and clinical guidelines [1, 3]. Importantly, the prognostic association of hemodynamic instability persisted in our cohort despite systemic thrombolytic treatment. This finding suggests that, once substantial circulatory compromise has developed, reperfusion therapy may not fully reverse the adverse consequences of right ventricular failure and systemic hypoperfusion. The strong

association between hemodynamic instability and early mortality has also been demonstrated in large observational cohorts and registry-based studies of acute PE [13–15].

Supplemental oxygen requirement also demonstrated a particularly strong unadjusted association with mortality. All 29 patients who died within 30 days required supplemental oxygen at presentation, whereas no deaths occurred among the 24 patients who did not require oxygen, resulting in complete separation in conventional logistic regression (Fisher's exact $p < 0.001$). This finding indicates that oxygen requirement was an important marker of acute physiological compromise in this cohort. When incorporated into the Firth penalized model, the point estimate remained large, although the confidence interval was extremely wide and the association did not reach conventional statistical significance. The imprecision of this estimate likely reflects the limited number of outcome events together with the absence of deaths in the non-oxygen group. Thus, oxygen requirement should not be interpreted as a precisely quantified independent predictor; rather, the observed pattern reinforces the potential prognostic relevance of impaired oxygenation as a marker of acute PE severity.

Age and Charlson Comorbidity Index were significantly associated with 30-day mortality in univariable analyses but were no longer significant after multivariable adjustment. Age and comorbidity are important components of clinical risk assessment in acute PE, and validated prognostic tools such as the Pulmonary Embolism Severity Index incorporate age and major comorbid conditions into mortality risk estimation [1, 16, 17]. However, the present cohort consisted exclusively of patients with high-risk or intermediate-high-risk PE who underwent systemic thrombolysis. Within this highly selected population, acute physiological derangements may exert a greater influence on short-term outcome than baseline demographic and comorbidity characteristics. Accordingly, loss of statistical significance after adjustment should not be interpreted as evidence that age or comorbidity are unimportant, but rather as an indication that their effects may be attenuated in the presence of more immediate markers of cardiopulmonary compromise.

Right ventricular dilatation showed a higher point estimate for mortality but did not reach statistical significance in either conventional or penalized multivariable analyses. The wide confidence intervals indicate substantial uncertainty regarding the magnitude of this association. This should be interpreted in light of several methodological considerations. Echocardiographic data were unavailable in a subset of patients, and examinations were performed within 24–48 hours of diagnosis, with some studies obtained after thrombolytic therapy. Consequently, treatment-related improvement in right ventricular loading conditions may have influenced subsequent echocardiographic measurements. These factors may have reduced the ability of the echocardiographic RV dilatation variable to capture the full prognostic importance of RV dysfunction, which remains a central component of guideline-based PE risk stratification and has established prognostic significance [1, 3, 17–19].

Thrombolytic treatment strategy was not associated with 30-day mortality in either the conventional multivariable model or the penalized sensitivity analyses. Systemic fibrinolysis has an established role in high-risk PE, whereas its risk–benefit profile in intermediate-risk PE is more complex because potential

prevention of hemodynamic deterioration must be weighed against bleeding complications [1, 3–5]. Reduced-dose systemic thrombolysis has therefore attracted considerable interest as a potential strategy to reduce bleeding while preserving reperfusion efficacy; however, the available evidence remains heterogeneous with respect to patient selection, thrombolytic agents, dosing strategies, and outcome definitions [6, 7]. Current international guidance does not establish reduced-dose systemic thrombolysis as therapeutically equivalent to standard-dose treatment across PE risk categories [1–3].

Our results should be interpreted within this context. The absence of an independent association between thrombolytic treatment strategy and mortality does not demonstrate equivalence between half-dose and full-dose therapy. The frequency of other documented bleeding events was numerically higher in the half-dose group than in the full-dose group (23.8% vs 9.6%), although the difference did not reach statistical significance ($p = 0.055$). This apparently counterintuitive finding may reflect confounding by indication, because clinicians may have preferentially selected reduced-dose therapy for patients perceived to have greater baseline bleeding risk that was not completely captured by the available variables. Treatment allocation was based on physician judgment rather than randomization, and residual differences between treatment groups therefore cannot be excluded. In addition, the full-dose group included both alteplase and reteplase, whereas half-dose therapy consisted of alteplase; therefore, the effects of thrombolytic dose could not be fully separated from those of the thrombolytic agent. Accordingly, the dose-related findings should be regarded as hypothesis-generating and should not be interpreted as evidence supporting therapeutic equivalence or superiority of reduced-dose systemic thrombolysis.

The present study has several strengths. It jointly evaluated inflammatory markers, hemodynamic variables, comorbidity burden, and thrombolytic treatment strategy in a cohort restricted to patients with acute high-risk and intermediate-high-risk PE receiving systemic thrombolysis. It provides real-world data reflecting routine clinical practice in a tertiary referral center and includes a clearly defined cohort of patients who all received systemic thrombolytic therapy. Complete follow-up for the primary outcome minimized outcome misclassification. In addition, the use of Firth penalized logistic regression as a sensitivity analysis allowed assessment of the robustness of the conventional regression estimates in the presence of a limited number of outcome events and permitted supplemental oxygen requirement to be evaluated despite complete separation.

Several limitations should be acknowledged. This was a retrospective single-center study and is therefore subject to the inherent limitations of observational research, including selection bias, information bias, and residual confounding. The relatively limited sample size may have reduced statistical power to detect modest differences between treatment strategies, particularly for secondary outcomes. Although the relatively low number of outcome events in relation to the number of covariates may have increased the risk of model overfitting and imprecision, sensitivity analyses using Firth penalized logistic regression yielded broadly consistent effect directions. However, after supplemental oxygen requirement was incorporated into the penalized model, the association between CRP and 30-day mortality was attenuated and no longer reached conventional statistical significance. Missing data

for some baseline variables necessitated complete-case multivariable analysis and may have reduced statistical precision or introduced selection bias. In addition, recurrent PE and CTEPH were identified from hospital medical records; therefore, events diagnosed exclusively outside the study center may have been underascertained. Although patients were followed for CTEPH according to guideline recommendations in routine clinical practice, no protocolized screening program was applied; therefore, the reported frequency should be interpreted as the frequency of clinically documented CTEPH rather than as an incidence estimate derived from protocolized surveillance. Treatment allocation was not randomized but was determined according to physician judgment and individual clinical characteristics, introducing the possibility of confounding by indication. Although multivariable adjustment was performed using clinically relevant variables, unmeasured confounders cannot be completely excluded. Furthermore, inflammatory biomarkers were evaluated using a single baseline measurement, and serial changes during hospitalization were not available. Echocardiography was performed within 24–48 hours of diagnosis and, in some patients, after thrombolytic therapy; therefore, RV measurements may have been influenced by treatment timing. Interobserver variability cannot be excluded because echocardiographic examinations were performed by different cardiologists. Finally, the findings should be externally validated in larger prospective multicenter cohorts before being generalized to broader patient populations.

CONCLUSIONS

In conclusion, among patients with acute high-risk and intermediate-high-risk pulmonary embolism treated with systemic thrombolysis, hemodynamic instability at presentation showed the most robust association with 30-day mortality across both conventional and penalized regression analyses. CRP was independently associated with mortality in the primary multivariable model and in the six-covariate Firth sensitivity analysis, although this association was attenuated after supplemental oxygen requirement was incorporated into the penalized model. Supplemental oxygen requirement was strongly associated with mortality in unadjusted analysis but could not be precisely estimated in multivariable analysis because of complete separation and the limited number of outcome events. Thrombolytic treatment strategy was not independently associated with 30-day mortality. These findings highlight the dominant prognostic importance of acute hemodynamic and respiratory compromise and suggest a potential adjunctive role for inflammatory markers in risk assessment. Larger prospective multicenter studies are needed to validate these findings and to further clarify the prognostic contribution of inflammatory biomarkers and reduced-dose thrombolytic strategies.

Abbreviations

aOR
adjusted odds ratio
CI
confidence interval
COPD

chronic obstructive pulmonary disease
CRP
C-reactive protein
CTEPH
chronic thromboembolic pulmonary hypertension
CTPA
computed tomography pulmonary angiography
ESC
European Society of Cardiology
FEU
fibrinogen equivalent units
IQR
interquartile range
NT-proBNP
N-terminal pro-B-type natriuretic peptide
OR
odds ratio
PE
pulmonary embolism
PESI
Pulmonary Embolism Severity Index
Q–Q
quantile–quantile
RV
right ventricular
RV/LV
right ventricular/left ventricular
SD
standard deviation
SMD
standardized mean difference
sPAP
systolic pulmonary artery pressure
sPESI
simplified Pulmonary Embolism Severity Index
SpO_2
peripheral oxygen saturation.

Declarations

Ethics approval and consent to participate

The study was approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee (meeting date: February 8, 2023; meeting no. 2023/03; decision no. 12). The approved protocol was retrospective and based on existing hospital records. Owing to the retrospective design, the requirement for informed consent was waived by the ethics committee. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Additional file

Additional file 1 (DOCX): Supplementary Table S1. Firth penalized logistic regression sensitivity analyses for 30-day mortality.

Funding

The authors received no specific funding for this work.

Author Contribution

GK contributed to study conception, data collection and curation, statistical analysis, visualization, and drafting of the manuscript. MMT conceptualized, designed, and supervised the study, contributed to interpretation of the results, and critically reviewed the manuscript. ATE and BA contributed to the clinical management and follow-up of the study patients and provided critical input on the interpretation of the findings during evaluation of the thesis on which this manuscript is based. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain clinical data subject to patient privacy and institutional/ethical restrictions. De-identified data may be available from the corresponding author on reasonable request and subject to approval by the relevant institution and ethics committee.

References

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543–603. 10.1093/eurheartj/ehz405.
2. Zuin M, Bikdeli B, Ballard-Hernandez J, Barco S, Battinelli EM, Giannakoulas G, et al. International clinical practice guideline recommendations for acute pulmonary embolism: harmony, dissonance, and silence. J Am Coll Cardiol. 2024;84(16):1561–77. 10.1016/j.jacc.2024.07.044.
3. Creager MA, Barnes GD, Giri J, Mukherjee D, Jones WS, Burnett AE et al. 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN guideline for the evaluation and management of acute pulmonary embolism in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2026;153(12):e977-e1051. 10.1161/CIR.0000000000001415
4. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402–11. 10.1056/NEJMoa1302097.
5. Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol. 2017;69(12):1536–44. 10.1016/j.jacc.2016.12.039.
6. Sharifı M, Bay C, Skrocki L, Rahimi F, Mehdipour M, MOPETT Investigators. Moderate pulmonary embolism treated with thrombolysis (from the MOPETT trial). Am J Cardiol. 2013;111(2):273–7. 10.1016/j.amjcard.2012.09.027.
7. Rojas Murguia A, Mukherjee D, Ojha C, Rajachandran M, Siddiqui TS, Nickel NP. Reduced-dose thrombolysis in acute pulmonary embolism: a systematic review. Angiology. 2024;75(3):208–18. 10.1177/00033197231167062.
8. Özdemir L, Özdemir B, Gegin S, Arslan Aksu E, Pazarlı AC. Can systemic inflammatory markers be used in pulmonary embolism risk assessment in patients with acute pulmonary thromboembolism? J Inflamm Res. 2025;18:5969–77. 10.2147/JIR.S514111.
9. Zhu N, Zhang L, Lin S, Mao F, Cao C, Chen L. Innovative Inflammatory Burden Index for identification of high mortality risk in patients with pulmonary embolism: a large retrospective cohort study. BMJ Open Respir Res. 2026;13(1):e003743. 10.1136/bmjresp-2025-003743.
10. Tukiendorf A, Feusette P. Does C-reactive protein exhibit high prognostic information value in acute pulmonary embolism? A novel structural pathway for disease progression beyond classical

statistical associations. PLoS ONE. 2026;21(2):e0343108. 10.1371/journal.pone.0343108.

11. Siddiqui F, Tafur A, Darki A, Kantarcioglu B, Hoppensteadt D, Walenga J, et al. Thromboinflammation and hemostatic activation drive early mortality risk in pulmonary embolism. Res Pract Thromb Haemost. 2026;10(4):106633. 10.1016/j.rpth.2026.106633.
12. Najarro M, Rodríguez C, Morillo R, Jara-Palomares L, Vinson DR, Muriel A, et al. C-reactive protein and risk of right ventricular dysfunction and mortality in patients with acute symptomatic pulmonary embolism. Arch Bronconeumol. 2024;60(6):344–9. 10.1016/j.arbres.2024.03.024.
13. Wolf S, Valerio L, Fumagalli RM, Konstantinides SV, Ulrich S, Klok FA, et al. Acute pulmonary embolism with and without hemodynamic instability (2003–2022): a Swiss nationwide epidemiologic study. J Thromb Haemost. 2025;23(4):1340–51. 10.1016/j.jtha.2024.12.040.
14. Jiménez D, Bikdeli B, Barrios D, Quezada A, Del Toro J, Vidal G, et al. Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism. Int J Cardiol. 2018;269:327–33. 10.1016/j.ijcard.2018.07.059.
15. Otero R, Trujillo-Santos J, Cayuela A, Rodríguez C, Barron M, Martín JJ, et al. Haemodynamically unstable pulmonary embolism in the RIETE Registry: systolic blood pressure or shock index? Eur Respir J. 2007;30(6):1111–6. 10.1183/09031936.00071007.
16. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the Pulmonary Embolism Severity Index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383–9. 10.1001/archinternmed.2010.199.
17. Leidi A, Bex S, Righini M, Berner A, Grosgurin O, Marti C. Risk stratification in patients with acute pulmonary embolism: current evidence and perspectives. J Clin Med. 2022;11(9):2533. 10.3390/jcm11092533.
18. Becattini C, Agnelli G, Lankeit M, Masotti L, Pruszczyk P, Casazza F, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Respir J. 2016;48(3):780–6. 10.1183/13993003.00024-2016.
19. Lyhne MD, Bikdeli B, Jiménez D, Kabrhel C, Dudzinski DM, Moisés J, et al. Right ventricular-pulmonary artery coupling for prognostication in acute pulmonary embolism. Eur Heart J Acute Cardiovasc Care. 2024;13(12):817–25. 10.1093/ehjacc/zuae120.

Figures

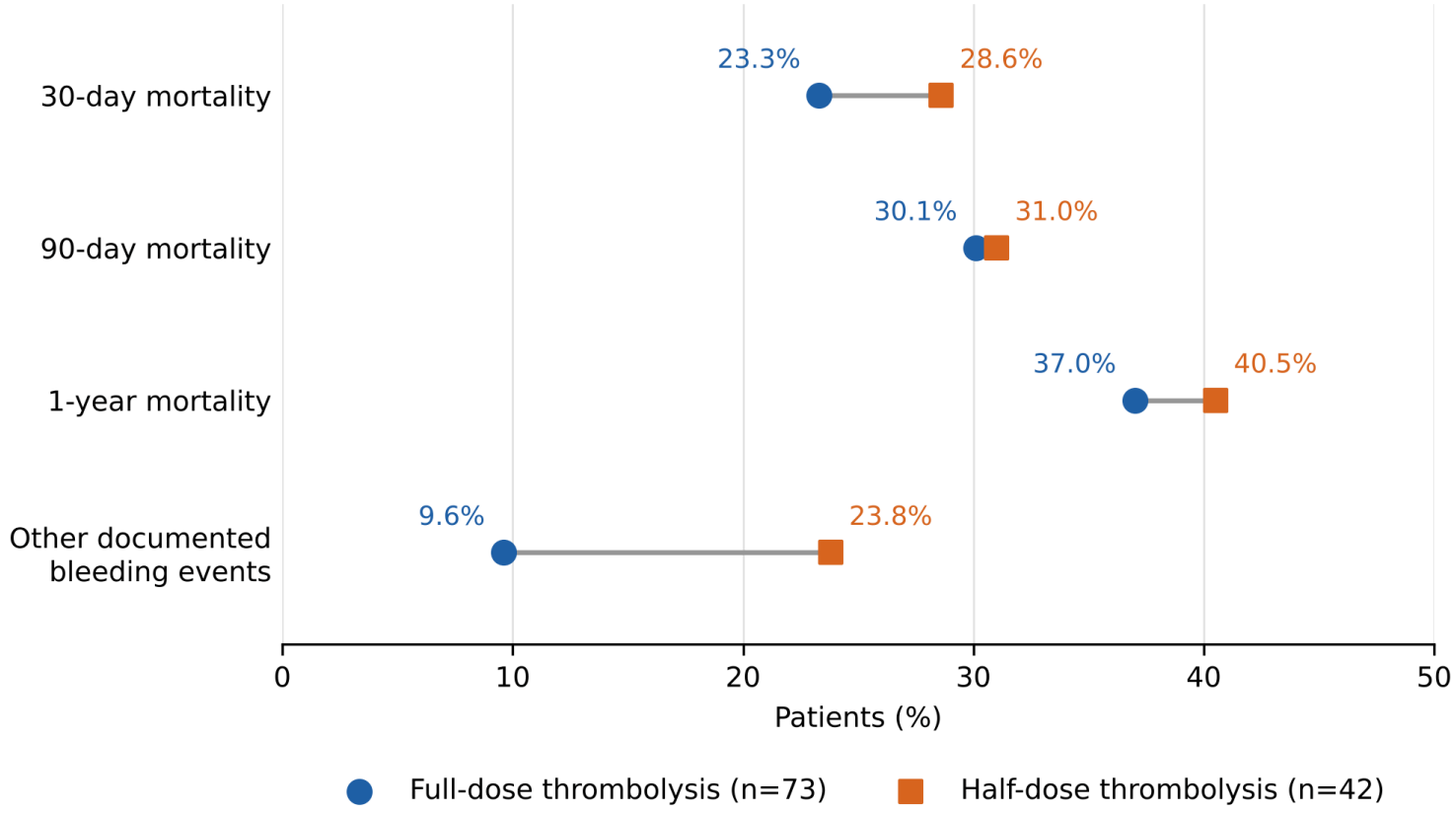


Figure 1

Clinical outcomes according to thrombolytic treatment strategy. Percentages of 30-day mortality, 90-day mortality, 1-year mortality, and other documented bleeding events are shown for the full-dose and half-dose thrombolysis groups.

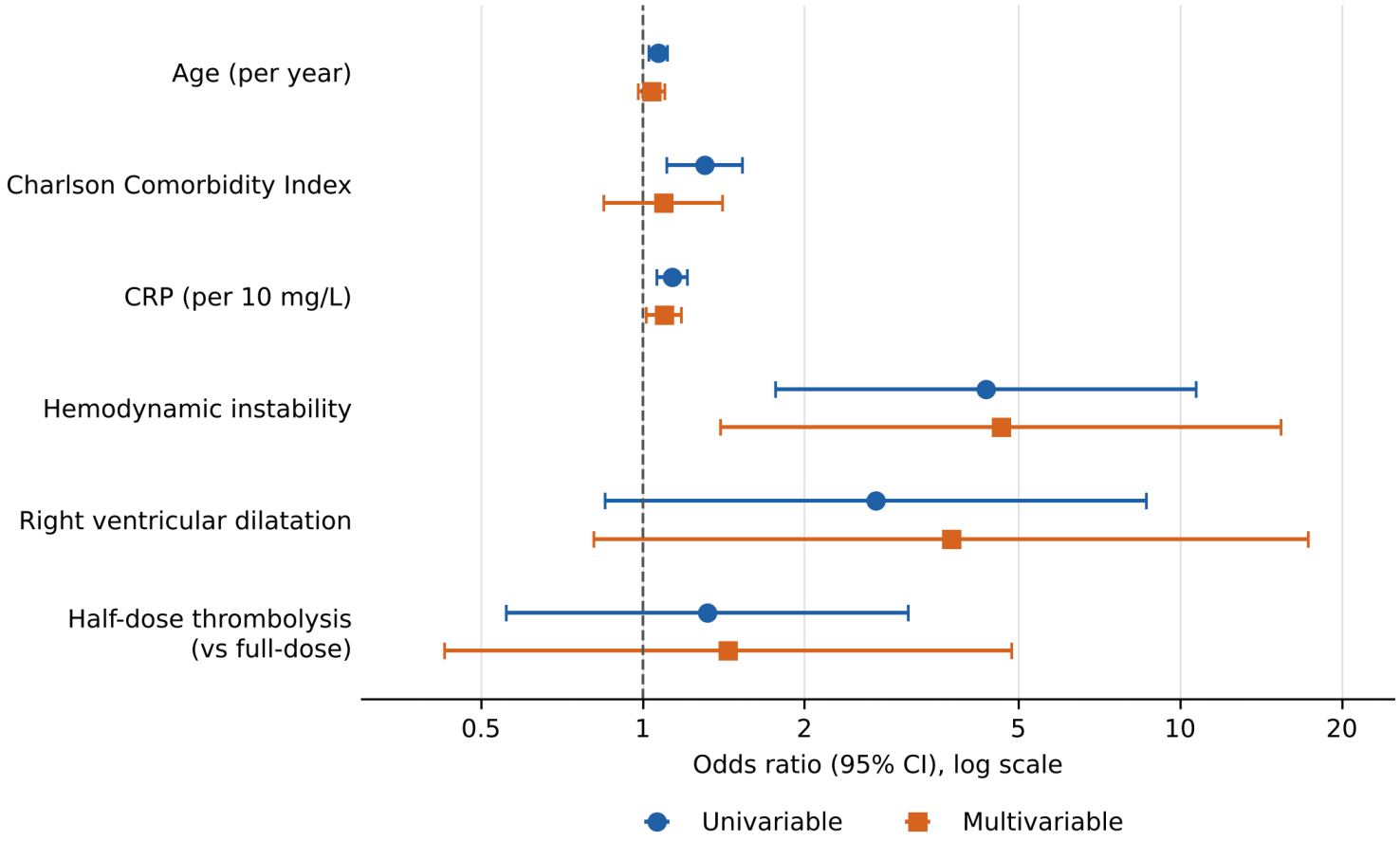


Figure 2

Univariable and conventional multivariable logistic regression analyses of factors evaluated for association with 30-day mortality. Forest plot showing odds ratios and 95% confidence intervals from univariable and conventional multivariable logistic regression analyses. CI, confidence interval; CRP, C-reactive protein.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1SupplementaryTableS1.docx