The Risk Factors of VTE and Survival Prognosis of Patients With Malignant Cancer: Implication for Nursing and Treatment

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Abstract

Venous thromboembolism (VTE) is very common in patients with malignant cancer. We aimed to conduct a retrospective analysis on the risk factors of VTE and its survival prognosis of patients with malignant cancer, to provide evidence into the management of VTE. Patients with malignant cancer treated in our hospital were selected. The characteristic of patients and related lab detection results including activated partial thromboplastin time (APTT), plasma prothrombin time (PT) and thrombin coagulation time (TT), fibrinogen (FIB), thrombin AT-III complex (TAT) and D-dimer (D-D) were collected and analyzed. And logistic regression analyses were performed to identify the potential risk factors. And ROC curves were established to evaluate their predictive ability of VTE for patients with malignant cancers. A total of 286 patients were included, of which 63 patients had VTE, the incidence of VTE in patients with malignant cancers was 22.03%. There were significant differences on the D-D, TAT level between VTE and no VTE patients (all P < 0.05). The survival condition of VTE patients was significantly worse than that of no VTE patients(P = 0.017). D-D (RR7.895, 3.228 ~ 19.286) and TAT (6.122, 2.244 ~ 16.695) were risk factors of VTE for patients with cancers (all P < 0.05). The area under the curve (AUC) of D-D, TAT and combined use was 0.764, 0.698, 0.794 respectively, and the cutoff value for D-D, TAT was 1.835mg/L and 4.58μg/L respectively. For cancer patients with D-D >1.835 mg/L and TAT >4.58 μg/L, early interventions are needed for the prophylaxis of VTE.

Background

It's been reported that venous thromboembolism (VTE) is increasing year by year.[1] At present, VTE-related deaths have been ranked as the third cause of death from cardiovascular diseases, second only to coronary heart disease and stroke.[2] The early symptoms of the disease are more concealed.[3] Once VTE occurs, it can affect venous circulation, causing swelling and pain in the limbs. At the same time, VTE has greatly increased the patient and social economic burden.[4] According to reports,[5,6] the incidence of VTE in China is also increasing with a range of 20%-70% among clinical patients. Therefore, the prevention and diagnosis of VTE has become the focus of health care providers.

Factors that can cause blood stasis, venous wall damage, and blood hypercoagulability are risk factors for the formation of VTE.[7] It is worth-noting that the incidence of VTE in various diseases is significantly different, and at the same time, the related risk factors may also be different.[8] It's been reported that oncology patients who suffered a surgery may have higher incidence of VTE, but there is a lack of studies on the risk factors of VTE in those population. Therefore, it is necessary to carry out research and analysis on the occurrence of VTE in

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Table 1. The Characteristics of 286 Included Patients.

Items		Cases (n = 286)	Percentage (%)
Gender	Male	157	54.90
	Female	129	45.10
Age (y)	≥60	102	35.66
	<60	184	64.34
Classification of cancers	Pancreatic cancer	38	13.29
	Lung cancer	72	25.17
	Ovarian cancer	25	8.74
	Breast cancer	34	11.89
	Gastric cancer	41	14.34
	Colorectal cancer	56	19.58
	Other cancers	22	7.69
TNM staging	Stage I-II	117	40.91
	Stage III-IV	169	59.09

various special populations, and identify their related risk factors, in order to provide reference for the prevention and treatment of clinical VTE. In this present study, we aimed to analyze the potential risk factors of VTE and survival prognosis of patients with malignant cancer, to provide evidence for VTE clinical nursing and treatment of patients with cancer.

Methods

Ethical Considerations

Our study had been approved by the ethical committee of our hospital, and written informed consents had been obtained from all the included patients.

Patients

Patients with malignant cancer who were treated in our hospital from May to November 2017 were selected. The inclusion criteria were: (1) Patients underwent cancer removal surgery and confirmed by pathological examination as malignant cancers after the operation; (2) Age ranged from 20 to 85 years old; (3) Functional status score of Performance Status (PS) varied from 0 to 2 points; (4) Expected bit survival time was > 1 month. (5) The patient was well informed and agreed to participant in this study. The exclusion criteria were: (1) Patient diagnosed with VTE upon admission; (2) Patients were using low molecular weight heparin and other anticoagulants for treatment upon admission; (3) Patients had significantly reduced platelets (platelets < 50000/μL) or have severe platelets disfunction;(4) patients disagreed to participant in this study.

The DVT Diagnosis

Ultrasound examination on the deep vein of patient's lower limb was performed for all the included patients, and the Doppler ultrasound (Philips 200) with a probe frequency of 7.5 MHz is used. We referred the Diagnosis and Treatment

Guidelines for Deep Vein Thrombosis of Chinese Medical Association as the diagnostic standard.[9]

Coagulation Index Detection

The baseline data of coagulation indexes every other day after admission were collected from all the patients. 6 ml venous blood in the morning on an empty stomach from patients, and we used 0.109 mol/L sodium citrate for anticoagulation. After inverting and mixing, they were placed in a centrifuge (Henmi S1250, China), centrifuged at 3000 r/min for 10 min, and the supernatant was placed and stored in the refrigerator at -20°C. The patients' activated partial thromboplastin time (APTT), plasma prothrombin time (PT) and thrombin coagulation time (TT), fibrinogen (FIB), thrombin AT-III complex (TAT) and D-dimer (D-D) were detected by the professionals in our laboratory. We have included PTT, PT, TT, FIB, TAT and D-D for consideration since it's the very common detected indicators in clinical setting.

Data Collection

We followed up all the included patients for 10 months. Two authors collected the characteristic of patients including age, gender, diagnosis, TNM staging, Wells score, Geneva score and related lab detection results. Any disagreements were further solved by discussion.

Statistical Analysis

All collected data were analyzed with SPSS 21.0 statistical software. All continuous data were expressed as "mean ± standard deviation," and t test was used for comparison between 2 groups. Categorical data was expressed as percentage, and Chi-square test or Fisher's exact probability method is used for comparison between groups. Moreover, we conducted univariate comparative analysis on the clinical data of VTE and no VTE patients. And logistic regression analyses were performed to identify the potential risk factors. In addition, the indicators with high correlation with VTE were selected and
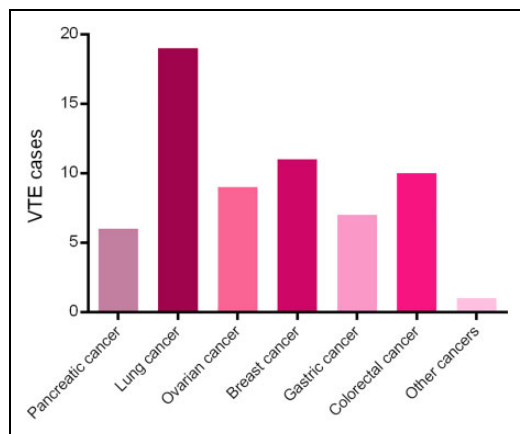
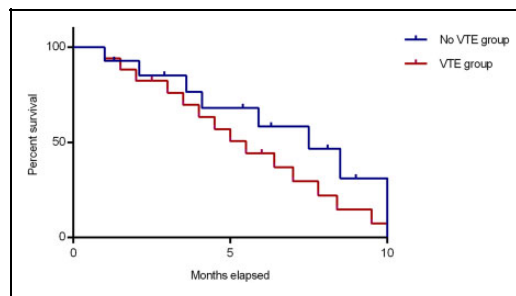**Figure 1.** VTE distribution among patients with different cancers.

Table 2. The Characteristics Comparison for VTE and No VTE Patients.

Variables	VTE patients (n = 63)	No VTE patients (n = 223)	χ^2/t	P
Male	37(58.73%)	120(53.81%)	1.297	0.058
Age (y)	62.38 ± 4.85	61.34 ± 5.01	8.334	0.195
TT (s)	21.02 ± 2.27	20.91 ± 2.40	5.299	0.212
APTT (s)	13.19 ± 1.97	13.12 ± 1.05	3.063	0.180
PT (s)	7.27 ± 0.46	7.26 ± 0.44	2.217	0.236
FIB (g/L)	2.41 ± 0.78	2.39 ± 1.07	1.121	0.175
D-D (mg/L)	1.91 ± 0.16	0.93 ± 0.11	1.092	0.041
TAT (μg/L)	4.67 ± 1.13	2.08 ± 0.75	1.124	0.036
Wells score	1.35 ± 0.22	1.32 ± 0.19	1.069	0.150
Geneva score	3.29 ± 1.04	3.16 ± 1.12	1.284	0.087

receiver operating characteristic (ROC) curves were established to evaluate their predictive ability of VTE for patients with malignant cancers. In this study, p < 0.05 was considered statistically significant.

Results

The Characteristics of Included Patients

A total of 286 patients were included. The characteristics of patients were presented in Table 1.

The VTE Distribution

As Figure 1 presented, a total of 63 patients had been detected with VTE, the incidence of VTE in patients with malignant cancers was 22.03%.

The Characteristics of VTE and No VTE Patients

As Table 2 showed, there were significant differences on the D-D, TAT level between VTE and no VTE patients(all P < 0.05), no significant difference on the gender, age, TT, APTT, PT, FIB, Wells score and Geneva score were found (all P > 0.05).

Figure 2. The survival curve of VTE and no VTE patients.

The Survival Condition of VTE and No VTE Patients

As Figure 2 showed, the survival condition of VTE patients was significantly worse than that of no VTE patients (P = 0.017).

Logistical Regression Analysis

As Table 3 presented, the logistical regression analysis indicated that D-D (RR7.895, 3.228~19.286) and TAT(6.122, 2.244~16.695) were the risk factors of VTE for patients with cancers (all P < 0.05).

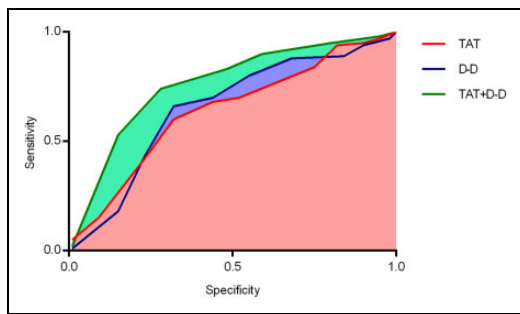### The Predicative Value of D-D and TAT

The ROC curve was used to further analyze the predictive value of D-D and TAT for VTE in patients with malignant cancers. As shown in Figure 3, The area under the curve (AUC) of D-D was 0.764, and the cutoff value was 1.835mg/L. The AUC of TAT was 0.698, and the cutoff value was 4.58μg/L. The AUC of combined use of D-D and TAT was 0.794, which was significantly higher than that of D-D and TAT alone use (all P < 0.05).

Discussions

Cancer plays an important role in the occurrence of VTE. Many clinical studies have found that malignant cancer cells can affect the body's coagulation system through various ways such as the expression of coagulation proteins, secretion of inflammatory factors, and adhesion to normal cells, which can lead to abnormal coagulation of the body.[10,11] At present, hypercoagulability, venous blood stasis, vascular wall damage are all high-risk factors that induce VTE.[12] For patients with malignant cancers that develop VTE, they have worse clinical prognosis and lower quality of life.[13] Many organizations including the American Society of Clinical Oncology[14] and the European Society of Medical Oncology[15] have formulated relevant guidelines for the prevention and treatment VTE. However, most clinical health care providers still underestimate VTE.[16] The incidence of VTE is rather high, in our study, the incidence of VTE in patients with malignant cancers was 22.03%, which is similar to previous reports.[17,18] It's noteworthy that even though we have made ecography to all patients, and all DVT were incidental, the incidence of VTE can be biased. Therefore, how to use practical and effective risk

Table 3. The Logistical Regression Analysis on the Risk Factors of VTE in Patients With Cancers.

Factors	β	SE	Wald	RR	95%CI	P
Male	1.214	0.180	2.286	0.482	0.112~1.249	0.140
Age (y)	0.975	0.225	4.301	0.287	0.101~0.745	0.197
TT (s)	-0.250	0.316	3.014	0.779	0.419~1.447	0.779
APTT (s)	-0.202	0.256	3.678	0.817	0.495~1.349	0.817
PT (s)	0.881	0.924	2.105	1.105	0.189~2.117	0.144
FIB (g/L)	1.416	0.735	3.779	4.124	0.976~17.400	0.058
D-D (mg/L)	2.066	0.456	7.879	7.895	3.228~19.286	0.005
TAT (µg/L)	1.812	0.512	6.539	6.122	2.244~16.695	0.011
Wells score	1.740	0.329	4.818	4.578	2.342~8.239	0.074
Geneva score	1.468	0.893	3.711	4.345	0.754~24.982	0.061

Figure 3. The ROC curve for the predicative value of D-D and TAT.

assessment criteria to determine whether a patient is a high risk for VTE, and to prevent, diagnose, and treat VTE high-risk patients as early as possible is a hot topic that needs to be resolved urgently in clinical practice.

In the process of coagulation, fibrinogen is converted into fibrin monomer by thrombin, and cross-linked with activating factor XIII to form cross-linked fibrin monomer.[19] Finally, the specific degradation product formed after hydrolysis by plasmin is D-D, so D-D is a specific marker that marks the body's hypercoagulability and fibrinolytic activity.[20,21] Several studies[22,23] have pointed out that D-D for VTE detection has high sensitivity, which can be as high as 92%-100%. Some scholars[24,25] have suggested that the clinical value of D-D is mainly reflected in the elimination of patients who may have VTE during the screening process. At present, it is generally believed that if the level of D-D is less than 0.5mg/L, patients with VTE can be basically ruled out.[26] The results of this present study have found that for patients with D-D >1.835mg/L, they may have higher risk for VTE, clinical heath workers should be alerted to prevent VTE for this kind of population.

TAT is a detection marker that indirectly reflects the body's thrombin level.[27] Clinically, the ELISA method is mainly used to measure TAT levels. This method has been developed to a relatively mature stage, and the sensitivity and specificity can be maintained at a high level.[28] The screening process is relatively simple and fast, and can be synchronized with the DD measurement process.[29] Therefore, TAT is a relatively simple and reasonable indicator for coagulation system. Several

studies[30,31] have pointed out that TAT measurement is of great clinical value in the early diagnosis of disseminated intravascular coagulation (DIC), acute myocardial infarction (AMI), and VTE, which can be used to evaluate changes in the body's coagulation system. It's been reported[32,33] that have pointed out that TAT >3.0ng/mL indicates that the level of thrombin in the body is increased, and the use of this level can help the diagnosis of the prethrombotic state. When the TAT level is higher than 4.2 ng/ml, the patient is considered to be in a pathological state.[34] At present, the TAT risk assessment criteria for the prethrombotic state have not been unified, and further researches are needed.

The survival of oncology patients with VTE must be considered. Even rough we only followed up the oncology patients for 10 months, we have found that the incidence of VTE in patients with malignant cancers was 22.03%, and no death case was found during our follow-up period, the association of VTE and related mortality in patients with oncology should be further assessed. Previous studies[35,36] have shown that patients with malignant cancer not only have a higher incidence of VTE than healthy people, but also have a lower quality of life. And the VTE shortens the survival time of cancer patients and seriously affects their quality of life. In the thrombosis risk assessment of cancer patients, various relevant laboratory indicators should be fully integrated to make the prevention and treatment of cancer-related VTE more targeted and individualized.[37] Several studies[38,39] have pointed out prophylactic anticoagulation therapy with low-molecular-weight heparin in patients with cancers can improve the patient's prognosis, reduce the risk of VTE and clinical mortality. All anticoagulation therapy should be closely observed for signs of bleeding during use.[40] Still, it's necessary to conduct long-term follow up to elucidate the survival conditions of oncology patients with VTE.

Several limitations in this present study must be considered. Firstly, the sample size is small, it may be underpowered to detect the potentially relevant risk factors, we will include more patients for consideration in the future study. Secondly, we only have conducted a 10 months follow-up, which may be not long enough to detect the mortality difference, the long-term survival conditions of patients with VTE should be further evaluated. Thirdly, we have not included the drug use for analysis limited by insufficient clinical data, future studies focused on the drug use and VTE are needed to guide the clinical prevention and treatment of VTE in oncology patients.

Conclusions

In conclusion, the incidence of VTE in patients with malignant cancers were 22.03%, and for patients with D-D >1.835mg/L and TAT >4.58µg/L, they may have higher risk for VTE, more attentions and early targeted strategies are needed for the prophylaxis of VTE.

List of Abbreviations

VTE   venous thromboembolism
APTT   activated partial thromboplastin time

PT	plasma prothrombin time
TT	thrombin coagulation time
FIB	fibrinogen
TAT	thrombin AT-III complex
D-D	D-dimer
ROC	receiver operating characteristic
AUC	under the curve
DIC	disseminated intravascular coagulation
AMI	acute myocardial infarction

Authors' Note

Declaration of Conflicting Interests

Funding

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