Retrospective matched cohort study comparing Unfractionated Heparin and Enoxaparin prophylaxis to the occurrence of Venous Thromboembolism among patients in surgical intensive care unit

Introduction/Background

Venous thromboembolism (VTE) is a collective term describing clot formation originating in the veins, namely deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT are blood clots found in the extremities, while PE is caused by dislodged blood clots which travel and occlude blood vessels in the lungs resulting in potentially fatal complications. Due to prolonged bed rest and immobilization after surgery, patients in the surgical intensive care unit (SICU) are prone to VTE. Furthermore, critically ill patients have risk factors unique to them, such as inflammation and high severity of illness (Fernando et al., 2022). The incidence of DVT in ICU patients ranges from 15-60% if no prophylaxis is given (Gurjar, 2014). Patients who undergo surgery are also at higher VTE risk, depending on individual predisposing factors and the type of surgery (Agnelli, 2004; O'Donnell & Weitz, 2003). Among the general surgical population, the VTE risk is about 10-50% (Ambra et al., 2022). VTE accounts for the top five most common causes of hospital-related deaths in the USA and Australia and is one of the most common preventable causes of hospital deaths (Hassan et al., 2014).

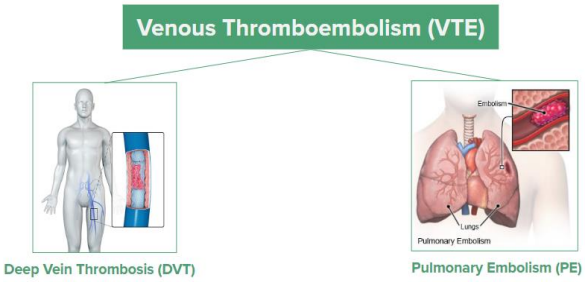

Figure 1: Venous thromboembolism consists of both deep vein thrombosis (DVT) and pulmonary embolism (PE)

The risk of VTE is significantly reduced when mechanical or pharmacological prophylaxis, or both, are administered (Ejaz et al., 2018; Fernando et al., 2022). As such, major guidelines such as the American College of Chest Physicians (ACCP) guidelines strongly recommend routine thromboprophylaxis in critically ill patients to reduce the risk of VTE (Kearon et al., 2012). Pharmacological prophylaxis with either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is widely used to prevent new clot formation in patients with high risk of VTE. Both UFH and LMWH work by inhibiting thrombin, an important coagulation factor in the clot formation process. In addition, they can inhibit other coagulation factors, naming coagulation factors IXa, Xa, XIa, XIIa, and plasmin, as well as the conversion of fibrinogen to fibrin (Drugbank, 2023). Based on their pharmacokinetics profiles, the use of LMWH is preferred to UFH due to its simplified dosing, lower risk of bleeding and heparin-induced thrombocytopenia (HIT) (Bounameaux, 1998), a potential life-threatening complication of taking heparin. UFH, however, is preferred in patients with kidney impairment (Kearon et al., 2012) since unlike LMWH, it is minimally cleared by the kidneys.

Currently, there is still a degree of uncertainty in the preference of agent for VTE prophylaxis among the critically ill patients in the SICU, and there exists variation in practices in the clinical setting (Fernando et al., 2022). In 4 randomized controlled trials involving critically ill patients, 1 recommended UFH over placebo, another recommended LMWH over placebo, while 2 others had inconclusive recommendations (Cook et al., 2011). A meta-analysis of trials involving medical-surgical intensive patients also concluded with no significant differences of 1 agent over the other in most efficacy and safety endpoints (Alhazzani et al., 2013). In view of the insufficiency of current evidence to guide the choice between UFH and LMWH among ICU patients (Gurjar, 2014), we conducted a retrospective cohort study to determine the association between treatment outcomes and safety in adult patients in the SICU given either UFH ("Heparin") or Enoxaparin (an LMWH). Enoxaparin is a commonly used LMWH in the United States since 1993, and is usually administered under the skin (Iqbal., 2022). The study is carried out using the Medical Information Mart for

Intensive Care (MIMIC-IV) database. MIMIC-IV comprises detailed information about 73,181 stays in the intensive care unit (ICU), such as patient encounter details, recorded observations, laboratory outcomes, microbiology data, prescribed medications, and hospital-level billing codes. The data from MIMIC has been applied in various research projects, covering a broad range of topics, from epidemiological inquiries to the creation of algorithms (Bennett et al., 2023).

All codes developed for this project can be found at: https://github.com/Ivan-LZY/Retrospective-study-on-healthcare-dataset-MIMIC-IV

Methods

Study hypothesis

H_0: There is **no difference** in VTE occurrence between patients taking Heparin or Enoxaparin for prophylaxis.

H_1: There is a **difference** in VTE occurrence between patients taking Heparin or Enoxaparin for prophylaxis.

Study population

We conducted a single-centre, retrospective matched-cohort study using the MIMIC-IV database, based on the electronic health record of the Beth Israel Deaconess Medical Center in Boston, Massachusetts.

All adult patients in the MIMIC-IV database meeting the following criteria were included:

1) Adults aged ≥18 years old, and
2) Admitted to either in Surgical Intensive Care Unit (SICU) or mixed Medical and Surgical Intensive Care Unit (MICU/SICU). For patients who had multiple ICU admissions in the MIMIC-IV database, only the first admission was taken, and
3) Received either Heparin or Enoxaparin as pharmacological prophylactic agent to prevent VTE.

A flowchart of the eligibility criteria and final sample size is shown in **Figure A1** in **Appendix (A)**.

Study outcomes

The primary endpoint examines the occurrence of Acute VTE, measured by the diagnosis entry in the respective patients in the specific hospital admission ID who received either Heparin or Enoxaparin. Secondary outcomes include occurrence of major bleeding events (defined as intracerebral, gastrointestinal, or pericardial hemorrhage also known as Hemopericardium) and in-hospital mortality (Lamberts et al., 2017). Heparin-induced thrombocytopenia (HIT) is also explored. These outcomes are highly studied in VTE studies to assess safety (major bleeding and HIT) and efficacy (VTE) between UFH and LMWHs (Cook et al., 2011).

Data extraction

Literature review on similar VTE studies was done to identify common covariates. Structured Query Language (SQL) was used to extract data relating to age, gender, ethnicity, laboratory results (serum creatinine and platelet counts), medications on concurrent antithrombotic, vasopressor usage, comorbidities, and outcomes of interest (VTE, major bleeding, and heparin-induced thrombocytopenia). Data on major bleeding was defined as intracerebral, gastrointestinal, or pericardial hemorrhage. Patients with missing weight values were excluded.

After data extraction, our dataset had an imbalanced split among patients who received Enoxaparin (n=311) and Heparin (n=7536), with the ratio being 1:24 respectively. This imbalanced exposure makes it challenging to perform some of the statistical analysis. The baseline characteristics of the original cohort are presented in **Table 1**.

Statistical Analysis

Propensity Score Matching. The first objective for our statistical analysis was to create a matched cohort to adjust for confounding effects. To do this, propensity score matching was done on the dataset with the following 12 identified covariates from relevant studies (Beitland et al., 2015; Flores et al., 2017; Gaitanidis et al., 2021; Meizlish et al., 2021; Samuel et al., 2023; Zou et al., 2022):

1. Age
2. Congestive Heart Failure
3. Cancer

4. Liver disease
5. ICU types
6. Gender
7. Sepsis
8. Mechanical ventilation
9. SOFA
10. Weight
11. Diabetes
12. Serum creatinine

To ensure that the effect size of our confounding covariates is small, we calculated the standardized mean difference (SMD) for all confounding covariates after matching. For an effect size to be considered small, the SMD needs to be in the range of 0.2-0.5(Andrade, 2020; Zhang, 2010). For our study, we aimed to get all confounding covariates to have a SMD < 0.25.

Subsequently, due to the high imbalance in our dataset, we trained a logistic regression model with a balanced class weights to predict propensity scores. With the treatment group being Enoxaparin and the control group being Heparin, the scores were then matched using a K-Nearest Neighbours algorithm with 1:N=20. A large N ratio of 20 was chosen to create a matched cohort that closely resembles the original dataset which had a ratio of 1:24.

However, the matches with N=20 were not ideal as it cannot meet our SMD requirements (**Appendix (A) Figure A2**). A matched cohort plot of the Density vs Propensity Score between the two groups also shows little overlap, signaling poor matches (**Appendix (A) Figure A3**). One explanation for this can be attributed to the poor training of the logistic regression model on the highly unbalanced dataset. This causes the propensity scores for Enoxaparin to concentrate on the lower end of 0.2.

To further validate this explanation, we can analyze the classification metrics for the trained logistic regression model. The train and test F1-score of the logistic regression model is in the ballpark of 0.48 while that of the model's accuracy is higher at 0.69. Ideally, for a model trained on a balanced dataset, both F1-score and accuracy must be similar in value. This indicates that the effect of an unbalanced dataset is not fully mitigated by the balanced class weights setting.

Hence, given the poor classification performance of our logistic regression model, to directly get better matches, we explored lower N ratios ranging from 4 to 20 in steps of 2. The results for this can be found in the appendix (**Figure 2**). For our finalized match cohort, we also aim to retain as large a cohort as possible, so that subsequent analysis has more datapoints to work with. Given that N=10 is the largest ratio that allows us to meet the SMD<0.25 requirement (**Figure 2**), a cohort matched with 1:N=10 is selected.

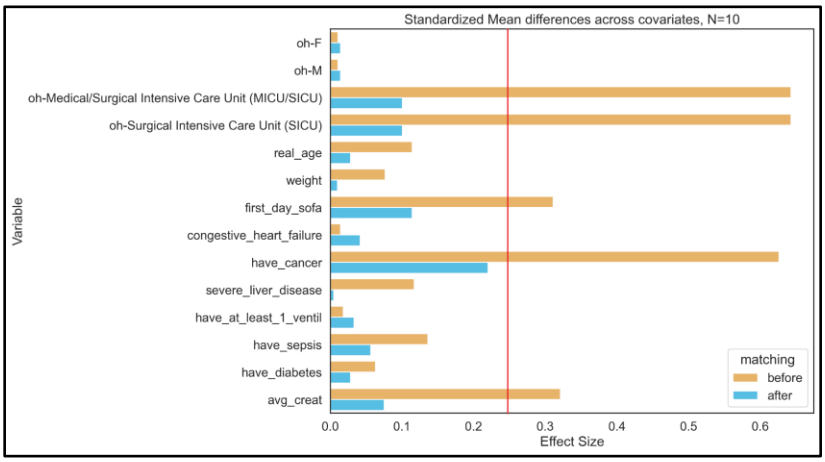

Figure 2: SMD plot with the finalized Propensity Score Matching with N=10, meeting the required SMD<0.25.

Pearson's Chi-square test/Fisher's exact test/Conditional logistic regression. To examine the association between exposure (Heparin and Enoxaparin) and outcomes (VTE, Major

bleeding events, HIT), odds ratio was generated. If sample size cell counts are large (less than 20% of cells have expected frequency < 5), Pearson's Chi-square test is employed. Otherwise, Fisher's exact test is used. Conditional logistic regression was also employed to generate odds ratio of outcomes between two treatment groups to account for 1:N matching.

Cox regression and Kaplan-Meier survival analysis. In-hospital survival curves for each treatment group were generated, while Cox proportional regression will be used to generate hazard ratio with the assumption that the two treatment groups have hazard functions that are proportional over time.

Continuous variables will be summarized in mean and standard deviations while categorical variables will be summarized in counts and proportions (%). Descriptive analysis will be used in the case of unanalyzable results. Data analysis was carried out using Python, STATA (version number 14), and R programming (R version 4.2.2). A two-sided level of significance of 5% is selected for statistical tests performed, unless stated otherwise.

Results and Discussion

Baseline characteristics

Based on our inclusion and exclusion criteria in (the methods section), we included (n = 7,638) patients in the analysis (**Figure A1**). Baseline characteristics before and after matching (**Table 1**) are summarized by covariates of interest.

Table 1 covariables were reported as mean (standard deviations) between the two treatment arms (Heparin vs. Enoxaparin) for continuous variables, and quantity (percentage) for categorical variables. Baseline characteristics were assessed to detect any potential imbalances between the two arms, and standardized mean differences were reported. In the original cohort, a larger percentage of patients taking Enoxaparin were admitted to SICU (81.9% vs. 51.9%) and had cancer (49.1% vs. 22.6%), while patients in Heparin group had higher mean serum creatinine level (1.29±1.3 mg/dL vs. 0.88±1.4 mg/dL) and SOFA score (4.23±3.2 vs. 3.21±2.4). Heparin group also had a higher proportion of patients with severe renal impairment (10.6% vs. 2.9%). After propensity matching with a 1:10 ratio, 3,421 patients were included in the cohort for further analysis, with 3,110 patients taking Heparin and 311 patients taking Enoxaparin. The standardized mean differences of all baseline characteristics between two groups after matching were all smaller than 0.25.

Table 1: Baseline characteristics table before and after propensity score matching (1:10)

Baseline Characteristics of Included Patients (before matching)				Baseline Characteristics of included patients (after 1:10 propensity score matching)		
Variables	**Heparin (N = 7,638)**	**Enoxaparin (N = 316)**	**SSMD**	**Heparin (N=3,110)**	**Enoxaparin (N = 311)**	**SSMD**
Demographics						
Age (years)	63.2 (17.3)	65.1 (13.2)	0.090	65.63 (16.3)	65.18 (13.3)	0.021
Gender (% Male)	3,889 (50.9)	162 (51.2)	0.005	1578 (50.7)	160 (51.4)	0.010

Body weight (kg)	81.5 (25.6)	83.3 (15.2)	0.048	83.02 (29.3)	83.25 (25.2)	0.006
ICU type (SICU%)	3,961 (51.9)	253 (80.06)	0.499	753 (24.2)	86 (27.7)	0.073
Labs						
Serum Creatinine (mg/dL)	1.29 (1.3)	0.88 (0.4)	0.302	0.908 (0.4)	0.878 (0.4)	0.055
Creatinine Clearance (mL/min) (<30 mL/min)	100.0 (69.5) 812 (10.6)	114.1 (57.2) 9 (2.9)	0.156 0.266	111.7 (69.7) 70 (2.3)	114.1 (57.2) 4 (1.3)	0.027 0.052
Platelet count (mm^3)	244.0 (113.9)	244.7 126.2)	0.004	249.7 (115.6)	243.9 (126.7)	0.034
Life support (%)						
Mechanical ventilation	6203 (82.3)	259 (81.8)	0.014	2510 (80.7)	255 (82.0)	0.023
Vasopressors	7611 (99.6)	314 (99.8)	0.028	3098 (99.6)	309 (99.4)	0.025
SOFA scores	4.23 (3.2)	3.21 (2.4)	0.251	3.53 (2.6)	3.24 (2.4)	0.083
Comorbidities						
Charlson Comorbidity Index	4.72 (3.1)	5.57 (3.0)	0.197	5.20 (3.2)	5.57 (3.0)	0.085
Cancer (%)	1,726 (22.6)	155 (49.1)	0.406	1187 (38.2)	159 (51.1)	0.154
Congestive Heart Failure (%)	1,406 (18.4)	60 (19.0)	0.011	642 (20.6)	59 (18.9)	0.030
Chronic Pulmonary Disease (%)	2,045 (25.9)	82 (25.7)	0.004	918 (29.5)	82 (26.4)	0.050
Diabetes Mellitus (%)	2,246 (23.1)	79 (23.2)	0.045	808 (26.0)	77 (24.8)	0.020
Sepsis (%)	1,705 (22.3)	52 (16.4)	0.105	588 (18.9)	52 (16.7)	0.040
Severe liver disease (%)	1,284 (4.2)	6 (1.9)	0.096	58 (1.9)	6 (1.9)	0.004
Use of antithrombotic medications (%)	879 (11.5)	44 (13.9)	0.051	324 (10.4)	44 (14.2)	0.080

Primary and secondary outcomes (Tables 2 and 3)

Patients who were on Heparin for VTE prophylaxis treatment had 0.13 lower odds of having VTE compared to patients given Enoxaparin, and this is statistically significant (p-value < 0.001, 95% CI 0.10 - 0.17).

In the Heparin-treated group, there is 69% lower risk of in-hospital mortality compared to Enoxaparin but is statistically not significant (p-value = 0.4, 95% CI 0.58 - 1.16). Major bleeding events were more prevalent in Heparin group, with 13 out of 3,110 patients reporting at least one occurrence, while only 1 out of 311 patients in Enoxaparin groups experienced the same adverse effect. The odds of major bleeding events is 1.3 higher in Heparin compared to Enoxaparin, however this is statistically not significant with p-value of 1.00 (95% CI 0.19-55.5). As for HIT outcome, there is 0.90 lower odds of having HIT event in patients treated with Heparin compared to Enoxaparin, this is statistically not significant with p-value of 1.00 (95% CI 0.58-1.16).

A subgroup analysis based on renal impairment for the primary outcome was performed. Patients with renal impairment were defined as creatinine clearance (CrCl) of <30 mL/min. Given that there was a cell count of '0' in CrCl <30mL/min group. For patients with normal renal function of CrCl >30 mL/min, those who were treated with Heparin have 0.116 lower odds of having VTE compared to Enoxaparin for patients without severe kidney impairment, and this is statistically significant (p-value<0.05) as the 95% CI do not overlap with 1 (**Appendix (A) Table A3**).

Whereas for patients with low renal function of creatinine clearance< 30mL/min group, there were 3 VTE events in Heparin group while Enoxaparin does not have any VTE occurrences. Hence, Pearson chi-square tests and Fisher exact tests were not conducted.

The primary and secondary outcomes conducted using Chi-square and Fisher exact methods are summarized in **Table 2.**

Table 2: Primary and secondary outcome analysis with propensity matched cohorts

Variables	Heparin (N = 3,110)	Enoxaparin (N = 311)	Effect size	95% Confidence Interval	p-value
Primary Outcome					
VTE (%)	319 (10.3)	145 (46.6)	OR 0.13	0.10-0.17	<0.001
Secondary Outcomes					
In-hospital mortality rate	-	-	HR 0.817	0.577-1.155	0.4
Major bleeding events (%)	13 (0.4)	1 (0.3)	OR 1.30	0.19-55.5	1.00
Heparin-Induced Thrombocytopenia	9 (0.3)	1 (0.3)	OR: 0.90	0.12-39.55	1.00

Conditional logistic regression was also used to provide the odds ratio of the primary and secondary outcomes between two treatment groups. This statistical method was used to account for 1:N (1:10) matching given that Pearson's chi-square and Fisher exact method do not account for matching. In this analysis, the cohorts were matched by age and ICU types. The model was also adjusted for confounders such as age, gender, weight, ICU types (based on first care unit in hospital admission), comorbidities (congestive heart failure, cancer, severe liver disease, diabetes), SOFA score, sepsis status, serum creatinine and use of mechanical ventilation. The rationale for only matching by age and ICU types instead of all the confounders was due to practical constraints from avoiding the singular matrices. Based on the conditional logistic regression results in Table 2, there is 0.12 lower odds of VTE events in patients treated with Heparin compared to Enoxaparin, after adjusting for confounders*****. This is statistically significant as well given that p-value < 0.01. The odds ratio reported here is similar to the earlier result using Pearson's Chi-square test (**Table 2**).

For secondary outcomes, the odds of having a major bleeding event is 1.94 higher in patients treated with Heparin compared to Enoxaparin after adjusting for confounders***,** but it is statistically not significant (p-value 0.536). While patients treated with heparin have 0.364 lower odds of having Heparin-induced thrombocytopenia compared to being treated with Enoxaparin after adjusting for confounders***** but are not statistically significant (p-value = 0.393).

Table 3: Primary and secondary outcome analysis with propensity matched cohorts using conditional logistic regression accounting for propensity matched cohorts by age and ICU types

Variables	Effect size (Odds ratio)	95% Confidence Interval	p-value
Primary Outcome			

VTE (%)	0.123	0.089-0.172	<0.001***
Secondary Outcomes			
Major bleeding events (%)	1.938	0.238-15.78	0.536
Heparin-induced thrombocytopenia (%)	0.364	0.0357-3.70	0.393

***Odds ratio after adjusting for age, gender, weight, ICU types (based on first care unit in hospital admission), comorbidities (congestive heart failure, cancer, severe liver disease, diabetes), SOFA score, sepsis status, serum creatinine and use of mechanical ventilation.*

Kaplan-Meier survival curves which analyze in-hospital mortality for each treatment group in the matched cohort was conducted (**Figure 3**). There were no statistically significant differences between the Enoxaparin and Heparin group for this secondary outcome as the log-rank test is statistically not significant (p-value=0.4).

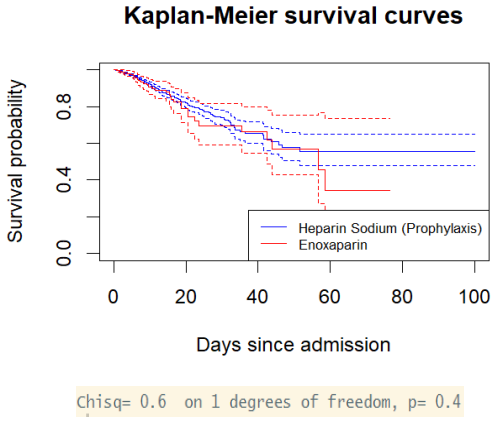

Figure 3. Kaplan-Meier survival curves for in-hospital mortality for propensity matched cohort, log-rank (displayed as chisq) has a p-value of 0.4.

In summary, we found that the use of Heparin for VTE prophylaxis in SICU patients was associated with lower incidence of VTE, and it is statistically significant. On the other hand, in-hospital mortality and risk of major bleeding were similar in these two groups. Compared to the largest head-to-head trial at the moment, our results are partly different from it. In the PROTECT Trial (2011) comparing the use of Dalteparin (as LMWH) and Heparin in critically ill patients, there was a significantly lower number of PE cases in patients taking Dalteparin (an LMWH in the same pharmacological class as Enoxaparin), compared to patients taking Heparin; but no significant difference in term of DVT occurrence was found. However, the same trial observed no significant differences in the occurrence of major bleeding or in-hospital mortality rates between the groups, which is also observed in our findings.

Study limitations

Our study had various limitations. We used average values for weight and laboratory readings throughout each subject's ICU stay, specifically, serum creatinine, weight, and platelet counts. It is possible that these values fluctuate widely during the ICU stay, and these fluctuations are not accounted for when an average is used. We also did not identify and exclude patients who were diagnosed for VTE at admission, as this number is likely to be small for patients admitted into the SICU and MICU/SICU.

The lack of data availability posed a problem in our research. The time of diagnosis was not recorded in

MIMIC-IV, so we were not able to study time to VTE occurrence, which is a suitable outcome to study. In many of the ICD-10 diagnostic names for VTE, DVT and PE were not differentiated within the same name. As such, we were unable to perform a subgroup analysis on outcomes based on either DVT or PE subgroups. We attempted to analyze Heparin-induced thrombocytopenia, a potentially life-threatening but rare known adverse effect of heparin and LMWH use and hence is clinically significant (Ahmed et al., 2007). However, counts in our final cohort were too low for any meaningful data analysis to be conducted. Additionally, given that VTE pharmacological prophylaxis is recommended based on the Caprini score based on the American Society of Hematology 2019 guidelines (Anderson et al., 2019), our study did not explore risk stratification according to Caprini scoring or bleeding risk to the occurrence of VTE due to the lack of data.

For the propensity score matching, the heavily unbalanced dataset makes it difficult to allocate good matches at higher ratios, especially if one group has a much lower distribution of propensity scores. The fitting of the unbalanced dataset onto the logistic regression model is likely to introduce bias in the score estimation as evident from its poor F1-score of 0.48. Propensity score matching is also known to have risk for selection bias. To combat these issues, we could have also explored using other classification models such as Gradient Boosted Trees to predict propensity scores as it is usually used for unbalanced dataset. Also, both Gradient Boosted Trees and Random Forest have been suggested to reduce selection bias more than logistic regression models (Ferri-García & Rueda, 2020) in propensity score matching.

With regards to the N-ratio used to obtain a matched cohort, we chose N=10 for 1:N propensity score matching to maximize the size of the matched cohort. However, based on the propensity score density plot (**Appendix (A) Figure A2**), N=4 might be a better match for data analysis as the distribution between the 2 matched groups are close to perfect.

Other Propensity score matching methods which could have been explored include Inverse Probability Weighting (IPTW) and doubly robust method, which could have helped to inform a more consistent average estimate and precise inference.

The MIMIC-IV dataset was also from one hospital setting, generalizability of the results may be limited as patients in Beth Israel Deaconess Medical Center (BIDMC) may not be representative of the general population. Factors which may vary are 1) medical professionals' experience (given that the hospital is in a world-class teaching hospital of Harvard Medical School), and 2) clinical protocols on VTE prophylaxis.

Conclusion

Evidence-based decision making in the choice of thromboprophylaxis agents in the surgical ICU patients must consider the pool of available studies. Based on our findings from the MIMIC-IV dataset, the use of Heparin is associated with a lower risk of VTE compared to Enoxaparin, but the strength of association may be limited by the data availability in MIMIC-IV. However, in view of the differences in outcomes between our study and other studies, these findings need to be interpreted carefully before considering its applications in clinical practice. Further studies to compare the effectiveness and safety of these two heparin treatments will need to be carried to guide decision-making in VTE thromboprophylaxis in post-surgical patients. Future studies may explore the occurrence of VTE among patients who received different types of surgery, as well as those who received thromboprophylaxis versus those who did not. There is also data availability to examine those with and without thromboprophylaxis to the readmission of Acute VTE given the clinical and economic relevance of having significant burden of nationwide readmissions in view of acute VTE in the United States (Secemsky et al., 2018). This is highly applicable in view of the real-world setting, where thromboprophylaxis is still underutilized despite evidence in existing studies which support the use (Skeik & Westergard, 2020). Future studies may wish to examine medical and medication history such as the history of VTE, or concurrent usage of hormonal therapy which, as well as comparing the different ICU types in MIMIC-IV dataset. Such studies can serve as real world evidence to shape clinical protocols for the use of thromboprophylaxis in critical care.

Appendix A

Table A1: Data extraction for covariates	
Age (years)	Actual age of patients were obtained from the MIMIC-IV derived dataset for age taken from GitHub. (https://github.com/MIT-LCP/mimic-code/tree/main/mimic-iv/concepts)
Gender (%Male)	Obtained from the "gender" column from the patients.csv table.
Body weight (kg)	The average weight of each subject throughout the ICU stay was calculated from the MIMIC-IV derived data set for first-day weight taken from GitHub.
ICU type (SICU%)	Obtained from the "first_careunit" from the icustays.csv table 1. Surgical Intensive Care Unit (SICU) 2. Medical/Surgical Intensive Care Unit (MICU/SICU)
Labs Serum Creatinine (mg/dL) Creatinine Clearance (mL/min) Platelet count (mm^3)	All labs obtained from labevents.csv. Values were averaged throughout each unique subject ID and hospital ID's ICU stay. Creatinine clearance was derived from the Cockcroft-Gault Equation (Botev et al., 2009), using patients' weight, age, and gender.
Life support (%)	
Mechanical ventilation Vasopressors	Data on mechanical ventilation was obtained from the mimiciv_derived dataset for "ventilation", by the following steps. 1. A new column "have_at_least_1_ventil" == 1 who are on mechanical ventilation, otherwise, "have_at_least_1_ventil" == 0 https://github.com/MIT-LCP/mimic-code/tree/main/mimic-iv/concepts Data on vasopressors were obtained by the following steps: 1. Filtering the "medication" column of the emar.csv dataset for the following: ["vasopressin", "norepinephrine", "dopamine", "epinephrine"] 2. Created a new column "if_vasopressin", if the filter is true, if_vasopressin == 1, otherwise if_vasopressin == 0

SOFA scores	Data on SOFA scores for the first day of admission was obtained from the mimiciv_derived dataset for “first_day_sofa”, under the SOFA column https://github.com/MIT-LCP/mimic-code/tree/main/mimic-iv/concepts
Comorbidities	
Charlson Comorbidity Index Cancer (%) Congestive Heart Failure (%) Chronic Pulmonary Disease (%) Diabetes Mellitus (%) Sepsis (%) Severe liver disease (%)	Data on comorbidities was obtained from “charlson” of the mimiciv_derived dataset. New columns were made for each comorbidity.
Use of antithrombotic medications (%)	Obtained from emar.csv “medication” column 1. The “medication” column was filtered for the following list of medications:['Aspirin', 'Clopidogrel', 'Prasugrel', 'Ticagrelor', 'Dipyridamole', 'Eptifibatide', 'Apixaban', 'Rivaroxaban', 'Edoxaban', 'Dabigatran', 'Warfarin'] 2. If “medication” is in the above list of medications, new column “if_antithrombotic == 1”, otherwise “if_antithrombotic == 0”

Table A2: Data extraction for outcomes	
Exposure and Treatment Groups	Obtained from merging d_items.csv and inputevents.csv This was done in 2 steps: 1. Identifying low-molecular weight heparins used in BIDMC A) Identified possible low molecular weight heparins used from inputevents.csv. B) Majority of hits came from "Enoxaparin", none from the other LMWHs. Therefore "Enoxaparin" was selected. 2. Ensuring agents used were for prophylaxis (and not treatment) Heparin and Enoxaparin can be used in either prophylaxis or treatment of VTE. As we are only interested in prophylactic use, A) Labels containing "hepa…" or "enoxa…" were identified B) Based on the results in 1, "Heparin" and "Enoxaparin" were filtered C) Ordercategoryname == "11-Prophylaxis (Non IV)" was filtered

VTE (%)	**Data extraction** Obtained from d_icd_diagnosis.csv with diagnosis_icd.csv 1. ICD names containing “acute”, “thrombosis”, “embolism”, or “thromboembolism”, “gastrointestinal hemorrhage” were first searched. ICD names related to gastrointestinal hemorrhage and pericardial hemorrhage were also manually searched and included. 2. Among these hits, those that contained the word “chronic” were excluded 3. Results obtained were screened manually and those relevant to VTE diagnosis were included. The list of relevant search terms are as follows: ['Nontraumatic intracerebral hemorrhage in brain stem', 'Nontraumatic intracerebral hemorrhage in cerebellum', 'Nontraumatic intracerebral hemorrhage in hemisphere, cortical', 'Nontraumatic intracerebral hemorrhage in hemisphere, subcortical', 'Nontraumatic intracerebral hemorrhage in hemisphere, unspecified', 'Nontraumatic intracerebral hemorrhage, intraventricular', 'Nontraumatic intracerebral hemorrhage, multiple localized', 'Nontraumatic intracerebral hemorrhage, unspecified', 'Other nontraumatic intracerebral hemorrhage', 'Nontraumatic subarachnoid hemorrhage from left anterior communicating artery', 'Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation', 'Nontraumatic subarachnoid hemorrhage from left middle cerebral artery', 'Nontraumatic subarachnoid hemorrhage from left posterior communicating artery', 'Nontraumatic subarachnoid hemorrhage from left vertebral artery', 'Nontraumatic subarachnoid hemorrhage from other intracranial arteries', 'Nontraumatic subarachnoid hemorrhage from right anterior communicating artery', 'Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation', 'Nontraumatic subarachnoid hemorrhage from right middle cerebral artery', 'Nontraumatic subarachnoid hemorrhage from right posterior communicating artery', 'Nontraumatic subarachnoid hemorrhage from right vertebral artery', 'Nontraumatic subarachnoid hemorrhage from unspecified anterior communicating artery', 'Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery', 'Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery', 'Nontraumatic subarachnoid hemorrhage, unspecified', 'Other nontraumatic subarachnoid hemorrhage', 'Gastrointestinal hemorrhage, unspecified', 'Esophageal varices with bleeding', 'Acute duodenal ulcer with hemorrhage', 'Acute peptic ulcer with hemorrhage', 'Acute gastrojejunal ulcer with hemorrhage', 'Acute gastrojejunal ulcer with both hemorrhage and perforation', 'Acute gastric ulcer with hemorrhage, without mention of obstruction', 'Acute gastric ulcer with hemorrhage, with obstruction', 'Acute gastric ulcer with hemorrhage and perforation, without mention of obstruction', 'Acute gastric ulcer with hemorrhage and perforation, with obstruction', 'Acute gastric ulcer with hemorrhage', 'Hemorrhage from respiratory passages', 'Hemorrhage from other sites in respiratory passages', 'Hemorrhage, not elsewhere classified', 'Hemopericardium']

In-hospital mortality rate	**Data extraction** Obtained from admissions.csv **Data analysis** Time-to-event is obtained from the following: 1. If discharge_location == "died", discharge_time - admit_time 2. Otherwise, death_time - admit_time
Major bleeding events (%)	Obtained from d_icd_diagnosis.csv with diagnosis_icd.csv. Gastrointestinal, Intracerebral, and pericardial bleeding were considered in identifying search terms. 1. ICD names containing "intracerebral hemorrhage", "thrombosis", "embolism", or "thromboembolism" were first searched 2. Among these hits, those that contained the word "chronic" were excluded 3. Results obtained were screened manually and those relevant to VTE diagnosis were included

Table A3: Subgroup analysis of primary outcome (risk of VTE) by renal function (measured by creatinine clearance), with propensity matched cohorts

Variables	Heparin	Enoxaparin	Effect size	95% Confidence Interval	p-value
VTE (%)					
No renal impairment (CrCl >=30 mL/min)	316/3,040 (10.4%)	145/307 (47.2%)	0.116	0.091-0.15	<0.001
Renal impairment (CrCl <30 mL/min)	3/70 (4.3%)	0/4 (0%)	-	-	-

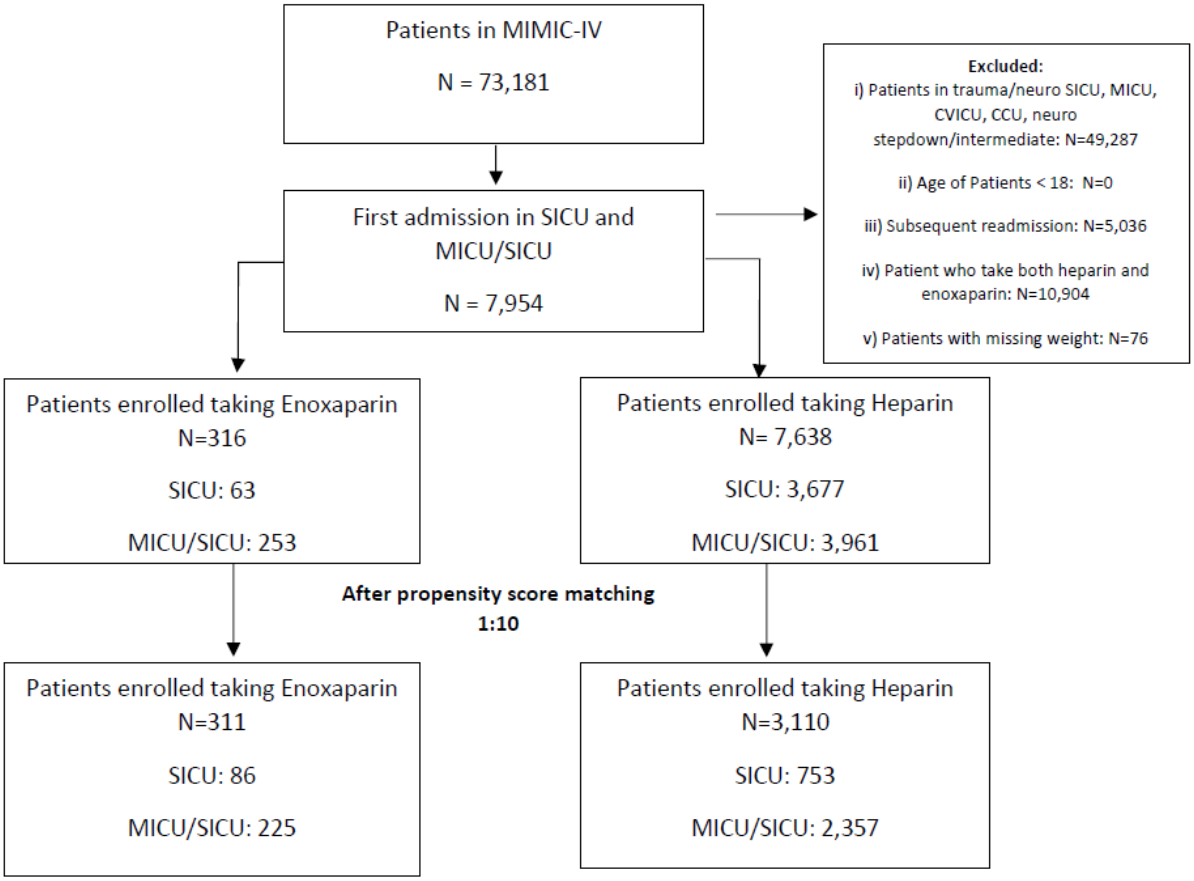

Figure A1: Flow diagram of filtered sample sizes in each treatment arms

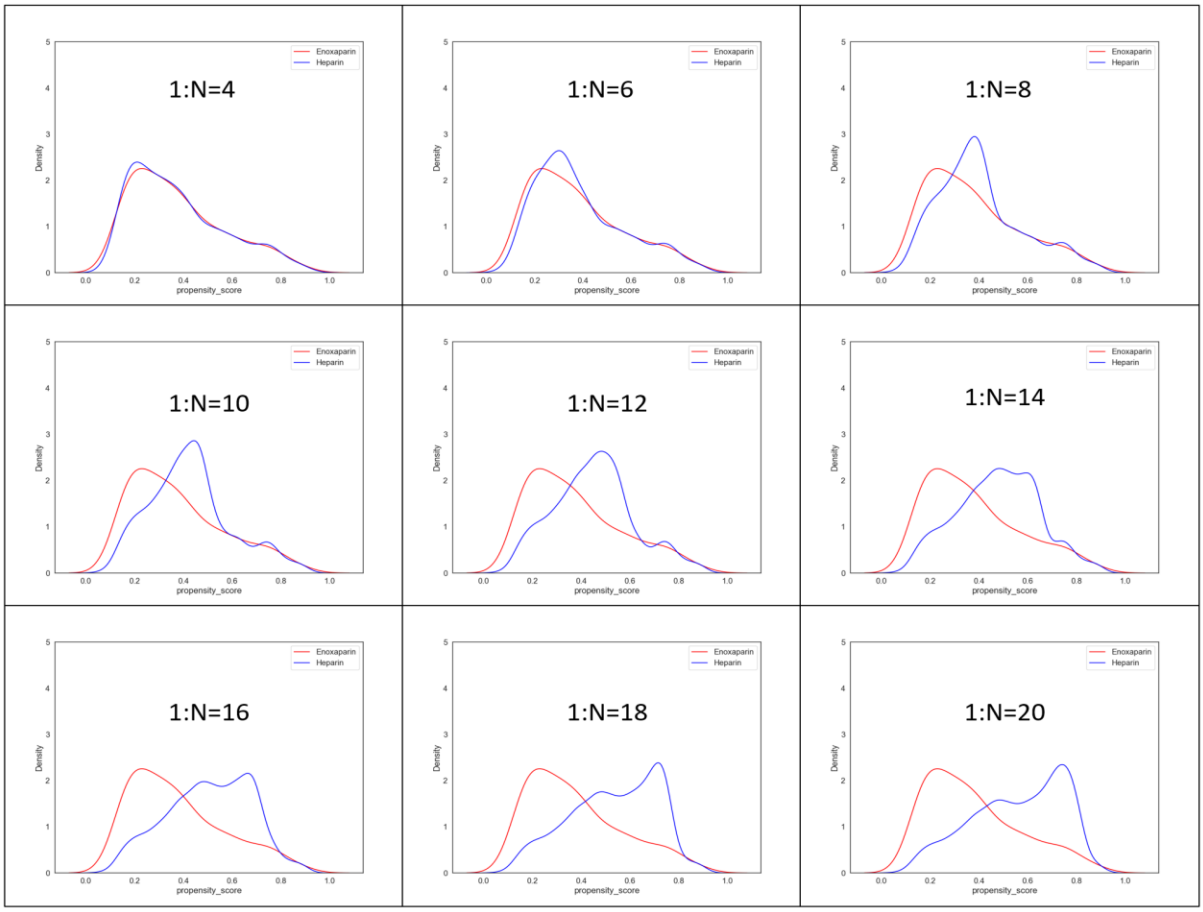

Figure A2: Density plots for Propensity Score Matching with 1:N=4 to N=20

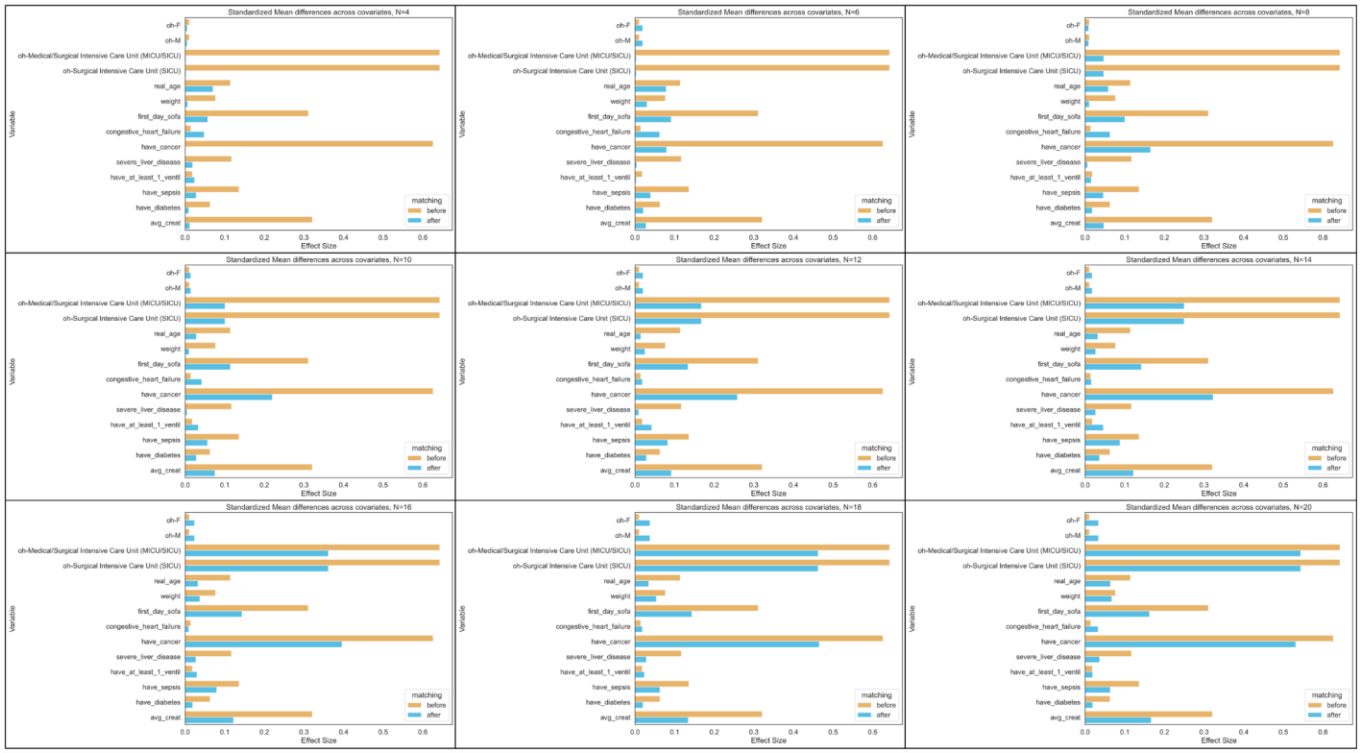

Figure A3: SMD plots for Propensity Score Matching with 1:N=4 to N=20

References

1. Agnelli, G. (2004). Prevention of venous thromboembolism in surgical patients. *Circulation*, *110*(24 Suppl 1), Iv4-12. https://doi.org/10.1161/01.CIR.0000150639.98514.6c
2. Ahmed, I., Majeed, A., & Powell, R. (2007). Heparin induced thrombocytopenia: diagnosis and management update. *Postgrad Med J*, *83*(983), 575-582. https://doi.org/10.1136/pgmj.2007.059188
3. Alhazzani, W., Lim, W., Jaeschke, R. Z., Murad, M. H., Cade, J., & Cook, D. J. (2013). Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med*, *41*(9), 2088-2098. https://doi.org/10.1097/CCM.0b013e31828cf104
4. Ambra, N., Mohammad, O. H., Naushad, V. A., Purayil, N. K., Mohamedali, M. G., Elzouki, A. N., Khalid, M. K., Illahi, M. N., Palol, A., Barman, M., Sharif, M., Chalihadan, S., Punnorath, A., Mostafa, A., Al Hariri, B., Khidir, T. G. M., & Varikkodan, I. (2022). Venous Thromboembolism Among Hospitalized Patients: Incidence and Adequacy of Thromboprophylaxis - A Retrospective Study. *Vasc Health Risk Manag*, *18*, 575-587. https://doi.org/10.2147/vhrm.S370344
5. Anderson, D. R., Morgano, G. P., Bennett, C., Dentali, F., Francis, C. W., Garcia, D. A., Kahn, S. R., Rahman, M., Rajasekhar, A., Rogers, F. B., Smythe, M. A., Tikkinen, K. A. O., Yates, A. J., Baldeh, T., Balduzzi, S., Brożek, J. L., Ikobaltzeta, I. E., Johal, H., Neumann, I., . . . Dahm, P. (2019). American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Advances*, *3*(23), 3898-3944. https://doi.org/10.1182/bloodadvances.2019000975
6. Andrade, C. (2020). Mean Difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis: As Simple as It Gets. *J Clin Psychiatry*, *81*(5). https://doi.org/10.4088/JCP.20f13681
7. Beitland, S., Sandven, I., Kjærvik, L. K., Sandset, P. M., Sunde, K., & Eken, T. (2015). Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*, *41*(7), 1209-1219. https://doi.org/10.1007/s00134-015-3840-z
8. Bennett, A. M., Ulrich, H., van Damme, P., Wiedekopf, J., & Johnson, A. E. W. (2023). MIMIC-IV on FHIR: converting a decade of in-patient data into an exchangeable, interoperable format. *Journal of the American Medical Informatics Association*, *30*(4), 718-725. https://doi.org/10.1093/jamia/ocad002
9. Botev, R., Mallié, J. P., Couchoud, C., Schück, O., Fauvel, J. P., Wetzels, J. F., Lee, N., De Santo, N. G., & Cirillo, M. (2009). Estimating glomerular filtration rate: Cockcroft-Gault and Modification of Diet in Renal Disease formulas compared to renal inulin clearance. *Clin J Am Soc Nephrol*, *4*(5), 899-906. https://doi.org/10.2215/cjn.05371008
10. Bounameaux, H. (1998). Unfractionated versus low-molecular-weight heparin in the treatment of venous thromboembolism. *Vasc Med*, *3*(1), 41-46. https://doi.org/10.1177/1358836x9800300109
11. Cook, D., Meade, M., Guyatt, G., Walter, S., Heels-Ansdell, D., Warkentin, T. E., Zytaruk, N., Crowther, M., Geerts, W., Cooper, D. J., Vallance, S., Qushmaq, I., Rocha, M., Berwanger, O., & Vlahakis, N. E. (2011). Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*, *364*(14), 1305-1314. https://doi.org/10.1056/NEJMoa1014475
12. Drugbank. (2023). *Heparin*. Retrieved 18 April 2023 from https://go.drugbank.com/drugs/DB01109
13. Ejaz, A., Ahmed, M. M., Tasleem, A., Rafay Khan Niazi, M., Ahsraf, M. F., Ahmad, I., Zakir, A., & Raza, A. (2018). Thromboprophylaxis in Intensive Care Unit Patients: A Literature Review. *Cureus*, *10*(9), e3341. https://doi.org/10.7759/cureus.3341
14. Fernando, S. M., Tran, A., Cheng, W., Sadeghirad, B., Arabi, Y. M., Cook, D. J., Møller, M. H., Mehta, S., Fowler, R. A., Burns, K. E. A., Wells, P. S., Carrier, M., Crowther, M. A., Scales, D. C., English, S. W., Kyeremanteng, K., Kanji, S., Kho, M. E., & Rochwerg, B. (2022). VTE Prophylaxis in Critically Ill Adults: A Systematic Review and Network Meta-analysis. *Chest*, *161*(2), 418-428. https://doi.org/https://doi.org/10.1016/j.chest.2021.08.050
15. Ferri-García, R., & Rueda, M. D. M. (2020). Propensity score adjustment using machine learning classification algorithms to control selection bias in online surveys. *PLoS One*, *15*(4), e0231500. https://doi.org/10.1371/journal.pone.0231500
16. Flores, B., Trivedi, H. D., Robson, S. C., & Bonder, A. (2017). Hemostasis, bleeding and thrombosis in liver disease. *J Transl Sci*, *3*(3). https://doi.org/10.15761/jts.1000182
17. Gaitanidis, A., Breen, K. A., Christensen, M. A., Saillant, N. N., Kaafarani, H. M. A., Velmahos, G. C., & Mendoza, A. E. (2021). Low-Molecular Weight Heparin is Superior to Unfractionated Heparin for Elderly

Trauma Patients. *Journal of Surgical Research*, *268*, 432-439. https://doi.org/https://doi.org/10.1016/j.jss.2021.06.074
18. Gurjar, M. (2014). Heparin thromboprophylaxis in critically ill patients: Is it really changing outcome? *Indian J Crit Care Med*, *18*(6), 345-347. https://doi.org/10.4103/0972-5229.133867
19. Hassan, A., Jack, C., Lixin, O., Stephanie, J. H., Kenneth, H., & Arthas, F. (2014). Rate of venous thromboembolism among surgical patients in Australian hospitals: a multicentre retrospective cohort study. *BMJ Open*, *4*(10), e005502. https://doi.org/10.1136/bmjopen-2014-005502
20. Iqbal., A. J. A. M. (2022). Enoxaparin. In *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing.
21. Kearon, C., Akl, E. A., Comerota, A. J., Prandoni, P., Bounameaux, H., Goldhaber, S. Z., Nelson, M. E., Wells, P. S., Gould, M. K., Dentali, F., Crowther, M., & Kahn, S. R. (2012). Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, *141*(2 Suppl), e419S-e496S. https://doi.org/10.1378/chest.11-2301
22. Lamberts, M., Staerk, L., Olesen, J. B., Fosbøl, E. L., Hansen, M. L., Harboe, L., Lefevre, C., Evans, D., & Gislason, G. H. (2017). Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients. *J Am Heart Assoc*, *6*(2). https://doi.org/10.1161/jaha.116.004517
23. Meizlish, M. L., Goshua, G., Liu, Y., Fine, R., Amin, K., Chang, E., DeFilippo, N., Keating, C., Liu, Y., Mankbadi, M., McManus, D., Wang, S. Y., Price, C., Bona, R. D., Ochoa Chaar, C. I., Chun, H. J., Pine, A. B., Rinder, H. M., Siner, J. M., . . . Lee, A. I. (2021). Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis. *Am J Hematol*, *96*(4), 471-479. https://doi.org/10.1002/ajh.26102
24. O'Donnell, M., & Weitz, J. I. (2003). Thromboprophylaxis in surgical patients. *Can J Surg*, *46*(2), 129-135.
25. Samuel, S., To, C., Ling, Y., Zhang, K., Jiang, X., & Bernstam, E. V. (2023). Enoxaparin may be associated with lower rates of mortality than unfractionated heparin in neurocritical and surgical patients. *Journal of Thrombosis and Thrombolysis*. https://doi.org/10.1007/s11239-022-02755-w
26. Secemsky, E. A., Rosenfield, K., Kennedy, K. F., Jaff, M., & Yeh, R. W. (2018). High Burden of 30-Day Readmissions After Acute Venous Thromboembolism in the United States. *J Am Heart Assoc*, *7*(13). https://doi.org/10.1161/jaha.118.009047
27. Skeik, N., & Westergard, E. (2020). Recommendations for VTE Prophylaxis in Medically Ill Patients. *Ann Vasc Dis*, *13*(1), 38-44. https://doi.org/10.3400/avd.ra.19-00115
28. Zhang, X. D. (2010). Strictly Standardized Mean Difference, Standardized Mean Difference and Classical t-test for the Comparison of Two Groups. *Statistics in Biopharmaceutical Research*, *2*(2), 292-299. https://doi.org/10.1198/sbr.2009.0074
29. Zou, Z. Y., Huang, J. J., Luan, Y. Y., Yang, Z. J., Zhou, Z. P., Zhang, J. J., Yao, Y. M., & Wu, M. (2022). Early prophylactic anticoagulation with heparin alleviates mortality in critically ill patients with sepsis: a retrospective analysis from the MIMIC-IV database. *Burns Trauma*, *10*, tkac029. https://doi.org/10.1093/burnst/tkac029