ORIGINAL ARTICLE

Clinical Study on the Screening of Lower Extremity Deep Venous Thrombosis by D-Dimer Combined with RAPT Score Among Orthopedic Trauma Patients

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Abstract

Background Among the causes of mortality in patients with lower extremity fracture following surgery, lower extremity deep venous thrombosis (DVT) is a leading one. To lower the morbidity and mortality, early screening and preventive anticoagulation therapy are essential in clinical study. Common screening methods, including risk prediction tools, imaging tests and D-dimer test, had various drawbacks. The study aimed to establish a new method, that is, D-dimer combined with Risk Assessment and Predictor Tool (RAPT) score, for screening the lower extremity DVT among patients with lower extremity fracture and evaluate its clinical value.

Materials and Methods The RAPT score, plasma D-dimer and lower extremity venous ultrasonography examination reports were collected from Department of Emergency Surgery & Orthopaedic Surgery from July 2019 to December 2019, and the data were analyzed retrospectively. Regarding the lower extremity venous ultrasonography examination report as the "gold standard" to determine whether DVT exists, the sensitivity, specificity and area under the curve (AUC) of RAPT score alone, plasma D-dimer alone and combination of them in screening lower extremity DVT were analyzed and evaluated.

Results 197 patients were enrolled in the study. There were significant differences in D-dimer level and RAPT score between DVT group and non-DVT group ($P < 0.01$). The sensitivity, specificity and AUC of RAPT score and D-dimer in screening lower extremity DVT were 78.12%, 56.44%, 0.723 and 97.71%, 25.74%, 0.803, respectively. The optimal diagnostic value of D-dimer decided by Youden's index was 1.125 µg/ml. The sensitivity and specificity of the method by combining RAPT score with this new D-dimer threshold were 96.88% and 42.57%, respectively, and AUC was 0.812.

Conclusion Higher diagnostic accuracy could be achieved by combining RAPT score with new D-dimer threshold. This novel diagnostic method is potential in the clinical diagnosis of DVT among orthopedic trauma patients.

Keywords Lower extremity · Deep venous thrombosis · RAPT score · D-dimer · Fractures · Bone

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of orthopedic trauma [1]. It was reported that the estimated incidence of DVT varies 5%–58% in orthopedic trauma patients [2, 3]. DVT mainly occurs in the lower extremity of orthopedic trauma patients, among which most patients are asymptomatic, bringing a big challenge to the clinical diagnosis [4]. In some severe cases, thrombus of DVT that sheds off may enter the pulmonary circulation and cause PE, even sudden death [5].

Anticoagulation is a primary therapy towards DVT [6]. However, it is not reasonable to apply anticoagulation agents to all suspected DVT patients, with the risk of hemorrhage

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associated with this therapy. Therefore, prompt and accurate identification of lower extremity DVT is crucial and urgent, which can help provide appropriate treatment and avoid thrombus extension and PE [7].

Screening methods for DVT mainly include imaging tests, risk prediction tools and D-dimer test. Among the common imaging tests, such as venography and ultrasound, venography is the gold standard for the diagnosis of DVT. However, invasion and requirement of potentially hazardous contrast agents of venography restricts its application in clinical [8]. Ultrasound is widely used for the diagnosis of DVT, whilst it is inconvenient for fracture patients and requires an experienced radiologist to complete it [9]. Risk Assessment and Predictor Tool (RAPT) is a simple DVT assessment scale specifically for orthopedic patients, including previous medical history, iatrogenic factors, injury-related factors and age. It categorizes patients as low-, moderate- and high-risk probability basing on their risk of developing DVT; however, its low sensitivity is a concern [10]. D-dimer is a degradation product of cross-linked fibrin, which reflects the fibrinolysis status of the system. D-dimer level screening is an exclusion test, with the reason that elevated D-dimer level can be seen in various diseases, including DVT as well [11].

A novel and more accurate diagnostic method of DVT is in urgent need in clinical. To the best of our knowledge, combination of D-dimer examination and RAPT score in screening lower extremity DVT is a debut report. We aimed to improve the diagnosis process of lower extremity DVT.

Materials and Methods

Setting

This was a retrospective study using data from patients hospitalized for lower extremity fracture in the Department of Emergency Surgery & Orthopaedic Surgery, from July 2019 to December 2019. This research has been approved by the IRB of the authors' affiliated institutions.

Patients

Inclusion criteria: (1) single lower extremity fracture; (2) closed fracture; (3) age ≥ 18 years.

Exclusion criteria: (1) old fracture (> 3 weeks); (2) pathological fracture; (3) coagulopathy; (4) incomplete information.

Study Design

In our department, patients received chemical thromboprophylaxis immediately after admission. D-dimer and ultrasound examination of lower extremity veins were routinely

performed within 24 h after admission and on the 2nd day after operation. Patients diagnosed as thrombosis by ultrasound would transfer to full anticoagulation therapy. Data of plasma D-dimer, lower extremity venous ultrasound report and RAPT score of the patients on the 2nd day after operation were retrospectively collected.

Patients were divided into DVT group and non-DVT group, based on ultrasound report as the gold standard. Age, sex, RAPT score and D-dimer were compared between the two groups. According to RAPT score, the diagnosis of DVT was ruled out for those patients in the low-risk group and further examination was needed for those in the intermediate and high-risk group. The sensitivity, specificity, positive and negative predictive value, and area under the receiver operating characteristic (ROC) curve (AUC) of RAPT score and D-dimer were evaluated, respectively.

Given the poor specificity of D-dimer threshold used widely nowadays ($0.5 \mu\text{g/ml}$), we put forward a new D-dimer threshold derived from ROC curve combined with Youden's index. The diagnosis of the lower extremity DVT was excluded for the patients whose RAPT score was estimated to be low-risk and D-dimer was less than the new D-dimer threshold, otherwise, the ultrasound examination of lower extremity veins was to be carried out. The sensitivity, specificity and AUC of this method in screening lower extremity DVT were evaluated.

Statistical Analysis

Normally distributed data are summarized as mean $\pm$ standard deviation (SD). Nonparametric data are reported as median and interquartile range (IQR). Differences between groups were analyzed using *t* test if in accordance with the normal distribution, otherwise, using a non-parametric test. Sensitivity, specificity, positive and negative predictive value of different diagnostic methods were assessed by χ^2 test.

Taking a series of continuous variables as the cut-off value, the ROC curve was established. AUC was used to evaluate accuracy of each diagnostic method. The best diagnostic point was accessed by Youden's index.

A *P* value of less than 0.05 was considered statistically significant. Data management and statistical analyses were performed using Statistical Package for the Social Sciences, version 22.0 (SPSS, Chicago, IL).

Results

Patients

197 patients were enrolled in the study, including 131 male patients and 66 female patients (51 ± 11 years). In terms of fracture types, there were 72 cases of middle and upper

Table 1 Patient profile

	All the patients	DVT group	Non-DVT group	<i>P</i>
Sex (male/female)	131/66	67/29	64/37	0.340
Age (y), mean $\pm$ SD	51 $\pm$ 19	53 $\pm$ 17	50 $\pm$ 21	0.20
D-dimer (ug/ml), median (IQR)	1.11(0.85, 2.95)	2.35 (1.10, 4.13)	0.98 (0.50, 1.12)	< 0.01
RAPT score, median (IQR)	7 (4,11)	10 (6,12)	4 (3,9)	< 0.01

Table 2 Comparison of different screening methods

	Sensitivity	Specificity	PPV*	NPV**
RAPT score	78.12%	56.44%	63.33%	74.02%
D-dimer (0.5 ug/ml)	97.71%	25.74%	55.62%	92.86%
D-dimer (1.25 ug/ml)	86.46%	57.43%	65.87%	81.69%
RAPT and D-dimer (1.25 ug/ml)	96.88%	42.57%	61.59%	93.48%

PPV positive predictive value, NPV negative predictive value

femoral fractures (including femoral neck, intertrochanteric fractures and middle and upper femoral shaft fractures), 37 cases of periarticular fractures, 43 cases of lower leg and ankle fractures, and 45 cases of both lower extremity.

Among all the 197 patients enrolled in the study, 96 patients were diagnosed with DVT, and the other 101 patients were included in non-DVT group. There were no significant differences in age and gender between DVT-group and non-DVT group (age $\chi^2=0.912$, $P>0.05$; gender: $\chi^2=1.367$, $P>0.05$) (Table 1). As to the type of DVT, there were 13 cases of proximal DVT and 83 cases of distal DVT. In the distal DVTs, there were 79 cases of intermuscular venous thrombosis, accounting for 95.18% (79/83). The median D-dimer level of DVT group and non-DVT group was 2.35 ug/ml (IQR 1.10–4.13 ug/ml) and 0.98 ug/ml (IQR 0.50–1.12 ug/ml), respectively, which showed significant difference ($Z=5.409$, $P<0.01$). Compared with non-DVT group (4, IQR 3–9), the RAPT score of DVT group (10, IQR 6–12) was significantly increased ($Z=7.317$, $P<0.01$).

Accuracy of Different Methods in Screening Lower Extremity DVT

RAPT Score

According to the RAPT score, the patients enrolled were divided into low-, intermediate- and high-risk groups. The thrombus incidence rates were 25.97% (20/77), 58.82% (60/102) and 88.89% (16/18), respectively.

The sensitivity and specificity of this method were 78.12% and 56.44%, respectively (Table 2). The AUC of RAPT score was 0.723 (Fig. 1), which showed that RAPT was valuable in diagnosing DVT of lower extremity in the orthopedic trauma patients.

Fig. 1 ROC curve of RAPT

D-Dimer

With 0.5 μ g/ml as the threshold of D-dimer to screen lower extremity DVT, the sensitivity and specificity were 97.71% and 25.74%, respectively. The AUC of D-dimer was 0.803 (Fig. 2). The new D-dimer threshold derived from ROC combined with Youden's index was 1.125 μ g/ml. The sensitivity and specificity of this new threshold were 86.46% and 57.43%, respectively.

Fig. 2 ROC curve of D-dimer

Fig. 3 ROC curve of RAPT combined with new threshold of D-dimer

Combination of RAPT Score and New Threshold of D-Dimer

The sensitivity, specificity and AUC of this method were 96.88%, 42.57% and 0.812 (Fig. 3), respectively. The diagnostic accuracy is higher than that of using RAPT score alone or D-dimer alone.

Discussion

Among the causes of mortality in patients with lower extremity fracture following surgery, lower extremity DVT is a leading one. To lower the morbidity and mortality [3], early screening and preventive anticoagulation therapy are essential in clinical study. Therefore, establishment of an effective early screening method for patients with lower extremity fracture is in urgent need.

Intermuscular vein thrombosis is isolated thrombosis in the soleal and gastrocnemial veins [1]. The main hazard of intermuscular vein thrombosis is thrombus organization and propagation [12]. Thrombus organization can lead to vascular cavity stenosis and occlusion, whilst propagation can cause secondary thrombosis in the proximal veins, even fatal PE in severe cases [13]. However, most patients with intermuscular vein thrombosis are not suffered with obvious symptoms due to collateral circulation. Although a small part of those patients present with local pain, it is easily masked by the pain caused by fracture. It is essential to build an effective screening method, as 82.29% of the total DVT in lower extremity was intermuscular vein thrombosis in our study.

High coagulation and hyperfibrinolysis state are found in DVT conditions, and serum D-dimer level increases in DVT patients as a specific degradative substrate of the crosslinked fibrin, which is significantly increased in hyperfibrinolysis state [14]. In clinical practice, D-dimer is widely used as an exclusion method for DVT [15]. However, the level of D-dimer can be affected by many factors, such as blood diseases, inflammation, tumor, pregnancy, and age [16]. Currently, the sensitivity and specificity of D-dimer varies in 75–100% and 26%–83%, respectively [17].

Patients with normal D-dimer level could be eliminated the possibility of DVT [18]; however, the low specificity of D-dimer test becomes a big concern. The main detection approach of D-dimer is enzyme-linked immunosorbent assay, whose detective threshold is 0.5ug/ml [19]. In this study, the first quartile of D-dimer in non-DVT group patients was 0.5 ug/ml, indicating that the D-dimer of the remaining 75% non-DVT patients was above threshold and led to the existence of a large number of false-positive results. It was also reported that 78% of hospitalized patients had a higher level of D-dimer than this threshold, while the incidence of lower extremity DVT was much lower [20]. In addition, it is difficult to apply further imaging studies to all patients with high level of D-dimer, which leads to a huge waste of medical resources. Although D-dimer test has been criticized for its low specificity in a long time, the high sensitivity and maneuverability make it commonly used in clinical practice.

As a screening tool, the balance between sensitivity and specificity of D-dimer is important. To improve the specificity of D-dimer, elevating the screening threshold or combining D-dimer with other tests have been tried. It was demonstrated that combination of D-dimer with ultrasonography could improve effective screening for asymptomatic venous thromboembolism [21]. It was also reported that a cut-off value adjusted to age combined with clinical features could greatly increase the utility of D-dimer test in the exclusive diagnosis of pulmonary embolism among elderly patients without reducing safety [22]. With regard to the selection of a new threshold value of D-dimer, the Youden's index only provided a reference. More investigation needs to be done to validate a new effective cut-off value of D-dimer.

Risk assessment scale is one of the major clinical screening methods for DVT. Effective assessment scale can greatly simplify the workflow and improve the efficiency and accuracy. Besides, it can also counteract the variations coming from uneven clinical experience of doctors. RAPT score, which was established by Greenfield in 1997 [23], has been endorsed by many orthopedists immediately after its issue because of its strong pertinence and high screening accuracy [24]. Surveys conducted by Hegsted et al. showed that the sensitivity of the method was 82% and specificity was 57%. In addition, there was a positive correlation between the incidence of venous thromboembolism and the score [25]. In our study, we used RAPT score as the lower extremity DVT screening assessment scale for patients. Consistently, the sensitivity, specificity and AUC of RAPT score method were similar to the results obtained by Damian and Michelle [25, 26]. It was demonstrated in our study that RAPT score has high accuracy in the detection and screening of DVT in patients with lower extremity fracture.

In clinical application, the ideal DVT screening methods should be featured with several characteristics. First, high sensitivity is required to avoid misdiagnosis of positive patients. Second, high specificity is needed to reduce unnecessary imaging tests, thus lowering the cost and attenuating mobile inconvenience of trauma patients. Basing on the comparison of the above two methods, we found that RAPT scoring method has a higher specificity, but its low sensitivity does not meet the requirements from clinicians. Conversely, the sensitivity of D-dimer is high, but its relatively low specificity results in the waste of medical resources. Because of the limitations of both methods, it is hard to apply them widely and a novel diagnostic approach is in urgent need [27]. Currently, many researchers have used combination of different methods to screen lower extremity thrombosis and confirmed that it could further improve DVT screening efficiency [25, 28, 29]. Several attempts using RAPT score in combination with D-dimer threshold of 0.5 ug/ml have been made. Although it could

increase the screening sensitivity, the specificity declined further simultaneously, not in favor of resolving the “low specificity” problem.

In this study, the combination of clinical risk assessment scale and elevated D-dimer threshold was introduced to increase the screening efficiency. One major advantage of this method was that the specificity increased with the upregulation of D-dimer threshold and the high sensitivity was ensured by RAPT score. The specificity of this new method was significantly increased compared with the D-dimer test alone and the accuracy was higher than the RAPT score or D-dimer alone. In addition, this screening method is beneficial to both clinicians and patients. As is well known, patients with lower extremity fracture usually have to stay in bed, making it inconvenient to go out for check. Compared with the traditional method, the new method here reduced 10.66% (21/197) of the ultrasound examination, which decreased the patient moving and hospitalized cost. Simultaneously, it attenuated the pressure of ultrasound department coming from huge workload and reduced waste of medical resources.

Inevitably, there are limitations of this novel method. The new threshold of D-dimer was put forward based on data from 197 patients in single center, which was a small number of patients, weakening its authority. Multi-center studies with large sample size should be performed to improve the authority in the future.

In conclusion, higher diagnostic accuracy could be achieved by the combination of RAPT score and new threshold of D-dimer. This novel diagnostic method is potential in the clinical diagnosis of orthopedic trauma patients.

Author Contributions All authors contributed to the study conception and design. XZ. analyzed the data and wrote the first draft of the manuscript; SA co-ordinated the study, collected the data and edited the manuscript; XS designed the study protocol, analyzed the data and edited the manuscript. All authors commented on previous versions of the manuscript and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical standard statement This article does not contain any studies with human or animal subjects.

Informed consent For this type of study, informed consent is not required.

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