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A Narrative Review of Prediction Models for Postoperative Recurrent Venous Thromboembolism

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Abstract

Venous thrombosis has a great impact on patients' quality of life after relapse. The present study summarizes the prediction model of recurrent venous thrombosis published in recent years regarding the applicable population, evaluation index, and predictive performance. It aims to provide a reference for the construction of a more reasonable predictive model and application of venous thrombosis recurrence. A query was conducted on EBSCO, Ovid, PubMed, Wanfang, and CNKI databases using the keywords "Venous Thromboembolism", "Recurrence", and "Prediction Models" to assess the prediction model of recurrent venous thrombosis. A total of five major models related to the recurrence of venous thrombosis were included. The models differed in reliability, validity, scoring method, evaluation method, and scope of application.

Keywords: Prognostic models, Recurrence, Venous thromboembolism

1. Background

Venous thromboembolism (VTE) is a common postoperative complication observed in hospitalized patients. The marked improvements in diagnosis and treatment measures has significantly increased the screening rate; nonetheless, based on the pathological characteristics of VTE itself, the recurrence rate of the disease is still high. The VTE recurrence refers to the detection of a new thrombus in a different or the same part of the previous VTE (1). The results of a prospective study (2) demonstrated that the cumulative recurrence rate of VTE patients within 10 years after discontinuing oral anticoagulants was as high as 40%. At the same time, the high recurrence rate is associated with a high mortality rate.

The mortality rate of elderly patients with VTE recurrence is 20.5%, and the mortality rate of patients with malignant tumors and VTE recurrence within 10 years is 88.1% (3-4). In response to this problem, the 10th edition of the guidelines issued by the American College of Chest Physicians (ACCP) recommends that the anticoagulation regimen should be selected on the premise of fully measuring the risk of recurrence and bleeding in patients (5). The VTE recurrence risk prediction model is based on a large sample of reliable data as a risk assessment tool obtained through different mathematical algorithms. Its core research groups are concentrated in Canada, the United States, Norway, and other regions.

In recent years, there has been a growth in the number of related articles. A total of 40%-60% of hospitalized patients in some countries are at risk of developing VTE; however, the prevention rate is significantly lower than that in other Asian countries (6), and no research has been retrieved on recurrence prediction models. The present article aims to review VTE recurrence risk prediction models from the applicable population and evaluation indicators, summarize the current research status of VTE recurrence prediction at home and abroad, and provide references for the construction of VTE recurrence prediction models suitable for various forms.

2. Prediction model for recurrence of venous thromboembolism

2.1. HERDOO2 score

The HERD002 score is a recurrence prediction model obtained by Rodger et al. (7) in 2008 through prospective follow-up of 600 VTE patients without obvious predisposing factors. The HERD002 score refers to hyperpigmentation, edema, or redness of the lower extremities; D-dimer level ≥250 μg/L; Obesity with body mass index ≥30; or Older age, ≥65 years. The sensitivity and accuracy of this model were reported as 0.88 and 0.57, respectively. Combining 1 risk index counts 1 point, a total score equal to 1 is low risk, and a total score greater than or equal to 2 is high risk. Subsequently, two studies (8-9) successively carried out external verification of the HERDOO2 score, confirming that this model has good repeatability. Low-risk patients, based on the HERDOO2 score, can safely discontinue the drug upon the completion of short-term anticoagulation therapy. Nevertheless, the HERDO02 score was only applicable to female patients with no obvious disease

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cause for the first occurrence of VTE at the beginning of the development. During the model validation process, attempts were made to use it in male patients, and no relevant results were reported. Due to the complex conditions of clinical patients, this model has simple entries, and the application population is relatively limited. It is more suitable for patients to self-assess the risk of recurrence outside the hospital. Further research is needed to determine the timing of drug withdrawal and adjust the anticoagulation time according to the risk of recurrence (10).

2.2. Vienna venous thromboembolism recurrence prediction model

In 2010, Austria Eichinger (11) et al. developed the Vienna VTE recurrence prediction model. The researchers followed up 929 patients with VTE for the first time and no obvious disease cause (average follow-up of 43.3 months) and collected common clinical and laboratory test results in advance. Cox regression analysis was used for multivariate analysis, and four independent risk factors were obtained: proximal deep venous thrombosis (DVT), male gender, pulmonary embolism, and abnormal increase in D-dimer concentration. This model predicts that the areas under the curve of the cumulative recurrence rate within 1 and 5 years are 0.674 and 0.646, respectively. At the same time, a nomogram was developed for calculating the patient's recurrence risk score and the corresponding expected cumulative recurrence rate within 1 and 5 years. Subsequently, Eichinger (12) et al. updated this model, and the results illustrated that with the passage of time, the corresponding risk ratio of each variable had a certain degree of reduction. Different columns are designed according to different time points after stopping taking anticoagulant drugs. The line chart also forms the corresponding calculation program based on the network algorithm, which makes up for the limitation of the more complicated calculation method and significantly improves the flexibility of this model.

However, Tritschler et al. (13) externally verified the updated model, and the areas under the curve of the cumulative recurrence rate within one and two years were only 0.39 and 0.43, respectively. They believed that the Vienna VTE recurrence prediction model is not suitable for the recurrence risk prediction of elderly VTE patients. In addition, genetic factors were ignored in the design process, and the effect of family history on patients was not analyzed. The clinical prediction may cause false negatives; the prediction result is the specific cumulative recurrence rate, and the researcher did not analyze the risk factors for the recurrence rate. Factors for recurrence rates and lacked corresponding preventive measures.

2.3. DASH score

In 2012, Tosetto et al. (14) in Italy followed up 1,818 patients who were treated with vitamin K antagonists and had no obvious disease cause for the first occurrence of VTE. According to the results of Cox regression analysis, the DASH score was obtained. The D-dimer concentration was abnormal, and the age was less than 50 years. Age, male gender, and hormone therapy are risk factors for recurrence. The area under the curve after internal verification was 0.71, signifying good accuracy. If the above risk factors were met, one point was counted. When the total score is less than or equal to 1, the annual recurrence rate is 3.1%; when the total score is 2, the annual recurrence rate is 6.4%; and when the total score is greater than or equal to 3, the annual recurrence rate is 12.3%.

Although researchers have stratified the age of patients with VTE recurrence, the risk factor is more controversial for the age range of less than 50. Tosetto et al. (15) found that even if the DASH score is less than or equal to 1, the annual recurrence rate of patients over 50 years old is still greater than 5%. MacDonald et al. (16) followed up 145 patients with primary VTE to discontinue regular anticoagulation therapy for three months based on the DASH score. After a 12-month follow-up, they found that the recurrence rate of patients with a DASH score less than or equal to 1 was 6.2%, which was much higher than the average level of the model. Moreover, the DASH score pays little attention to clinical diseases that may cause VTE recurrence, and its clinical predictive efficacy needs further verification.

2.4. Ottawa venous thromboembolism recurrence prediction model

The recurrence rate of VTE in cancer patients is three times higher than that in noncancer patients (17). Louzada et al. (18) conducted a retrospective study on cancer-related VTE patients and obtained the Ottawa VTE recurrence prediction model. The model has a total score of -3-3 points, 1 point for high-risk predictors (female, lung cancer, previous VTE history), and negative points for low-risk predictors (breast cancer = -1 point, breast cancer tumor stage I = -2 points); the risk of VTE recurrence of patients with a score less than or equal to 0 is less than or equal to 4.5%. The risk of VTE recurrence in patients with a score greater than or equal to 1 is greater than or equal to 19%, the sensitivity of the model is 100%, and the negative predictive value is 98.1%, which is low. The risk elimination rate was 48.1%, and the negative likelihood ratio was 0.155.

Astruc et al. (19) adjusted the predictive indicators of the model on the basis of external verification and the revised scores (1 point each for the female gender, lung cancer and VTE previous history, breast cancer and breast cancer tumor stage I and II stage -1 each). The risk of recurrence was divided into three levels: low (-1 point), medium (0 points), and high (1 point). Delluc et al. (20)

conducted a meta-analysis on the accuracy of the Ottawa VTE recurrence model, including nine eligible studies and 14,963 patients. The results proved that the sensitivity and discrimination of the modified prediction model are better than those of the previous model, which is suitable for use in clinical cancer patients. However, this model only recognizes that lung cancer is a risk factor for VTE recurrence. Pancreatic cancer, ovarian cancer, and brain tumors are all related to VTE recurrence (21, 22), which was not discussed in the study. The researchers calculated that women are VTE recurrence independent risk factors, and this result is different from other models. The reason for this situation can be ascribed to the fact that the researchers failed to take into account the complexity of cancer location and tumor classification during the data collection process, resulting in false negatives for some risk factors.

2.5. Leiden thrombosis recurrence risk prediction model

Regarding the complexity of the patient's disease, in 2019, Timp et al. (23-25) extracted patient data from five cohort studies and developed a Leiden Thrombosis Recurrence Risk Prediction model (L-TRRiP), which includes four versions. The predictive indicators come from three aspects: clinical, laboratory test indicators, and genetic factors. The researchers discussed the performance and clinical applicability of the model and believed that Model C is the most suitable for popularization. The risk factors include male gender and venous thrombosis. The risk factors include male gender and venous thrombosis.proximal DVT, pulmonary embolism+slapped fossa DVT, surgery, pregnancy/ puerperium, hormone therapy, plaster immobilization,bed rest, cardiovascular history, blood type (type O or non-type O), and Leiden mutations in the clotting factor V gene, which only contains two laboratory inspection indicators.

Its suitability for the recurrence risk assessment of all VTE patients other than cancer-related thrombosis has made it advantageous to the above prediction model. The predictive index is composed of a set of comprehensive variables and has good discriminative performance, as well as a wider predicted absolute risk range. The result is that the specific value indicates the patient's risk of recurrence within two years. The disadvantage is that the calculation method of the recurrence risk of this model is more complicated, and each variable corresponds to different correlation coefficients. At the time of application, it needs to be combined with applications or install professional calculation software in the electronic medical record. This model was developed in 2019, and further research is needed for accuracy and applicability.

Some prediction models have their own characteristics, and the prediction performance of all models needs to be further externally verified in a large sample of people. From the perspective of the applicable population, the inclusion and exclusion criteria of each model are different. The same applies to the three models without obvious disease triggers. The HEROOD2 score is only applicable to female patients, and the DASH score is included in patients taking hormones. There is a lack of a universal version of the VTE recurrence risk prediction model. Based on the results of the stratification of outcome indicators, most models are binary classifications. An overly rough outcome stratification may lead to insufficient or excessive anticoagulation, further aggravating the risk of VTE recurrence or bleeding in patients. From the perspective of research status, most of the research types in the relevant literature are observational studies, and no relevant studies have been retrieved to guide patients to take drugs based on the prediction results of a model, indicating that researchers in various countries are still in the exploratory stage of research on predicting the performance of models. From the point of view of drug guidance, the developer simply stated that it can decide whether to continue treatment based on risk stratification; nonetheless, the relevant content, such as the choice of anticoagulant drugs and anticoagulant treatment time, as well as risk assessment nodes, have not been elaborated.

3. Current research status of venous thromboembolism recurrence prediction

Foreign researchers have conducted a wide range of studies on the prediction of VTE recurrence, and the identified risk factors include basic patient characteristics, laboratory test indicators, genetic indicators, and many other issues (26). Large-sample follow-up cohort studies are relatively mature. At the same time, foreign scholars will gradually refine the research on this basis and improve the prediction performance by limiting the target population, treatment plan, underlying disease, or the type of first VTE (27-28). To reduce the recurrence rate, the guidelines (5) recommend that patients with cancer-related thrombosis and those with the recurrence of VTE can choose low-molecular-weight heparin drugs for anticoagulation therapy and at the same time extend the duration of anticoagulation therapy. Nevertheless, the results of a multicenter randomized controlled study (29) indicated that the incidence of the postthrombotic syndrome and quality of life in the extended anticoagulation treatment group were not significantly different from those in the conventional treatment group. The clinical utility in patients with coagulation is low; therefore, in the application process of the VTE recurrence prediction model, it is necessary to combine it with the actual clinical situation. During anticoagulation treatment, close attention should be devoted to preventing the occurrence of anticoagulant-related bleeding events.

At present, numerous studies focus on VTE treatment, risk factor analysis, prevention, and management. Some researchers have introduced VTE risk assessment models for middle-aged and elderly patients, as well as children (30-33). There are few studies on VTE recurrence. The recurrence rate of VTE patients in internal medicine is 15.4% within 2 years (32). High-risk factors included severe lung disease, nephrotic syndrome, malignant tumors, and nonstandard anticoagulation therapy. D-dimer, high-sensitivity C-reactive protein, fibrin Proto, platelet, and Caprini scores were all independent risk factors for cancer-related thrombosis recurrence ($P<0.01$). Regarding the study of VTE recurrence prediction models, multiple countries are still in their infancy. The possible reasons are as follows:① insufficient storage and utilization of medical information big data (33), the construction of predictive models requires the support of large-scale scientific data. However, due to the imperfect medical information system, as well as fragmentation of medical data and patient disease information, relevant data are only used briefly and lack in-depth research. ② It is related to researchers' insufficient attention to VTE recurrence. In recent years, relevant guidelines have mostly studied VTE as a complication of surgery or other diseases. Recommendations are mostly focused on the diagnosis of VTE, the use of anticoagulant drugs, and physical preventive measures. In all aspects (34-36), there are few contents, such as recurrence risk stratification and early diagnosis, in VTE patients. ③ It is related to the medical staff's insufficient knowledge of VTE-related issues (37, 38).

Therefore, researchers can build on the experience of establishing the VTE recurrence prediction model reported in the current literature and cooperate with the medical big data platform to establish an early follow-up cohort of VTE patients, set up a special institution to be responsible for the follow-up of patients, refine the risk factor classification, and form a suitable VTE recurrence risk prediction model for the local population. Load the mature model into the electronic medical record system and the out-of-hospital follow-up system to improve the primary prevention effect of patients at high risk of VTE recurrence and take corresponding treatment measures as soon as possible to improve the prognosis of patients.

4. Conclusion

Due to the different research objects and applicable environments of VTE recurrence by researchers, the VTE recurrence prediction model presents a diversified development trend, and different populations with different disease characteristics apply different prediction models. Many countries have not yet developed the relevant models. The effective identification of the high-risk groups of VTE recurrence and the full-process VTE management of patients is the key to reducing the VTE recurrence rate. In future research on VTE recurrence, the following issues should be considered. 1) Further integrate the existing literature report models, compare and analyze the risk factors and outcome indicators, extract common factors, and provide guidance for establishing a suitable VTE recurrence model. 2) In the development process, full consideration should be given to clinical applicability, convenience, and economy. Moreover, the included laboratory test indicators should be specific to effectively screen high-risk groups without increasing the economic burden of patients. 3) Consider developing a patient self-evaluation model and using gradually improved mobile medicine as a carrier to encourage patients to participate in the prevention and management of VTE recurrence.

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