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Thromboprophylaxis and Intensive Care Unit Mortality in Critically Ill Patients: A Severity-Adjusted Retrospective Cohort Study

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Abstract

Background

As venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), is a serious complication of critical illness, prophylaxis is considered for each patient. In everyday ICU practice, the choice of thromboprophylaxis follows the same patient characteristics that determine whether someone survives, so any observational comparison of outcome is confounded by indication unless illness severity is taken into account. We aimed to describe thromboprophylaxis practice in a tertiary ICU, compare clinically detected DVT and PE between prophylaxis strategies (primary outcome), and examine the association between prophylaxis strategy and ICU mortality after adjustment for comorbidity and day-1 severity of illness (secondary outcome).

Methodology

We conducted a retrospective cohort study in an adult ICU in Oman between January 2021 and June 2022. Of the 912 admissions screened, 859 admissions (739 patients) were analyzed. Four admissions with another anticoagulant were excluded; 855 admissions were grouped by the thromboprophylaxis received: low-molecular-weight heparin (LMWH; enoxaparin, n = 381), unfractionated heparin (UFH, n = 220), or no pharmacological prophylaxis (n = 254). A day-1 Sequential Organ Failure Assessment (SOFA) score was calculated for all. DVT and PE were compared using the Fisher-Freeman-Halton exact test, with Holm-adjusted pairwise Fisher's exact tests. ICU mortality was modeled by logistic regression with LMWH as the reference group, before and after adjustment for comorbidity and SOFA. Landmark, first-admission, and propensity-stratified sensitivity analyses and E-values were used to examine the robustness of the mortality association.

Results

DVT was found in 1.3% of admissions and PE in 2.0%, with no statistically significant difference between groups (Fisher-Freeman-Halton exact test, DVT: $p = 0.172$; PE: $p = 0.099$). Median day-1 SOFA was 8 (IQR = 5-13) with LMWH, 14 (8-17) with UFH, and 12 (7-16) with no pharmacological prophylaxis (Kruskal-Wallis $H = 67.46$, $p < 0.001$). ICU mortality was 14.2%, 48.6%, and 47.6%, respectively ($\chi^2 = 110.05$, $p < 0.001$). Against LMWH, the odds ratio for death with UFH was 5.73 unadjusted, 3.92 after adjustment for comorbidity, and 4.94 (95% CI: 2.73-8.93) once SOFA was added; for no pharmacological prophylaxis, the corresponding figure was 5.16 (95% CI: 3.05-8.72). On the risk scale, adjustment for comorbidity and SOFA reduced the difference between UFH and LMWH from 34.4 to 16.9 percentage points (95% CI: 10.5-24.5). The association persisted within every severity stratum and among admissions still in the ICU at 48 and 72 hours; across analyses, the odds ratio for UFH ranged from 2.91 (propensity-stratified) to 5.59 (72-hour landmark). The comparison with no pharmacological prophylaxis is confounded by design, as 98% of these patients had a documented contraindication.

Conclusions

No statistically significant difference in clinically detected thrombotic events was observed between prophylaxis strategies, although the study was not powered to detect modest differences. ICU mortality was considerably higher among patients given UFH or no pharmacological prophylaxis. This association persisted after adjustment for measured comorbidity and day-1 organ dysfunction, but residual confounding, including by unrecorded treatment-limitation decisions and treatment timing, remains possible. The mortality finding should be regarded as hypothesis-generating.

Categories: Hematology, Internal Medicine, Anesthesiology
Keywords: confounding by indication, low-molecular-weight heparin (lmwh), sofa score, thromboprophylaxis, unfractionated heparin (ufh), venous thromboembolism (vte)

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Introduction

Venous thromboembolism is common in critical illness and easy to miss. Patients in the intensive care unit (ICU) accumulate risk from immobility, sedation, vasopressors, mechanical ventilation, and central venous access, while the same sedation and severity of illness that raise that risk also mask its signs. Minet et al. described how readily thrombosis goes unrecognized in this setting [1]. Thrombosis occurs even when prophylaxis is given. Ibrahim et al. found deep vein thrombosis (DVT) during prolonged ventilation at rates far above those picked up on clinical suspicion alone [2].

The American Society of Hematology 2018 guidelines recommend pharmacological prophylaxis for patients whose bleeding risk is acceptable and mechanical prophylaxis for those in whom it is not [3]. The PROTECT trial randomized 3,764 critically ill patients to dalteparin or unfractionated heparin (UFH) and found dalteparin no better for proximal DVT, though it did reduce pulmonary embolism (PE). Heparin-induced thrombocytopenia was less frequent with dalteparin, a difference that was statistically significant in the prespecified per-protocol analysis but not in the primary intention-to-treat analysis (0.3% versus 0.6%; hazard ratio 0.47; $p = 0.16$) [4]. The meta-analysis by Alhazzani et al. reached the same conclusion: low-molecular-weight heparin (LMWH) lowers the rate of PE but not of DVT, major bleeding, or death [5]. The PREVENT trial, reported by Arabi et al., found that adding pneumatic compression to pharmacological prophylaxis does not lower DVT rates either [6].

What trials cannot tell us is how prophylaxis behaves in ordinary practice, where the agent is chosen rather than allocated. The multicenter audit by Lauzier et al. showed that ICU clinicians pick prophylaxis according to renal function, bleeding risk, and perceived contraindication [7]. Patients on different regimens therefore differ in ways that also determine whether they survive, and any observational comparison of outcome is confounded by indication unless severity of illness is measured and accounted for.

Regional data from the Arabian Gulf are sparse; published reports have described hospital-wide prophylaxis practice [8] or ICU cohorts restricted to COVID-19 [9], and few describe a general adult ICU population. Any comparison of outcomes between prophylaxis groups needs a measure of how sick the patients were. Lauzier et al. showed that prophylaxis is chosen according to the very characteristics that also determine survival [7], and Sjoding et al. showed that inadequate risk adjustment can by itself produce mortality differences of considerable size [10]. To adjust for the severity of illness, we extracted a day-one Sequential Organ Failure Assessment (SOFA) score, as originally described by Vincent et al. [11], for every case in this cohort.

The study had three objectives. The first was to describe thromboprophylaxis practice in the adult ICU of a tertiary university hospital in Oman. The primary objective was to compare clinically detected DVT and PE between prophylaxis strategies. The secondary objective was to examine the association between prophylaxis strategy and ICU mortality after adjustment for comorbidity and day-one severity of illness. ICU mortality was specified as a secondary outcome in the original ethics protocol; the severity-adjusted analysis was added later, for the reasons given above. The study was designed to identify associations, not to estimate causal treatment effects.

Materials And Methods

Design, setting, and approval

This retrospective cohort study covered the 18 months from January 2021 to June 2022 in the adult multidisciplinary ICU of Sultan Qaboos University Hospital, a tertiary center in Muscat, Oman. Reporting follows STROBE [12], and the completed checklist is provided in Appendix 8. The Medical Research Ethics Committee approved the study (approval number: MREC #2693, February 24, 2022) and waived individual consent, as the work involved routinely collected records with no patient contact and no change to management. Data were collected and analyzed between January 2023 and December 2025.

Participants

Every patient aged 13 years or older admitted to the ICU during the study period was screened. Adolescents aged 13 years and older are admitted to the adult ICU under hospital policy and were therefore included; a sensitivity analysis excluded patients younger than 18. We excluded those under 13 years of age, those with DVT or PE diagnosed before admission, those admitted with COVID-19-related complications, and those whose records did not show which prophylaxis had been given. Four duplicate data entry records and five entries carrying an erroneous medical record number were also removed. The cohort is therefore one of admissions rather than individuals: 96 patients were admitted more than once.

Exposure, outcomes, and covariates

Patients were grouped by the pharmacological thromboprophylaxis they received: LMWH (enoxaparin), UFH, or none. Each admission was coded with a single agent. The data collection form recorded the agent used for prophylaxis during the ICU stay; as it did not capture each patient's time of first dose, interruptions, or switching between agents, classification reflects the agent prescribed for the admission rather than the agent received on a given day. Following the unit protocol, enoxaparin was administered

subcutaneously at 40 mg once daily to patients weighing under 100 kg and 1 mg/kg once daily to those over 100 kg, and UFH subcutaneously at 5,000 units twice daily. The enoxaparin dose was reduced according to estimated glomerular filtration rate, following the unit protocol. By unit practice, prophylaxis was started 24 to 36 hours after ICU admission, with the same timing for both agents. Only prophylactic-dose subcutaneous anticoagulation was counted as exposure; the UFH group comprised subcutaneous prophylactic-dose heparin only, and no admission was classified as UFH based on a therapeutic infusion or heparin used to anticoagulate a renal replacement or extracorporeal circuit. A few patients given another anticoagulant are described but left out of the comparisons, as the group was too small to support inference. The third group was named for what its members did not receive rather than calling it a mechanical prophylaxis group, as it held both patients with a device and patients with nothing at all; these two subgroups are also described separately.

Primary outcomes were DVT on compression Doppler ultrasonography and PE on computed tomography pulmonary angiography, both imaged on clinical indication and reported by consultant radiologists. DVT was defined as non-compressibility of a deep venous segment and PE as an intraluminal filling defect in a pulmonary artery. Events were ascertained from ICU admission to ICU discharge or death. The number of imaging studies performed in each group was not recorded. Secondary outcomes were ICU mortality, ICU length of stay, and duration of invasive mechanical ventilation, recorded as zero days for admissions that were not ventilated. Hospital mortality was not captured by the data collection form.

Bleeding, thrombocytopenia, and heparin-induced thrombocytopenia occurring after prophylaxis had started were not captured by the data collection form. The variables recorded under these headings (bleeding, thrombocytopenia, and bleeding risk) describe the reason prophylaxis was withheld at baseline, not complications of treatment.

Covariates were age, sex, hypertension, diabetes, heart failure or ischemic heart disease, acute kidney injury or chronic kidney disease, stroke, sepsis, hematological disease, immunological disease, and shock. All patients were assessed by the referring medical or surgical team before ICU admission, and each condition was recorded as present when it was documented as a diagnosis in the medical record at or before admission following standard criteria. Abstractors recorded these diagnoses as documented and did not re-apply formal diagnostic criteria such as Sepsis-3 or Kidney Disease: Improving Global Outcomes (KDIGO). Admission category (medical, elective or emergency surgical, trauma), admission source, renal replacement therapy, extracorporeal support, and treatment-limitation decisions were not recorded. The reasons for withholding prophylaxis were recorded (bleeding, thrombocytopenia, and bleeding risk) wherever appropriate. They describe the baseline state and not the complications of treatment.

Patient data were extracted from the hospital electronic record (TrakCare) by two ICU registrars (AP, NA) using a predesigned data collection form; both registrars were trained in intensive care medicine. Abstractors were not blinded to outcome. No formal audit or double data entry was performed, but entries were checked periodically against source records by the principal investigator. Repeat admissions were confirmed against source records and recoded before analysis. None of the analyzed variables had missing values.

Statistical analysis

Software

Analyses were performed using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). A few analyses that SPSS 26 cannot run (models that allow for repeat admissions, spline curves, standardized risks, and propensity balance checks) were performed using Python 3 (statsmodels 0.15). Technical details are given in the Appendices.

Describing and Comparing the Groups

Age, day-one SOFA, ICU days, and ventilator days were not normally distributed, so they are shown as median (interquartile range (IQR)), with mean (standard deviation (SD)) also given for age. They were compared across the three groups with the Kruskal-Wallis test, and between two groups with the Mann-Whitney U test. Yes/No characteristics are shown as numbers (percentages) and compared with the chi-square test.

Thrombotic Events

DVT and PE were rare, with between one and twelve events per group. Standard methods are unreliable for such small numbers, so exact methods were used throughout. Confidence intervals (CIs) for event rates are exact (Clopper-Pearson) intervals [13]. The three groups were compared with the Fisher-Freeman-Halton exact test, which extends Fisher's exact test to three groups. Each pair of groups was then compared with Fisher's exact test. Making three comparisons for each outcome raises the chance of a false-positive finding, so these p-values were adjusted with the Holm method [14]; all six are reported before and after adjustment

(Appendix 5). DVT and PE were not analyzed in a regression model adjusted for other variables, because with only 11 and 17 events such a model would give unstable results [15].

Sample Size

The study included every eligible admission during the 18-month study period, so no sample size was calculated in advance. To show what the study could and could not detect, we calculated that, comparing 381 LMWH with 220 UFH admissions, it had 80% power (two-sided $\alpha = 0.05$) to detect a difference in DVT of 0.9% versus 4.5%, or in PE of 1.4% versus 5.6%. Smaller differences, which could still matter clinically, could not be ruled out.

Intensive Care Unit Mortality

Logistic regression was used to compare the odds of dying in the ICU between groups, with LMWH as the comparison group. Because 96 patients were admitted more than once, and admissions of the same patient are likely to have related outcomes, we used robust standard errors clustered by patient. This widens the CIs to allow for repeat admissions without changing the odds ratios. Variables were added in four steps (no adjustment; then age and sex; then comorbidities; then day-one SOFA), so that the effect of each step on the result could be seen directly. ICU length of stay and ventilator days were not included: both are determined after admission, partly by how ill the patient becomes, and they were almost perfectly correlated with each other ($r = 0.96$) (Appendix 1).

Modeling Day-One Sequential Organ Failure Assessment

The risk of death does not rise evenly with the SOFA score; it changes little at low scores and climbs steeply at high ones. To capture this curve, we compared four ways of entering SOFA into the model (a straight line, a quadratic curve, five bands, and a flexible restricted cubic spline with knots at the 5th, 35th, 65th, and 95th centiles) using the Akaike information criterion (AIC), for which a lower value means a better fit [16]. The quadratic curve and the spline fitted almost equally well (AIC = 594.5 and 593.6; differences below 2 are not meaningful), so the quadratic, which was the original plan, was kept for the main model and the spline was used as a check. The five-band model used quintiles of the score (1-5, 6-8, 9-12, 13-16, 17-22).

How Well the Model Performs

We report how well the model separated patients who died from those who survived (the c statistic, where 0.5 is no better than chance and 1.0 is perfect), how closely predicted and observed deaths agreed (calibration, assessed with the Hosmer-Lemeshow test and a calibration plot), Nagelkerke R^2 [17], and −2 log likelihood. To keep the model stable, we checked that it had at least 10 deaths for every variable included [15]. We also tested whether the difference between groups depended on severity (a prophylaxis × SOFA interaction), and whether the apparent effect of hypertension did (a hypertension × SOFA interaction). As a simple check that does not depend on any model, mortality was compared between groups within three SOFA bands (1-9, 10-15, 16-22).

Results on the Risk Scale

Odds ratios can change when variables are added to a model even when those variables are not confounders, a mathematical property called noncollapsibility [18]. A rise or fall in the odds ratio after adjustment therefore cannot on its own show how much confounding was removed. To give a more direct answer, we also estimated adjusted ICU mortality for each group as a percentage. The model predicted every patient's risk of death as if all patients had received LMWH, then UFH, then no pharmacological prophylaxis, and the predictions were averaged. The differences between these percentages are the adjusted risk differences. Their 95% CIs were obtained by repeating the calculation in 500 random resamples of patients (bootstrapping).

How Strong Would Unmeasured Confounding Need to Be?

Because prophylaxis was chosen by clinicians rather than assigned at random, factors we did not record could explain the results. The E-value expresses how strongly such an unmeasured factor would need to be linked to both the choice of prophylaxis and death to explain away the association [19]; the larger the E-value, the stronger that factor would need to be. E-values are calculated on the risk-ratio scale, and because ICU death was common (33%), odds ratios were first converted to approximate risk ratios by taking their square root [20]. We calculated the E-value for each estimate and for the end of its CI nearer to no effect, and compared these with the strongest factors we did measure. E-values only show how sensitive the result is to unmeasured confounding. They do not prove that confounding has been controlled, and they do not address errors in recording exposure, selection bias, or treatment timing.

Checking the Robustness of the Result

The severity-adjusted analysis and the checks below were set out in a written analysis plan after the first, unadjusted analysis and before the SOFA-adjusted models were fitted; they were not registered in advance. We repeated the main model in several ways to see whether the result held: using only each patient's first admission; entering SOFA as five bands or as a spline instead of a quadratic curve; excluding patients younger than 18 years; and leaving hypertension out of the model. All admissions were kept in the main analysis, because dropping readmissions would discard information and leave a cohort made up only of patients admitted once.

Timing of Prophylaxis

Prophylaxis was started 24 to 36 hours after admission. A patient who died before that point could have been counted as untreated, which would make the untreated group look worse than it really was, a problem known as immortal time bias [21]. To guard against this, we repeated the analysis including only patients who were still in the ICU 48 hours and 72 hours after admission (landmark analysis) [22]. By 48 hours, patients who were going to receive prophylaxis had normally started it, so in this analysis every patient had had the chance to receive it.

Comparing Similar Patients (Propensity Scores)

This analysis was added after the main analyses, as another way of comparing like with like. We estimated each patient's probability of receiving UFH rather than LMWH from their age, sex, comorbidities, and day-one SOFA (the propensity score) [23], and did the same for no pharmacological prophylaxis versus LMWH. Patients were divided into five equal groups by this probability, mortality was compared within each group, and the results were combined using the Mantel-Haenszel method (Appendix 3). We checked that this made the groups comparable by calculating a standardized difference for each characteristic before and after stratification, where a value below 0.1 indicates good balance [24], and by checking that the propensity scores of the two groups overlapped (Appendix 7). All p-values are two-sided, and a p-value <0.05 was taken as statistically significant.

Results

Study population

Of the 912 admissions screened, 53 were excluded, and 859 were analyzed, representing 739 patients; 120 records were repeat admissions, contributed by 96 patients admitted two to five times each. The comparative set of 855 admissions represented 737 patients (Figure *1*).

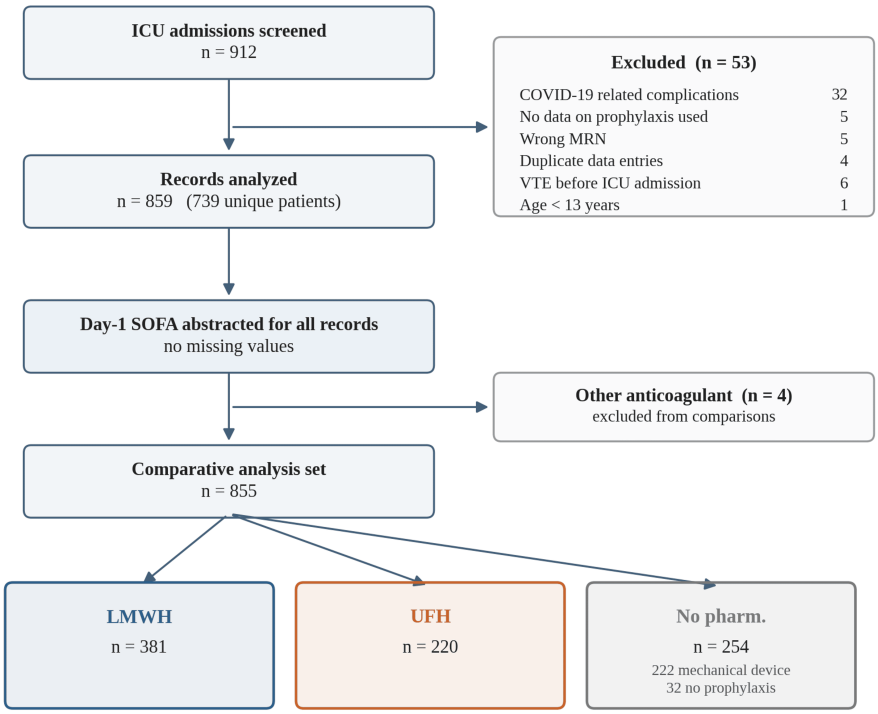


FIGURE 1: Flow of cases through the study.

DVT: deep vein thrombosis; ICU: intensive care unit; LMWH: low-molecular-weight heparin; MRN: medical record number; No pharm.: no pharmacological prophylaxis; PE: pulmonary embolism; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin; VTE: venous thromboembolism

The mean age was 53.8 years (SD = 20.0), median age was 55 years (IQR = 37-69), and 529 (61.6%) patients were male. In total, 33 (3.9%) admissions were of patients aged 13 to 17 years. The median ICU stay was 3 days (IQR = 2-9), and the median ventilation was 2 days (IQR = 1-7); this figure includes unventilated admissions as zero days, and 694 of the 855 (81.2%) admissions received invasive ventilation (LMWH: 308, UFH: 189, no pharmacological prophylaxis: 197). LMWH was given to 381 (44.4%) patients, UFH to 220 (25.6%), and 254 (29.6%) received no pharmacological prophylaxis (222 with a mechanical device and 32 with nothing at all). Only four patients on an anticoagulant also had a device. Day-one SOFA was extracted for all 859 records with no missing values. Four patients given another anticoagulant were excluded from the comparisons, leaving 855.

Severity of illness and baseline characteristics

Comorbidity burden differed sharply between the groups (Table *1*).

Characteristics	LMWH (n = 381)	UFH (n = 220)	No pharmacological (n = 254)	Test statistic (df = 2)	P-value
Day-1 SOFA, median (IQR)	8 (5–13)	14 (8–17)	12 (7–16)	H = 67.46	<0.001
Age, mean (SD), years	51.4 (20.4)	60.4 (17.8)	51.2 (20.0)	H = 34.60	<0.001
Age, median (IQR), years	52 (34–67)	63.5 (48.5–74)	52 (35–68.75)	H = 34.60	<0.001
Age 13–17 years, n (%)	13 (3.4)	4 (1.8)	16 (6.3)	—	—
Male, n (%)	242 (63.5)	128 (58.2)	156 (61.4)	$\chi^2 = 1.68$	0.43
Hypertension, n (%)	146 (38.3)	133 (60.5)	92 (36.2)	$\chi^2 = 35.38$	<0.001
Diabetes mellitus, n (%)	119 (31.2)	112 (50.9)	76 (29.9)	$\chi^2 = 29.09$	<0.001
Heart failure/IHD, n (%)	110 (28.9)	115 (52.3)	62 (24.4)	$\chi^2 = 47.84$	<0.001
AKI or CKD, n (%)	79 (20.7)	155 (70.5)	96 (37.8)	$\chi^2 = 145.57$	<0.001
Stroke, n (%)	59 (15.5)	28 (12.7)	25 (9.8)	$\chi^2 = 4.30$	0.12
Sepsis, n (%)	166 (43.6)	137 (62.3)	124 (48.8)	$\chi^2 = 19.70$	<0.001
Hematological disease, n (%)	45 (11.8)	28 (12.7)	74 (29.1)	$\chi^2 = 36.27$	<0.001
Immunological disease, n (%)	34 (8.9)	13 (5.9)	35 (13.8)	$\chi^2 = 8.77$	0.012
Shock, n (%)	117 (30.7)	108 (49.1)	116 (45.7)	$\chi^2 = 24.70$	<0.001
Invasive ventilation, n (%)	308 (80.8)	189 (85.9)	197 (77.6)	—	—

TABLE 1: Baseline characteristics and day-one severity by thromboprophylaxis group.

Data are median (IQR), mean (SD), or number (percentage), as marked in each row. Continuous variables are compared across the three groups by the Kruskal–Wallis test (H statistic) and categorical variables by the Pearson chi-square test (χ^2), each with 2 degrees of freedom and two-sided p-values. Age is shown both as mean (SD) and median (IQR); the Kruskal–Wallis test applies to both rows.

AKI: acute kidney injury; CKD: chronic kidney disease; IHD: ischemic heart disease; IQR: interquartile range; LMWH: low-molecular-weight heparin; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

Patients on UFH were nine years older on average and far more often had renal disease (70.5% versus 20.7%), cardiac disease (52.3% versus 28.9%), or sepsis (62.3% versus 43.6%) than those on LMWH. Those receiving no anticoagulant had the most hematological (29.1%) and immunological (13.8%) disease, as their contraindications would predict. Sex did not differ between groups.

Severity followed the same pattern. Median day-one SOFA was 11 across the cohort (IQR = 6-16, range = 1-22), and 8 (IQR = 5-13) with LMWH, 12 (IQR = 7-16) with no pharmacological prophylaxis, and 14 (IQR = 8-17) with UFH (Kruskal-Wallis H = 67.46, df = 2, $p < 0.001$) (Figure *2A*). The score performed as expected, with ICU mortality rising steadily from 7.3% at scores of 1-6 to 86.0% at 16 or above (Figure *2B*).

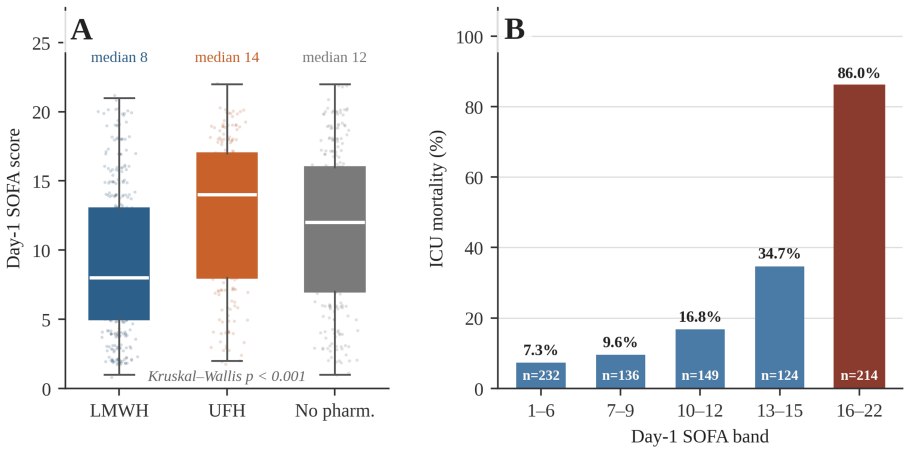


FIGURE 2: Day-1 SOFA score and ICU mortality. (A) SOFA scores in each thromboprophylaxis group. (B) ICU mortality by SOFA band in the comparative analysis set (n = 855), with the number of admissions in each band shown in the bars.

(A) Each box covers the interquartile range, with the median marked by the line inside it, and the whiskers reach the 5th and 95th centiles. Dots are individual patients. Groups were compared by Kruskal–Wallis test (H = 67.46, df = 2, p < 0.001). (B) Mortality climbs steadily as the score climbs, which is one indication that the scores were abstracted reliably.

ICU: intensive care unit; LMWH: low-molecular-weight heparin; No pharm.: no pharmacological prophylaxis; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

Reasons for Withholding Pharmacological Prophylaxis

Among the 254 patients without pharmacological prophylaxis, the reason recorded was empirical bleeding risk in 110 (43.3%, 95% CI = 37.1-49.6), thrombocytopenia in 94 (37.0%, 95% CI = 31.1-43.3), and active bleeding in 45 (17.7%, 95% CI = 13.2-23.0). Five (2.0%) had no reason documented. Two UFH patients had thrombocytopenia recorded as a reason for initial deferral before heparin was started. The 222 admissions with a mechanical device and the 32 with neither were similar in age (mean 50.9 versus 52.9 years) and ICU mortality (106/222, 47.7% versus 15/32, 46.9%); one DVT and two PEs occurred in the device subgroup and none in the other (Appendix 4).

Primary outcomes: deep vein thrombosis and pulmonary embolism

DVT was diagnosed in 11 of 859 patients (1.3%, 95% CI = 0.6-2.3) and PE in 17 (2.0%, 95% CI = 1.2-3.1). Neither differed across groups on the Fisher-Freeman-Halton exact test (DVT: statistic 3.34, p = 0.172; PE: statistic 4.48, p = 0.099). No pairwise comparison on Fisher's exact test survived Holm adjustment either (Table *2*; all six pairwise p-values are listed in Appendix 5).

Outcome	LMWH (n = 381)	UFH (n = 220)	No pharmacological (n = 254)	Test statistic	P-value
DVT, n (%)	8 (2.1)	2 (0.9)	1 (0.4)	3.34	0.172
95% CI	0.9–4.1	0.1–3.2	0.0–2.2	—	—
PE, n (%)	12 (3.1)	3 (1.4)	2 (0.8)	4.48	0.099
95% CI	1.6–5.4	0.3–3.9	0.1–2.8	—	—

TABLE 2: Incidence of DVT and pulmonary embolism by thromboprophylaxis group.

Events were found on compression Doppler ultrasonography (DVT) or computed tomography pulmonary angiography (PE), ordered on clinical suspicion. Confidence intervals are exact (Clopper–Pearson) binomial intervals. The p-values and test statistics are from the Fisher–Freeman–Halton exact test (the extension of Fisher's exact test to three groups), used in place of chi-square because three of six cells in the DVT table had expected counts below five. All three pairwise comparisons (Fisher's exact test) for each outcome were non-significant before and after Holm adjustment; the lowest adjusted value was 0.164 for PE between LMWH and no pharmacological prophylaxis.

CI: confidence interval; DVT: deep vein thrombosis; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; UFH: unfractionated heparin

Nor was day-one SOFA any different in patients who developed a thrombotic event (Mann-Whitney U test; DVT, median 8 versus 11, U = 3573, p = 0.181; PE, 11 versus 11, U = 6687, p = 0.642). Of the 28 thrombotic events, 21 occurred in patients who survived the ICU stay (DVT: 10 of 11; PE: 11 of 17).

Secondary outcomes

Overall ICU mortality was 32.9% (283/859). By group, it was 14.2% with LMWH, 48.6% with UFH, and 47.6% with no pharmacological prophylaxis ($\chi^2 = 110.05$, df = 2, $p < 0.001$). The median ICU stay was 4, 5, and 2 days, and the median ventilator days were 3, 4, and 1 (Kruskal-Wallis H = 55.26 and 30.96, respectively, df = 2, both $p < 0.001$). The group without pharmacological prophylaxis had the shortest stays: 80 of 254 (31.5%) left the ICU within 48 hours, 26 of them by death (Table *3*).

Outcome	LMWH (n = 381)	UFH (n = 220)	No pharmacological (n = 254)	Test statistic (df = 2)	P-value
ICU mortality, n (%)	54 (14.2)	107 (48.6)	121 (47.6)	$\chi^2 = 110.05$	<0.001
95% CI	10.8–18.1	41.9–55.4	41.4–54.0	—	—
ICU days, median (IQR)	4 (2–10)	5 (2–11)	2 (1–5)	H = 55.26	<0.001
Ventilator days, median (IQR)	3 (1–8)	4 (1–10)	1 (1–4)	H = 30.96	<0.001

TABLE 3: Secondary outcomes.

Confidence intervals for mortality are exact (Clopper–Pearson) binomial intervals. Mortality was compared by Pearson chi-square test (χ^2) and the continuous variables by Kruskal–Wallis test (H), each with 2 degrees of freedom and two-sided p-values. Ventilator days are days of invasive mechanical ventilation, counted as zero for unventilated admissions (LMWH: 73, UFH: 31, no pharmacological: 57).

CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin

Severity-adjusted predictors of intensive care unit mortality

We modeled day-one SOFA with a quadratic term, which fitted better than a linear one (likelihood-ratio $\chi^2 = 35.1$, 1 df, $p < 0.001$; AIC 594.5 versus 627.6, and 627.1 for five bands). The effect of each additional point therefore grows as the score climbs: roughly 1.03 at a score of 5, 1.37 at 10, and 1.83 at 15. The quadratic implies a slight fall in predicted mortality between scores of 1 and 5, which is not plausible and is not seen in the observed data (Figure *2B*); a restricted cubic spline, which does not impose this shape, fitted no better (AIC = 593.6 versus 594.5), tracked the quadratic closely across the observed range, and gave prophylaxis estimates of 4.98 (95% CI = 2.74-9.04) for UFH and 5.20 (3.06-8.82) for no pharmacological prophylaxis (Appendix 6A). Adding severity improved the model substantially, with Nagelkerke R^2 rising from 0.338 to 0.636, the c statistic from 0.804 to 0.917, and −2 log likelihood falling from 846.6 to 562.5. Calibration was good (Hosmer-Lemeshow $\chi^2 = 5.61$, df = 8, p = 0.69; Appendix 6B). Sepsis, shock, and renal disease all lost significance at the same time. This is consistent with their association with death being captured by the organ dysfunction measured in SOFA, but the analysis cannot demonstrate such mediation. The model contained 282 deaths and 15 variables, or 18.8 events per variable. Age and hematological disease remained

independent predictors (Table 4, Figure 3A).

Variable	Adjusted OR	95% CI	Wald χ^2	P-value
No pharmacological prophylaxis (vs LMWH)	5.16	3.05–8.72	37.42	<0.001
UFH (vs LMWH)	4.94	2.73–8.93	27.82	<0.001
Hematological disease	2.20	1.22–3.98	6.81	0.009
AKI or CKD	1.28	0.78–2.09	0.98	0.32
Immunological disease	1.10	0.53–2.25	0.06	0.80
Shock	1.08	0.67–1.76	0.11	0.75
Male sex	1.04	0.65–1.66	0.03	0.87
Age, per year	1.016	1.002–1.030	5.16	0.023
Sepsis	1.00	0.62–1.59	<0.01	0.98
Heart failure/IHD	0.84	0.48–1.48	0.35	0.55
Stroke	0.72	0.36–1.45	0.84	0.36
Diabetes mellitus	0.69	0.39–1.24	1.56	0.21
Hypertension	0.29	0.15–0.56	13.38	<0.001
Day-1 SOFA, linear term	0.75	0.60–0.93	6.59	0.010
Day-1 SOFA, quadratic term	1.029	1.019–1.040	32.07	<0.001

TABLE 4: Multivariable logistic regression: predictors of ICU mortality (n = 855, 282 deaths)

Logistic regression of ICU mortality on baseline covariates, ordered by descending odds ratio, with LMWH as the reference category for prophylaxis. ICU length of stay and duration of mechanical ventilation were left out as they were collinear with each other (r = 0.96). Day-1 SOFA enters as a linear and a quadratic term, which should be read together rather than one at a time. The odds ratio per additional point rises with the score, from about 1.03 at a score of 5 to 1.83 at 15. Model fit: Nagelkerke R^2 = 0.636, −2 log likelihood = 562.5, c statistic 0.917, 18.8 events per variable. Confidence intervals are Wald intervals based on robust standard errors clustered by patient (odds ratios are unchanged by clustering), and p-values are from the Wald χ^2 test with 1 degree of freedom.

AKI: acute kidney injury; CI: confidence interval; CKD: chronic kidney disease; ICU: intensive care unit; IHD: ischemic heart disease; LMWH: low-molecular-weight heparin; OR: odds ratio; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

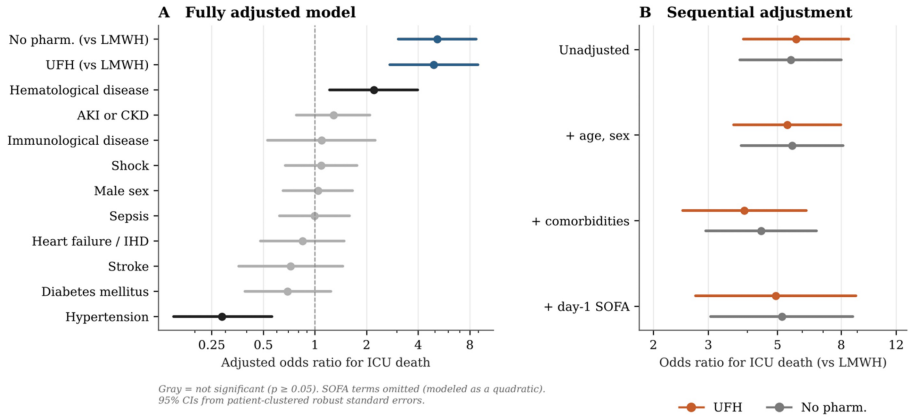


FIGURE 3: Logistic regression estimates for ICU mortality.

(A) Odds ratios from the fully adjusted model, ranked by size; intervals in gray are not significant (Wald χ^2 test, $p \geq 0.05$). (B) Odds ratios for the two prophylaxis groups against LMWH as covariates are added step by step. Both panels use a logarithmic scale, with 95% confidence intervals from robust standard errors clustered by patient and a dashed line at the null.

In the fully adjusted model, ICU death odds are about five times higher with UFH or no pharmacological prophylaxis than with LMWH. Hematological disease is also associated with higher odds, while hypertension is associated with lower odds. The other listed factors have confidence intervals crossing one. Across successive adjustments, odds ratios for both prophylaxis groups remain above one. They decrease after adding comorbidities, then rise after adding day-one SOFA score.

AKI: acute kidney injury; CKD: chronic kidney disease; ICU: intensive care unit; IHD: ischemic heart disease; LMWH: low-molecular-weight heparin; No pharm.: no pharmacological prophylaxis; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

Adding day-one SOFA did not attenuate the odds ratios. Against LMWH, the odds ratio for ICU death with UFH was 5.73 unadjusted; 3.92 after age, sex, and comorbidity; and 4.94 once day-one SOFA was added; for no pharmacological prophylaxis, the figures were 5.51, 4.42, and 5.16, respectively. Because the odds ratio is noncollapsible, its rise from 3.92 to 4.94 does not by itself show that severity fails to explain the association [18]. On the risk scale, which is collapsible, adjustment did attenuate the comparison. Crude ICU mortality differed from LMWH by 34.4 percentage points for UFH and 33.4 for no pharmacological prophylaxis. Standardized on comorbidity, the differences were 23.2 (95% CI = 14.4-31.5) and 25.7 (95% CI = 18.1-32.6) points; standardized on comorbidity and day-one SOFA, model-standardized mortality was 22.8% (95% CI = 18.3-26.7) with LMWH, 39.7% (95% CI = 33.9-45.3) with UFH, and 40.3% (95% CI = 34.8-45.1) with no pharmacological prophylaxis, risk differences of 16.9 (10.5-24.5) and 17.5 (11.4-22.9) percentage points. Severity therefore accounts for part of the crude difference, but not all of it (Table *5*, Figure *3B*).

Model	UFH vs LMWH	UFH Wald χ^2	No pharmacological vs LMWH	No pharm. Wald χ^2
Unadjusted	5.73 (3.88–8.47)	77.21	5.51 (3.79–8.00)	80.50
+ age and sex	5.37 (3.62–7.97)	69.65	5.57 (3.82–8.11)	80.06
+ comorbidities	3.92 (2.48–6.18)	34.31	4.42 (2.94–6.66)	50.78
+ day-1 SOFA (quadratic), primary model	4.94 (2.73–8.93)	27.82	5.16 (3.05–8.72)	37.42
SOFA in five quintile bands (sensitivity)	4.67 (2.61–8.37)	26.88	5.49 (3.30–9.15)	42.79
SOFA as restricted cubic spline	4.98 (2.74–9.04)	27.74	5.20 (3.06–8.82)	37.24
One admission per patient (n = 736)	4.62 (2.50–8.52)	23.97	4.51 (2.55–7.98)	26.87
Adults ≥18 years (n = 822), comorbidity-adjusted	4.05 (2.55–6.44)	35.04	4.58 (3.01–6.97)	50.26
Adults ≥18 years, + day-1 SOFA	5.05 (2.77–9.19)	28.02	5.25 (3.05–9.03)	35.97
Hypertension omitted, + day-1 SOFA	4.59 (2.55–8.26)	25.88	5.19 (3.09–8.74)	38.47
Landmark ≥48 hours (n = 665), comorbidity-adjusted	3.37 (2.03–5.59)	22.18	5.41 (3.35–8.76)	47.27
Landmark ≥48 hours, + day-1 SOFA	4.20 (2.17–8.15)	18.01	6.04 (3.32–10.99)	34.62
Landmark ≥72 hours (n = 513), comorbidity-adjusted	4.29 (2.42–7.61)	24.76	9.83 (5.37–17.98)	54.99
Landmark ≥72 hours, + day-1 SOFA	5.59 (2.67–11.70)	20.84	11.73 (5.83–23.64)	47.50

TABLE 5: Prophylaxis group odds ratios for ICU mortality before and after severity adjustment.

Every row is a separate logistic regression of ICU mortality, with LMWH as the reference group, and the covariates build up as the table descends. Odds ratios are shown with 95% confidence intervals; all are significant at $p < 0.001$ by the Wald χ^2 test with 1 degree of freedom. The quadratic model is the primary one. All rows use robust standard errors clustered by patient, except the one-admission-per-patient row, which needs no clustering. The rows below the primary model ask whether the result depends on how the analysis was set up: how day-1 SOFA is modeled, whether repeat admissions, adolescents, or hypertension are included, and whether admissions that ended within 48 or 72 hours are retained (landmark analyses, which limit immortal time bias). Rows marked comorbidity-adjusted are adjusted for age, sex, and the comorbidities without SOFA. Because odds ratios are noncollapsible, differences between rows should not be read as measures of confounding.

CI: confidence interval; ICU: intensive care unit; LMWH: low-molecular-weight heparin; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

Mortality within severity strata

The difference between groups turned up in every severity band. Among patients scoring 1-9, ICU mortality was 2.9% with LMWH, 15.9% with UFH, and 14.6% with no pharmacological prophylaxis. In the 10-15 band, it was 11.8%, 30.3%, and 39.7%, respectively. At 16 or above, it was 64.2%, 91.4%, and 95.0%, respectively. A prophylaxis × SOFA interaction term did not improve the model (likelihood-ratio $\chi^2 = 0.87$, df = 2, $p = 0.65$), so there was no evidence that the association differed by severity (Figure *4*).

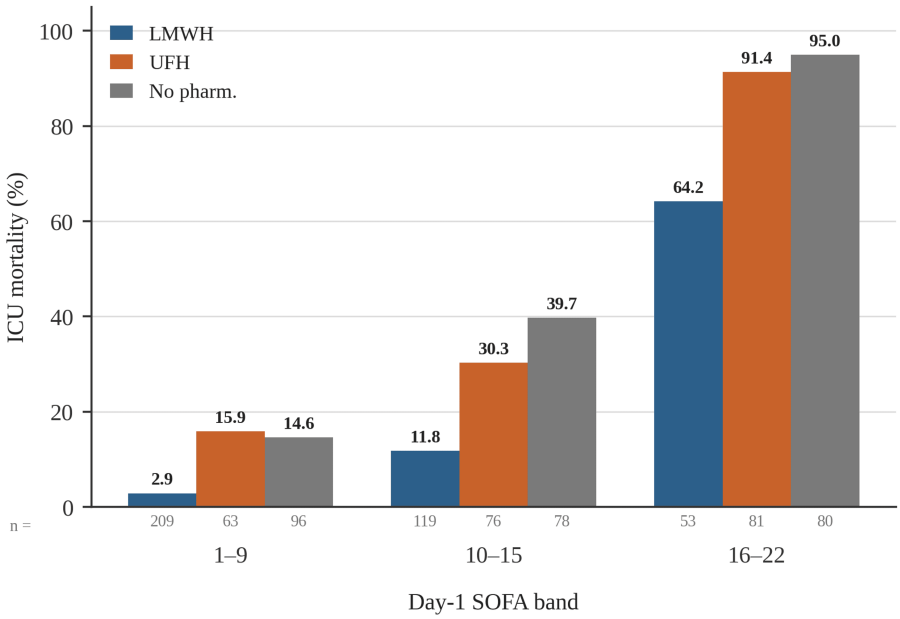


FIGURE 4: ICU mortality by thromboprophylaxis group within day-1 SOFA bands.

Each bar shows the percentage of admissions in that thromboprophylaxis group and SOFA band who died before ICU discharge. The figures above the bars are these percentages, and the numbers below the axis are the admissions contributing to each bar. Mortality was higher with UFH and with no pharmacological prophylaxis than with LMWH in all three bands.

ICU: intensive care unit; LMWH: low-molecular-weight heparin; No pharm.: no pharmacological prophylaxis; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

Quantitative bias analysis

For UFH against LMWH, the E-value was 3.87, falling to 2.69 at the confidence limit nearer the null; for no pharmacological prophylaxis, the figures were 3.97 and 2.89. Expressed on the same risk-ratio scale, renal disease carried a risk ratio for death of 1.76, shock 1.80, hematological disease 2.24, and a SOFA score above the median 3.78. These comparisons indicate how strong an unmeasured confounder would need to be; they do not show that the measured covariates have controlled confounding.

Sensitivity analyses

When the cohort was restricted to each patient's first ICU admission (n = 736; the chronologically first admission of each of the 739 patients, less three patients whose first admission received another anticoagulant), the adjusted odds ratio for UFH was 4.62 (95% CI = 2.50-8.52). Modeling day-one SOFA in five bands rather than as a quadratic produced a similar estimate of 4.67 (95% CI = 2.66-8.20). Excluding patients younger than 18 years, omitting hypertension, and restricting to admissions still in the ICU at 48 or 72 hours left the association in the same direction and of similar size (Table *5*). Propensity stratification gave a smaller estimate than the primary model. The Mantel-Haenszel common odds ratio was 2.91 (95% CI = 1.86-4.54; Mantel-Haenszel $\chi^2 = 22.22$, df = 1, $p < 0.001$). Mortality was higher with UFH in all five strata, and the Breslow-Day test found no sign that the effect varied between them ($\chi^2 = 5.60$, df = 4, p = 0.23). Stratification balanced the covariates well: standardized differences fell from 1.15 to −0.01 for renal disease and from 0.69 to 0.03 for day-one SOFA, and were below 0.1 for 11 of 12 covariates (immunological disease, 0.14) (Appendix 3B). The score distributions overlapped across most of their range; 48 admissions (47 LMWH, 1 UFH) lay outside the region of common support, nearly all LMWH patients with very low scores (Appendix 7A), and excluding them gave a Mantel-Haenszel odds ratio of 2.97 (95% CI = 1.90-4.64). The same approach for no pharmacological prophylaxis versus LMWH gave a Mantel-Haenszel odds ratio of 4.14 (95% CI = 2.67-6.41; Breslow-Day p = 0.93), with all standardized differences at or below 0.11 after stratification (Appendix 3B, Appendix 7B).

Discussion

Among 859 ICU admissions, DVT was detected clinically in 1.3% and PE in 2.0%, with no statistically significant difference between prophylaxis strategies. Mortality was 14.2% with LMWH, against 48.6% with UFH and 47.6% with no pharmacological prophylaxis, and the latter two groups were considerably sicker,

with median day-one SOFA scores of 14 and 12 compared with 8. The association persisted after adjustment for the measured confounders and within every severity stratum, but, as discussed below, it remains open to residual confounding and time-related bias.

Thrombotic outcomes

Our DVT rate of 1.3% is low, but that is expected in units which scan only when a clinician suspects thrombosis. Minet et al. noted how often thrombosis in the critically ill is silent, and how readily it passes unrecognized without protocolized imaging [1]. Our finding of no difference between agents also fits the randomized record. PROTECT found dalteparin no better than UFH for proximal DVT [4], and the meta-analysis by Alhazzani et al. found no difference in DVT rates between the two [5]. Studies that screen systematically tell a different story. Ibrahim et al. reported DVT during prolonged ventilation, despite prophylaxis, at rates far above ours [2]. PROTECT scanned within two days of admission and twice weekly after that, and found proximal DVT in a much greater share of patients [4]. What our figure measures, then, is most likely our diagnostic pathway rather than the true burden of thrombosis. The comparison between groups is also imprecise. With 11 DVT and 17 PE events, the study had 80% power only for differences of the order of 0.9% versus 4.5% for DVT and 1.4% versus 5.6% for PE; smaller but clinically relevant differences could not be excluded, and the absence of a statistically significant difference should not be read as evidence that the strategies are equivalent.

The difference in the PE result in our study, across the three prophylaxis groups, is not significant (Fisher-Freeman-Halton exact test, $p = 0.099$), and no pairwise comparison survived the Holm correction for multiple testing (Fisher's exact test); the lowest adjusted value was 0.164. The crude rates nonetheless run counter to the trial evidence. Alhazzani et al. found that LMWH reduces PE relative to UFH, not the reverse (risk ratio = 0.62, 95% CI = 0.39-1.00, and 0.58, 0.34-0.97, respectively, for symptomatic PE) [5]. Haut and Pronovost offered a simpler explanation in surveillance bias: a diagnosis gets made more often when it is looked for more often [25]. LMWH recipients survived the ICU stay more often, which gave more time in which thrombosis could be suspected and imaged; 21 of the 28 thrombotic events occurred in ICU survivors. We did not record imaging rates by group, so this explanation remains a hypothesis.

Patients who received no anticoagulant

This group carried the heaviest burden of contraindications, although median day-one SOFA was higher in the UFH group (14 versus 12): hematological disease in 29.1%, and bleeding, thrombocytopenia, or perceived bleeding risk documented in 98% of cases. That fits the multicenter audit by Lauzier et al., who found that prophylaxis decisions track patient characteristics rather than being applied uniformly [7]. Their low apparent DVT rate reflects the same detection limits affecting everyone else, compounded by short survival. That low rate is not evidence that a mechanical device suffices. PREVENT found no reduction in proximal DVT when pneumatic compression was added to pharmacological prophylaxis [6], and no trial has shown mechanical prophylaxis to substitute for anticoagulation here. Our data cannot resolve it, the comparison being wholly confounded by the contraindications that created the group. The odds ratio for this group is therefore reported for completeness and should not be interpreted as an effect of withholding anticoagulation. Thirty-two patients received nothing at all; their mortality (46.9%) was similar to that of patients with a device (47.7%). Whether prophylaxis was truly contraindicated in each case could not be found in the records.

This group is also the one most exposed to immortal time bias [21]: a patient who died before prophylaxis could be started would be classified as untreated. In the landmark analyses restricted to admissions still in the ICU at 48 or 72 hours, the association for this group strengthened rather than weakened (SOFA-adjusted odds ratios 6.04 and 11.73) (Table *5*), the opposite of what immortal time bias alone would produce. Because prophylaxis was started 24 to 36 hours after admission, the 48-hour landmark corresponds closely to the point at which exposure was assigned, though individual start times would be needed to remove the bias entirely.

Intensive care unit mortality

The mortality difference was present in every model we tried and in every severity band. Among the least unwell patients, 2.9% died on LMWH against 15.9% on UFH. Adding SOFA did not attenuate the odds ratio, but because odds ratios are noncollapsible, this does not show that severity fails to explain the association [18]. On the risk scale, adding SOFA reduced the adjusted difference between UFH and LMWH from 23.2 to 16.9 percentage points: severity explains part of the gap, and a substantial part remains. For the adjusted UFH estimate, the E-value was 3.87, falling to 2.69 at the confidence limit nearer the null [19]. In other words, to explain the finding away, an unmeasured confounder would need to be linked to both prophylaxis choice and death about as strongly as day-one organ dysfunction, and be largely independent of it. The propensity-stratified analysis sets a lower bar still. Its odds ratio of 2.91 gives an E-value of 2.80, weaker than the severity score itself, which carried a risk ratio of 3.78, and a ceiling-of-care decision would clear that easily.

Treatment timing matters less for the UFH comparison than for the untreated group, because both UFH and

LMWH recipients received an anticoagulant; immortal time bias would arise only if UFH were started systematically later. By unit practice, both agents were started in the same window, 24 to 36 hours after admission, and among admissions still in the ICU at 72 hours the SOFA-adjusted odds ratio for UFH was 5.59 (95% CI = 2.67-11.70), no smaller than in the full cohort.

Against this, the randomized evidence contradicts a causal reading. PROTECT found no mortality difference between agents [4], and the pooled estimate was null (risk ratio = 0.93, 95% CI = 0.82-1.04) [5]. When a large trial and an observational cohort disagree this sharply, the cohort is usually the one at fault, and the mechanism has been quantified for exactly this setting. Sjoding et al. simulated ICU studies in which a treatment is given more often to sicker patients. In their simulations, imperfect risk adjustment produced mortality odds ratios of 1.4 or more even when the treatment genuinely helped, at levels of adjustment normally thought acceptable [10]. Their work is a direct warning against our interpretation.

Residual confounding can come from factors we measured inadequately and from factors we did not measure at all. Among the former, renal disease combined acute kidney injury with chronic kidney disease without staging, and bleeding risk was recorded only as a reason for withholding prophylaxis. Among the latter are admission category and source, operative status, renal replacement therapy, extracorporeal support, platelet count, the trajectory of illness after day one, and treatment-limitation decisions. Day-one SOFA describes admission physiology and nothing after it. Ferreira et al. showed that serial measurement, not a single score, is what carries prognostic weight in critical illness [26], and two patients with the same admission score may diverge completely. We suspect the LMWH group was enriched for planned postoperative admissions, who tend to be less unwell and to survive, but could not verify this. More important still, we have no record of decisions to limit or withdraw life-sustaining treatment. Such a decision predicts death almost deterministically and would also discourage starting an anticoagulant, putting it on both arms of the confounding triangle. Code status could not be retrieved retrospectively. Formal do-not-resuscitate (DNR) orders are documented in about 2-3% of admissions to our unit. Under deliberately extreme assumptions, that every such admission (about 26 at 3%) died and all fell in the UFH group, a confounder of this prevalence would reduce the UFH risk ratio from 2.22 to 1.76, corresponding to an odds ratio of about 3.1 [27]; the same calculation for no pharmacological prophylaxis gives about 3.4. Formal DNR orders alone are therefore too infrequent to explain the association. Informal decisions not to escalate or to withdraw treatment are likely more common than documented DNR orders, however, and could still meet the E-value threshold; we cannot rule them out.

There is a pharmacological reason to doubt a drug effect too. UFH is chosen preferentially in renal impairment, and 70.5% of our UFH group had acute kidney injury or chronic kidney disease, compared with 20.7% on LMWH. That preference rests on concern about accumulation of LMWH. DIRECT found no bioaccumulation of dalteparin at creatinine clearance below 30 mL/minute [28], and the companion analysis found no bleeding signal [29], but these studies concern dalteparin and cannot be extended to enoxaparin, the agent used in our unit. For enoxaparin, accumulation and excess bleeding at therapeutic doses in severe renal insufficiency are documented, while data at prophylactic doses are limited [30]; in our unit, enoxaparin doses were reduced according to estimated glomerular filtration rate. Whatever the pharmacological merits of the preference, it means that UFH use in this cohort partly marks renal failure and clinical caution, which complicates its interpretation as an exposure.

Severity, length of stay, and what we could not measure

SOFA performed as the literature says it should. It was built to quantify organ dysfunction rather than to predict death [11], but Ferreira et al. showed that admission and serial scores both track mortality closely [26]. Mortality rose steadily from 7.3% at scores of 1-6 to 86.0% at 16 or above, which suggests the scores were abstracted reliably. Sepsis, shock, and renal disease lost significance once SOFA entered the model; this is consistent with, but does not demonstrate, their effect being captured by the organ dysfunction it measures. Its weakness here is that a single timepoint cannot capture trajectory, as Ferreira et al. demonstrated [26].

ICU stay and ventilator days were kept out of the mortality model on purpose. Both are fixed after admission and sit on the path between severity and death. They were also collinear here at r = 0.96, which gave uninterpretable coefficients when both were entered. Minet et al. identify both as genuine risk factors for thrombosis [1], and we accept them in models of thrombosis, but not of mortality, where the direction of causation cannot be untangled retrospectively.

Bleeding and heparin-induced thrombocytopenia could not be assessed, because the data collection form did not capture these events after prophylaxis had started. Had these outcomes been captured, the findings of PROTECT and the meta-analysis of Alhazzani et al. would lead us to expect a modest advantage for LMWH on thrombocytopenia and none on bleeding [4,5]. Crowther et al. found thrombocytopenia common in critical illness regardless of anticoagulation [31], so attributing it to heparin without confirmatory testing would be unsound in any case.

The hypertension coefficient

Hypertension appeared strongly protective once SOFA was in the model (odds ratio = 0.29, 95% CI = 0.15-0.56). Hypertensive patients scored 2.6 SOFA points higher on average yet died at the same rate (33% in both groups). One possible explanation, which these analyses do not demonstrate, is that the cardiovascular component of SOFA, as Vincent et al. defined it, turns on a mean arterial pressure below 70 mmHg [11], a threshold chronically hypertensive patients cross at a lower level of relative compromise, so that adjustment for SOFA sets them against less unwell normotensive patients. Because hypertension was more common with UFH (60.5% versus 38.3%), a coefficient coding hypertension as protective could inflate the UFH estimate. Omitting hypertension lowered the UFH odds ratio from 4.94 to 4.59 (95% CI = 2.55-8.26). A hypertension × SOFA interaction was of borderline significance (odds ratio = 0.89 per SOFA point, 0.80-1.00; likelihood-ratio $\chi^2 = 4.00$, df = 1, p = 0.046), so the apparent protection grew with the score, as the explanation above would predict; with the interaction in the model, the UFH estimate was 5.13 (2.81-9.39). Only the total day-one SOFA score was recorded in the master chart, not its organ components, so the cardiovascular component could not be replaced with vasopressor use as a further check. In the model without SOFA, hypertension had an odds ratio of 0.59, and omitting it changed the UFH estimate only from 3.92 to 3.83.

Limitations

This is a retrospective, single-center study. Prophylaxis was started 24 to 36 hours after admission by unit practice, but each patient's time of first dose, dosing changes, interruptions, and switching between agents were not recorded, so exposure misclassification and some immortal time bias cannot be excluded; landmark analyses timed to the usual start of prophylaxis limit but do not remove the latter. Severity was measured once, on the first ICU day, and we have no record of what happened afterward: no trajectory, no treatment-limitation decisions. Admission category, operative status, and extracorporeal support were not recorded. Thrombotic events came from imaging ordered on clinical grounds, so the true incidence is certainly higher than what we report. It may also differ between groups according to how long each spent under investigation, the surveillance bias described by Haut and Pronovost [25]. Bleeding and heparin-induced thrombocytopenia could not be assessed at all. Overall, 120 records are repeat admissions, which we confirmed against source records; restricting the analysis to first admissions changed nothing, and the primary model used patient-clustered standard errors. The study period overlapped the COVID-19 pandemic; although COVID-19 admissions were excluded, case mix, staffing, and prophylaxis practice may have differed from other periods. Adolescents aged 13 to 17 years were included because they are admitted to the adult ICU, although excluding them did not change the result. Data were abstracted without blinding to outcome and without a formal audit or double entry. The severity-adjusted analyses were not registered in advance, and ICU rather than hospital mortality was recorded, which depends in part on discharge practice.

Conclusions

Clinically detected venous thromboembolism was not very common in this cohort, with DVT in 1.3% and PE in 2.0% of admissions, and no statistically significant difference was observed between prophylaxis strategies, although the study was not powered to detect modest differences. Mortality was considerably higher among patients given UFH or no anticoagulant than among those given LMWH. The association persisted after adjustment for measured comorbidity and day-one organ dysfunction and within every severity stratum, with odds ratios for UFH of 2.91 to 5.59 depending on how confounding was handled; on the risk scale, adjustment for severity reduced the difference from LMWH but did not remove it. Its explanation remains uncertain: residual confounding, particularly by treatment-limitation decisions, and time-related bias could account for it, and the randomized evidence does not support a mortality difference between agents. The comparison with no pharmacological prophylaxis is confounded by design. These findings are hypothesis-generating and do not establish a mortality benefit of LMWH. Prospective studies with systematic thrombosis screening, recorded treatment timing, and serial severity scoring are needed to determine whether the association reflects the agent or the patients who receive it.

Appendices

Supplement

This supplement records the model specification decisions, the E-value calculation, and the propensity-stratified sensitivity analysis, and gives the additional descriptive and sensitivity results requested on review. All analyses were performed in IBM SPSS Statistics version 26 and Python 3 (statsmodels 0.15); the syntax is available from the corresponding author on request.

Four decisions about model specification were taken before fitting, and are set out below with the results that support them. Each is a judgement about which variables belong in a model of ICU mortality, rather than a finding (Appendix 1).

Decision	Reason	Supporting results
ICU length of stay and ventilator days excluded from the mortality model	Both are fixed after admission and lie on the path between severity and death; the two are also collinear (r = 0.96)	Entered together: 0.318 per ICU day and 3.235 per ventilator day, which cannot both be true. Entered separately: 1.008 per ICU day (Wald $\chi^2 = 1.03$, df = 1, p = 0.310) and 1.028 per ventilator day
Day-1 SOFA entered as a curve (linear plus quadratic terms)	Fitted better than a straight line or five bands	−2 log likelihood 562.451, against 597.580 (straight line) and 591.123 (five bands); likelihood-ratio $\chi^2 = 35.1$, df = 1, p < 0.001. AIC 594.5 (quadratic, 16 parameters), 627.6 (linear, 15), 627.1 (five quintile bands, 18), 593.6 (restricted cubic spline, 17). Prophylaxis estimates differ little between the specifications (UFH 4.94, 4.54, 4.67, 4.98)
No multivariable model of DVT or pulmonary embolism	Too few events per variable for stable estimates	11 DVT and 17 PE events; a five-variable PE model gives 3.4 events per variable against a threshold of 10
All admissions retained rather than one per patient	Prophylaxis was prescribed, and outcomes accrued, at the level of the admission	96 patients were admitted more than once; the primary model uses patient-clustered standard errors; the first-admission model (n = 736) gave UFH 4.62 (95% CI 2.50–8.52) and no pharmacological prophylaxis 4.51 (2.55–7.98)

TABLE 6: Appendix 1: Model specification decisions

Specification decisions were made before fitting the mortality model, with the results supporting each. All models were adjusted for age, sex, comorbidities, and prophylaxis group. The events-per-variable threshold of 10 follows Peduzzi et al. [15]. Wald and likelihood-ratio tests each have 1 degree of freedom. AIC = −2 log likelihood + 2 × number of parameters (including the intercept).

CI: confidence interval; DVT: deep vein thrombosis; ICU: intensive care unit; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

An E-value is the minimum strength of association, on the risk-ratio scale, that an unmeasured confounder would need with both prophylaxis choice and death to account for the association we observed. The strongest predictors we did measure are shown on the same scale for comparison (Appendix 2).

Estimate or predictor	OR (95% CI)	Approximate RR	E-value, point estimate	E-value, limit nearer null
UFH vs LMWH, primary model	4.94 (2.73–8.93)	2.22	3.87	2.69
No pharmacological vs LMWH, primary model	5.16 (3.05–8.72)	2.27	3.97	2.89
No pharmacological vs LMWH, propensity-stratified	4.14 (2.67–6.41)	2.03	3.48	2.65
UFH vs LMWH, propensity-stratified	2.91 (1.86–4.54)	1.71	2.80	2.07
Day-1 SOFA above median (12–22)	14.31 (9.72–21.07)	3.78	—	—
Hematological disease	5.03 (3.41–7.41)	2.24	—	—
Shock	3.26 (2.42–4.39)	1.80	—	—
Renal disease (AKI or CKD)	3.09 (2.29–4.18)	1.76	—	—

TABLE 7: Appendix 2: E-value analysis.

E-values follow VanderWeele and Ding [19]. Because ICU mortality was common (33%), odds ratios were converted to approximate risk ratios as RR = √OR [20], and the E-value was calculated as E = RR + √(RR × (RR − 1)). The lower four rows are the strongest measured predictors of death, each from a separate logistic regression adjusted for age and sex, shown on the same scale for comparison. The E-value for the primary estimate (3.87) slightly exceeds the strongest measured predictor (3.78); the propensity-stratified E-value (2.80) is lower than it. Primary-model confidence limits use patient-clustered standard errors. E-values describe sensitivity to unmeasured confounding only; they do not establish that confounding has been controlled and do not address exposure misclassification, selection bias, or treatment timing.

AKI: acute kidney injury; CI: confidence interval; CKD: chronic kidney disease; ICU: intensive care unit; LMWH: low-molecular-weight heparin; OR: odds ratio; RR: risk ratio; SOFA: Sequential Organ Failure Assessment; UFH: unfractionated heparin

Because prophylaxis was chosen rather than allocated, we also compared mortality only between patients who were similarly likely to receive UFH in the first place (Appendix 3A).

Likelihood of receiving UFH	Score range	LMWH, deaths/n (%)	UFH, deaths/n (%)
Group 1 (lowest)	0.036–0.117	1/111 (0.9)	1/8 (12.5)
Group 2	0.117–0.199	13/106 (12.3)	3/15 (20.0)
Group 3	0.200–0.382	16/86 (18.6)	20/35 (57.1)
Group 4	0.385–0.690	11/44 (25.0)	30/76 (39.5)
Group 5 (highest)	0.691–0.878	13/34 (38.2)	53/86 (61.6)
Total	-	54/381 (14.2)	107/220 (48.6)

TABLE 8: Appendix 3A: Propensity-stratified sensitivity analysis.

Restricted to the 601 patients who received one of the two anticoagulants. A logistic regression on age, sex, comorbidities, and day-1 SOFA estimated each patient's probability of receiving UFH (Nagelkerke $R^2 = 0.366$; renal disease was the strongest factor, odds ratio 6.69, 95% CI 4.43–10.10). Patients were divided into five equal groups by this score, and every group contained patients from both arms. Mantel–Haenszel common odds ratio 2.91 (95% CI 1.86–4.54; $\chi^2 = 22.22$, df = 1, $p < 0.001$); Breslow–Day $\chi^2 = 5.60$, df = 4, $p = 0.23$. The estimate is smaller than the primary model's 4.94 but in the same direction; taken together, the analyses place the odds ratio for UFH between 2.91 and 5.59. Only eight UFH admissions fell in the lowest stratum, so the estimate there is imprecise. Restricting to the region of common support (n = 553) gave a Mantel–Haenszel odds ratio of 2.97 (1.90–4.64).

CI: confidence interval; ICU: intensive care unit; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin

Covariate balance before and after stratification is shown in Appendix 3b.

Covariate	UFH vs LMWH, before	UFH vs LMWH, after	No pharm. vs LMWH, before	No pharm. vs LMWH, after
Age	0.47	0.06	-0.01	0.00
Male sex	-0.11	0.04	-0.04	0.01
Hypertension	0.45	-0.03	-0.04	0.01
Diabetes mellitus	0.41	0.04	-0.03	-0.01
Heart failure/IHD	0.49	0.01	-0.10	-0.01
AKI or CKD	1.15	-0.01	0.38	0.06
Stroke	-0.08	-0.02	-0.17	-0.03
Sepsis	0.38	0.05	0.10	0.03
Hematological disease	0.03	0.03	0.44	0.07
Immunological disease	-0.12	-0.14	0.15	0.05
Shock	0.38	0.07	0.31	0.04
Day-1 SOFA	0.69	0.03	0.47	0.11

TABLE 9: Appendix 3B: Covariate balance before and after propensity stratification.

Standardized differences before and after propensity-score stratification into quintiles, using stratification weights; values below 0.1 indicate adequate balance [24]. For no pharmacological prophylaxis versus LMWH, the propensity score was estimated from the same covariates (n = 635; Nagelkerke R^2 = 0.153), and the Mantel–Haenszel common odds ratio was 4.14 (95% CI 2.67–6.41; χ^2 = 43.56, df = 1, p < 0.001; Breslow–Day χ^2 = 0.85, df = 4, p = 0.93).

LMWH: low-molecular-weight heparin; UFH: unfractionated heparin

Admissions without pharmacological prophylaxis by use of a mechanical device are presented in Appendix 4.

Characteristic	Mechanical device (n = 222)	Neither (n = 32)
Age, mean, years	50.9	52.9
Reason for withholding: active bleeding	36	9
Reason: thrombocytopenia	87	7
Reason: empirical bleeding risk	97	13
Reason: none documented	2	3
DVT, n	1	0
PE, n	2	0
ICU deaths, n (%)	106 (47.7)	15 (46.9)

TABLE 10: Appendix 4: Admissions without pharmacological prophylaxis by use of a mechanical device.

Descriptive only; no formal comparison was made given the size of the second group.

DVT: deep vein thrombosis; ICU: intensive care unit; PE: pulmonary embolism

Pairwise comparisons of thrombotic events are shown in Appendix 5.

Comparison	DVT, unadjusted p	DVT, Holm-adjusted p	PE, unadjusted p	PE, Holm-adjusted p
LMWH vs UFH	**0.339**	**0.679**	**0.277**	**0.554**
LMWH vs no pharmacological	0.093	0.280	0.055	0.164
UFH vs no pharmacological	0.599	0.679	0.667	0.667

TABLE 11: Appendix 5: Pairwise comparisons of thrombotic events.

Two-sided Fisher's exact tests, with Holm adjustment computed from unrounded p-values across the three comparisons for each outcome [14].

DVT: deep vein thrombosis; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; UFH: unfractionated heparin

Functional form and calibration of the primary mortality model are shown in Appendix 6.

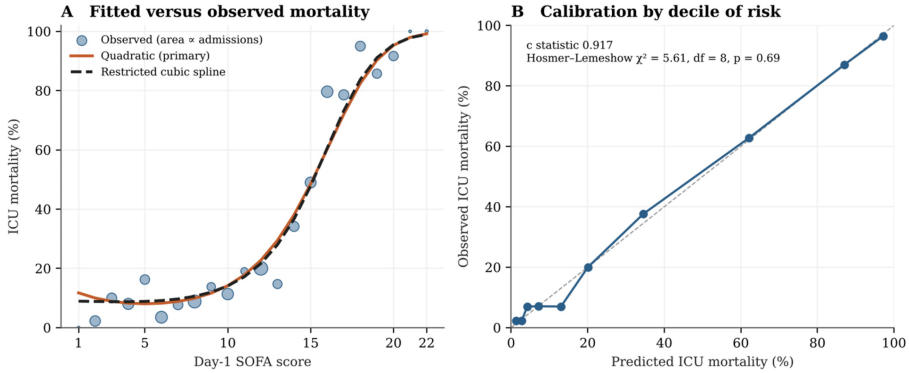


FIGURE 5: Appendix 6: Functional form and calibration of the primary mortality model.

(A) ICU mortality at each day-1 SOFA score (circles, area proportional to the number of admissions) with model-standardized predictions from the quadratic (primary) and restricted cubic spline (four knots at scores 2, 8, 14, and 19.3) specifications. The quadratic dips slightly between scores 1 and 5, where few admissions lie; the two curves otherwise coincide. (B) Observed against predicted mortality by decile of predicted risk; the dashed line is perfect calibration.

ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment

The propensity score distribution is shown in Appendix 7.

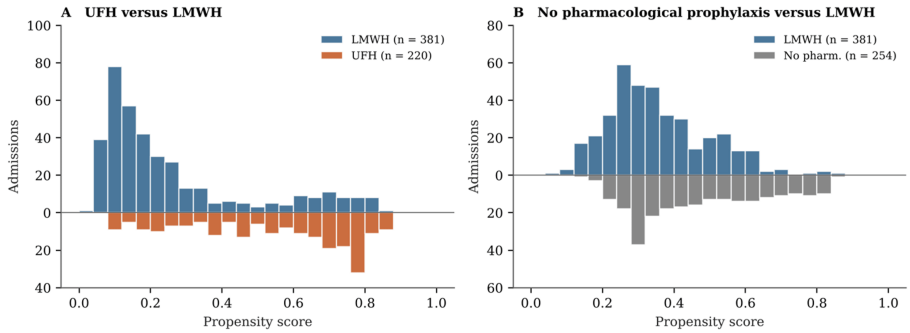


FIGURE 6: Appendix 7: Propensity score distributions.

(A) Probability of receiving UFH rather than LMWH (n = 601); 48 admissions (47 LMWH, 1 UFH) fall outside the region of common support. (B) Probability of receiving no pharmacological prophylaxis rather than LMWH (n = 635). LMWH admissions are plotted above the axis and the comparison group below.

LMWH: low-molecular-weight heparin; UFH: unfractionated heparin

The completed STROBE checklist for cohort studies [12] is given in Appendix 8, with the location of each item in the manuscript.

Section/Topic	Item	Recommendation	Where reported in the manuscript
Title and abstract	1a	Indicate the study design with a commonly used term in the title or abstract	Title (“Retrospective Cohort Study”); Abstract, Methods
	1b	Provide an informative and balanced summary of what was done and what was found	Abstract (Background, Methods, Results, Conclusions)
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation	Introduction, paragraphs 1–4
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, final paragraph (descriptive objective; primary outcome DVT/PE; secondary outcome ICU mortality); Abstract, Background
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, Design, setting, and approval
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, Design, setting, and approval (SQUH adult ICU, January 2021–June 2022; data collected and analyzed January 2023–December 2025); Methods, Outcomes (follow-up from ICU admission to ICU discharge or death)
Participants	6a	Give the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up	Methods, Participants (inclusion and exclusion criteria, age policy, repeat admissions); Methods, Outcomes (follow-up to ICU discharge or death)
	6b	For matched studies, give matching criteria and number of exposed and unexposed	Not applicable (no matching)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if applicable	Methods, Exposure (agents, doses, timing, classification); Methods, Outcomes (DVT and PE imaging criteria; secondary outcomes); Methods, Severity of illness and covariates (day-1 SOFA, comorbidity definitions); Methods, Statistical analysis (effect modification)

Data sources/Measurement	8	For each variable of interest, give sources of data and details of methods of assessment; describe comparability of assessment methods if there is more than one group	Methods, Data abstraction (TrakCare, abstractors, checking); Methods, Severity of illness and covariates (SOFA abstraction, admission panel, GCS before sedation); Methods, Outcomes (imaging and radiologist reporting, identical for all groups)
Bias	9	Describe any efforts to address potential sources of bias	Methods, Statistical analysis (confounding: sequential adjustment, propensity scores, E-values; immortal time bias: landmark analyses; repeat admissions: clustered standard errors); Discussion, Thrombotic outcomes (surveillance bias); Limitations
Study size	10	Explain how the study size was arrived at	Methods, Statistical analysis, Sample size (all eligible admissions; minimum detectable differences)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses; if applicable, describe which groupings were chosen and why	Methods, Statistical analysis, Modeling day-1 SOFA (quadratic, spline, quintile bands, descriptive bands); Appendix 1
Statistical methods	12a	Describe all statistical methods, including those used to control for confounding	Methods, Statistical analysis (all subsections); Supplement, Appendix 1–3
	12b	Describe any methods used to examine subgroups and interactions	Methods, Statistical analysis, How well the model performs (prophylaxis × SOFA and hypertension × SOFA interactions; mortality within SOFA bands)
	12c	Explain how missing data were addressed	Methods, Data abstraction (“None of the analyzed variables had missing values”); Methods, Severity of illness and covariates (no SOFA component imputed)
	12d	If applicable, explain how loss to follow-up was addressed	Not applicable: outcomes were ascertained in hospital records to ICU discharge or death, with no loss to follow-up
	12e	Describe any sensitivity analyses	Methods, Statistical analysis, Checking the robustness of the result; Timing of prophylaxis; Comparing similar patients (propensity scores)
Results			
Participants	13a	Report numbers of individuals at each stage of study	Results, Study population; Figure 1
	13b	Give reasons for non-participation at each stage	Methods, Participants; Figure 1 (exclusions with reasons)
	13c	Consider use of a flow diagram	Figure 1
Descriptive data	14a	Give characteristics of study participants and information on exposures and potential confounders	Results, Study population; Results, Severity of illness and baseline characteristics; Table 1; Figure 2A; Results, Reasons for withholding pharmacological prophylaxis; Appendix 4
	14b	Indicate number of participants with missing data for each variable of interest	Results, Study population (no missing values, including day-1 SOFA for all 859 records)
	14c	Summarize follow-up time	Results, Study population (median ICU stay 3 days, IQR 2–9); Table 3 (ICU days by group)
Outcome data	15	Report numbers of outcome events or summary measures over time	Results, Primary outcomes (Table 2); Results, Secondary outcomes (Table 3)
Main results	16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision; make clear which confounders were adjusted for and why they were included	Results, Severity-adjusted predictors of ICU mortality; Tables 4 and 5 (unadjusted and sequentially adjusted odds ratios with 95% CIs); Figure 3
	16b	Report category boundaries when continuous variables were categorized	Methods, Statistical analysis, Modeling day-1 SOFA and How well the model performs; Figures 2B and 4; Appendix 3
	16c	If relevant, consider translating estimates of relative risk into absolute risk	Results, Severity-adjusted predictors (model-standardized mortality and adjusted risk differences)

Other analyses	17	Report other analyses done, e.g., analyses of subgroups and interactions, and sensitivity analyses	Results, Mortality within severity strata (Figure 4); Quantitative bias analysis; Sensitivity analyses; Table 5; Appendix 2–4 and Appendix 6
Discussion			
Key results	18	Summarize key results with reference to study objectives	Discussion, opening paragraph
Limitations	19	Discuss limitations, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias	Discussion, Limitations; Discussion, ICU mortality (residual confounding, DNR bounding calculation, E-values); Discussion, Thrombotic outcomes (power, surveillance bias)
Interpretation	20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion (comparison with PROTECT, PREVENT, and meta-analyses); Conclusions
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion, Limitations (single-center design, pandemic-era study period, inclusion of adolescents, ICU rather than hospital mortality)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No external funding was received; declared in the Cureus submission disclosures (Financial relationships)

TABLE 12: Appendix 8: STROBE checklist for cohort studies.

Locations are given by section, table, and figure.

CI: confidence interval; DVT: deep vein thrombosis; GCS: Glasgow Coma Scale; ICU: intensive care unit; PE: pulmonary embolism; SOFA: Sequential Organ Failure Assessment; SQUH: Sultan Qaboos University Hospital

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Medical Research Ethics Committee issued approval MREC #2693. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other

relationships or activities that could appear to have influenced the submitted work.

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