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Original Article

Comparison of Quantitative and Semi-quantitative D-dimer in the Diagnosis of Deep Venous Thrombosis

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ABSTRACT

Objective: To compare sensitivity along with the specificity of quantitative and semi-quantitative D-dimer tests in patients of Deep venous thrombosis.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Mar 2021 to Feb 2022.

Methodology: A total of 176 patients were recruited using a nonprobability consecutive sampling technique. Patients with age <60 years and suspected of having deep venous Deep venous thrombosis were included. Patients with age >60 years and who were on anticoagulation therapy or have raised D-dimer due to other causes were excluded. The sample obtained in the trisodium citrate tube was analyzed both by semi-quantitative and quantitative methods. A value above 200ng/ml was considered positive. Sensitivity, specificity, and negative and positive predictive values were measured. Receiver Operating Characteristic was made taking Doppler ultrasound as a gold standard.

Results: In our study males 116(60%) and females 60(34%). Based on the gold standard test, and Doppler ultrasound, 24(14%), patients did not have Deep venous thrombosis while 152(86%) were diagnosed with Deep venous thrombosis. The Quantitative D-dimer test has a sensitivity of 98.7% and a specificity of 73.1%. Whereas sensitivity, specificity, positive and negative predictive value of the semiquantitative test was 92.7%, 100%, 92.1%, and 52.1% respectively. The area under the Receiver Operating Characteristic curve was 0.911 for the semiquantitative test and 0.873 for a quantitative test.

Conclusions: Semiquantitative D-dimer test has acceptable sensitivity and better specificity as compared to quantitative assay using Doppler ultrasound as a gold standard for diagnosis of Deep venous thrombosis.

Keywords: Deep venous thrombosis (DVT), D-dimer, Quantitative, Semiquantitative.

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INTRODUCTION

Venous thromboembolism (VTE) means blood clots in the vein. It is a multifactorial condition. It leads to morbidity and mortality in both, the community, and hospitalized patients. On average number of individuals affected annually is 1 - 2 per 1000 persons and the annual death rate because of VTE is 60,000 to 100,000.[1,2] VTE manifests in two forms, one is deep venous thrombosis (DVT) and the other is pulmonary embolism(PE). DVT can be unprovoked or provoked. When there is no identifiable provoking environmental event or factor that can lead to DVT then its unprovoked DVT.[3] However factors or events like hospitalization or surgery provoked DVT. Risk factors for provoked DVT are immobility >3 days, major surgery >30 minutes, and cesarean section. Sometimes minor risk factors like pregnancy, estrogen therapy, minor surgery <30 minutes, or some persistent risk factors like chronic heart disease, malignancies, inherited thrombophilia, and inflammatory bowel disease may lead to DVT.[4] DVT occurs when blood clot forms in deep veins usually in the lower leg, thigh or sometimes in the pelvis. Patients with DVT usually present with throbbing or cramping pain in one or rarely both legs. Usually, pain is in the calf or thigh muscles. Swelling in one leg (rarely both) with warm and red skin around the painful area is also noted. In a patient with DVT, the involved area veins are swollen, tender, and hard to touch. If there is no contraindication, then the mainstay of treatment of DVT is anticoagulation e.g., the use of warfarin, heparin, or rivaroxaban. Patients of DVT are on long-term anticoagulation to prevent future recurrence, embolism, and thrombosis-related deaths. If anticoagulant therapy is not suitable then filters are put in large veins.[5]

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Several diagnostic approaches to DVT have been proposed but the most commonly followed include clinical pretest probability(PTP), and laboratory and radiological investigations.[6] Radiological investigations include Doppler ultrasonography, contrast venography, and Magnetic resonance imaging (MRI).[7] Among laboratory investigations D-dimer level testing is the first lined Dimer assays vary in the method of detection, antibody used, instrumentation, and calibrations. A negative D-dimer test decreases the probability of DVT. However, a positive result needs further investigation as a positive result may be seen in other conditions like malignancy, sepsis, trauma, surgery, and pregnancy.[8] D-dimer is a fibrin degradation product, a small protein that is formed after a blood clot is degraded by fibrinolysis. Its structure consists of two D fragments of the fibrin protein, both joined by cross-linking. A fibrin clot is formed, and this cross-linking by the covalent bond is done by factor XIII which helps in the stabilization of the clot. Then plasmin causes a breakdown of cross-linked fibrin and D-dimers are formed. D-dimer levels can be determined either by qualitative, semi-quantitative, or quantitative methods.[9]

Initially, venography was used as a gold standard test for DVT but with the passage of time Doppler ultrasonography, a more noninvasive test has replaced venography. However, it is also time-consuming.[10] So, a quick, accurate, and noninvasive test for prompt and accurate screening and diagnosis of DVT is under discussion. Keeping in view this need of the era we decided to compare the sensitivity as well as the specificity of quantitative and semi-quantitative methods of D-dimer analysis in patients with DVT using Doppler ultrasound as a gold standard test.

METHODOLOGY

A total of 176 patients were recruited in this cross-sectional study after taking approval from the institutional review board (IRB), AFIP Rawalpindi reference no. (FC-HEM 19-14/READ-IRB/22/881). This study was conducted at the Department of Haematology, AFIP Rawalpindi from Mar 2021 to Feb 2022).

After a thorough literature search, a sample size of 114 was calculated using a WHO calculator, keeping a 5% margin of error, 95% confidence interval, and prevalence of Deep venous thrombosis (DVT) 8%.[11] Sampling was done using the nonprobability consecutive sampling technique. A maximum number of available participants during the study period were recruited.

Inclusion Criteria: Patients aged below 60 years and with suspected Deep venous thrombosis (DVT) of both genders were included and underwent clinical examination and laboratory and radiological investigations.

Exclusion Criteria: Patients older than 60 years and patients who were on anticoagulation therapy and have raised D-dimer due to other causes like pregnancy, malignancy, and sepsis were excluded from the study.

Before enrolling all patients, we obtained their written consent, and the confidentiality of the patients was ensured at all levels. Doppler ultrasound was taken as the gold standard and findings were noted as positive or negative for DVT.

About 2ml of venous sample was collected from subjects in trisodium citrate vacutainers keeping blood to anticoagulant ratio as 9:1. Plasma was separated from cells by centrifugation at 15000RPM for 10 minutes and platelet-poor plasma is formed and then separated plasma was stored at -20^{o}C for subsequent analysis. Separated plasma was then analyzed by both semi-quantitative D-dimer assay and quantitative D-dimer assay. The semi-quantitative D-dimer method used was the latex agglutination technique using Atlas D-dimer semi-quantitative test strips. Quantitative D-dimer levels were analyzed using INNOVANCE® D-dimer Reagent on Sysmex® CS-5100 Haemostasis System, which is random access, fully automated high-volume coagulation analyzer based on immunoturbidimetry. In it monoclonal antibodies form aggregates when mixed with a sample containing D-dimer and aggregation is then detected by turbidimetry. All parameters were analyzed according to the standard operating principles of the laboratory. Internal quality controls were run with each batch. Results of the D-dimers assay were compared with a gold standard of Doppler ultrasound for the diagnosis of DVT. Data were entered in Microsoft excel and later analyzed using Statistical Package for Social Sciences (SPSS) 23.0. Descriptive statistics were expressed as mean±SD. Sensitivity, Specificity, and Negative and positive predictive values were measured. The area under the ROC curve was determined for both semi-quantitative and quantitative D-dimer tests taking Doppler ultrasound as a gold standard.

RESULTS

A total of 176 patients were included in the study with distribution among both genders (Figure-1). The mean age of the study population was 46.02±16.59 years. Based on a gold standard of Doppler ultrasound 24(14%) patients did not have DVT while 152(86%) were diagnosed with DVT. In comparison based on semi-quantitative D-dimer analysis, 23(13%) people had a value of <200ng/ml indicating a negative result of DVT. 14(8%) patients had values of >200<400ng/ml , 47(27%) patients had D-dimer >400<800ng/ml, and 92(52%)patients had values >800<1600ng/ml. All D-dimers above 200ng/ml were considered positive. Whereas based on the quantitative D-dimer test, 21(12%) patients had negative values and 155(88%) had positive results. Based on these results quantitative D-dimer test has a sensitivity of 98.7% and a specificity of 73.1% with a positive predictive value of 96.8% and a negative predictive value of 90.5%. Whereas the semi-quantitative analysis of the D-dimers test had a sensitivity of 92.7% and specificity of 100% and a positive predictive value of 92.1% and a negative predictive value of 52.1%.The area under the ROC curve of semiquantitative 0.911 (Confidence interval 95%, 0.802-0.944) and quantitative test 0.873 (Confidence interval 95%, 0.854-0.967) taking Doppler ultrasound as the gold standard (Figure-2).

These study results indicate that absolute quantification of D-dimer has slightly better sensitivity, but it is less specific than semi-quantitative analysis of D-dimer. Whereas semi-quantitative D-dimer analysis may have a lesser sensitivity, it is 100% specific when compared with a gold standard of Doppler ultrasound. However, the positive and negative predictive values of the absolute quantification of the D-dimer test are much better than the semi-quantitative analysis.

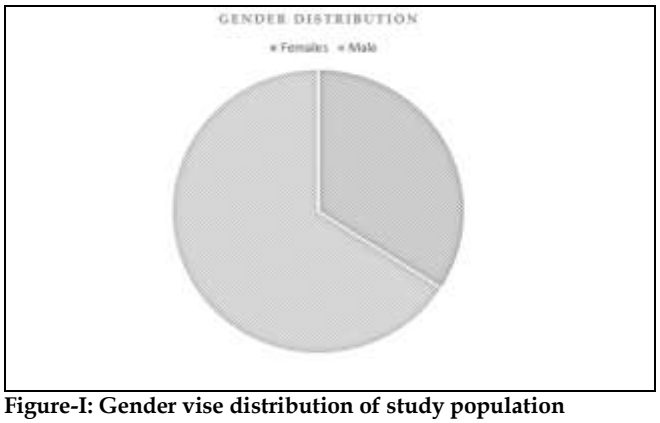

Figure-I: Gender vise distribution of study population

DISCUSSION

D-dimer is a marker of fibrin turnover and fibrinolysis. It is a unique biological marker of haemostatic abnormalities as well as it is an indicator of intravascular thrombosis.[1] Systemic degradation of vascular thrombi via fibrinolytic mechanism leads to the generation of this soluble fibrin degradation product. Because of this, it serves as a valuable marker in various clinical scenarios. Usually, D-dimer testing is conducted for DVT. D-dimer assays provide a fast and cost-effective way of diagnosis of DVT.[12]

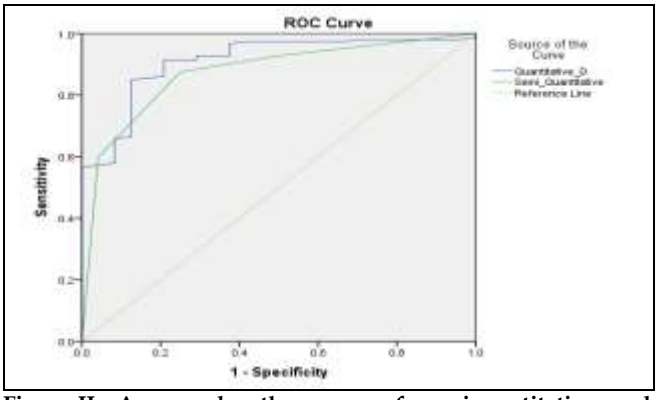

Figure-II: Area under the curve of semiquantitative and quantitative D Dimer test-taking Doppler as Gold standard

In our study population, gender distribution comprised 60 females and 116 males with a mean age of 46.02±16.59 years. In a local study conducted in Rawalpindi in the year, 2005 males were 80 and females were 107 with mean age noted 28.3±12.4 years, which is quite different from that observed in our study.[13] In an international study conducted by Boyd.S. *et al.*,[14] in the year 2020 to determine the incidence of DVT, more males than females were noted which is similar to that observed in our study.

In our study, the quantitative D-dimer test had a sensitivity of 98.7% and a specificity of 73.1% whereas the semi-quantitative analysis of the D-dimer test had a sensitivity of 92.7% and specificity of 100%. Nicoletta Riva *et al.*,[15] in a systematic review and meta-analysis in the year 2021 to determine the diagnostic accuracy of quantitative D-dimer assay in high-risk patients for splanchnic vein thrombosis noted D dimer sensitivity to be 96% but a specificity of 25% was noted. The sensitivity noted by them (96%)[15] is comparable to that noted by us (98.7%), but their specificity was quite low (25%) as compared to that observed by us (73.2%). Aparajeeta Bora and Wilma Delphine Silvia C[16] in a meta-analysis conducted in India in the year 2021

noted semiquantitative latex agglutination assay to be 96% sensitive and 92%specific. They also observed quantitative D-dimer immunoturbidimetric assay to be 100% sensitive and 45 % specific. They mentioned that comparing D-dimer assays are usually challenging and D-dimer assays should be adjusted for age as D-dimer increase naturally with age in the body. D-dimer testing in our study wasn't adjusted for age but we avoided such false-positive cases by excluding cases with age >60 years.

In another point of care testing, quantitative D-dimer immunoturbidimetric assay sensitivity of 95% with a specificity of 62% was observed.[17] We also observed slightly high sensitivity of quantitative D-dimer assay, but low specificity as compared to qualitative D-dimer assay.

Standardizing the D-dimer assay is a big challenge.[18] Different assay show different sensitivity and specificity due to differences in technique and method of analysis. Enzyme-linked immunosorbent (ELISA)-based D-dimer assay showed sensitivity and a negative predictive value of 100%.[19,20] Our immunoturbidimetric quantitative D-dimer method showed slightly low but comparable sensitivity and negative predictive values which were 98.7% and 90.5% respectively. But this sensitivity and negative predictive value are higher than that noted in the semiquantitative latex agglutination test (sensitivity 92.7%, negative predictive value, 52.1%). However, the specificity of the semiquantitative D-dimer assay (100%) is higher than that of the quantitative D-dimer assay (specificity 73.1%, Positive predictive value, 96.8%). The area under the curve of quantitative D-dimer assay was 0.873(95%CI 0.854-0.967) and semiquantitative D-dimer assay was 0.911(0.802-0.944) which is comparable to that noted by John J *et al.*[21]

Semiquantitative D-dimer assay is cheaper than quantitative D-dimer assay in terms of cost.[22] Having comparable sensitivity but being a more specific and cost-effective test, semiquantitative D-dimer assay can be used for DVT diagnosis instead of a more expensive quantitative D-dimer assay or before more time-consuming Doppler ultrasound is carried out. This can be particularly useful in a developing country like Pakistan which has a limitation of resources.

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LIMITATION OF STUDY

This was a single-centered study with time constraints. We recommend further studies on large populations with the involvement of multiple centers for more generalization of results and formulation of new guidelines for diagnosis and approach to DVT cases.

CONCLUSION

Semiquantitative D-dimer assay has acceptable sensitivity and better specificity as compared to quantitative D-dimer assay using Doppler ultrasound as a gold standard test for diagnosis of DVT. So, in a developing country like Pakistan which faces the issue of limitations of resources, the semiquantitative D-dimer test is cost-effective and can be used for prompt diagnosis and timely treatment of DVT, before going to expensive and time-consuming Doppler ultrasound or quantitative D-dimer assay results.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SI & FA: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZH & ZZ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MS & SZ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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