Original Article

Venous thromboembolism risk factors and prophylaxis of elderly intensive care unit patients in a Chinese general hospital

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Background: To analyze the venous thromboembolism (VTE) risk factors and prophylaxis of elderly patients in the intensive care unit (ICU).

Methods: We retrospectively recruited 200 elderly patients with VTE and 234 non-VTE patients. VTE risk factors were got from data of all patients. The sensitivity and specificity of the Caprini scores and Padua scores were calculated. We use the receiver operating characteristic (ROC) curve and the area under the curve (AUC) to evaluate each score.

Results: We found that male sex, sepsis, being bedridden (>72 hours), pneumonia, history of deep vein thrombosis (DVT), diabetes mellitus, coronary heart disease, heart failure, glucocorticoid treatment, PaO_2, hemoglobin (Hb), prothrombin time (PT), and international normalized ratio (INR), D-dimer (D-D), mechanical ventilation, and continuous renal replacement therapy (CRRT) were significantly associated with VTE in elderly ICU patients ($P<0.05$). For elderly patients in the ICU, the predictive ability of Caprini risk assessment model was better than that of the Padua risk assessment model. Among the high VTE risk elderly patients, the number of patients receiving mechanical prophylaxis in the high bleeding-risk group was higher than that in the low bleeding-risk group ($P<0.0001$).

Conclusions: Elderly patients in the ICU have the highest risk of VTE and high bleeding risk; decisions concerning clinical prophylaxis should be made after appropriate information on the risk and benefit on an individual level is considered.

Keywords: Venous thromboembolism (VTE); risk factors; prophylaxis; elderly intensive care unit (ICU); Chinese general hospital

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Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PE). The prevalence of VTE in medical inpatients is 12%, the peak of VTE incidence is 65–75 years old, and the elderly are usually the patients at highest risk of VTE (1). VTE causes more than 100,000 deaths every year, with more than half of deaths occurring during hospitalization, especially in elderly patients. Approximately 18% to 65% of VTE-associated mortality has been reported as being preventable (2). Multimorbidity, which is defined as the co-occurrence of 2 or more chronic comorbidities is the common characteristic in the majority of elderly patients. We present the following article in accordance with the STARD reporting checklist

(available at http://dx.doi.org/10.21037/apm-21-464).

Methods

Patients

We conducted a retrospective case-control study in which the data from 200 patients with VTE and 234 non-VTE patients were consecutively collected from January, 2019 to December 31, 2019 from the intensive care unit (ICU) in Beijing Shijitan Hospital. In the VTE group, the inclusion criteria were the following: ≥65 years, ≥2 days in the ICU, DVT diagnosed by lower extremity venous duplex compression ultrasonography and PE diagnosed by computed tomography (CT) angiography of the pulmonary artery or ventilation-perfusion imaging. The exclusion criteria were as follows: <65 years, DVT and PE diagnosed before admittance to the ICU or <2 days in ICU, and superficial vein thrombosis. This study was approved by the Medical ethics committee of Beijing Shijitan Hospital Affiliated to Capital Medical University (No. 2020-2). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Study methods

The clinical data, laboratory examination results, and treatment of the patients in the VTE group and non-VTE group admitted to the ICU in 2019 were obtained through the hospital's medical record system. The Caprini risk assessment model (RAM) and the Padua RAM were used for the 2 groups. The Caprini RAM includes 41 risk factors, with each factor being scored between 1 and 5 points and being classified into one of the following categories: low risk [0–1], moderate risk [2], high risk [3–4], or highest risk [≥5]. The Padua RAM includes 11 risk factors, with each factor being scored between 1 and 5 points and being classified into one of the following categories: low risk (<4) or high risk (≥4). Two trained investigators were responsible for collecting data.

Statistical analysis

All data were analyzed by SPSS version 25 (IBM Corp., Armonk, NY, USA), and the count data are expressed as a percentage. χ^2 test and Fisher's exact probability test were used for comparison between groups. The measurement data are expressed as $\overline{X} \pm S$. If the distribution of data was normal, a parametric model was used to calculate the P value and confidence interval. For a nonnormal distribution of data, a nonparametric rank-sum test was used calculate the P value and confidence interval. We used logistic regression to analyze the risk factors in the VTE group. We drew receiver operating characteristic (ROC) curves and calculated the sensitivity, specificity and the value of the area under the curve (AUC).

Results

Comparison of clinical characteristics between VTE and non VTE elderly ICU patients

The number of male patients in the VTE group was 152 (76%), which was greater than that in the 128 (54.7%) in the non-VTE group (P<0.05). We found that in the VTE group, the proportion of patients suffering from sepsis (<1 month), bed rest (>72 hours), history of DVT were higher than that in the non-VTE group (P<0.05). However, the number of patients receiving glucocorticoid treatment in the non-VTE group was more than that in the VTE group (P<0.05). In terms of laboratory examination, levels of PaO_2, hemoglobin (Hb), prothrombin time (PT), and international normalized ratio (INR) in the VTE group were lower than those in the non-VTE group (P<0.05); however, D-dimer (D-D), creatinine (Cr), APACHE II (Acute Physiology And Chronic Health Evaluation II), mechanical ventilation, hemofiltration, nutritional risk score, Caprini score, and Padua score in the VTE group were much higher than those in the non-VTE group (P<0.05). The number of elderly patients receiving mechanical prevention and anticoagulation therapy in the non-VTE group was greater than that in the VTE group (P<0.05; *Table 1*).

Risk factors of VTE in elderly ICU patients

Before the logistic regression analysis, the data were standardized. The results showed that male sex, sepsis, being bedridden (>72 hours), history of DVT, glucocorticoid treatment, PaO_2, Hb, PT, INR, D-D, mechanical ventilation, and continuous renal replacement therapy (CRRT), were significantly associated with VTE in

Table 1 Characteristics of elderly ICU patients in the ICU in the VTE and non-VTE groups

Characteristic	VTE (n=200)	Non-VTE (n=234)	P value
Age (years)	80.42±7.68	79.9±7.93	0.4915
Male, n (%)	152 (76.00)	128 (54.70)	<0.0001
Acute myocardial infarction (<1 month), n (%)	26 (13.07)	17 (7.26)	0.0529
Sepsis (<1 month), n (%)	114 (57.29)	85 (36.32)	<0.0001
Bed rest (>72 h), n (%)	170 (85.43)	134 (57.26)	<0.0001
History of DVT, n (%)	77 (38.50)	54 (23.01)	0.0004
History of PE, n (%)	6 (3.00)	12 (5.13)	0.3373
Stroke (<1 month), n (%)	10 (5.00)	11 (4.70)	1.0000
Chemotherapy, n (%)	19 (9.50)	27 (11.54)	0.5341
Central venous access, n (%)	98 (49.00)	114 (48.72)	1.0000
Glucocorticoid therapy, n (%)	10 (5.00)	42 (17.95)	<0.0001
Major surgery (<1 month), n (%)	9 (4.50)	19 (8.12)	0.1695
Varicose veins, n (%)	2 (1.00)	8 (3.42)	0.1161
Swollen legs, n (%)	53 (26.50)	77 (32.91)	0.1717
PaO_2 (mmHg)	78.35 [63, 114]	94 [61, 140]	0.0109
lactic acid (mmol/L)	1.69±1.07	1.67±1.13	0.0908
WBC ($\times10^9$/L)	8.74 [6.26, 12.04]	8.26 [6.18, 11.46]	0.5401
Percentage of neutrophils (%)	79.9 [70.5, 85.8]	79.45 [67.7, 87.7]	0.9871
Hb (g/L)	87 [76,1 14.5]	106 [86, 122]	<0.0001
PLT ($\times10^9$/L)	206 [132.5, 285]	200.5 [139, 285]	0.8601
APTT (s)	30.25 [27.5, 33.7]	30.6 [28.1, 33.3]	0.7379
PT (s)	12.94±1.68	13.59±3.23	0.0108
INR	1.19±0.15	1.25±0.3	0.0084
D-D (mg/L)	800 [371, 1,960.5]	620 [366, 1,175]	0.0438
Cr (mmol/L)	98 [66, 131]	82 [60, 118]	0.0479
CRP (mg/L)	51.33 [11.75, 104.77]	46.19 [12.14, 110.76]	0.7674
PCT (ng/mL)	0.2 [0.08, 0.90]	0.18 [0.08, 0.98]	0.9027
APACHE II	17.3±3.36	16.75±3.41	0.0174
Mechanical ventilation, n (%)	134 (67.00)	105 (44.87)	<0.0001
CRRT, n (%)	31(15.50)	21(8.97)	0.0390
Nutrition score ≥3, n (%)	199 (99.50)	232 (99.13)	0.0093
Caprini score	9 [6, 12]	7 [5, 10]	<0.0001
Padua score	6 [5, 8]	5 [4, 8]	0.0073
High bleeding risk, n (%)	113 (56.50)	136 (58.12)	0.7705
Mechanical prophylaxis, n (%)	46 (23.00)	120 (51.28)	<0.0001
Anticoagulation, n (%)	61 (30.50)	143 (61.11)	<0.0001
Bleeding after anticoagulation, n (%)	8 (13.79)	20 (14.18)	1.0000
Prognosis (recovery), n (%)	149 (74.50)	175 (74.79)	1.0000

ICU, intensive care unit; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary thromboembolism; WBC, leukocyte; Hb, hemoglobin; PLT, blood platelet; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; D-D, D-dimer; Cr, creatinine; CRP, C-reactive protein; PCT, procalcitonin; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy.

Table 2 VTE risk factors of elderly patients in the ICU

Characteristic	OR	CI (2.5%)	CI (97.5%)	P value
Male (%)	2.61	1.72	3.96	<0.001
Sepsis (<1 month) (%)	2.87	1.90	4.34	<0.001
Bed rest (>72 h) (%)	5.36	3.25	8.85	<0.001
History of DVT (%)	0.47	0.30	0.73	0.001
Glucocorticoid therapy (%)	0.23	0.11	0.47	<0.001
PaO_2 (mmHg)	0.99	0.99	1.00	<0.001
Hb (g/L)	1.02	1.01	1.03	<0.001
PT (s)	1.13	1.03	1.25	0.013
INR	3.97	1.40	11.27	0.010
D-D (mg/L)	1.00	1.00	1.00	0.031
Cr (mmol/L)	1.00	1.00	1.00	0.473
APACHE II	0.94	0.89	1.00	0.055
Mechanical ventilation (%)	2.37	1.59	3.54	<0.001
CRRT (%)	2.09	1.13	3.86	<0.001
Nutrition score ≥3 (%)	0.52	0.04	6.04	0.599

VTE, venous thromboembolism; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; DVT, deep-vein thrombosis; Hb, hemoglobin; PT, prothrombin time; INR, international normalized ratio; D-D, D-dimer; Cr, creatinine; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy.

Table 3 Comparison of elderly ICU patients in the ICU in the VTE and non-VTE groups with different disease

Disease	VTE (n=200)	Non-VTE (n=234)	P value
Currently pneumonia, n (%)	172 (86.87)	181 (77.35)	0.0124
COPD, n (%)	28 (14.07)	37 (15.81)	0.6860
Hypertension, n (%)	124 (62.31)	152 (64.96)	0.6163
Cancer, n (%)	65 (32.66)	54 (23.08)	0.0307
Diabetes, n (%)	128 (64.00)	107 (45.73)	0.0002
Coronary heart disease, n (%)	174 (87.00)	164 (70.09)	<0.0001
Cardiac failure, n (%)	156 (78.00)	147 (62.82)	0.0008

VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease;

elderly ICU patients (P<0.05; *Table 2*).

Comparison between VTE and non VTE elderly ICU patients with different disease

We found in the VTE group, pneumonia, and incidence of tumor was higher than that in the non-VTE group (P<0.05). The number of patients in the VTE group with diabetes mellitus, coronary heart disease, and heart failure was greater than that in the non-VTE group (P<0.05; *Table 3*). We documented that pneumonia, diabetes mellitus, coronary heart disease, heart failure were significantly associated with

Table 4 VTE risk factors of elderly patients with different disease in the ICU

Disease	OR	CI (2.5%)	CI (97.5%)	P value
Currently pneumonia (%)	1.77	1.05	3.01	0.033
Cancer (%)	1.45	0.94	2.24	0.095
Diabetes (%)	2.37	1.59	3.56	<0.001
Coronary heart disease (%)	3.08	1.84	5.15	<0.001
Cardiac failure (%)	2.15	1.38	3.37	0.001

OR, odds ratio; CI, confidence interval.

Table 5 The comparison between Caprini and Padua RAMs in elderly ICU patients

Measure	Caprini	Padua	P value
Sensitivity	0.687	0.350	<0.0001
Specificity	0.540	0.815	<0.0001
AUC	0.6303	0.5719	0.0495

RAM, risk assessment model; ICU, intensive care unit; AUC, area under the curve.

VTE in elderly ICU patients (P<0.05; *Table 4*).

Comparing the Padua and Caprini RAMs in elderly ICU patients

The sensitivity of the Caprini RAM (0.687) was higher than that of the Padua RAM (0.35) (P<0.0001), but compared with the Caprini RAM (0.54), the specificity of the Padua RAM (0.815) was significantly higher (P<0.0001) (*Table 5*). The AUC value of Caprini RAM was significantly greater than that of the Padua RAM (0.6303 *vs.* 0.5719, P<0.05). For elderly ICU patients, the Caprini RAM has a higher sensitivity but a lower specificity than the Padua RAM. Overall, the predictive ability of the Caprini RAM was better than that of the Padua RAM (*Figure 1*).

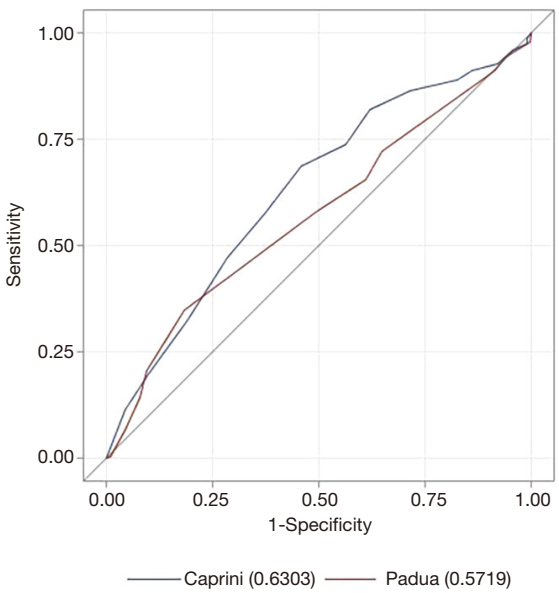

Figure 1 The performance of the Caprini and Padua RAMs in elderly ICU patients. RAM, risk assessment model; ICU, intensive care unit.

Comparing prophylaxis in high VTE risk patients with bleeding risk among elderly ICU patients

Among the elderly high VTE risk patients, mechanical prophylaxis alone was much more common in high bleeding-risk patients than in low bleeding-risk patients (27.35% *vs.* 13.14%, P<0.0001). Another 2 prophylaxis types, including anticoagulation prophylaxis alone and mechanical + anticoagulation, showed no significant difference between the different bleeding risks (P>0.05; *Table 6*).

Discussion

Many large multicenter studies exclude elderly patients due to the multiple diseases present in many elderly patients. At present, there are few studies on VTE in elderly patients, especially in elderly ICU patients. Engbers *et al.* found the annual incidence of VTE in elderly patients to be nearly 8,000, which is 8 times higher than that in patients under 50 years old (3). It is well known that elderly patients often have multiple diseases. Pleuritic chest pain, hemoptysis, tachycardia, swollen extremities, and difficulty walking, which are typical signs and symptoms of VTE, are more

Table 6 Prophylaxis types and bleeding risk in elderly ICU patients with high VTE risk

Bleeding risk	Mechanical prophylaxis alone, n (%)	Anticoagulation prophylaxis alone, n (%)	Mechanical + anticoagulation, n (%)
High bleeding risk (n=245)	67 (27.35)	33 (13.47)	20 (8.16)
Low bleeding risk (n=175)	23 (13.14)	22 (12.57)	22 (12.57)
χ^2	12.233	0.072	2.204
P value	<0.0001	0.454	0.094

ICU, intensive care unit; VTE, venous thromboembolism.

prevalent in elderly patients than in younger patients. A few researchers have reported that the prevalence of asymptomatic DVT is 17.8% among patients over 80 years old, and for ICU patients the prevalence of DVT is as high as 33% (4-6). A large prospective multicenter Chinese trial confirmed that the prevalence of VTE during ICU stay was about 7.3% (7). Alessandro summarized some studies of COVID-19 and VTE, found that the incidence of VTE was about 30% in hospitalized COVID-19 patients, the incidence of DVT alone and PE alone was about 20% and 18% respectively (8). Huang *et al.* reported the incidence of VTE sharply increased among those older than 75 years old (9). Zhang *et al.* confirmed that the incidence of VTE within 7 days of ICU admission was as high as 4.45% (10).

Our study found that the proportion of male patients in the VTE group was much higher than that in the non-VTE group, while sepsis, being bedridden (>72 hours), pneumonia, and presence of tumor were also significantly higher; with sepsis, being bedridden (>72 hours), and pneumonia were associated with VTE. Hypercoagulability and blood stasis are the basis of thrombosis (11). Blood clot occurs frequently due to increased coagulation factor activity in elderly patients (12). Furthermore, interleukin 6 (IL-6) cytokine is secreted by monocyte macrophages and T lymphocytes after infection. The high concentration of IL-6 can damage vascular endothelial cells, promote immune adhesion and micro thrombosis, inhibit endothelial repair, and damage blood vessels (13). In the addition, a large number of other inflammatory cell infiltrates release inflammatory factors and inflammatory mediators, resulting in systemic inflammatory response syndrome, leading to lung tissue damage, which can initiate endogenous coagulation and form microthrombosis in the blood circulation (14). Kaplan *et al.* demonstrated that the incidence of VTE in patients with sepsis is higher than in those without sepsis; it has also been found that the deposition of platelet-fibrin thrombi and the development of disseminated intravascular coagulation are dysregulated in these patients (15).

In the VTE group, there were more patients with a history of DVT, diabetes, coronary heart disease, and heart failure, which were significantly correlated with the incidence of VTE in elderly ICU patients. Wang *et al.* showed that the proportion of hypertension, active malignant tumor/chemotherapy, diabetes, coronary heart disease, heart and/or respiratory failure, acute myocardial infarction, and/or ischemic stroke to be significantly increased in elderly patients with VTE in the ICU (16). Our study was consistent with the above findings. In terms of laboratory examination, PaO_2, Hb, PT, and INR in the VTE group were lower than those in the non-VTE group ($P<0.05$), while PaO_2, Hb, PT, and INR were significantly correlated with the occurrence of VTE. Wang *et al.* reported that PaO_2 level is an important factor affecting the occurrence of VTE in elderly acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients (17). D-D, Cr, APACHE-II, mechanical ventilation, hemofiltration, nutritional risk score, Caprini score, and Padua score were significantly higher in the VTE group than in the non-VTE group. D-D, mechanical ventilation, and CRRT were important risk factors for VTE in elderly ICU patients. Fu *et al.* found D-D to be an independent factor of VTE in ICU patients. Laboratory examinations and Caprini risk assessment scale can increase the predictive ability of VTE in ICU patients (18). However, the specificity of D-D is poor, and it increases in the cases of tumor, infection, and trauma. Multiple diseases coexist in elderly patients. For physicians, it is necessary to dynamically observe the level of D-D. Liu *et al.* found that D-D was significantly associated with VTE in elderly AECOPD patients (19). Li *et al.* confirmed that, with the increase of APACHE II score, the mortality rate gradually increases: when the score is ≥25, the mortality rate increases significantly; when the score is ≥35, the mortality rate increases to 100%. The actual mortality rate is significantly

and positively correlated with APACHE II score (20). Studies by An *et al.* evaluated the APACHE II score of a death group 24 hours after admission and found that their score was higher than that of the survival group. It has also been found that the higher the Nutrition Risk Screening 2002 (NRS-2002) value is, the worse the prognosis (21). Another retrospective study by Adimi Naghan *et al.* demonstrated that if the APACHE II score is greater than 17.6, most cases develop VTE in the first 2 weeks of ICU stay (22). Development of acute respiratory distress syndrome (ARDS) and higher positive end-expiratory pressure (PEEP) were associated with an increased risk for development of VTE (23). Prabhakaran *et al.* demonstrated that increased ventilator days were also associated with higher risk of developing VTE (24).

In our study, the number of elderly patients receiving mechanical prophylaxis and anticoagulation therapy in the non-VTE group was significantly higher than that in the VTE group. The 9th edition of US guidelines on the prevention of venous thrombosis pointed out that prevention of VTE should be given to elderly patients at high risk of VTE (25). High risk factors such as age, bedridden, coexistence of multiple diseases and central venous catheterization lead elderly ICU patients to be high or highest-risk group of VTE. If there is no contraindication, low dose unfractionated heparin (LDUH) (5,000 u subcutaneous injection, twice a day) or low molecular weight heparin (LMWH) (such as enoxaparin 40 mg subcutaneous injection, once a day; dalteparin 5,000 u subcutaneous injection, once a day) should be recommended for high-risk patients in ICU to prevent the occurrence of VTE. And mechanical prophylaxis should be combined with chemoprophylaxis. For patients with high risk of bleeding, graduated compression stockings (GCS) and (or) intermittent pneumatic compression (IPC) were used to prevent thrombosis until the risk of bleeding was reduced, and then chemoprophylaxis should be prescribed or both were used in combination. ICU patients should be evaluated dynamically according to the development of the disease (26). García-Olivares and other researchers discovered that establishing a prophylaxis protocol in the ICU can reduce the incidence of VTE from 11.9% to 4.5% (27,28). In regard to mechanical prophylaxis, Vignon *et al.* showed that, compared with those receiving GCS alone, there was no difference in the incidence of VTE in those who received IPC together with GCS (29). For nursing strategy in the our intensive care unit, the patients without consciousness will be given GCS and IPC, the patients with consciousness will be given health education of VTE besides the above mechanical prophylaxis.

There is no specific VTE risk assessment model for elderly patients in ICU. We used the Caprini RAM and Padua RAM which were used commonly in clinic. And found that the sensitivity of the Caprini RAM was higher than that of the Padua RAM in elderly ICU inpatients, and that the Caprini RAM was a good predictor of VTE risk in elderly ICU patients. Our previous research discovered similar conclusions across different departments. We compared the sensitivity and specificity of the 2 scales in VTE risk patients between different departments (internal *vs.* surgical, oncological *vs.* nononcological) in a general hospital. We found that the Caprini RAM had a higher sensitivity but a lower specificity than the Padua RAM and had better VTE predictive ability among hospitalized Chinese patients (30).

Most of the elderly ICU patients are at high-risk of VTE. Furthermore, due to the coexistence of multiple diseases in elderly patients, the interaction between drugs and the decline of liver and kidney function, the risk of bleeding is significantly increased. Parikh *et al.* found that only 20.2% of medical ICU patients received VTE prophylaxis which were recommended by American College of Chest Physicians (ACCP) (31). In this study, we found that mechanical prophylaxis was the main prophylaxis method for high bleeding-risk patients, which was consistent with the recommendations of the Caprini RAM (32). Arabi *et al.* found that only using IPC was associated with a significantly decreased incidence of VTE. The ACCP recommend that IPC can be used for patients with contraindication to drug thromboprophylaxis (33). In addition, our study found no significant difference between the VTE group and non-VTE group in bleeding after anticoagulation. Another trial suggested that patients older than 75 years who were treated with novel oral anticoagulants (NOACs) had a greater reduction in the risk of major bleeding than those treated with vitamin K antagonists (VKAs) (34). In the recent multiple centers research including 41 tertiary hospitals in China, Zhou found that 85.4% ICUs completed VTE risk assessment within 24 hours after admission. 71.4% ICUs used the Caprini score to assess VTE risk. 97.6% of ICUs used IPC as mechanical prophylaxis. LMWH was the initial chemoprophylaxis in ICUs (35).

Our study had a few limitations which should be mentioned. First, the discharged patients were not followed up, we will follow-up the discharged patients in our further research to evaluate the prognosis of the elderly

ICU patients. Second, because there was no similar study in the past, we used retrospective study to explore. In the future, large cohort study will be needed to verify. VTE is a preventable death related to hospitalization, and it is also one of the main causes of medical complications. With the aging global population, elderly patients are becoming a high-risk VTE group due to their age, fragility, frequent bed rest, presence of other diseases, etc., and the elderly ICU patients are the key population for VTE prevention and control. However, balancing the benefit and risk of treatment requires us to dynamically assess the risk of VTE and bleeding in elderly patients. In the next phase of our research, we plan to conduct a prospective study on the individualized comprehensive management of VTE in elderly ICU patients. Combined with biomarkers, imaging, VTE risk assessment scale, and bleeding risk assessment scale, a precise treatment plan for elderly ICU patients can be formulated.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-464). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Medical ethics committee of Beijing Shijitan Hospital Affiliated to Capital Medical University (No. 2020-2). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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