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ORIGINAL ARTICLE

Prothrombin Fragment 1 + 2 in Urine and Plasma and D-dimer in Patients with Clinically Suspected Venous Thromboembolism

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Abstract

In recent years, several biomarkers have been found to be associated with deep vein thrombosis (DVT). D-dimer is a degradation product of a cross-linked fibrin blood clot and has a negative value in the diagnosis of DVT. Prothrombin fragment 1 + 2 (p F1 + 2) is a non-thrombotic polypeptide that is cleaved from Prothrombin during its conversion to thrombin. The study aims to evaluate the D-dimer and to evaluate Prothrombin fragment 1 + 2 in urine and plasma in clinically suspected DVT patients. This study comprised of 30 patients who are clinically suspected cases of deep vein thrombosis, carried out from July 2018 to May 2020 in the Department of General Surgery, IMS BHU, Varanasi. In our study, D-dimer and plasma F1 + 2 both showed comparable results in patients of venous thromboembolism (VTE). Proximal DVT tended to have higher levels of D-dimer and had significantly higher levels of F1 + 2 than patients with distal DVT. In our study, a positive correlation was found between D-dimer and plasma F1 + 2 ($r = 0.588$ and p-value 0.006) in DVT-positive patients. There is no correlation between plasma D-dimer and urine F1 + 2 ($r = -0.0.07$ and p-value 0.769) In conclusion, Prothrombin F1 + 2 is an important marker raised in patients with DVT.

Keywords Veins · Venous thromboembolism · Biomarker · Deep vein thrombosis · Evaluation

Introduction

Deep vein thrombosis has an estimated annual incidence of 1–2 per thousand among the general population. Despite adequate therapy, approximately 6–9% mortality is seen in these patients who develop complications like pulmonary embolism. Compression ultrasonography is the imaging test of choice to diagnose deep vein thrombosis (DVT). The addition of Doppler along with lack of compressibility of a venous segment is the diagnostic criteria. In many centers, ultrasound testing is limited to the proximal veins, for which the sensitivity is 97%. In the calf for diagnosing DVT, the sensitivity is only 73%. Several biomarkers are elevated in DVT and have been tested as D-dimer, P-selectin, interleukins and cytokines, von Willebrand factor, thrombin, fibrin monomers, plasmin activators uPA and tPA, myeloperoxidase, osteoprotegerin, homocysteine, neutrophil extracellular traps, oxidative stress markers, microparticles, ADAMTS13, plasma DNA, micro-RNA, apo-lipoprotein M, galectin-3-binding protein/receptor, etc.

D-dimer is a degradation product of a cross-linked fibrin blood clot. Levels of D-dimer are typically elevated in patients with acute venous thromboembolism, as well as in patients with a variety of non-thrombotic conditions (e.g., recent major surgery, trauma, pregnancy, or cancer). D-dimer assays are, in general, sensitive but nonspecific marker of DVT. The value of D-dimer assay is that a negative result suggests a lower likelihood of DVT. Thus, it is a good test to rule out DVT with the appropriate pretest probability [1, 2].

Prothrombin fragment 1 + 2 (F1 + 2) is a non-thrombotic polypeptide that is cleaved from prothrombin during its conversion to thrombin. F1 + 2 is released into the bloodstream where it has a half-life of approximately 90 min. Due to the low molecular weight of F1 + 2 (~ 31 kDa), it is excreted in the urine where it can be detected by enzyme-linked immunosorbent assay (ELISA). The plasma half-life of F1 + 2 was calculated as approximately 90 min in healthy individuals. Plasma levels of F1 + 2 increase with age [3]. Our study aimed to detect D-dimer values and Prothrombin fragment 1 + 2 in plasma and urine in suspected patients of DVT.

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Patient and Methods

A prospective study of patients with clinical suspicion of deep vein thrombosis was carried out in the Department of General Surgery, Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, India, from July 2018 to May 2020. Clinical assessment of all cases was carried out and all the details were recorded in performa. Inclusion criteria were clinically suspected patients of DVT and subjects who gave informed consent. The patients excluded were subjects who are unwilling to give consent. All patients were interviewed on the duration of symptoms, comorbidities, and use of medications. Patients who have coronary vascular disease had met trauma in the previous 3 months or underwent surgical procedure within the past 3 months are said to have comorbidity.

Blood and urine samples (10 ml each) were collected before the duplex scan and divided into two aliquots after centrifugation at $3000 \times g$ for 20 min within 1 h and stored at − 80 °C until the analysis after completion of the required number of patients. Urine and plasma levels of Prothrombin fragment F1 + 2 were measured using a commercially available ELISA kit (Human Prothrombin Fragment 1 + 2 (F1 + 2) ELISA Kit supplied by My Biosource San Diego, CA, USA) and in accordance with the manufacturer's instructions. The same kit was used for both plasma and urine samples.

A total of 3.5 ml blood was collected in sodium citrate vial, centrifuged for 10 min at $2000 \times g$, aliquoted, and stored at − 80 °C for ELISA assay of D-dimer. The D-dimer assay was done using the Nycocard D-dimer single test, based on immunometric flow through. The plasma sample was applied to test the well of the device. The conjugate solution is then added. The D-dimer on the membrane will bind to conjugate in a sandwich type reaction. In the presence of D-dimer levels above 0.1% mg/l in the sample, the membrane appears reddish with a color intensity proportional to the D-dimer concentration.

For duplex evaluation, patients were examined using Siemens Xario Ultrasound Machine and 5–8 MHz linear or 3–5 MHz curvilinear transducer venous compressibility, intraluminal echoes, and venous flow characteristic, and luminal color filling were evaluated.

Statistical Analysis

A standard curve was made by plotting the mean absorbance for each standard on the *x*-axis against the concentration on the *y*-axis. The statistical analysis was done using SPSS for Windows version 23.0 software. For categorical data, chi-square and Fisher's exact test were used. For comparing two groups of mean independent, Student's "*t*" test was used. For paired samples, paired "*t*" test was applied for statistical analysis. Spearman's correlation coefficient was used to correlate two continuous variables. A receiver operator characteristic (ROC) curve was used for the prediction of confirmed DVT. The critical value of "*p*" indicating the probability of significant difference was taken as < 0.05 for comparison.

Results

This study comprised of 30 patients who are clinically suspected cases of deep vein thrombosis, carried out from July 2018 to May 2020 in the Department of General Surgery, IMS BHU, Varanasi. Cases were divided into two groups:

Group A - Those who are color Doppler confirmed cases of DVT or VTE.
Group B - Those who are not color Doppler confirmed cases of DVT or VTE.

The total number of male patients was 17 (56%) of which 14 were from group A and 3 were from group B and the total number of female patients was 13 (44%) of which 6 (20%) were from group A and 7 (24%) from group B. In group A, 8 (40%) were in the age group 20–40 years, 10 (50%) were in the age group 41–60, and 2 (10%) were > 60 years of age. In group B, 2 (20%) were in the age group 20–40 years, 7 (70%) were in the age group 41–60, and 1 (10%) was > 60 years of age (Table 1). As per the risk factors, 14 cases out of 20 were immobilized for the past 3 days in group A. Three patients of group A have previous VTE, 3 had taken oral contraceptives, 3 patients have some inflammatory condition, and 2 patients had taken chemotherapy. In group B, 7 cases were immobilized for > 3 days, 1 patient had diabetes mellitus, and 2 patients were in sepsis (Table 2). As per Wells score, in group A, 1 (5%) case had Wells score 2, 5 (25%) cases had a score between 3 and 5, and 14 (70%) had a score between 6 and 8, and corresponding values in group B were 2 (20%), 5 (50%), and 3 (30%), respectively (Table 3). According to

Table 1 Distribution of cases according to age and sex

	Group A (20)	Group B (10)	Total
Sex			
Male	14 (70%)	3 (30%)	17
Female	6 (30%)	7 (70%)	13
Age			
20–40	8 (40%)	2 (20%)	10
41–60	10 (50%)	7 (70%)	17
> 60	2 (10%)	1 (10%)	3

Table 2 Distribution of cases based on risk factors

Risk factor	Group A	Group B	*p*-value
Inactivity and immobilization	14 (70%)	7 (70%)	1.000
Pregnancy and the postpartum period	1 (5%)	1 (10%)	0.605
Previous VTE	3 (15%)	0 (0.0%)	0.532
Combined oral contraceptives	3 (15%)	0 (0.0%)	0.532
Diabetes mellitus	9 (45%)	1 (10%)	0.055
Autoimmune disease	3 (15%)	3 (30%)	0.333
Chemotherapy	2 (10%)	0 (0.0%)	0.540
Sepsis	0 (0.0)	2 (20%)	0.103

Table 3 Distribution of cases as per Wells score

Wells score	Group A	Group B
1–2	1 (5%)	2 (20%)
3–5	5 (25%)	5 (50%)
6–8	14 (70%)	3 (30%)
Total	20 (100%)	10 (100%)

Table 4 Distribution of cases with respect to involvement of vein segment in group A patient

Segment involved	No. of cases
IVC	4 (20%)
Femoral	15 (75%)
Popliteal	18 (90%)
Infrapopliteal	3 (15%)

Table 5 Distribution of D-dimer value (quantitative) among group A and B cases

D-dimer (ng/ml)	Group A	Group B
< 500	1 (5%)	5 (50%)
500–2000	4 (20%)	5 (50%)
2000–3500	7 (35%)	0
> 3500	8 (40%)	0
Total	20 (100%)	10 (100%)

$\chi^2 = 16.250$, $p = < 0.001$

the involvement of segment based on color Doppler finding in group A patients which shows that IVC was involved in 4 (20%) cases, femoral segment involvement was present in 15 (75%) cases and popliteal segment involvement was in 18 (90%) cases and infrapopliteal segment involvement was present in 3 (15%) cases (Table 4).

As per D-dimer values, in group A, 1 (5%) had D-dimer value < 500 (ng/ml), 4 (20%) had value between 500 and 2000 ng/ml, 7 (35%) had value between 2000 and 3500 ng/ml, 8 (40%) had value > 3500 ng/ml, and corresponding values in group B were 5 (50%), 5 (50%), 0, and 0, respectively

Table 6 Distribution of Prothrombin fragment 1 + 2 in plasma among group A and B cases

Prothrombin fragment 1 + 2 in plasma (pmol/l)	Group A	Group B
< 200	0 (0%)	2 (20%)
200–500	2 (10%)	7 (70%)
500–1000	7 (35%)	1 (10%)
> 1000	11 (55%)	0 (0%)
Total	20 (100%)	10 (100%)

$\chi^2 = 19.063$a, $p = < 0.001$

Table 7 Distribution of prothrombin fragment 1 + 2 in urine among group A and B cases

Prothrombin fragment 1 + 2 in urine (pmol/l)	Group A	Group B
< 20	0 (0%)	3 (30%)
20–60	2 (10%)	7 (70%)
60–100	10 (50%)	0 (0%)
> 100	8 (40%)	0 (0%)
Total	20 (100%)	10 (100%)

$\chi^2 = 23.000$a, $p = 0.001$

(Table 5). As per Prothrombin fragment 1 + 2 in plasma, in group A, no patient had Prothrombin fragment 1 + 2 in plasma value < 200 (pmol/l), 2 (10%) had value between 200 and 500 pmol/l, 7 (35%) had value between 500 and 1000 pmol/l, and 11 (55%) had value > 1000 pmol/l, and corresponding values in group B were 2 (20%), 7 (70%), 1 (10%), and 0, respectively (Table 6). As per Prothrombin fragment 1 + 2 in urine, in group A, no patient had Prothrombin fragment 1 + 2 in urine of value < 20 (pmol/l), 2 (10%) had value between 20 and 60 pmol/l, 10 (50%) had value between 60 and 100 pmol/l, and 8 (40%) had value > 100 pmol/l, and corresponding values in group B were 3 (30%), 7 (70%), 0, and 0 (Table 7).

There is a positive correlation between Wells score and D-dimer, and Prothrombin fragment markers strongest correlation is seen with D-dimer ($r = 0.172$ and p-value 0.468) (Table 8). The mean value for D-dimer in patients with pulmonary embolism was 3069.76 ± 1301.927. Prothrombin fragment 1 + 2 in plasma was 1165.88 ± 473.049 and Prothrombin fragment 1 + 2 in urine was 92.82 ± 28.437; the corresponding values in cases without pulmonary embolism were 2473.33 ± 670.398, 1143.33 ± 390.171, and 125.33 ± 40.067. It shows that there is an increased level of plasma D-dimer and Prothrombin fragment 1 + 2 in plasma in cases with pulmonary embolism (Table 9). Looking at the correlation between markers, there was a positive co-relation between D-dimer and plasma F1 + 2 ($r = 0.588$, $p = 0.006$).

Table 8 Correlation of Wells score with D-dimer, Prothrombin fragment 1 and 2 in plasma, and Prothrombin fragment 1 and 2 in urine

Marker	Wells score		
		Group A	Group B
D-dimer	*r*-value	0.172	0.560
	p-value	0.468	0.092
Prothrombin fragment 1 and 2 in plasma	*r*-value	1.000	0.385
	p-value		0.272
Prothrombin fragment 1 and 2 in urine	*r*-value	0.388	0.096
	p-value	0.091	0.792

Table 9 Correlation of D-dimer, Prothrombin fragment 1 and 2 in plasma, and Prothrombin fragment 1 and 2 in urine in pulmonary embolism group versus DVT cases in group A

	With PE Mean ± SD $N=3$	Without PE Mean ± SD $N=17$	*p*-value
D-dimer	3069.76 ± 1301.927	2473.33 ± 670.398	0.455
Prothrombin fragment 1 and 2 in plasma	1165.88 ± 473.049	1143.33 ± 390.171	0.939
Prothrombin fragment 1 and 2 in urine	92.82 ± 28.437	125.33 ± 40.067	0.100

Table 10 Co-relation between p D-dimer and p F1 + 2 and u F 1 + 2 in group A

		D-dimer
Prothrombin fragment 1 + 2 in plasma	*r*	0.588
	p	0.006
Prothrombin fragment 1 + 2 in urine	*r*	− 0.070
	p	0.769

There is no correlation between D-dimer and urine F1 + 2. Table 10 shows the positive co-relation between D-dimer in plasma and prothrombin fragment 1 + 2 in plasma in group A patients (Fig. 1). The scatter diagram shows there is no co-relation between D-dimer in plasma and prothrombin fragment 1 + 2 in urine in group A patients (Fig. 2).

At the cutoff value of 685 ng/ml for D-dimer values, the sensitivity and specificity were 80% and 95%. For Prothrombin fragment in plasma at the cutoff value of 410 pmol/l, the sensitivity and specificity were 90% and 95%, respectively and for Prothrombin fragment in urine at the cutoff value of 45.0 pmol/l, it was 90% and 95.0% sensitivity and specificity (Table 11) (Fig. 3).

Discussion

In recent years, the advances in the management of patients with suspected VTE have both improved both in diagnosis and management. Several diagnostic algorithms are available based on clinical pretest probability, D-dimer measurement, and imaging tests, mainly compression ultrasound (CUS) for suspected DVT, and computed tomography pulmonary angiography or lung ventilation-perfusion scan for pulmonary embolism. These diagnostic algorithms allow a safe and cost-effective diagnosis with suspected VTE.

Deep vein thrombosis has an estimated annual incidence of 1–2 per thousand in the general population. Despite adequate therapy, about 6–9% mortality is observed especially in pulmonary embolism. Other complications are post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension. Anticoagulant therapy decreases the risk of recurrent disease but there is a chance of bleed also [4].

Acute thrombosis increases D-dimer levels and it is a sensitive marker of thrombosis generally. The high negative predictive value of D-dimer is utilized in the clinical conditions to rule out PE. The D-dimer levels increase with age and in other clinical conditions like cancer, pregnancy, and inflammatory states, hence limits its positive predictive values for diagnosis of VTS [5].

There are several biomarkers of DVT including D-dimer, P-selectin, factor VIII, thrombin generation, inflammatory cytokines, microparticles, fibrin monomer, and leukocyte count [6]. Prothrombin fragments F1 + 2 fragment, produced during the conversion of prothrombin to thrombin, has been proposed as a potentially useful clinical marker of thrombogenesis during arthroplasty and can be measured by enzyme-linked immune sorbent assay (ELISA) [7]. This small molecule, with a half-life in plasma of 90 min, is excreted in the urine, and both blood and urine levels of F1 + 2 are increased for several days after arthroplasty [8]. Furthermore, studies have demonstrated increased levels of urine F1 + 2 in patients with venous thromboembolism [9].

In our study, it was a prospective hospital-based study comprising of 30 patients who were clinically suspected cases of deep vein thrombosis included during the time period between Sept 2018 and April 2020. The total study subjects were categorized into two groups; first, those who were imaging confirmed cases of deep vein thrombosis, and second, those who are not confirmed, i.e., group A and group B, respectively.

Various studies have shown the significantly higher levels of plasma D-dimer and prothrombin fragment 1 + 2 in plasma and urine in image confirmed venous

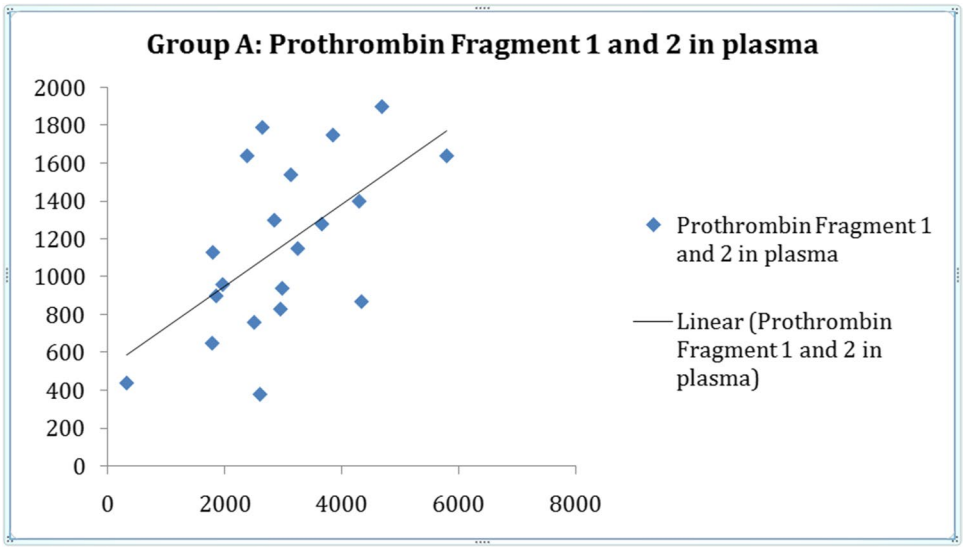

Fig. 1 Distribution of Prothrombin fragment 1 + 2 in urine in group A patients

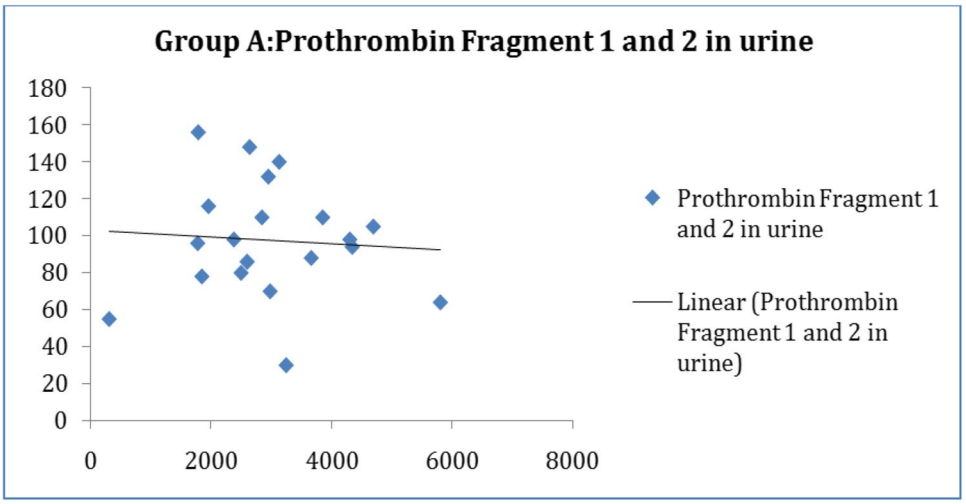

Fig. 2 Showing ROC curve delineating specificity and specificity of D-dimer, Prothrombin fragment 1 + 2 in plasma and urine

Table 11 Diagnostic criteria for diagnosing DVT with D-dimer, Prothrombin fragment 1 + 2 in plasma and urine

Variables	Cutoff	Sensitivity	Specificity	*P*-value
D-dimer	685 ng/ml	80%	95%	< 0.001
Prothrombin fragment 1 + 2 in plasma	410 pmol/l	90%	95%	< 0.001
Prothrombin fragment 1 + 2 in urine	45 pmol/l	90%	95%	< 0.001

thromboembolism versus those without ($P < 0.001$). The three biomarkers were statistically correlated significantly. Plasma D-dimer had the highest diagnostic accuracy followed by prothrombin fragment 1 + 2 in plasma. Further development of ELISA analyses for urine testing of prothrombin fragment 1 + 2 may improve its diagnostic accuracy [3].

It has been shown that the diagnostic accuracy of prothrombin F1 + 2 in patients with suspected pulmonary embolism is less efficient than the D-dimer tests [10]. In our study, D-dimer and p F1 + 2 both in plasma and urine showed comparable results. Patients who had pulmonary embolism had raised values of D-dimer and Prothrombin 1 and 2 as compared to patients without pulmonary embolism.

Patients with proximal DVT tended to have higher levels of D-dimer and had significantly higher levels of F1 + 2 than patients with distal DVT. It has been also reported that the thrombus extension is associated with higher D-dimer and p F1 + 2. In our study, similar result is found with patients who have proximal DVT [11].

Patients with image-verified DVT had significantly higher urinary F1 + 2 levels compared to those without, both in patients with and without, known comorbidities. Patients

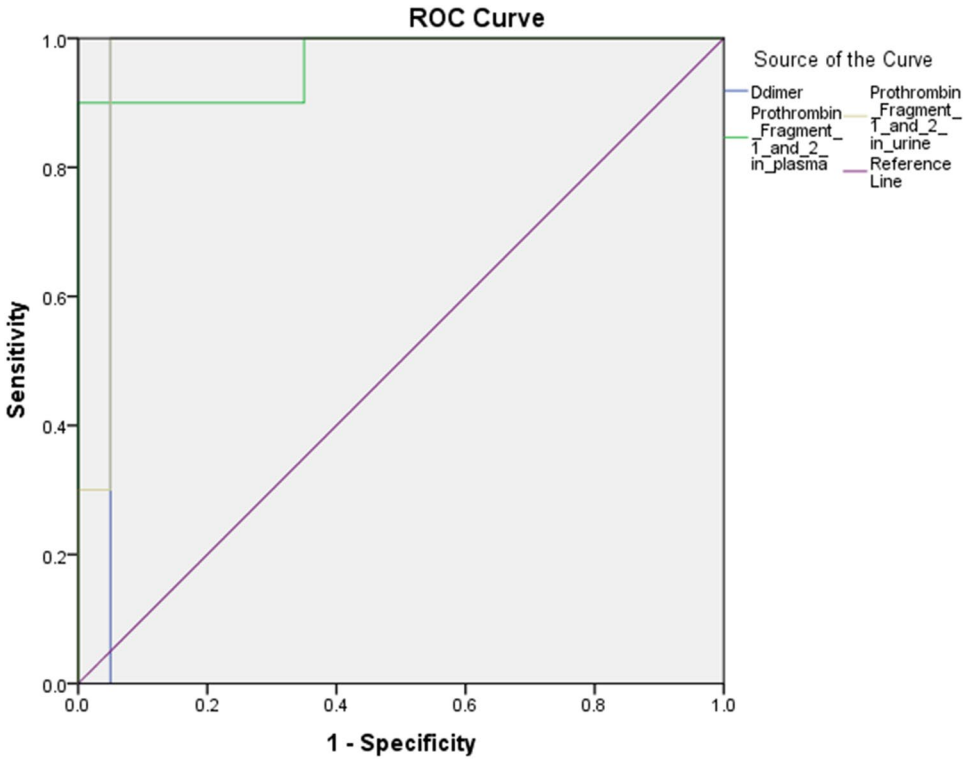

Fig. 3 Distribution of Prothrombin fragment 1 + 2 in plasma

with image verified PE had increased, however, not statistically significant, levels of urinary F1 + 2 compared to the PE negative patients. D-dimer and F1 + 2 levels measured in plasma and urine from patients with suspected VTE were significantly higher in those with image confirmed VTE compared to those without. In addition, there was a significant and positive correlation between D-dimer and F1 + 2 levels in plasma and between F1 + 2 in plasma and urine. The D-dimer had a better predictive value for VTE than plasma F1 + 2 followed by urinary F1 + 2 and there was no overlap in the ROC curves [12].

The patients with DVT have a higher level of value of D-dimer but it may be even raised even in other conditions. In our study, the level of plasma D-dimer (mean value) in group A patient was 2980.3 ± 1233.86 while in group B, it was 588.00 ± 278.36 with a *p*-value of < 0.001, which was significant. Similarly level of Prothrombin fragment 1 + 2 in the plasma of group A patient was 1162.5 ± 452.256 while in group B, it was 330.00 ± 216.744 with a *p*-value of < 0.001, which was significant. The level of prothrombin fragment 1 + 2 in the urine of group A patient was 97.7 ± 31.496 while in group B, it was 27.40 ± 19.254 with a *p*-value of < 0.001, which was significant. Comorbidities were noted in 14 (46.6%) patients in for which the mean value of D-dimer, plasma F1 + 2, and urine F1 + 2 was 2509.36 ± 1168.122, 939.29 ± 435.775, and 95.50 ± 39.816, respectively. Patients who have no co-morbidity were 16 (53.4%) in number for which the mean value of D-dimer, plasma F1 + 2, and urine F1 + 2 was 1897.19 ± 1774.651, 837.50 ± 652.344, and 55.69 ± 38.887 [13].

In our study, we found a positive co-relation between D-dimer and plasma Prothrombin F1 + 2 ($r = 0.588$ with *p*-value of 0.006). There is no co-relation between D-dimer and urinary Prothrombin F1 + 2 ($r = -0.07$ and *p*-value 0.769). High D-dimer and F1 + 2 levels independently predict the occurrence of VTE in patients with cancer [14].

Increased urine levels of F1 + 2 were observed immediately after the surgery and reached a peak level on postoperative day 3 before decreasing toward day 7 and normalizing at follow-up on day 35 ± 5. A ROC curve with area under the curve (AUC) of urinary F1 + 2 levels performed on postoperative day 5 showed that F1 + 2 levels in urine could accurately discriminate patients with and without increased risk of developing a VTE. Levels of F1 + 2 in urine were significantly higher in patients who developed a VTE or death compared to the event-free patients [15].

Conclusion

D-dimer is an important biomarker in DVT and it has its negative value, but the value of D-dimer is high in patients with comorbidities, proximal DVT, and in the presence of pulmonary embolism. Similarly, the Prothrombin F1 + 2 in plasma and urine is high. We found a positive correlation between D-dimer and plasma Prothrombin fragment level

but we did not find a good correlation between D-dimer and urinary Prothrombin fragment level.

Declarations

Conflict of Interest The authors declare no competing interests.

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