ORIGINAL ARTICLE

Incidence and risk assessment of venous thromboembolism in cancer patients admitted to intensive care unit for post-operative care

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Summary

Purpose: *The occurrence of venous thromboembolism (VTE) in Chinese cancer patients admitted to intensive care unit (ICU) for postoperative care is poorly characterized. This study was designed to investigate the incidence of VTE in this polulation and to evaluate the utility of the Caprini score in risk stratification.*

Methods: *We conducted a retrospective cohort study of 2127 consecutive adult patients admitted to a 10-bed surgical ICU in a tertiary care academic hospital during a 4-year period (January 1,2013 to December 31,2016). Demographic and VTE data were collected. Data for the Caprini risk assessment model (RAM) was used to stratify patients on their risk of VTE.*

Results: *Of the 2127 patients admitted to ICU after cancer surgery, 66 (3.1%) developed symptomatic VTE. There were a total of 32 patients with pulmonary embolism (PE), 51 patients with deep vein thrombosis (DVT), and 17 patients with both conditions. Based on the original Caprini RAM, 99.5% of the patients scored in the "highest risk" category (score≥5), all patients with VTE were in the "highest risk" category. Further substratification in the "highest risk" category showed the risk of developing VTE events were significantly higher among patients with Caprini score >10 ,as compared with patients with Caprini score of 5 to 6 (OR*

5.63; 95%CI 1.27-24.94), 7 to 8 (OR 2.36; 95%CI 1.23-4.52) or 9 to 10 (OR 2.28; 95%CI 1.17-4.44). The percentage of patients receiving double prophylaxis was 16.8% (358/2127), 20 of the 66 VTE patients (30.3%) received double prophylaxis before VTE was diagnosed. Patients with higher Caprini score were more likely to receive double thrombo-prophylaxis than patients with lower Caprini score (23.4% of patients with Caprini score>10 vs 10.8% with Caprini score 5-6).

Conclusions: *Though accompanying with the sub-utilizing of chemoprophylaxis, the overall incidence of VTE was relatively low in Chinese cancer patients admitted to ICU for postoperative care. In contrast, the Caprini score was high in this population. The original Caprini RAM was limited to stratify this population, but further substratification of "highest risk" category demonstrated the risk of developing VTE events was significantly higher in patients with Caprini score >10. Future research with high quality evidence should be performed targeting on the accurate risk stratification and optimizing VTE prophylaxis for this population.*

Key words: *cancer surgery, Caprini score, intensive care unit, risk stratification, venous thromboembolism*

Introduction

Venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT) and pulmonary embolism (PE), is the major source of postopera-tive morbidity and mortality in cancer patients, contributing to prolonged length of hospital stay and incremental hospital costs [1,2]. When can-

cer patients are admitted to ICU for postoperative care, the risk of VTE is substantially higher than other patient populations. Administration of chemoprophylaxis can significantly reduce the risk of VTE, but the benefits of chemoprophylaxis may be counterbalanced by the risk of postoperative bleeding and coagulopathy in this population. Risk stratification is urgently needed for physicians to optimize thromboprophylaxis regimens. Well-validated in postsurgical patient population, the Caprini RAM is the most widely used tool for VTE risk prediction and recommended in VTE guidelines for VTE risk stratification [3,4]. Since the occurrence of VTE in Chinese cancer patients admitted to ICU for postoperative care is poorly characterized, we conducted this retrospective study to 1) investigate the incidence of symptomatic VTE in this patient population; and 2) examine the utility of the Caprini RAM for VTE risk stratification.

Methods

This retrospective cohort study was performed in the Peking University Cancer Hospital, a tertiary care academic hospital ranked top 5 in cancer specialty in China. Approval for this study was obtained from the Institutional Review Board. All admissions to a 10-bed surgery intensive care unit (SICU), undergoing surgery for malignancy between January 1,2013 and December 31,2016 were included. Patients younger than 18 years were excluded. The enrolled patients were retrospectively identified with the electronic medical records, data including demographics, malignancy characteristics, concomitant diseases, APACHE II score, and length of ICU and hospital stay were collected.

Data regarding thromboprophylaxis were also recorded. According to the protocol of VTE prevention at Peking University Cancer Hospital, perioperative mechanical prophylaxis such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices was recommended unless contraindicated. Chemoprophylaxis was not routinely used unless the attending physicians considered the patient at high risk of VTE and low risk of bleeding.

Originally derived from surgical patients, the Caprini RAM is a convenient method to stratify VTE risk by summing individual risk factors. In this model, different patient and procedure risk factors are assigned weighted points (ranging from 1 to 5) based on the risk of VTE for each factor as listed in Table 1. A total risk factor score is calculated and stratify patients into 4 risk levels based on reported incidence of VTE: "very low risk" (0 points), "low risk" (1-2 points), "moderate risk" (3-4 points), and "high risk" (≥5 points), leading to stratified prophylaxis. In this study, the Caprini score was calculated for individual patient based on comorbidities and perioperative risk factors immediately at admission to ICU.

Table 1. 2005 Caprini risk model

Each risk factor represents 1 point

Age 41–60 years

Swollen legs (current)

Varicose veins

Obesity (BMI >25)

Minor surgery planned

Sepsis (<1 month)

Acute myocardial infarction

Congestive heart failure (<1 month)

Medical patient currently at bed rest

History of prior major surgery (<1 month)

History of inflammatory bowel disease

Abnormal pulmonary function (COPD)

Serious lung disease including pneumonia (<1 month)

Oral contraceptives or hormone replacement therapy

Pregnancy or postpartum (<1 month)

History of unexplained stillborn infant, recurrent spontaneous abortion (>3),

Premature birth with toxemia or growth-restricted infant

Each risk factor represents 2 points

Age 61–74 years

Arthroscopic surgery

Malignancy (present or previous)

Laparoscopic surgery (>45 min)

Patient confined to bed (>72 h)

Immobilizing plaster cast (<1 month)

Central venous access

Major surgery (>45 min)

Each risk factor represents 3 points

Age 75 years or older

History of DVT/PE

Positive factor V Leiden

Elevated serum homocysteine

Heparin-induced thrombocytopenia (HIT)

Elevated anticardiolipin antibodies

Positive prothrombin 20210A

Positive lupus anticoagulant

Other congenital or acquired thrombophilia

Each risk factor represents 5 points

Stroke (<1 month)

Multiple trauma (<1 month)

Elective major lower extremity arthroplasty

Hip, pelvis, or leg fracture (<1 month)

Acute spinal cord injury (paralysis) (<1 month)

The primary outcome of this study was 30-day VTE occurring after the admission to ICU. As routine screening protocol for VTE was not performed in our hospital, investigation for VTE was at the discretion of the attending physicians if patients got suspected symptoms related to VTE (such as extremity edema, pain, unexplained shortness of breath or hypoxia). DVT was defined as acute thrombosis of lower-extremity veins (iliac, femoral, popliteal, or calf veins) or upper-extremity veins (axillary, subclavian, brachial, or internal jugular veins) by compression ultrasonography. PE was defined as acute thrombosis within the pulmonary vasculature based on spiral computed tomography.

Statistics

Statistical analyses were carried out with SPSS software, version 22. Continuous variables with a normal distribution were described as means with standard deviations, while continuous variables with skewed distribution were presented as median values with interquartile ranges. Comparisons between two groups were performed with 2-tailed Student's t test. Discrete variables were presented as frequencies and percentages, and group comparisons were performed using the chi-square or Fisher's exact test. Patients were categorized into risk categories based on the calculated Caprini score and the incidence of venous thromboembolism for each risk groups was estimated along with a 95% confidence interval. A p value <0.05 was considered to indicate statistical significance.

Results

A total of 2127 consecutive cancer patients admitted to ICU for postoperative care were included in this study. The baseline characteristics of the included patients are presented in Table 2. Of the total 2127 patients, 1918 underwent radical surgery amd 209 palliative or emergency surgery before admission to the ICU. Patients had a median age of 67 years (range 59-75), with most patients being male (64.2%). The majority of the patients in this cohort had a colorectal cancer (38.3%), followed by gastric cancer (19.9%), lung cancer (10.4%) and esophageal cancer (8.0%), with median APACHE II score of 8 (range 7-11), ICU length of stay of 3 days (range 2-5), and hospital length of stay 17 days (range 12-25).

The observed rate of VTE in ICU was 3.1% (66/2127; Table 3). There was a total of 32 patients with PE (1.5% of the overall population, 48.5% of the VTE population), 51 patients with DVT (2.4% of the overall population, 77.3% of the VTE population), 17 (0.8% of the overall population, and 25.8% of the VTE population) experienced both conditions. In the 51 DVT patients, 6 were with proximal DVT (2 located in inner jugular vein and 4 in femoral vein) and 45 with distal DVT (throm-

Table 2. Demographic and clinical characteristics of enrolled patients

Characteristics	Patients, n (%)
Gender, male	1366 (64.2)
Age, years	67 (59.75)
Site of malignancy	
Esophagus	170 (8.0)
Gastric	423 (19.9)
Colorectal	814 (38.3)
Pancreatic	62 (2.9)
Hepatobiliary	90 (4.3)
Genital urinary tract	64 (3.0)
Lung	222 (10.4)
Breast	47 (2.2)
Gynecologic	52 (2.5)
Sarcoma	66 (3.1)
Medical co-morbidity	
Hypertension	872 (41.0)
Arrhythmia	277 (13.0)
Coronary heart disease	406 (19.1)
COPD	133 (6.3)
Diabetes	367 (17.3)
Cerebrovascular disease	184 (8.7)
APACHE II score*	8 (7.11)
Length of ICU stay	3 (2.5)
Length of hospital stay	17 (12.25)

*Acute Physiology and Chronic Health Evaluation II score

Table 3. Venous thromboembolism data

| Variables	Patients, n (%)
Total VTE events	66 (3.1)
VTE location	
PE	32 (1.5)
PE+DVT	17 (0.8)
PE only	15 (0.7)
DVT	51 (2.4)
Proximal extremity	6 (0.3)
Distal extremity	51 (2.1)

For abbreviations see text

bus located below the knee in the calf vein). The median time from surgery to VTE development was 3 days (range 1-7). There were 2 postoperative sudden deaths recorded. Unfortunately, the autopsy was refused. Both DVT and severe right ventricular enlargement were detected under bedside echocardiography in these 2 cases, so DVT with PE were diagnosed based on the indirect evidence and attending physician's clinical judgment.

According to the original Caprini RAM (also recommended in ACCP guidelines), patients were classified into different risk groups by their

Caprini scores in this study (Table 4). As a result, only 10 patients (0.5% of the overall population) were classified into low to moderate risk and the remaining 99.5% were high risk (score ≥5). Given the majority of patients classified into the high risk group, this group was substratified by Caprini score and the VTE incidence was calculated for each subgroup. Patients with Caprini score of 10 or greater were significantly more likely to develop VTE events compared with those with Caprini score of 5 to 6 (odds ratio 5.63; 95%CI 1.27-24.94; p=0.01), 7 to 8 (odds ratio 2.36; 95%CI 1.23-4.52; p=0.02) or 9 to 10 (odds ratio 2.28; 95%CI 1.17-4.44; p=0.02). However, there was no significant difference between 5 to 6, 7 to 8 and 9 to 10 group (Table 5).

Of enrolled patients 14.8% (315/2127) received preoperative double thromboprophylaxis
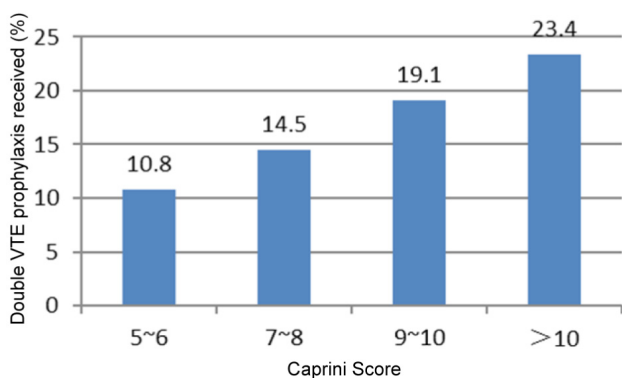
Figure 1. Double VTE prophylaxis received according to Caprini score.

(pharmacological combined with mechanical prophylaxis), this proportion increased to 16.8% (358/2127) after admission to ICU and 20 of the 66 VTE patients (30.3%) received double prophylaxis before VTE was diagnosed. As shown in Figure 1, patients with greater Caprini score were more likely to receive double prophylaxis (23.4% of patients with Caprini score >10, 19.1% with Caprini score 9-10, 14.5% with Caprini score 7-8, 10.8% with Caprini score 5-6).

Discussion

VTE is a frequent complication in patients with cancer and is associated with significant morbidity and mortality. Published data confirmed that the risk of developing VTE is increased up to 6-7 fold in cancer patients compared to the general population, and if undergoing surgical procedure, the risk will go even higher [5]. Hence, thromboprophylaxis for cancer patients after major surgery was strongly recommended according to the VTE risk assessment [6].

In the current study we found the incidence of VTE events in Chinese cancer patients admitted to ICU for postoperative care was 3.1%. Due to the lack of results from high quality studies, the real VTE incidence of cancer patients in Asia is still controversial [7,8]. Data from retrospective studies based on Asian patients undergoing major cancer surgery showed a VTE incidence of 0.06-0.85% [9,10]. Even with the genetic inhomogeneity,

Table 4. Observed VTE incidence for each group substratified by Caprini score

Caprini score	Patients, n (%)	Observed VTE rate (%)	95%CI
Low risk (0-1)	0 (0)		
Moderate risk (2)	1 (0.1)		
High risk (3-4)	9 (0.4)		
Highest risk (≥5)	2117 (99.5)		
Caprini 5-6	167 (7.9)	1.20 (2/167)	0.21-4.71
Caprini 7-8	924 (43.4)	2.81 (26/924)	1.75-3.87
Caprini 9-10	791 (37.2)	2.91 (23/791)	1.74-4.08
Caprini >10	235 (11.0)	6.38 (15/235)	3.26-9.50

Table 5. Odds for VTE substratified by Caprini score

	Caprini 7-8	Caprini 9-10	Caprini >10
Caprini 5-6	2.39 (0.56-10.16) p=0.29	2.47 (0.58-10.58) p=0.29	5.63 (1.27-24.94) p=0.01
Caprini 7-8		1.034 (0.59-1.83) p>0.99	2.36 (1.23-4.52) p=0.02
Caprini 9-10			2.28 (1.17-4.44) p=0.02

Data are presented as odds ratios (95% CI)

a recently published review including Chinese, Koreans, Japanese, Malaysians and Indians, demonstrated no significant differences in VTE risk between studies from different regions in Asia [11]. One of the studies from Taiwan, which is comparable to the population in our study, indicated the VTE rate was lower than in Caucasian cancer patients [12]. Certainly, the possibility of underdiagnosis due to the limitation of retrospective study should be noticed. When we look at the data from prospective studies, the incidence varied greatly up to 42% [7,13]. These studies were likely to overestimate the VTE risk as DVT scan was routinely performed even in asymptomatic patients in all these studies and two studies which observed VTE incidence at 38 and 42% had a very small sample size. A recent prospective observational study by Lee et al. with 548 Korean colorectal cancer patients undergoing major abdominopelvic surgery with only mechanical prophylaxis revealed a postoperative DVT incidence of 3.0% in the screening group compared with 0.7% in the non-screening group [7]. Based on these observations, it is reasonable to conclude the VTE rate in Asian cancer patients undergoing major surgery is about 2-3%, equal to the VTE incidence at moderate risk (about 3%) according to the American College of Chest Physicians (ACCP) VTE guideline risk categories. All the above results indicated differences in the epidemiologic profile of VTE in Asian compared with Western population and a proportion of cancer patients may be exposed to possibly unnecessary costs and risk of bleeding. This highlights the importance of appropriate risk stratification in Asian cancer populations undergoing major surgery.

The Caprini score is the most widely used VTE RAM developed from a large retrospective study, with a database including a representative sample of general, vascular, and urological surgery patients. Taking into account the total number of risk factors which are associated with the patient's condition and the nature of the surgery being performed, the Caprini VTE RAM is validated in Western surgical patient populations and is recommended in guidelines for VTE prevention [4]. However, in our study we found the original Caprini score was of limited ability to discriminate the VTE risk among Chinese cancer patients admitted to ICU for postoperative care. Since the majority (99.5%) of the enrolled patients were categorized into the highest risk group (Caprini score ≥5), we can't distinguish between different risk levels. This is consistent with the results on patients with gynecologic malignancies [14]. This can be partially explained based on that all in-cluded patients had 2 risk factors: major surgery and malignancy, which contributed to 4 points together according to the original Caprini score. If any additional risk factors, such as advanced age, central lines and other complications exist, which are quite common in ICU patients compared with patients in general care wards, the patients would be classified into the highest-risk category (Caprini score ≥5).

One solution is increasing the cutoff point for stratifying cancer patients. Bahl et al. modified the Caprini RAM and added a separate "super high risk" group (>8) and recommended an extended duration of chemoprophylaxis for this group [15]. Similar to cancer patients, a raised cutoff point of 8 had already been used in risk stratification in patients undergoing plastic and orthopedic surgery [16]. In the current study, sub-stratification of the "highest risk" category showed the risk of developing VTE events were significantly higher among patients with Caprini score >10, as compared with patients with Caprini score of 5 to 6 (OR 5.63;95%CI 1.27-24.94), 7 to 8 (OR 2.36;95%CI 1.23-4.52) or 9 to 10 (OR 2.28;95%CI 1.17-4.44). This suggests if the cutoff points are elevated, the Caprini score may be more effective in discriminating the relative risk of VTE between different cancer patients.

Risk assessment tools customized for cancer patients may be another way out. The current Caprini RAM considers malignancy as a single risk factor regardless of the primary cancer, while the risk of VTE may have great variations in different cancers (thinking about the VTE risk of a patient with early stage colorectal cancer *in situ* compared with a pancreatic cancer patient with distant metastasis). One universal VTE RAM cannot solve all the problem just like one size cannot fit all. More tumor-specific factors should be considered in VTE risk stratification for cancer patients. For example, Khorana score is a tumor-specific RAM recommended in National Comprehensive Cancer Network (NCCN) guideline [17]. Unfortunately, this RAM was only verified in cancer patients receiving chemotherapy, there are no similar RAMs recommended for cancer patients undergoing surgery. Future development of RAMs customized for cancer patients could allow us to tailor our VTE prophylaxis regimen.

In our study, the observed ratio of chemoprophylaxis in ICU was at a relatively low level of 16.8%. Though patients with higher Caprini score were more likely to receive double prophylaxis (23.4% of patients with Caprini score >10, 19.1% with Caprini score 9-10, 14.5% with Caprini score 7-8, 10.8% with Caprini score 5-6), which was still

not concordant with guideline recommendations. Actually, sub-utilizing the coagulant agent is not uncommon in Asia. In a survey of opinions and practices of surgical and intensive care specialists towards perioperative venous thromboembolism prophylaxis from 191 responses in 8 Asian countries, only half of the respondents practised routine thromboprophylaxis in moderate and high risk operations [18]. In an study including 2967 patients in 52 hospitals from Michigan, US, Krell et al. found that only 40.4 % of eligible patients had perioperative pharmacologic thromboprophylaxis for abdominal cancer surgery, and 25.3% of the highest-risk patients had inadequate postoperative prophylaxis [19]. Meanwhile, cancer patients receiving chemoprophylaxis are under a high risk of bleeding. A recent meta-analysis provided evidence that for cancer patients undergoing surgery, pharmacological thromboprophylaxis is had limited impact on VTE-related fatal events (RR 1.77, 95% CI 0.76-4.14; p=0.19) and could lead to a significantly increased incidence of bleeding events (RR 2.51, 95% CI 1.79-3.51; p<0.0001) despite a relatively reduced incidence of DVT [20]. A retrospective study using the database of RIETE (an international, prospective registry on patients treated for VTE) observed that the 30-day cumulative incidence of major bleeding and fatal bleeding in cancer patients receiving anticoagulant therapy was 1.8% and 0.74%, respectively, suggesting that a substantial proportion of cancer patients may be exposed to a possibly unnecessary risk of bleeding [21]. Challenging of counterbalancing risks of VTE and bleeding is still the main concern before physicians making the decision. Therefore, the benefits and risks of VTE prophylaxis should be weighed for the individual patient to get the optimal prophylactic regimen. VTE prevention should be tailored to patients individually based on appropriate risk assessment.

Limitations

Several limitations of our study should be noted. First, though a sizeable patient population was enrolled, the current study was limited to a mono-center retrospective design. Inherent limitations of a retrospective study involving medical data missing result in potential underscoring or inclusion bias. Second, we observed the VTE incidence only for 30 days after surgery. Though it was reported the VTE incidence was at its peak in the first 4 to 6 weeks after the surgery, it may underestimate, to a certain extent, the VTE risk in this population without long follow-up time [22]. In our study, colorectal and gastric cancer patients accounted for a major proportion of all enrolled patients. Actually, colorectal and gastric cancer patients do represent those undergoing major surgery with perioperative risk factors for VTE development. In NCCN guideline for VTE prevention and treatment, abdominal/pelvic cancer surgery patients with anesthesia time more than 2 hrs are defined as VTE high risk population, for whom an extended VTE prophylaxis for up to 4-6 weeks is recommended [6]. However, patient distribution is certainly a potential source of bias. Further well-designed, prospective, multi-center investigations are desired to estimate the real incidence of VTE among this population and optimize their VTE risk stratification.

Conclusions

Though accompanied with sub-utilizing chemoprophylaxis, the overall incidence of VTE was relatively low in Chinese cancer patients admitted to ICU for postoperative care.

In contrast, the Caprini score was high in this population. The original Caprini RAM was limited to stratify this population, but further substratification of "highest risk" category demonstrated the risk of developing VTE events was significantly higher in patients with Caprini score >10. Future research with high quality evidence should be performed targeting on the accurate risk stratification and optimizing VTE prophylaxis for this population.

Conflict of interests

The authors declare no conflict of interests.

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