Original Article

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Serum Levels of Factor XIII, D-dimer, and Fibrinogen as A non-Invasive Diagnostic Biomarkers in Patients with Venous Thromboembolism

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ABSTRACT

Background & Objective: Using new diagnostic methods to help quickly diagnose VTE disease is important. It is well known that treatment of VTE is based on radiological methods, but the main purpose of this research was to investigate the relationship between blood coagulation factor XIII(FXIII), D-dimer, and fibrinogen levels in patients with VTE**.**

Materials & Methods: Seventy patients initially suspected of having VTE were included and determined their D-dimer, fibrinogen, and (FXIII)levels. The diagnosis of VTE was based on the CT-Angiography. The blood samples were prepared from the patients during the first 6 hours of admission and before using anticoagulant.

Results: The mean level of D-dimer in VTE patients was higher than those without VTE (1770± 764.49 vs. 430.66± 263.98ng / ml) (p <0.001). The mean factor XIII level in patients with VTE was significantly lower than those without VTE(55.03±13.61 vs. 88.57±18.14ng / ml) (p <0.001). The mean fibrinogen level in patients with VTE was significantly lower than in non-VTE patients (140.49± 36.03 vs. 214.69± 69.73 mg/dl) (p <0.001). The cut-off value of D-dimer was 500 ng/ml, and the sensitivity and specificity were 97% and 74%, respectively. The cut-off point of fibrinogen was 168 mg/dl, with a sensitivity of and a specificity of 77% and 77%, respectively. The cut-off point of XIII was 70 ng/ml, with a sensitivity of and specificity85% and 82%, respectively.

Conclusion: Our findings suggest that combined measurement of serum levels of D-dimer, factor XIII, and fibrinogen can be used to confirm clinical suspicion for VTE.

Keywords: D-dimer, Fibrinogen, Factor XIII, Venous thromboembolism.

Introduction

VTE is a disease related to health problems **(1)**. No therapy within 72 hours after damage may raise the extent of deep vein thrombosis **(2)**. Risk factors for venous thrombosis include surgery, malignancy, trauma, immobility, pregnancy, and previous history of deep vein thrombosis **(3, 4)**. VTE causes a major burden of disease across countries. VTE is a major lower limb orthopedic surgery **(5, 6)**. DVT can happen in the injured and uninjured leg, with a clearly developed incidence in the injured leg. The probability of occurrence of proximal DVT in an uninjured leg is rare **(7)**. Silent pulmonary embolism sometimes involves central pulmonary arteries **(8)**.

VTE in pregnancy and postpartum is the main reason for maternal morbidity and mortality **(9-11)**. Therefore,

it is not reasonable to invoke it in these cases. For this reason, using new laboratory methods or imaging procedures seems reasonable.

FXIII is operated at the end of the coagulation cascade and strongly cross-links between the fibrin strands, giving clot vigor and defiance to fibrinolysis **(12)**. Interrelationship of factor 13antigen concentrations with pulmonary occlusion scale, fibrinogen, D-dimer, and clot firmness was reported **(13)**. Replaces in platelet functions, coagulation, and fibrinolysis in unchallenging patients of acute myocardial infarction reported **(14)**. Factor XIII activity *arbitrate*s red blood cell keeping in VTE(15). RBC *relation*s with fibrinogen and cells, *containing* platelets and endothelial cells, may also *advance* thrombus formation **(16)**.

There is no developed risk of transfusion or hematoma and a low overall ***extent*** of VTE after implementing a chemoprophylaxis administration **(17).** Patients who maintain orthopedic trauma are at risk for evolving deep venous thrombosis and symptomatic pulmonary emboli **(18)**. Aspirin may be advised as a reasonable choice for *elongated* thrombus prophylaxis after THA **(19)**. Merged with a negative D-dimer test consequence, deep vein thrombosis can be left out in cases with a not likely outcome on the Wells rule **(20).**

Fondaparinux, indirect subordinate activated factor VII *constraint*, appears to be effective for starting medication and averting VTE, but even so needs parenteral management. On the other hand, Ximelagatran, an oral direct thrombin *constraint*, has also been demonstrated to be effective for medication and *avert* of VTE . VTE is a *frequent* and potentially fatal difficulty that happens in 4 to 15% of cases confess to ICUs *even though* the normal use of pharmacological prophylaxis **(21,22)**. Nearly all operatively and non-operatively treated EGS cases have an average to high risk of expanding a VTE **(23)**. Acute pulmonary embolism (PE) puts a considerable burden on health and survival. Early diagnosis and treatment of pulmonary embolism can reduce the risk of serious complications and mortality **(24)**. Infection was considerably matched up with concurrent DVT and PE **(25)**. Increased coagulation due to hormonal changes formation and acquired thrombophilia **(26).**

Discriminating testing is *convolute*d, as *biological* markers, like the D-dimer, are regularly false positive, and imaging, like computed tomography pulmonary angiography, carries chances of radiation and contrast dye *disclosure* **(27).** Utilize an age-adjusted D-dimer break-off for cases above 50 years of old for ruling out DVT seems as safe as using a standard D-dimer cut-off **(28, 29)**, previous history of VTE, blood coagulation, and fibrinolysis **(30).**

Yan et al. discussed the acquired factor 13 deficiency **(31)**. Lugo et al. reported ethnic/geographic variation of the val 34 leu polymorphism of coagulation factor 13 and its distribution in American admixed populations **(32)**. VTE, incorporating both deep vein thrombosis and pulmonary embolism**.** Diagnosis requires D-dimer testing and imaging **(33)**. D-dimer allows to safely avert VTE in abundant women with suspected VTE **(34)**.

.In another study carried out by Cushman et al., FXIII-A antigen status was determined in prevent conditions; they suggested that coagulation factors IX through 13 and the hazard of future VTE **(35)**. Based on the literature review, there are contradictory results regarding these factors. Therefore, further study is necessary in cases with VTE. Current research investigated the correlation between factor XIII, D-dimer, and fibrinogen levels within individuals with suspected venous thromboembolism.

Materials and Methods

This research was a prospective case-control research. Seventy sufferers who underwent radiologic evaluation with CT angiography for possible clinical diagnosis of venous thromboembolism were selected as the study sample.

Inclusion criteria: All patients were included in the study after being evaluated with pulmonary CT-Angiography who were admitted to Ayatollah Rouhani Hospital in Babol, Iran, without any cardiovascular disease.

Exclusion criteria: underlying malignancy, cirrhosis, well-known bleeding coagulopathy, and Alzheimer's disease, surgery, trauma.

Sample Preparation and Measurement

Due to the possibility of interfering with the anti-coagulant treatment on factor XIII and fibrinogen levels, blood samples were taken during the first 6 hours before and before administration of the drug and tested in a test tube containing 3.2% sodium citrate and ethylene diamide tetra acetic acid. Samples of the coagulation test were centrifuged at 2700* g for 10 minutes to obtain platelet-poor plasma. Plasma samples were also sent to a single laboratory for measurement. Fibrinogen concentration was determined by ACL TOP analyzer and Hemos ILPT Fibrinogen HS PLUS reagents (Instrumentation Laboratory, Kirchheim, Germany) by ELISA method. Factor XIII's concentration was also determined by the ELISA method by ACL TOP analyzer and HemosIL FXIII Antigen reagent (Instrumentation Laboratory, Bedford, MA, USA).

Ethical Consideration

The patient’s written informed consent was obtained before collecting samples from all patients and healthy controls. The Babol University of Medical Sciences Ethics Committee approved the research protocol and written consent procedures on Human Research (IR.MUBABOL.HRI.REC.1397.158).

Method of Sample Size Determination

To calculate sample size with a 95% confidence level, the standard deviation of 0.5, and margin of error of -0.5% based on Tang study according to formula n≥ (2 × Z1-α / 2√p (p-1) / 2) sampling error, a sample size of 70 was determined.

Statistical Analysis

Data were evaluated using SPSS V.18. Chi-square and T-tests were used. P-values less than 0.05 were considered statistically significant. Continuous variables were presented as median and categorical variables were expressed as prevalence and percentage. Comparison between non-parametric variables was performed using the Mann-Whitney test.

Results

In this study, 70 patients with suspected VTE who were referred to Ayatollah Rouhani Hospital in Babol for 12 months were included.35 patients (50%) with VTE and 35 (50%) without VTE were as healthy control by using CT angiography. Of these, 40 (57.1%) were male, and 30 (42.9%) were female. The mean age of patients in this study was 60.26 ±14.00 years (minimum age 29 and maximum age 89 years). The characteristics of the subjects with and without venous thromboembolism are demonstrated in **Table 1**. According to the results of **Table 1**, there was no considerable discrepancy between the age and gender variables in subjects with VTE and those without VTE(p = 0.63 and p = 0.62, respectively).

A quantitative comparison of D-dimer, factor XIII, and fibrinogen levels was shown in subjects with VTE and healthy controls **(Table 2).** According to the results of Table 2, the mean D-dimer level in subjects with venous thromboembolism was higher than in subjects with no VTE (1770± 764.49vs. 430.66± 263.98ng / ml). This difference was statistically significant (p <0.001). According to available sources, the cut-off scale of D-dimer was 500 ng/ml, and based on this cut-off point, sensitivity was 97% with a 92 to 100% confidence interval and 74% specificity with a 60-89% confidence interval. D-dimer with a 1.08 odds ratio has also been suggested as a hazard factor for VTE. In Table 3 comparison of D-dimer cut-off points in individuals with and without VTE was demonstrated. Based on Table 3 the results of 35 patients with venous thromboembolism, 34 patients (97.1%) had D-dimer levels greater than 500 ng/ml, and this correlation was important (p <0.001). A comparison of the fibrinogen cut-off scale in individuals with and without VTE was shown **(Table 4).**

Table 1 .The characteristics of subjects under study venous thromboembolismand non-venous thromboembolism

Variables	With venous thromboembolism	Withot venous thromboembolism	Total (%)	P-value*
Age (year)				
≤60	(42.9) 15	(48.6) 17	(45.7) 32	0.63
>60	57.1) 20	(51.4) 18	(54.3) 38	
Gender				
Male	(60.0)21	(54.3) 19	(57.1) 40	0.63
female	(40.0) 14	(45.7) 16	(42.9) 30	

*Chi-square

Table 2.Quantitative comparison of D-dimer ,factor XIII and fibrinogen levels in subjects with venous thromboembolism and healthy controls .

Variables	With venous thromboembolism	Without venous thromboembolism	*P -Value
D-dimer (ng/ml)	1770.29 ± 764.49	430.66 ± 263.98	<0.001*
F XIII (ng/ml)	55.03 ± 13.61	88.57 ± 18.14	<0.001**
Fibrinogen (mg/dl)	140.49 ±36.03	214.69 ± 69.73	<0.001*

Mann-Whitney *,T-test **

Table 3. Comparison of D-dimer cut-off point in individuals with and without venous thromboembolism

D-dimer (ng/ml)	With venous thromboembolism(%)	Withot venous thromboembolism(%)	P-value*
500≤	(2.9)1	(74.3)26	0.001<
500≤	97.1)34	(25.7)9	

Chi-square*

Table 4.Comparison of fibrinogen cut off point in individuals with and without venous thromboembolism.

Fibrinogen (mg/dl)	Groups: Pulmonary embolism) (%)	Groups: non-pulmonary embolism(%)	*P value
168≤	(77.1)27	(22.9)8	<0.001
168≥	(22.9)8	(77.1)27	

Chi-square*

Based on Table 4, the results of 35 patients with VTE, 27 (77.1%) had a factor XIII level less than 168 mg/dl, and this correlation was important (p <0.001) and given the odds ratio of 0.97.

Mean factor XIII in subjects with VTE was significantly lower than non-venous thromboembolism (55.03±*13.61 vs.88.57±18.14*ng / ml) (p <0.001). The mean fibrinogen level in patients with venous thromboembolism was significantly lower than in non-venous thromboembolism patients (140.49± 36.03 vs. 214.69± 69.73 mg/dl) (p <0.001)—comparison of Factor XIII cut-off point in individuals with and without VTE (Table 5). Based on Table 5, the results of 35 patients with VTE, 29 (82.9%) had a factor XIII level less than 70 ng/ml, and this correlation was important (p <0.001) and given the odds ratio of 0.89, factor XIII is considered as a preventive factor.

Table 5. Comparison of Factor XIII cut-off point in individuals with and without VTE

Factor XIII(ng/ml)	Groups: Pulmonary embolism) (%	Groups: non-pulmonary embolism(%)	P *value
70≤	(82.9)29	(14.3)5	<0.001
70≥	(17.1)6	(85.7)30	

Chi-square*

ROC curve showing the correlation between specificity and sensitivity of fibrinogen in diagnosing VTE (figure 1). Based on the ROC curve's evaluation, the fibrinogen's cut-off point is 168 mg/dl, with a sensitivity of 77% and a specificity of 77%. Area under curve 0.83, p <0.001 / 95% confidence interval = 0.73 - 0.92.

ROC curve showing the correlation between specificity and sensitivity of factor XIII in diagnosing VTE (Figure 2). The study's cutoff point for factor XIII was 70 ng/ml. The sensitivity and the specificity are 85% and 82%, respectively. Area under curve = 0.92,p<0.001, confidence interval = 0.85 - 0.98.

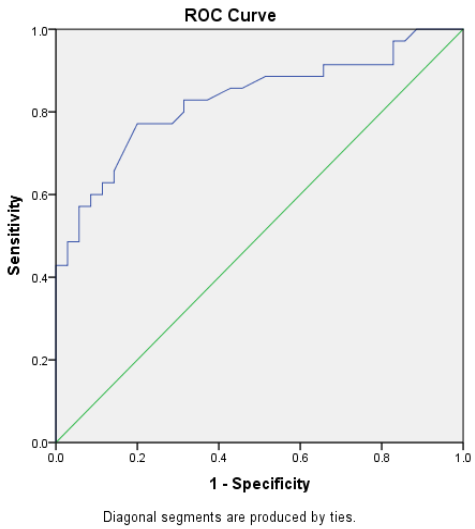

Figure 1 .**ROC curve showing the relationship between specificity and sensitivity of fibrinogen in diagnosis of venous thromboembolism**.

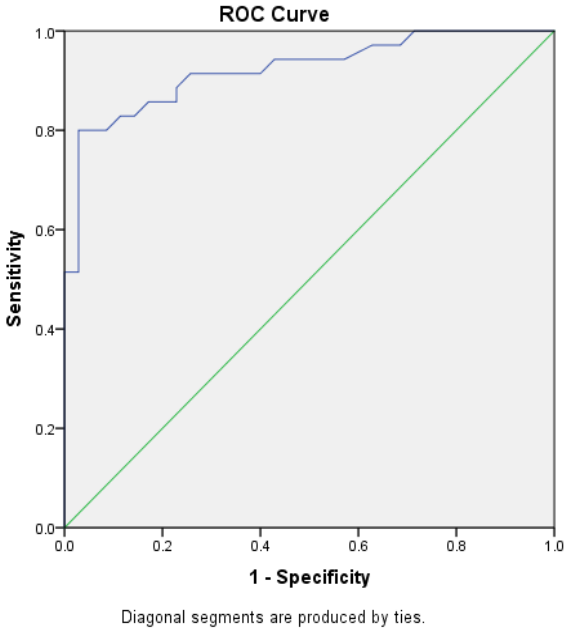

Figure 2. ROC curve showing the relationship between specificity and sensitivity of factor XIII in diagnosing venous thromboembolism.

Discussion

There are conflicting views regarding the relationship between factor XIII and fibrinogen with VTE. Some researchers have reported that elevation of these factors is a biomarker for pulmonary thromboembolism. Nevertheless, other researchers reported the protective effect of factor XIII and fibrinogen in pulmonary thromboembolism. The third view has suggested the lack of association between thromboembolism with factor XIII and fibrinogen level (33). The results of the mentioned studies are consistent with the present study's findings. Studies show that increased levels of D-dimer can be effective in raising the risk of pulmonary thromboembolism.

The primary finding of the present research, which is itself a major challenge, is that serum levels of factor XIII and fibrinogen are reduced in patients with VTE. Conversely, elevated serum levels of these two factors might prevent lung embolism.

Also, a study carried out by Cushman et al. reported that Factor XII deficiency was not associated with VTE hazard. Amid pro-coagulant factors, only elevated factor XI was a hazard factor for VTE(35). Like our study, Vleig found that increased Factor XIII levels were associated with reduced thromboembolic risk (34). This finding is quite consistent with the findings of the current study.

The results contradictory to the findings of the present research may be due to many reasons such as type of kit used, type of laboratory factor measuring device, and most importantly measurement of these factors in patients with acute or chronic phase of disease or before disease onset. However, given the limited time of disease studies and measurement of these factors in the acute phase before anti-coagulant initiation, it can be argued that this research is one of the first studies in this field. The present study's strengths were determining the cut-off scales of fibrinogen, XIII, and D-dimer factors. Their sensitivity and specificity in disease diagnosis were obtained following the cut-off scales obtained for factor XIII, fibrinogen, and D-dimer. The sensitivity and specificity of D-dimer at the cut-off point of 500 ng/ml in the diagnosis of venous thromboembolism were 97 and 74%, respectively. In a review study by Janssen et al., the sensitivity of D-dimer in detecting pulmonary embolism was 94%, and the specificity was 93%. In our study, sensitivity was higher than Janssen's result but with lower specificity. In the present study, the cut-off point for fibrinogen was 168 mg/dl, which, according to the results, decreased the fibrinogen level in patients with venous thromboembolism. However, further studies are needed to use this cut-off point for screening patients with suspected embolism. The sensitivity and specificity of fibrinogen at the cut-off point 168 mg/dl were 77% and 77%, respectively.

Regarding the specificity of fibrinogen, it should be noted that out of every 100 people who were healthy based on CT angiography results, 77 had fibrinogen levels above 168. The cut-off point for factor XIII was 70 ng/ml, which decreased the factor XIII level in patients with embolism. Of course, further studies are needed to use this cutoff point to screen for patients with suspected embolism. Based on this cut-off point, factor XIII had a sensitivity of 85% and specificity of 82%.

Conclusion

Early diagnosis and treatment of VTE can reduce the risk of serious complications and mortality. For early diagnosis of VTE, single diagnostic testing as biomarkers is complicated; it is frequently false positives. Therefore, the combination of D-dimer, factor XIII, and fibrinogen levels for the detection of venous could be useful in the early diagnosis of VTE. These results revealed that changed D-dimer levels, factor XIII, and fibrinogen can effectively raise the risk of pulmonary thromboembolism. Larger sample sizes will be required to detect these associations reliably.

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Authors' Contribution

DQ conceived and designed the experiments. HOB performed the experiments. HOB and MM analyzed the data. MR and MM contributed to the writing of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

The samples were collected with the consciously written consent of patients after approval by the Ethics

Committee of Babol Medical University (IR.MUBABOL.HRI.REC.1397.158).

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