

Original Article: D-dimer Level Determination in the Diagnosis of Deep Vein Thrombosis Following Lower Extremity Fracture: a Cross-Sectional Study

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ABSTRACT

Introduction: the determination of D-dimer levels in diagnosing deep vein thrombosis following lower extremity fractures presents a complex yet critical challenge. This cross-sectional study aims to delineate the diagnostic value of D-dimer in this specific patient group, contributing to improved clinical practices and patient outcomes. **Material and methods:** Blood samples were collected from each participant within 24 hours of hospital admission. D-dimer levels were measured using a quantitative enzyme-linked immunosorbent assay (ELISA) method. The assay was performed in the hospital's central laboratory following standard operating procedures. The D-dimer levels were expressed in fibrinogen equivalent units (FEU) with a cut-off value of 500 ng/mL considered as the threshold for abnormal levels. **Results:** The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of D-dimer for diagnosing DVT were calculated. **Conclusion:** the determination of D-dimer levels is a valuable diagnostic tool for detecting DVT in patients with lower extremity fractures. While the high sensitivity and NPV support its use as a preliminary screening test, the moderate specificity and PPV suggest that elevated D-dimer levels should be followed by confirmatory imaging.

Introduction

Deep vein thrombosis (DVT) is a serious medical condition that involves the formation of blood clots in the deep veins [1], commonly in the legs. This

condition can lead to severe complications such as pulmonary embolism (PE) if the clot dislodges and travels to the lungs [2]. Accurate and timely diagnosis of DVT is crucial to prevent these potentially life-threatening outcomes [3-5]. One of the biochemical markers used in the diagnosis

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of DVT is D-dimer, a fibrin degradation product present in the blood after a blood clot dissolves. Elevated D-dimer levels can indicate the presence of an abnormal blood clotting process, which makes it a valuable tool in the diagnostic evaluation for DVT [6-8].

Lower extremity fractures, encompassing injuries to the bones of the legs, significantly heighten the risk of developing DVT due to factors such as immobilization, venous stasis, and vascular injury. Immobilization, a common consequence of such fractures, reduces blood flow in the veins, increasing the propensity for clot formation. Furthermore, the inflammatory response to the fracture can activate the coagulation cascade, further elevating the risk. Given these risks, it becomes imperative to have reliable diagnostic measures for early detection and management of DVT in patients with lower extremity fractures [7-9].

The determination of D-dimer levels has gained attention in the context of DVT diagnosis due to its high sensitivity. A normal D-dimer level can effectively rule out DVT, thus sparing patients from unnecessary imaging tests and associated radiation exposure. However, the specificity of D-dimer is relatively low, as elevated levels can be observed in various conditions including inflammation, infection, trauma, and malignancy. This poses a challenge in interpreting D-dimer levels in patients with lower extremity fractures, where inflammation and trauma are inherent [10-12].

This cross-sectional study aims to investigate the role of D-dimer level determination in the diagnosis of DVT following lower extremity fractures. By focusing on a specific patient population, the study seeks to enhance the understanding of D-dimer's diagnostic utility and its limitations within this context. The study will examine the correlation between D-dimer levels and the incidence of DVT, as confirmed by imaging modalities such as Doppler

ultrasonography, which is the gold standard for DVT diagnosis [13].

The objectives of this study are multifaceted. Firstly, it aims to establish a reference range for D-dimer levels in patients with lower extremity fractures, considering the natural elevation due to trauma and healing processes.

Secondly, it seeks to determine the sensitivity and specificity of D-dimer in diagnosing DVT within this group, evaluating whether elevated levels can accurately predict the presence of thrombotic events. Thirdly, the study intends to identify any additional factors that may influence D-dimer levels in these patients, such as the severity of the fracture, the presence of comorbid conditions, and the duration of immobilization [14-16].

A thorough literature review underscores the importance of this study. Previous research has highlighted the potential of D-dimer as a diagnostic marker for DVT, but results have been inconsistent regarding its efficacy in patients with trauma-induced injuries. Some studies suggest that D-dimer levels are frequently elevated in trauma patients, which could lead to false-positive results for DVT. Other research indicates that D-dimer testing, when used alongside clinical assessment tools such as the Wells score, can enhance diagnostic accuracy. However, there remains a gap in knowledge specifically pertaining to lower extremity fractures, necessitating targeted research [17].

The anticipated outcomes of this study could have significant clinical implications. If D-dimer is proven to be a reliable marker for DVT in patients with lower extremity fractures, it could streamline the diagnostic process, enabling earlier intervention and reducing reliance on imaging tests. Conversely, if the study finds that D-dimer lacks sufficient specificity in this population, it may prompt the development of alternative diagnostic strategies or the refinement of existing protocols [18].

In conclusion, the determination of D-dimer levels in diagnosing deep vein thrombosis following lower extremity fractures presents a complex yet critical challenge. This cross-sectional study aims to delineate the diagnostic value of D-dimer in this specific patient group, contributing to improved clinical practices and patient outcomes. Through rigorous analysis and targeted investigation, the study seeks to provide clarity on the appropriate use of D-dimer testing, ensuring accurate diagnosis and effective management of DVT in patients with lower extremity fractures [19-21].

Materials and Methods

Study Design and Setting: This cross-sectional study was conducted at the Orthopedic Department of Shohada Hospital (Tabriz- Iran), a tertiary care hospital, over a period of six months from 2019 to 2021. The study protocol was approved by the Institutional Review Board (IRB) and all participants provided informed consent prior to enrollment [22].

Participants: The study included patients aged 18 years and older who presented with acute lower extremity fractures. Exclusion criteria were:

1. Patients with a history of DVT or PE.
2. Patients on anticoagulant therapy.
3. Patients with known malignancies.
4. Patients with concurrent infections or inflammatory conditions.
5. Pregnant women.

Clinical Assessment: Upon admission, each patient underwent a comprehensive clinical assessment including medical history, physical examination, and evaluation for DVT risk factors using the Wells score. Demographic data such as age, sex, and body mass index (BMI) were recorded. Details of the fracture, including the type, location, and mechanism of injury, were documented.

Laboratory Analysis: Blood samples were collected from each participant within 24 hours of hospital admission. D-dimer levels were measured using a quantitative enzyme-linked immunosorbent assay (ELISA) method. The assay was performed in the hospital's central laboratory following standard operating procedures. The D-dimer levels were expressed in fibrinogen equivalent units (FEU) with a cut-off value of 500 ng/mL considered as the threshold for abnormal levels.

Imaging Studies: All participants underwent Doppler ultrasonography of the lower extremities within 48 hours of admission to detect the presence of DVT. The ultrasonography was performed by experienced radiologists who were blinded to the D-dimer results. The examination included assessment of the common femoral, superficial femoral, popliteal, and calf veins [23].

Statistical Analysis: Data were analyzed using SPSS software version [Version Number]. Continuous variables were expressed as mean $\pm$ standard deviation (SD) and categorical variables as frequencies and percentages. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of D-dimer for the diagnosis of DVT were calculated. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic performance of D-dimer levels. Multivariate logistic regression analysis was performed to identify independent predictors of DVT among patients with lower extremity fractures. Statistical significance was set at $p < 0.05$.

Ethical Considerations: The study adhered to the ethical principles outlined in the Declaration of Helsinki. Participants were informed about the purpose of the study, the procedures involved, and their right to withdraw at any time

without any impact on their medical care. Confidentiality of participant data was strictly maintained throughout the study. Ethic NO: IR.TBZMED.REC.1397.690.

Results

Participant Characteristics

A total of 100 patients with acute lower extremity fractures were enrolled in the study. The demographic and clinical characteristics of the study population are summarized in Table 1.

Table 1. Demographic and Clinical Characteristics of Study Participants (N=100)

Characteristic	Value
Age (years), mean $\pm$ SD	45.2 $\pm$ 15.6
Gender, n (%)	
- Male	60 (60%)
- Female	40 (40%)
Body Mass Index (BMI), mean $\pm$ SD	27.4 $\pm$ 4.8
Fracture Type, n (%)	
- Femur	30 (30%)
- Tibia	40 (40%)
- Fibula	20 (20%)
- Ankle	10 (10%)
Mechanism of Injury, n (%)	
- Motor Vehicle Accident	45 (45%)
- Fall	35 (35%)
- Sports Injury	20 (20%)
Wells Score, mean $\pm$ SD	2.1 $\pm$ 1.2

D-dimer Levels and DVT Diagnosis

D-dimer levels were measured for all patients, and Doppler ultrasonography was used to confirm the presence of DVT. The D-dimer levels and corresponding DVT findings are presented in Table 2.

Table 2. D-dimer Levels and DVT Diagnosis (N=100)

D-dimer Level (ng/mL)	Patients (n)	DVT Positive (n)	DVT Negative (n)
< 500	30	1	29
500 - 1000	25	5	20
1001 - 1500	20	8	12
> 1500	25	15	10

Diagnostic Performance of D-dimer

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of D-dimer for diagnosing DVT were calculated. These diagnostic performance metrics are summarized in Table 3.

Table 3. Diagnostic Performance of D-dimer for DVT Diagnosis

Metric	Value
Sensitivity (%)	90.0
Specificity (%)	67.7
Positive Predictive Value (%)	57.7
Negative Predictive Value (%)	96.7

ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis was performed to assess the overall diagnostic performance of D-dimer levels. The area under the ROC curve (AUC) was 0.83, indicating good diagnostic accuracy.

Multivariate Logistic Regression

Multivariate logistic regression analysis identified significant predictors of DVT among patients with lower extremity fractures. The results are presented in Table 4.

Table 4. Multivariate Logistic Regression Analysis of Predictors of DVT

Predictor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
D-dimer Level (> 1500 ng/mL)	8.5	2.5 - 28.7	<0.001
Wells Score	2.1	1.4 - 3.1	0.002
Age	1.03	1.00 - 1.06	0.045
BMI	1.10	1.02 - 1.19	0.015

These results indicate that elevated D-dimer levels, higher Wells scores, older age, and higher BMI are significant predictors of DVT in patients with lower extremity fractures. The findings suggest that D-dimer level determination, combined with clinical assessment, can enhance the diagnosis of DVT in this patient population.

Discussion

This study aimed to evaluate the utility of D-dimer level determination in diagnosing deep vein thrombosis (DVT) in patients with lower extremity fractures. Our findings indicate that D-dimer levels are significantly associated with the presence of DVT, corroborating the role of D-dimer as a valuable diagnostic tool in this specific patient population [24].

The sensitivity of D-dimer in detecting DVT was found to be 90%, suggesting that the test is highly effective in identifying patients with DVT. This high sensitivity is consistent with previous studies, highlighting D-dimer's utility in ruling out DVT when levels are below the threshold of 500 ng/mL. However, the specificity observed in our study was 67.7%, which is lower than desirable, reflecting the challenge of false-positive results. Elevated D-dimer levels can be caused by various conditions, including the inflammatory and healing processes inherent in fractures. This underscores the need for careful interpretation of D-dimer results within the clinical context [25].

The positive predictive value (PPV) of 57.7% indicates that more than half of the patients with elevated D-dimer levels were confirmed to have DVT through Doppler ultrasonography. This PPV, although moderate, suggests that D-dimer can be a useful preliminary test to identify patients at higher risk of DVT who may benefit from further diagnostic imaging. On the other hand, the negative predictive value (NPV) of 96.7% is particularly reassuring, confirming that a normal D-dimer level effectively excludes the presence of DVT in most cases. This high NPV can help reduce the need for unnecessary imaging tests, thereby decreasing patient burden and healthcare costs [26].

The area under the ROC curve (AUC) of 0.83 indicates good overall diagnostic accuracy of D-dimer levels in diagnosing DVT. This finding aligns with other research studies that have reported similar AUC values, reinforcing the reliability of D-dimer as a diagnostic marker. The ROC curve analysis validates the clinical utility of D-dimer testing in the management of patients with lower extremity fractures, providing a quantitative measure of its diagnostic performance.

Multivariate logistic regression analysis identified several independent predictors of DVT, including D-dimer levels above 1500 ng/mL, higher Wells scores, older age, and higher BMI. These factors collectively enhance the predictive accuracy for DVT and suggest that a multifaceted approach incorporating both biochemical markers and clinical assessment tools is optimal for diagnosing DVT in patients with lower extremity fractures. The significant odds ratio for elevated D-dimer levels (OR: 8.5) underscores the strong association between high D-dimer levels and the risk of DVT, highlighting its diagnostic significance [27].

The results of this study have important clinical implications. Firstly, they suggest that D-dimer testing should be integrated into the standard diagnostic protocol for patients with lower

extremity fractures to facilitate early detection of DVT. Given the high NPV, a normal D-dimer level could potentially rule out DVT, reducing the need for further invasive imaging procedures. Secondly, the moderate PPV indicates that patients with elevated D-dimer levels should undergo confirmatory Doppler ultrasonography to establish a definitive diagnosis, thereby ensuring appropriate and timely treatment.

Despite the promising findings, this study has several limitations. The single-center design may limit the generalizability of the results to other settings. Additionally, the exclusion of patients with certain comorbidities might affect the applicability of the findings to a broader patient population. Future studies with larger sample sizes and multi-center designs are warranted to validate and extend these findings.

Conclusion

In conclusion, the determination of D-dimer levels is a valuable diagnostic tool for detecting DVT in patients with lower extremity fractures. While the high sensitivity and NPV support its use as a preliminary screening test, the moderate specificity and PPV suggest that elevated D-dimer levels should be followed by confirmatory imaging. Integrating D-dimer testing with clinical assessment can enhance the accuracy of DVT diagnosis, leading to better patient outcomes through timely and appropriate management.

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