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Review Article

Advances in research on personalized venous thromboembolism risk assessment tools

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ABSTRACT

This paper describes the definition of venous thromboembolism and introduces to personalized venous thromboembolism risk assessment tools overseas. Thoughts are given on the development, amendment, application and validation of these tools. The paper provides a reference for building personalized venous thromboembolism risk assessment tools in China.

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1. Introduction

The incidence of venous thromboembolism (VTE) is up to 0.0816% in the United States,[1] and the incidence of VTE is also increasing each year in Asian populations.[2,3] VTE has become a public issue that seriously threatens human health and economic development.[4] It is therefore critical to timely perform VTE risk assessment and undertake VTE prevention in patients.[5] Relevant guidelines[6,7] suggest that it is necessary to use VTE risk assessment models (RAMs) for VTE risk assessment and stratification in patients and to take appropriate preventive measures to reduce the incidence of VTE. There are numerous studies on VTE RAMs overseas, but such research efforts still lack a systematic and effective system in China. This paper reviews the current state of the science and advances in research on personalized VTE RAMs overseas to provide a reference for building personalized VTE RAMs in China.

2. Definition of VTE

VTE includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PE). DVT refers to abnormal blood coagulation in a deep vein that blocks the lumen and results in venous reflux disorder.[8] Typical symptoms of DVT include swelling, pain, and even ulcers in the affected limbs. If thrombi detach and reach the lungs through the circulation, they may block pulmonary arteries and result in PE. PEs manifest as chest pain, dyspnea, and even sudden death. This condition is extremely harmful, and 25% of DVT patients suffer from sudden death due to PE.[9]

3. Personalized VTE risk assessment tools overseas

3.1. Caprini RAM

In the late 1980s, Joseph et al from the United States designed the Caprini VTE RAM based on clinical experience and the results of existing studies. The Caprini RAM, which has been translated and published in 12 languages,[10,11] includes approximately 40 risk factors. Each factor is given a score of 1–5 points by which the risk of VTE for patients is ranked into four grades: low risk (<3 points), moderate risk (3–4 points), high risk (5–8 points), and extremely high risk (>8 points); appropriate preventive measures and duration of therapy are recommended accordingly. Large-sample retrospective studies demonstrated the feasibility and effectiveness of the Caprini RAM for preventing VTE in patients.[12–14] In China, retrospective and prospective studies have also shown that this model is an effective tool to screen high-risk populations for

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VTE.[15] The generalizability of the Caprini RAM for VTE risk assessment in cancer patients was noted in the latest "Guidelines on Prevention and Treatment of Tumor-associated Venous Thromboembolism in China". The model has been widely used since it was developed. The greatest feature of this model is that it comprises more than 40 specific risk factors, including objective laboratory tests, while it also takes into account the effect of special physiological and pathological conditions in women on VTE. The model is comprehensive, specific, and highly feasible to use. Study on this scale is instructive for building VTE RAMs, particularly when VET risk assessment is still in its infancy in China.

3.2. Autar scale

The Autar scale, which was designed by Autar in 1996,[16] includes seven risk factors: age, body mass index (BMI), activity, special risks (use of contraceptives and pregnancy), trauma, surgery, and high-risk disease. Each risk factor is given a score of 1–7 points by which patients are divided into three groups: low risk (7–10 points, incidence <10%), intermediate risk (11–14 points, incidence 11%–40%), and high risk (≥15 points, incidence >40%); the aim is to provide a simple and convenient VTE assessment scale for paramedics. Small-sample reliability testing of the model showed a Pearson coefficient of 0.98, a sensitivity of 100%, and a specificity of 81%.[16] Test-retest reliability evaluation showed a Cronbach's α coefficient of 0.88–0.95 and an internal correlation coefficient of 0.94–0.99.[17] Additionally, test-retest reliability evaluations showed a Cronbach's α coefficient of 0.78–0.90.[18] These studies indicate that the Autar scale can appropriately classify the risk of VTE in patients. This scale is characterized by a detailed division of BMI, activity, and trauma. In particular, it details the effect of trauma to different parts of body on the incidence of VTE for common traumas in surgical patients, which provides a theoretical and practical basis for the scale's division of trauma.

3.3. Risk assessment profile (RAP) score

The RAP score,[19] which was designed in 1997, includes four risk factors: age, underlying diseases, iatrogenic factors, and trauma-related factors. Each risk factor is given a score of 2–4 points by which patients are divided into two groups: high risk (≥5 points) and low risk (2–4 points); it is mainly for VTE risk assessment in trauma patients.[19] Currently, there are two views on the RAP score in clinical application. One view is that this score can achieve effective risk stratification for VTE in trauma patients. Supporting this idea, one study found that the RAP score had a sensitivity of 0.82 and a specificity of 0.57 in the moderate-risk group, while it had a sensitivity of 0.15 and a specificity of 0.97 in the high-risk group.[20] This result indicates that the RAP score is highly correlated with the risk of VTE in trauma patients and thus is an effective risk assessment tool. The other view is that this score cannot achieve effective risk stratification of VTE in trauma patients. Supporting this idea, a retrospective study reported three cases of VTE in 26 low-risk patients and suggested the critical score of 5 points being invalid. Anticoagulation is recommended for all trauma patients, unless there is a clear contraindication.[21] Although further investigation is still needed to determine whether the RAP score can be used as a VTE risk assessment method in trauma patients, this score presents the relationship between abbreviated injury scale (AIS) and VTE, while it also proposes transfusion, repair, or ligation of large blood vessels as a risk factor for VTE, thus providing a theoretical reference for the prevention of VTE.

3.4. Kucher scale

The Kucher scale was published in 2005 and includes eight common risk factors. These factors are assigned to the following scores in accordance with the level of risk: malignant tumor, history of VTE, and hypercoagulable state of blood – 3 points each; moderate surgery – 2 points; and old age, obesity, bedridden, and estrogen replacement therapy or oral contraceptives – 1 point each. When a patient scores ≥4 points, the risk of developing VTE increases.[22] Kucher combined this scale with a computer information system and programmed an early warning procedure for risk that automatically scores based on relevant information from patient admission and discharge records. When the total score is ≥4 points, the computer sends an early warning and reminds medical personnel of an increased risk of VTE for the patient. This scale combines with computer systems and performs dynamic assessment of the risk of VTE in patients. It can remind clinicians and paramedics of the risk of VTE in patients in a timely manner and thus greatly reduce the workload of medical staff.

3.5. Padua prediction score

In 2010, Barbar et al[23] designed the Padua prediction score by adding thrombosis-related clinical scenarios based on the Kucher model. The Padua prediction score includes 11 risk factors: active cancer, history of VTE, decreased activity, thrombophilia, trauma or surgery in the last month, old age (≥70 years), heart/lung failure, acute myocardial infarction/stroke, acute infection/rheumatic disease, obesity (BMI ≥30 kg/m^2), and ongoing hormone therapy. Each risk factor is assigned a score of 1–3 points, by which patients are divided into two levels of risk: low risk (<4 points) and high risk (≥4 points) to assess the risk of VTE in internal medicine inpatients. One study showed that the Padua prediction score is highly associated with patients who died from VTE.[24] This score was recommended for VTE risk assessment in internal medicine inpatients by the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Antithrombotic Therapy and Prevention of Thrombosis.[25] The Padua prediction score is characterized by the inclusion of heart/lung failure, acute myocardial infarction/stroke and acute infection/rheumatic disease among the various thrombotic clinical diseases.[23] This focus suggests that certain special diseases raise the risk of developing VTE. Moreover, the population previously thought to be at high risk of DVT was surgical and trauma patients. Caution is needed when evaluating and intervening for high-risk medical patients.

3.6. The IMPROVE RAM

In 2011, Spyropoulos et al[26] reported the IMPROVE RAM that was developed based on multiple regression analysis of the risk factors for VTE in 15,156 patients from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE).[27] The IMPROVE RAM includes seven risk factors: age >60 years, history of VTE, stay in intensive care unit (ICU) or coronary care unit (CCU), paralysis of the lower limbs, immobilization, thrombosis physique, and cancer. Each risk factor is scored 1–3 points, and a total score ≥2 is defined as high risk. In 2014, Rosenberg et al[28] performed external validation of the IMPROVE RAM in 19,217 patients. This group yielded an area under the receiver operating characteristic (ROC) curve of 0.7, and the authors recommended defining patients with a score of ≥3 points as the high-risk population for VTE. This model was created and validated using large sample populations. It particularly emphasizes a higher risk of VTE in the population in the ICU or CCU and warns clinicians to pay attention to the risk of VTE in critically ill patients.

3.7. Woller model

To simplify the VTE assessment model and improve the rate of implementing VTE prevention, Woller et al[29] established and validated the Woller model, which included four risk factors: history of VTE, bedridden, central venous catheter placement, and cancer. Compared with the area under the ROC curve (AUC) of the Kucher score, the Woller model had a greater AUC of 0.843. In 2012, members of the IMPROVE model questioned the Woller model, and it was noted that the predicted rate of VTE would be exaggerated by using ICD-9 codes as an outcome measure.[30] In the same year, Woller et al[31] responded that the model could be corrected by changing the risk factors to history of VTE, physician-prescribed bed rest, central venous catheter placement, and cancer. After these changes, the AUC of the model was corrected to 0.74. Meanwhile, Woller et al noted that the risk of VTE in patients is constantly changing, making it necessary to design dynamic RAMs and use electronic means to assess the patients. This group also admitted that further prospective trials are needed to verify the model's validity, irrespective of the Woller or IMPROVE model.

4. Conclusions

Virchow proposed that the three elements for DVT formation are impaired blood flow, injured vein wall, and hypercoagulable state.[32] Throughout the history of the development of VTE assessment tools overseas, the risk of VTE has been found to be elevated not only in surgical and trauma patients. In recent years, there have also been many studies on VTE risk assessment and intervention in internal medical patients. Currently, the work on VTE risk assessment in China is still in its initial exploration stage. Although clinical and healthcare workers have been aware of the importance of personalized risk assessment and preventive intervention for VTE in patients, there remains a lack of reliable, effective, and practical risk assessment tools.[33] The risk assessment tools overseas are relatively mature; however, owing to the large differences in race, types of illnesses, lifestyles, and genetic factors, the risk factors included in foreign scales cannot reflect the risk of VTE in Chinese patients. Therefore, we cannot directly apply these assessment tools in Chinese patients. It is necessary to build suitable personalized RAMs by combining the characteristics of Chinese population.

4.1. Collecting RAM risk factors

According to the content of foreign VTE risk assessment tools, the following factors are being emphasized: age, gender, medical history and family history of thrombosis, surgical site, time, chronic diseases, activity level, risk of bleeding, fractures and trauma, genetic factors, cancer, hormone replacement therapies, blood transfusion, thrombosis physique, ICU patients,[34] mechanical ventilation, chemotherapy, heart/lung failure, acute myocardial infarction/stroke, acute infections/rheumatic disease, among other clinical diseases. In China, research has also found that smoking,[35] hypertension,[36] diabetes,[37] and stroke[38] are among the risk factors inducing VTE. To ensure the completeness and effectiveness of risk factors, it is critical to collect as much relevant clinical information and data as possible, with a tendency to prefer objective, reliable risk indicators.

4.2. Determining a RAM building method

Multi-center, large-sample retrospective studies need to be conducted in China, which, by learning from the assessment tools overseas, can use multiple stepwise regression to analyze the clinical data of patients, screen for VTE risk factors, determine their degree of influence, divide the corresponding risk levels, and determine the appropriate prevention methods. Thus, we can ultimately build RAMs suitable for Chinese patients, followed by verification of clinical reliability and validity and subsequent clinical validation. Once the RAM is built, optimization analysis needs to be conducted to improve the rate of implementation of the model.

4.3. Considerations in RAM building

In the course of intervening for patients at risk for VTE, the first thing to consider is the balance between bleeding and anticoagulation. Therefore, it is necessary to take into consideration the risk of bleeding in patients when building RAMs.[39] The bleeding risk score can be developed by referring to foreign bleeding risk scores[40] in combination with the conditions of Chinese patients.

4.4. Prospects for RAMs

With the constant development of electronic health information systems, it will become increasingly preferred by healthcare workers to program RAMs into specialized medical computer systems and thereby develop specialized medical tools for risk assessment for VTE. Such specialized medical tools have multiple advantages such as easy access to the database and effective, continuous, dynamic tests, making it possible to balance the risk of bleeding, timely and dynamic assessment of the risk of VTE in patients, and implementation of appropriate preventive measures. Therefore, the construction of VTE RAMs suitable for the national conditions in China and the further development of these conditions into electronic assessment tools for different populations will become the future trend in the development of VTE RAMs.

Conflict of interest

All contributing authors declare no conflicts of interest.

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