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A retrospective cohort study of disease-related risk factors for central venous catheter-related symptomatic thrombosis in intensive care unit inpatients

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Abstract

Central venous catheters (CVC) are widely used in critically ill patients given their benefits in monitoring vital signs, treatment administration, and renal replacement therapy in intensive care unit (ICU) patients, but these catheters have the potential to induce symptomatic catheter-related venous thrombosis (CRVT). This study reported the rate of symptomatic CRVT in ICU patients receiving CVC and analyzed the disease-related risk factors for symptomatic CRVT in ICU patients.

A retrospective analysis was performed on the consecutive ICU 1643 critically ill patients with CVCs inserted from January 2015 to December 2019. Symptomatic CRVT was confirmed by ultrasound. CVCs were divided into 2 groups based on the presence of symptomatic CRVT, and the variables were extracted from the electronic medical record system. Logistic univariate and multivariate regression analyses were used to determine the disease-related risk factors of symptomatic CRVT.

A total of 209 symptomatic CRVT events occurred among 2114 catheters. The rate of CRVT was 9.5 per 1000 catheter days. Univariate analysis revealed that trauma, major surgery, heart failure, respiratory failure, and severe acute pancreatitis were risk factors for symptomatic CRVT in the ICU. Multivariate analysis showed that trauma (odds ratio [OR], 2.046; 95% confidence interval [CI] [1.325–3.160], $P = .001$), major surgery (OR, 2.457; 95% CI [1.641–3.679], $P = .000$), and heart failure (OR, 2.087; 95% CI [1.401–3.111], $P = .000$) were independent disease-related risk factors for symptomatic CRVT in ICU. The C-statistic for this model was 0.61 (95% CI [0.57–0.65], $P = .000$).

The incidence rate of symptomatic CRVT in the ICU population was 9.5 per 1000 catheter days. Trauma, major surgery, and heart failure are independent disease-related risk factors of symptomatic CRVT.

Abbreviations: APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, CI = confidence interval, CRVT = catheter-related venous thrombosis, CVC = central venous catheter, ICU = intensive care unit, OR = odds ratio, VTE = venous thromboembolism.

Keywords: catheter-related venous thrombosis, critically ill, symptomatic, venous thromboembolism

1. Introduction

Hospital-acquired venous thromboembolism (VTE) has received increasing attention in medical institutions due to its increased morbidity and mortality among hospitalized patients.[1–4] A number of studies have identified several important risk factors for hospital-acquired thrombosis, of which central venous catheter (CVC) is an important risk factor.[5–7] Symptomatic catheter-related venous thrombosis (CRVT) is a special type of hospital-acquired VTE. Due to the convenience of CVC in intravenous drug injection, renal replacement therapy, monitor-

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ing of vital signs, and other aspects, the use of catheters in clinical practice is becoming increasingly common, and the occurrence of CRVT events is also increasing.[8]

CVCs were used more frequently in intensive care unit (ICU) inpatients given their critical illness.[3,9–11] Many studies on CRVT in ICU patients have been reported, and it has been found that venous catheter diameter, number of lumens, intubation site, blood transfusion, parenteral nutrition, sedation, and other factors are related to CVC-related thrombosis.[12–14] Critical and severe patients are usually treated in the ICU. To our knowledge, no studies have been conducted on the correlation between CVC-related thrombosis and major diseases in ICU patients. The purpose of this study was to investigate disease-related risk factors for symptomatic CRVT in ICU inpatients.

2. Patients and methods

2.1. Ethics statement

The retrospective cohort study was approved by the Medical Ethics Committee of Ganzhou People's Hospital, and the methods were performed in accordance with the approved guidelines. Written informed consent was signed by the patients' direct relative.

2.2. Study design

This 5-year retrospective cohort study was conducted at a regional medical center, a 3200-bed university-affiliated hospital. Data of the consecutive critically ill patients hospitalized in the ICU from January 2015 to December 2019 were collected by clinician review through electronic medical record retrieval to analyze disease-related risk factors for symptomatic CRVT in ICU inpatients. The inclusion criteria were as follows: Age $\geq$ 18 years; $>$ 3-day stay in the ICU; With CVCs inserted into the deep vein of the patients. And the exclusion criteria were the presence of thrombus in the CVC before ICU admission or the duration of CVC intubation was less than 3 days.

According to the research needs, we collected baseline demographics and variables previously shown to increase the risk of VTE, including gender, age, hypertension, drinking, smoking, diabetes, history of malignant tumor, chronic obstructive pulmonary disease, body mass index (BMI), and acute physiology and chronic health evaluation II (APACHE II) score. In addition, indicators related to hospitalization were collected, including ICU stay, endotracheal intubation time, CVC indwelling time, anticoagulant therapy, and anticoagulant contraindication. Most importantly, the primary diseases that necessitated admission to the ICU were collected according to the International Classification of Diseases, Ninth Revision.

2.3. Definitions

The primary disease referred to the most important disease that caused patients to be admitted to the ICU, and this information was determined by the chief complaint of admission to the ICU. However, patients hospitalized in the ICU generally had multiple coexisting diseases, and the diseases that were difficult to identify as the primary diseases were discussed and decided by the research group members based on the patient diagnostic information provided by the medical records. Trauma patients referred to patients admitted to the ICU after trauma, including severe injuries to the brain, chest, abdomen, and/or limbs, regardless of whether the trauma was accompanied by other mild or severe diseases. Major surgery referred to the operation performed under general anesthesia, the operation time was more than 2 hours, patients' breathing, circulation and other organ function instability might occur and the patients need life support treatment after the operation.

Multiple catheterizations could be included from a single patient. According to the therapeutic needs, intravenous catheterization was performed by qualified doctors under ultrasound guidance, or nonultrasound guidance. The insertion sites included the internal jugular vein, subclavian vein, or femoral vein.

Symptomatic CRVT was defined as the thrombosis with symptoms at the insertion site of the CVC. These symptoms included redness, swelling, and pain in the catheter insertion site or the area of the venous flux. The administering physician depending on the symptoms of thrombus decided whether to perform an ultrasound examination to determine the presence of a catheter-related thrombosis. Venous duplex ultrasonography was performed by certified ultrasonography technologists and interpreted by an attending radiologist. The thrombus was described as complete thrombus, mural thrombus, and no thrombus according to the relationship between thrombus volume and vascular lumen.

2.4. Data analysis

The catheters were divided into 2 groups based on the presence of symptomatic CRVT. The continuous data of the 2 groups are described by means $\pm$ standard deviations and compared using t tests for 2 independent samples. Nonparametric data are expressed as median (interquartile range) and compared using the Mann–Whitney test. The categorical data were presented as percentages and compared with the $\chi 2$ test or Fisher exact test. The incidence of CRVT was normalized per 1000 CVC days. Kaplan–Meier curves were applied to analyze the cumulative incidence of symptomatic CRVT. Univariate and multivariate logistic regression analyses were used for disease risk factor analysis. Variables with a 2-tailed $P < .1$ on univariate analysis were included in a multivariate regression model to identify independent predictors of symptomatic CRVT. Odds ratios (ORs) and 95% CIs are reported. Area under the receiver operator curve (c-statistic) is used to assess predictive value of the model. All tests were 2-sided with a significance level of 0.05 and were performed using SPSS software (ver. 24.0; IBM Corp, Armonk, NY).

3. Results

3.1. Patient baseline characteristics

From January 2015 to December 2019, a total of 4904 patients were admitted to the ICU, including 329 patients $<$ 18 years old, 2099 patients whose length of stay in the ICU $<$ 3 days, 31 patients with CVC complicated thrombosis before admission to the ICU, 802 patients without CVC, and 1643 patients with CVC. Among them, 1187 patients had 1 catheter, 380 patients had 2 catheters, 76 patients had 3 or more catheters. The total number of CVC was 2196. In total, 82 catheters with an intubation duration of $<$ 3 days were excluded from the study. Thus, 2114 catheters were included in the analysis, and each catheter was analyzed as a case (Fig. 1).

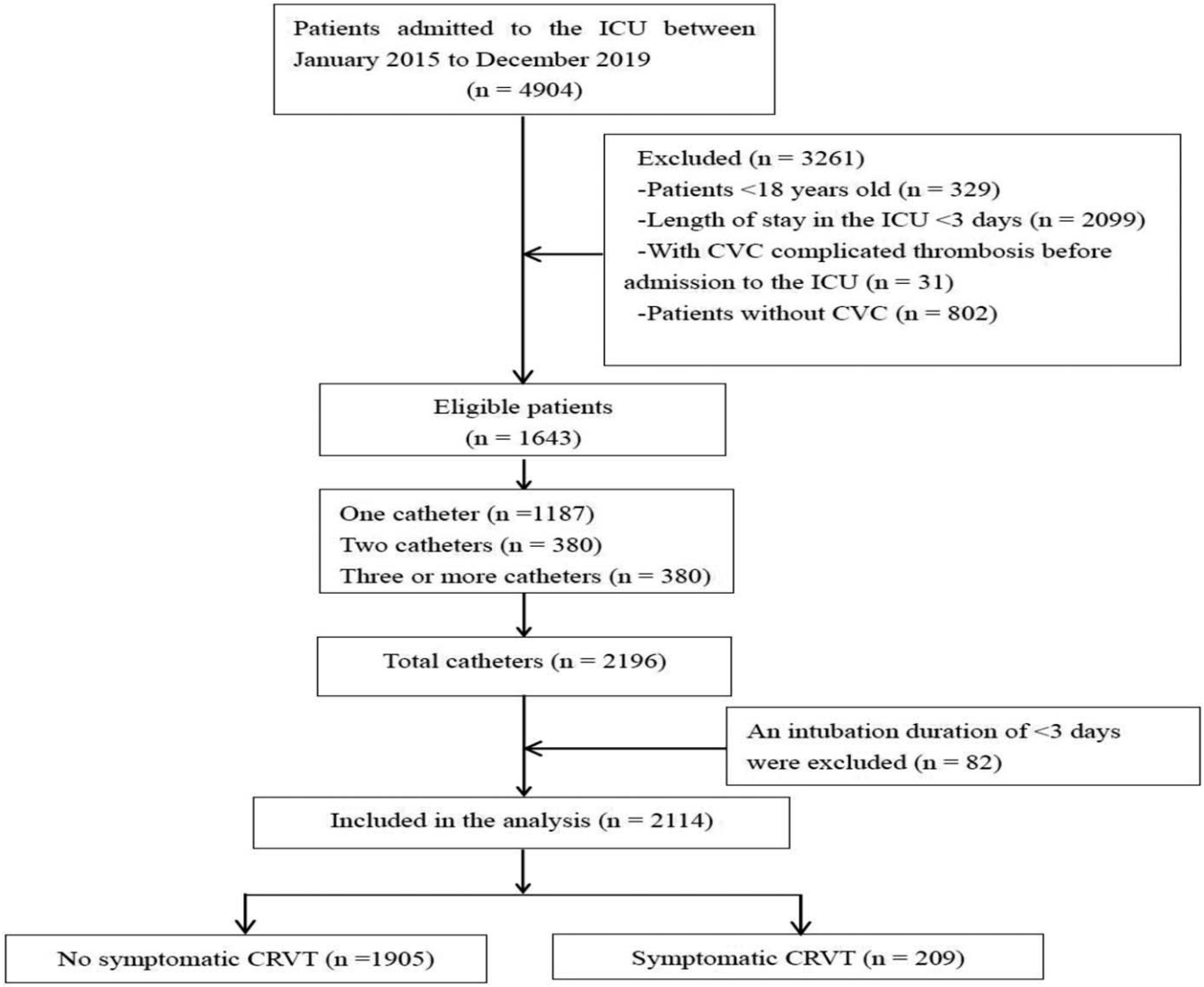

Figure 1. Patient flowchart.

Symptomatic CRVT occurred in 209 CVCs. The amount CVC days were 21,972 days and the incidence rate of symptomatic CRVT in the ICU population was 9.5 per 1000 catheter days. Approximately 75% of thrombotic events occurred within 17 days of catheter placement (Fig. 2). The 2114 CVCs were divided into 2 groups according to whether symptomatic CRVT occurred. We found significant differences in age ($P = .000$), BMI ($P = .000$), APACHE II score ($P = .001$), length of ICU stay ($P = .000$), endotracheal intubation time ($P = .000$), CVC indwelling time ($P = .000$), anticoagulation therapy ($P = .034$), and anticoagulant contraindications ($P = .005$) between the 2 groups. Patient clinical characteristics are presented in Table 1.

3.2. Predictive factors of SCRVT

Figure 3 shows the distribution of the primary diseases of patients admitted to the ICU, in which respiratory failure is the most frequent (n = 386 [18.3%]) followed by sepsis, heart failure, major surgery, trauma, hypovolemic shock, renal failure, cerebrovascular disease, severe acute pancreatitis, hepatic failure, and intestinal obstruction. Symptomatic CRVT occurred in 7.3%, 7.8%, 13.9%, 16.1%, 14.0%, 10.6%, 5.9%, 11.8%, 4.4%, 13.3%, and 15.0% of patients in each disease group, respectively. Univariate analysis revealed that trauma, major surgery, heart failure, respiratory failure, and severe acute pancreatitis were disease-related risk factors for symptomatic CRVT in the ICU (Table 2). Then, these 5 factors were incorporated into the multivariate analysis. As a result, a risk model was established including the 5 diseases. Trauma (OR, 2.046; 95% CI [1.325–3.160], $P = .001$), major surgery (OR, 2.457; 95% CI [1.641–3.679], $P = .000$), heart failure (OR, 2.087; 95% CI [1.401–3.111], $P = .000$) were independent risk factors for symptomatic CRVT in ICU (Table 3). The c-statistic for this model was 0.61 (95% CI, 0.57–0.65, $P = .000$) (Fig. 4).

4. Discussion

The study indicated that the incidence rate of symptomatic CRVT in the ICU population was 9.5 per 1000 catheter days and revealed that the independent disease-related risk factors of

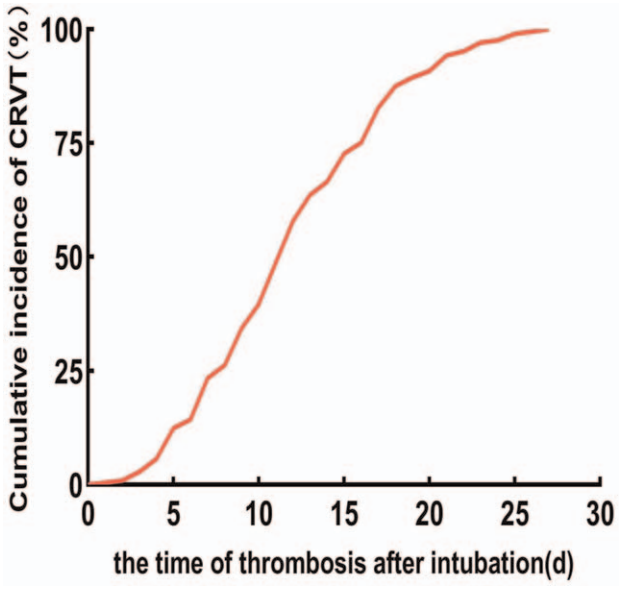

Figure 2. Cumulative incidence of CRVT. CRVT = catheter-related venous thrombosis.

symptomatic CRVT included trauma, major surgery, and heart failure based on the ICU primary disease risk model (c-statistic = 0.610).

Given the high risk of developing VTE, hospital-acquired VTE is extremely high in ICU patients, but its incidence has been reported differently by various medical institutions. One study analyzed ICU patients with duplex sonography performed during CVC placement or within 7 days after CVC removal and found that 59 CRVTs were diagnosed in 28% of patients.[15] Gibson et al retrospectively analyzed the occurrence of vein thrombosis among hospitalized patients in the medical ICU, and selected patients with suspected limb thrombosis for ultrasound examination. The incidence of thrombosis was 16%, and the catheter usage rate of patients with thrombosis was 55.26%. However, the incidence of symptomatic CRVT was not further analyzed.[16] Chen et al[17] studied symptomatic thrombosis associated with peripherally inserted CVC in cancer patients and found that the incidence of symptomatic CRVT was 6.7%. The incidence rate of symptomatic CRVT in the ICU population was 9.5 per 1000 catheter days. The difference may be related to the study population and statistical methods. The population in this study was dominated with surgical diseases.

The traumatically injured are at an especially high risk for VTE.[18–21] In the absence of pharmacologic prophylaxis, those with severe injuries have a risk of VTE that surpasses 50%.[22] Immediately after the injury, the delicate homeostasis balance of coagulation in the system is disturbed by the reduction of functional protein C, the reduction of antithrombin, and the cessation of acute fibrinolysis, leading to the state of hypercoagulability.[23–25] The combination of endothelial and tissue injury, vascular stasis, and hypercoagulability[26] represents a high risk factor for early VTE in this population, especially in patients with severe multiple trauma.[27,28] Hamada et al[27] prospectively studied 153 patients with severe trauma from an ICU of a university level 1 trauma center and found that the prevalence of VTE was 30.7%. CVC was an independent risk factor for VTE occurrence in this group of cases (OR 4.39, 95% CI [1.1–29]). Most of the wounds in the population in our study involved multiple injuries, including major compound injuries of head, neck, chest, and/or abdomen. The incidence of symptomatic CRVT was 16.1%, which did not seem high. However, the VTE here did not include thrombosis unrelated to CVC.

Given that major surgery may result in unstable respiratory, circulatory, and other organ functions, patients need to be admitted to ICU for life support after surgery. The major operations of the center mainly include abdominal surgery,

Table 1

Baseline characteristics of the study population.

Variable	Overall (n = 2114 CVCs)	NO symptomatic CRVT (n = 1905 CVCs)	Symptomatic CRVT (n = 209 CVCs)	*P* value
Male, No. (%)	1423 (67.3)	1278 (67.1)	145 (69.4)	.503*
Age, median (IQR), yr	62 (50–74)	63 (50–73)	67 (53–79)	.000†
BMI (kg/m^2), median (IQR)	22 (20–24)	22 (20–24)	24 (21.8–25)	.000†
APACHE II score, median (IQR)	25 (21–31)	26 (21–31)	28 (23–32)	.001†
Comorbidities				
Hypertension, No. (%)	867 (41.0)	772 (40.5)	95 (45.5)	.169*
Diabetes, No. (%)	464 (21.9)	420 (22.0)	44 (21.1)	.742*
Malignant tumor, No. (%)	205 (9.7)	184 (9.7)	21 (10.2)	.857*
COPD, No. (%)	494 (23.4)	444 (23.3)	50 (23.9)	.842*
Medical history				
Drinking, No. (%)	430 (20.3)	394 (20.7)	36 (17.2)	.238*
Smoking, No. (%)	705 (33.3)	645 (33.9)	60 (28.7)	.134*
ICU length of stay, median (IQR), d	8 (5–17)	8 (5–17)	16 (7–27)	.000†
Endotracheal intubation time, median (IQR), d	6 (3–14)	6 (3–14)	10 (4–22.5)	.000†
CVC indwelling time, median (IQR), d	10 (6–14)	10 (6–14)	14 (11–20)	.000†
Anticoagulant contraindication, No. (%)	620 (29.3)	541 (28.4)	79 (37.8)	.005*
Anticoagulant therapy, No. (%)	716 (33.9)	659 (34.6)	57 (27.3)	.034*

APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CVC = central venous catheters, ICU = intensive care unit, score.
* Independent-sample *t* test.
† Mann–Whitney *U* test.

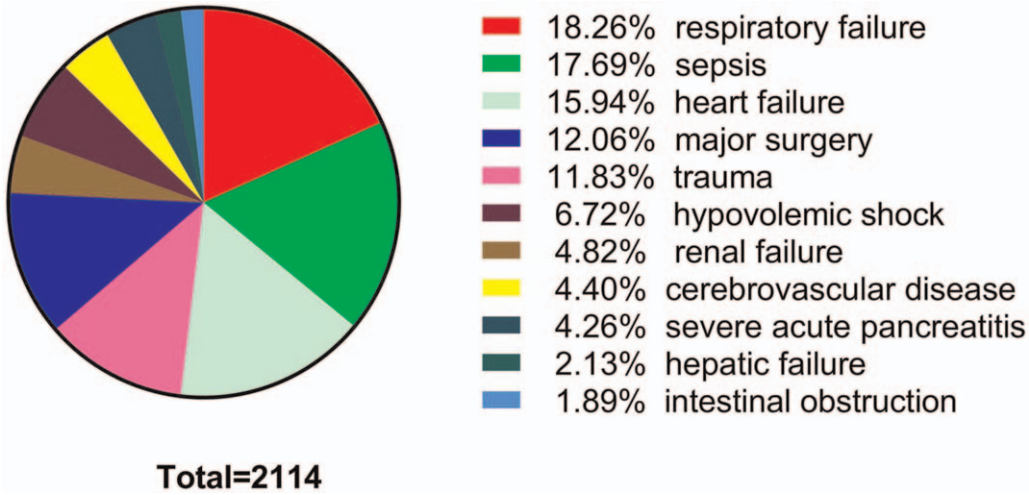

Figure 3. The distribution of the primary diseases of patients admitted to the ICU. ICU = intensive care unit.

cardiac surgery, open brain surgery, and multiple injury repair surgery. These types of operations are characterized by long operation time, a large amount of blood loss, need for blood transfusion, and the need to be performed under general anesthesia, and all of these parameters contribute to the risk of venous thrombosis formation.[29,30] At present, clinical researchers in different surgical specialties, including general surgery,[31] orthopedics,[32] thoracic surgery,[33] urology,[34] tumor surgery,[35] and neurosurgery[36] found that the incidence of VTE after major surgery is relatively high, ranging from 3.6%[31] to 21.3%.[36] They believe that major surgery is a risk factor for VTE and that active prevention is needed.[8] The current study population included 255 patients admitted to the ICU due to major surgery, among which 41 patients (13.9%) had SCRVT. Major surgery was an independent risk factor for symptomatic CRVT in this group.

Heart failure accounts for a high proportion of ICU inpatients, and symptomatic CRVT was noted in 16.2% (47/290) in patients admitted to ICU due to heart failure in this study. Basnet et al[37] found that the incidence of heart failure associated with VTE increased yearly by analyzing inpatient with heart failure from 2000 to 2013. Wilson et al[38] analyzed the risk factors for thrombosis associated with peripherally inserted CVC in inpatients and found that heart failure (OR, 2.62; 95% CI, 1.01–6.83) was associated with the occurrence of a CRVT. Heart failure is characterized by a prothrombotic state, which not only increases the risk for cardioembolic events and ischemic stroke[39] but also increases the risk for deep venous thrombosis and pulmonary embolism, which together constitute VTE.[40] In a study of 13,728 subjects, Fanola et al reported that over a 22-year period, heart failure occurred in 2696 (20%) patients, and 729 VTE events were identified. Heart failure was associated with an increased long-term risk of VTE (OR 4.39, 95% CI [2.58–3.80]) that was independent of multiple risk factors for VTE.[41]

This study also noted that a long duration of CVC intubation[42] and long endotracheal intubation[16,18] could increase symptomatic CRVT occurrence in ICU patients. In this study population, anticoagulation therapy was insufficient due to anticoagulation contraindication, and the comparison of anticoagulation therapy between the 2 groups was statistically significant ($P = .005$), which may also increase the occurrence of symptomatic CRVT. Therefore, especially after major surgery[8] or trauma,[26] patients should undergo active measures to prevent thrombosis, and anticoagulation drugs should be given if there is no anticoagulation contraindication. Otherwise, mechanical prophylaxis to prevent thrombus should be performed. In

Table 2

Univariate analysis of disease-related risk factors for CRVT (n = 1905 CVCs).

Variable	NO symptomatic CRVT (n = 1905)	Symptomatic CRVT (n = 209)	OR	95% CI	*P* value
Respiratory failure, No. (%)	358 (18.8)	28 (13.4)	0.668	0.442–1.012	.057
Sepsis, No. (%)	345 (18.1)	29 (13.9)	0.729	0.484–1.097	.129
Heart failure, No. (%)	290 (15.2)	47 (22.5)	1.414	1.141–2.288	.007
Major surgery, No. (%)	214 (11.2)	41 (19.6)	1.928	1.332–2.791	.001
Trauma, No. (%)	215 (11.3)	35 (16.7)	1.581	1.071–2.335	.021
Hypovolemic shock, No. (%)	127 (6.7)	15 (7.2)	1.082	0.621–1.886	.780
Renal failure, No. (%)	96 (5.0)	6 (2.9)	0.557	0.241–1.287	.171
Cerebrovascular disease, No. (%)	82 (4.3)	11 (5.3)	1.235	0.647–2.357	.522
Severe acute pancreatitis, No. (%)	86 (4.5)	4 (1.9)	0.413	0.150–1.136	.087
Liver function failure, No. (%)	39 (2.0)	6 (2.9)	1.616	0.592–3.381	.436
Intestinal obstruction, No. (%)	34 (1.8)	6 (2.9)	1.626	0.675–3.921	.279

CI = confidence interval, CRVT = catheter-related venous thrombosis, OR = odds ratio.

Table 3

Disease-related risk factors for symptomatic CRVT in ICU inpatients (multivariate logistic regression analysis).

Risk factor	OR	95% CI	*P* value
Model (c-statistic 0.61; 95% CI 0.57–0.65)			
Trauma	2.046	1.325–3.160	**.001**
Major surgery	2.457	1.641–3.679	**.000**
Heart failure	2.087	1.401–3.111	**.000**
Respiratory failure	0.913	0.583–1.428	.690
Severe acute pancreatitis	0.581	0.207–1.632	.303

Bold values indicate independent risk factors for symptomatic CRVT in ICU. CI = confidence interval, OR = odds ratio.

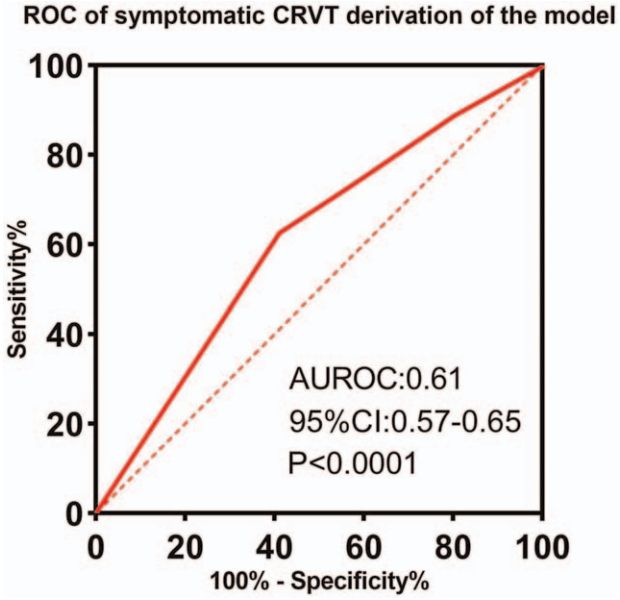

Figure 4. ROC of symptomatic CRVT derivation of the model. CRVT = catheter-related venous thrombosis.

addition, this study also suggested that age, BMI, APACHE II score, length of ICU stay, and other factors were significantly different in the comparison between the 2 groups, which was basically consistent with the results of previous studies.[12,16,17,43]

Our study has several limitations. First, it involved a single center and a relatively small number of patients. Second, this was a retrospective study performed using electronic medical records, and the study population was heterogeneous, which possibly introduced the potential for information bias. In addition, only symptomatic CRVT was analyzed in this study. Non-symptomatic CRVT was not included in the analysis, which might potentially result in the incidence of CRVT being underestimated.

5. Conclusions

The incidence of symptomatic CRVT in the ICU population was 9.5 per 1000 catheter days. Trauma, major surgery, and heart failure are independent disease-related risk factors for symptomatic CRVT. For patients hospitalized in the ICU, especially those admitted with these 3 conditions, thromboprophylaxis, and/or mechanical prophylaxis should be actively provided to reduce the occurrence of symptomatic CRVT (Supplemental Digital Content: http://links.lww.com/MD/G293.).

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Author contributions

Yuanfei Liu contributed to the study design, data analysis, and the writing of the manuscript. Hailiang Xie, Yunlin Zhu and Zhiming Kuang contributed to data collection, and translation of the manuscript. Yuanfei Liu and Xiaochun Liu revised the manuscript. All authors agreed with the decision to submit the manuscript for publication. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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