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 (RR 7.895, 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 1.835 mg/L and 4.58 mg/L respectively. For cancer patients with D-D >1.835 mg/L and TAT >4.58 mg/L, early interventions are needed for the prophylaxis of VTE.

Keywords
VTE, cancer, risk, thrombus, diagnosis, nursing, treatment

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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...
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 participate 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 participate 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 (Henni 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

Table 1. The Characteristics of 286 Included Patients.

| Items                  | Cases (n = 286) | Percentage (%) |
|------------------------|----------------|---------------|
| Gender Male            | 157            | 54.90         |
| Age (y) ≥60            | 102            | 35.66         |
| Age (y) <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         |
| TNM staging Stage III-IV | 169         | 59.09         |

Clinical and Applied Thrombosis/Hemostasis
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 ($all \ P > 0.05$).

**Logistical Regression Analysis**

As Table 3 presented, the logistical regression analysis indicated that D-D (RR7.895, $3.228 \times 19.286$) and TAT (6.122, $2.244 \times 16.695$) 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 4.58mg/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. At present, hypercoagulability, venous blood stasis, vascular wall damage are all high-risk factors that induce VTE. For patients with malignant cancers that develop VTE, they have worse clinical prognosis and lower quality of life. Many organizations including the American Society of Clinical Oncology and the European Society of Medical Oncology have formulated relevant guidelines for the prevention and treatment VTE. However, most clinical health care providers still underestimate VTE. 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. 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
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. 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. Several studies have pointed out that D-D for VTE detection has high sensitivity, which can be as high as 92%-100%. Some scholars 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. 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. 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. The screening process is relatively simple and fast, and can be synchronized with the DD measurement process. Therefore, TAT is a relatively simple and reasonable indicator for coagulation system. Several studies 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 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. 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 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. Several studies 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. 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

| Abbreviation | Description |
|--------------|-------------|
| 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
All data generated or analyzed during this study are included in this published article. Yan Qi and Xin Hu are equal contributors. Y Q, Hu, X H, Y S contributed to the conception and design of the research; Y Q, X H, J C contributed to the collection and analysis of the data; Y Q, X H and X Y contributed to the analysis and interpretation of the data; Y Q wrote the first draft of manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript. Our manuscript has been approved by the ethical committee of Shanghai tenth people’s hospital (2016-93), and written informed consents had been obtained from all the included patients.

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References
1. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-1424.
2. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol. 2020;7(5):e362-e363.
3. Cheng K, Faye AS. Venous thromboembolism in inflammatory bowel disease. World J Gastroenterol. 2020;26(12):1231-1241.
4. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020;382(17):1599-1607.
5. Huang D, Wong E, Zuo ML, et al. Risk of venous thromboembolism in Chinese pregnant women: Hong Kong venous thromboembolism study. Blood Res. 2019;54(3):175-180.
6. Liew NC, Alemany GV, Angchaisukiri P, et al. Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism. Int Angiol. 2017;36(1):1-20.
7. Law Y, Chan YC, Cheng SWK. Epidemiological updates of venous thromboembolism in a Chinese population. Asian J Surg. 2018;41(2):176-182.
8. Zhai Z, Kan Q, Li W, et al. VTE risk profiles and prophylaxis in medical and surgical inpatients: the identification of Chinese hospitalized patients’ risk profile for venous thromboembolism (DissoVE-2)—a cross-sectional study. Chest. 2019;155(1):114-122.
9. Vascular Surgery Group SBoCMA. Guidelines for the diagnosis and treatment of deep vein thrombosis (third edition). Chinese J General Surg. 2017;32(9):13-19.
10. Wu X, Li Z, Cao J, et al. The association between major complications of immobility during hospitalization and quality of life among bedridden patients: a 3 month prospective multi-center study. PLoS One. 2018;13(10):e0205729.
11. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology. 2019;156(6):1582-1599 e1581.
12. Watson HG, Keeling DM, Laffan M, Tait RC, Makris M. British Committee for Standards in H: guideline on aspects of cancer-related venous thrombosis. Br J Haematol. 2015;170(5):640-648.
13. Timp JF, Braeken SK, Versteeg HH, Canneiger SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-1723.
14. Tendas A, Scaramucci L, Cupelli L, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer: comment. J Thromb Haemost. 2014;12(5):805-807.
15. Mandala M, Falanga A, Roila F, ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2011;22(Suppl 6):vi85-92.
16. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2020;38(5):496-520.
17. Kruger PC, Eikelboom JW, Douketis JD, Hankey GJ. Deep vein thrombosis: update on diagnosis and management. Med J Aust. 2019;210(11):516-524.
18. Rafii H, Frere C, Benzidia I, et al. Management of cancer-related thrombosis in the era of direct oral anticoagulants: a comprehensive review of the 2019 ITAC-CME clinical practice guidelines. On behalf of the Groupe Francophone Thrombose et Cancer (GFTC). J Med Vasc. 2020;45(1):28-40.
19. Chen H, Tao R, Zhao H, Jiang J, Yang J. Prevention of venous thromboembolism in patients with cancer with direct oral anticoagulants: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99(5):e19000.
20. Samama CM, Laporte S, Rosencher N, et al. Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. N Engl J Med. 2020;382(20):1916-1925.
21. Qi Y, Hu X, Cui J, et al. Combined use of insoluble beta-glucan from the cell wall of Candida albicans and cyclophosphamide: validation in S180 tumor-bearing mice. Biomed Pharmacother. 2018;97:1366-1372.
22. Fu Y, Liu Y, Jin Y, Jiang H. Value of coagulation and fibrinolysis biomarker in lung cancer patients with thromboembolism [in Chinese]. Zhongguo Fei Ai Za Zhi. 2018;21(8):583-587.
23. Yin Q, Xue H, Jie C, et al. Identification of molecular markers for pre-thrombotic state: validation in rabbits with tibia fracture or lung cancer. Transl Cancer Res. 2019;9(44):10-19.
24. Cosmi B, Legnani C, Cini M, Favaretto E, Palareti G. D-dimer and factor VIII are independent risk factors for recurrence after anticoagulation withdrawal for a first idiopathic deep vein thrombosis. *Thromb Res.* 2008;122(5):610-617.

25. Wada M, Iizuka M, Iwadate Y, Yamakami I, Yoshinaga K, Saeki N. Effectiveness of deep vein thrombosis screening on admission to a rehabilitation hospital: a prospective study in 1043 consecutive patients. *Thromb Res.* 2013;131(6):487-492.

26. Jin J, Tan Z, Qiao L, et al. Clinical characteristics and prognosis of patients with venous thromboembolism after malignant tumor surgery. *Int J Respir Med.* 2019;29(3):201-206.

27. Rimpo K, Tanaka A, Ukai M, Ishikawa Y, Hirabayashi M, Shoyama T. Thrombin-antithrombin complex measurement using a point-of-care testing device for diagnosis of disseminated intravascular coagulation in dogs. *PLoS One.* 2018;13(10):e0205511.

28. Innocenti F, Gori AM, Giusti B, et al. Prognostic value of sepsis-induced coagulation abnormalities: an early assessment in the emergency department. *Intern Emerg Med.* 2019;14(3):459-466.

29. Innocenti F, Bianchi S, Guerrini E, et al. Prognostic scores for early stratification of septic patients admitted to an emergency department-high dependency unit. *Eur J Emerg Med.* 2014;21(4):254-259.

30. Hirano A, Suzuki Y, Umegaki H, et al. Relationship between blood coagulability and sense of burden among caregivers of patients with dementia. *Geriatr Gerontol Int.* 2019;19(8):804-808.

31. Mei H, Jiang Y, Luo L, et al. Evaluation the combined diagnostic value of TAT, PIC, tPAIC, and sTM in disseminated intravascular coagulation: a multi-center prospective observational study. *Thromb Res.* 2019;173:20-26.

32. Boccalon H, Boneu B, Emmerich J, Thalamas C, Ruidavets JB. Long-haul flights do not activate hemostasis in young healthy men. *J Thromb Haemost.* 2005;3(7):1539-1541.

33. Eilertsen AL, Qvigstad E, Andersen TO, Sandvik L, Sandset PM. Conventional-dose hormone therapy (HT) and tibolone, but not low-dose HT and raloxifene, increase markers of activated coagulation. *Maturitas.* 2006;55(3):278-287.

34. Ling K, Pang L, Chen Z, Lin M. Clinical analysis of the difference between male and female incidence of venous thrombosis disease with lower limb fracture. *Chinese J Bone Joint Injury.* 2013;28(10):941-943.

35. Mittal P, Heuft T, Richter DF, Wiedner M. Venous thromboembolism (VTE) prophylaxis after abdominoplasty and liposuction: a review of the literature. *Aesthetic Plast Surg.* 2020;44(2):473-482.

36. Skeik N, Westergard E. Recommendations for VTE prophylaxis in medically ill patients. *Ann Vasc Dis.* 2020;13(1):38-44.

37. Murphy RF, Williams D, Hogue GD, et al. Prophylaxis for pediatric venous thromboembolism: current status and changes across pediatric orthopaedic society of North America From 2011. *J Am Acad Orthop Surg.* 2020;28(9):388-394.

38. Sebaaly J, Covert K. Enoxaparin dosing at extremes of weight: literature review and dosing recommendations. *Ann Pharmacother.* 2018;52(9):898-909.

39. Novo-Veleiro I, Alvela-Suarez L, Costa-Grille A, Suarez-Dono J, Ferron-Vidan F, Pose-Reino A. Compliance with current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical inpatients: a prospective cohort study in a Spanish internal medicine department. *BMJ Open.* 2018;8(5):e021288.

40. Li J, Wu X, Li Z, et al. Nursing resources and major immobility complications among bedridden patients: a multicenter descriptive study in China. *J Nurs Manag.* 2019;27(5):930-938.