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FUTURE DIRECTION: NOVEL INFLAMMATORY MARKERS TO ENHANCE DEEP VEIN THROMBOSIS DIAGNOSTIC SPECIFICITY

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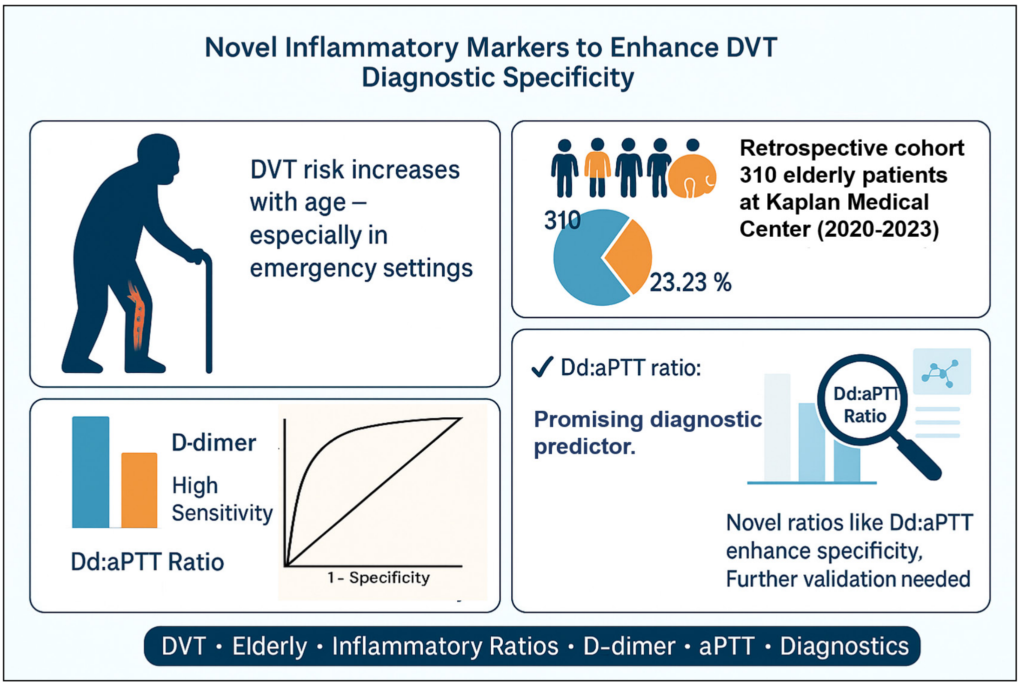
ABSTRACT – ***Objective:*** Deep vein thrombosis (DVT) poses a critical health risk, especially among the elderly. This study aims to enhance the specificity of DVT diagnosis by integrating novel inflammatory ratios and hematological markers.

Materials and Methods: We conducted a retrospective cohort study at Kaplan Medical Center, analyzing data from 310 patients aged 65 and older, following strict inclusion and exclusion criteria. Hematological and biochemical parameters, including D-dimer, C-reactive protein (CRP), and various inflammatory markers, were evaluated. Statistical analyses involved logistic regression, Receiver operating characteristic (ROC) curve, and K-Nearest Neighbors (KNN) algorithm for missing data imputation, ensuring robust results for DVT diagnostics.

Results: Out of 500 patients aged 65 and older evaluated for DVT admitted to the Emergency room at Kaplan Medical Center between January 1, 2020, and January 30, 2023, 310 were included in the analysis, with 23.23% positive for DVT. The DVT group's mean age was significantly higher (78.6 ± 9.1 years) than the non-DVT group (76.4 ± 4.65 years, $p < 0.01$). Significant predictors of DVT included D-dimer ($p < 0.01$, OR 1.33) and the D-dimer to activated partial thromboplastin time (aPTT) ratio ($p < 0.01$, OR 1.07). While achieving 100% sensitivity for both markers comes with low specificity, D-dimer and the Dd:aPTT ratio demonstrated strong potential in identifying DVT.

Conclusions: D-dimer to aPTT ratio is a promising diagnostic tool for DVT, warranting further investigation.

KEYWORDS: Deep vein thrombosis, D-dimer, Novel inflammatory ratios, Elderly patients, Diagnostic tools.



Graphical Abstract. Schematic representation of the study workflow evaluating hematological and inflammatory markers for DVT diagnosis in elderly patients. The graphical abstract illustrates how D-dimer and the D-dimer/aPTT ratio improve diagnostic specificity for DVT in patients aged 65 and above, integrating biochemical and inflammatory data analysis.

INTRODUCTION

Deep vein thrombosis (DVT) is a significant health challenge, especially in the aging population, where physiological and pathological changes increase the risk of developing blood clots in deep veins, most commonly in the legs. If left undiagnosed or untreated, DVT can lead to life-threatening complications such as pulmonary embolism. With an aging population and rising prevalence of age-related risk factors[1,2], there is a pressing need to enhance diagnostic and prognostic methods for DVT to better address the needs of this vulnerable group.

Sex-related differences and the role of coagulation markers further underscore the complexity of DVT diagnosis[1,2]. Elevated D-dimer levels, a well-known marker of fibrinolytic activity, are widely used in clinical settings to assess thrombotic activity[3]. Similarly, inflammatory markers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet indices have shown promise in evaluating systemic inflammation associated with DVT. These parameters not only provide insight into the pathophysiology of DVT but also highlight the intricate interplay between coagulation and inflammation in thrombus formation[4-8].

In line with precision and personalized medicine, integrating hematological and biochemical biomarkers can refine diagnostic and prognostic assessment in thromboembolic disease[9-11]. This framework supports combining coagulation measures with inflammatory indices to improve diagnostic specificity in older adults evaluated for suspected deep vein thrombosis[9-11].

This study explores the potential of integrating hematological and biochemical markers to improve the specificity of DVT diagnosis, particularly in elderly patients. By examining markers such as fibrinogen, activated partial thromboplastin time (aPTT), and novel inflammatory ratios, the research aims to contribute to the development of robust diagnostic tools.

MATERIALS AND METHODS

Study design and population

This retrospective cohort study was conducted at Kaplan Medical Center, Rehovot, Israel. Data were collected from patients admitted to the emergency department between January 12, 2020, and January 12, 2023. All patients aged 65 years and older who underwent lower-limb Doppler ultrasound for suspected deep vein thrombosis (DVT) were screened. A total of 500 patients were initially identified from the electronic medical records. Following the application of exclusion criteria, 102 patients were removed due to inadequate or incomplete data, leaving 398 patients eligible for further evaluation (Figure 1). Additional exclusions included 14 patients with D-dimer levels > 20 mg/L, 4 patients with platelet counts < 50 × 10^3/µL, 66 patients with age-adjusted normal D-dimer levels, and 4 patients with missing clinical data. After all exclusions, 310 patients were included in the final analysis. The cohort was subsequently divided into two diagnostic groups: a positive DVT cohort (n = 72) and a negative DVT cohort (n = 238), based on Doppler ultrasound findings.

Hematological and biochemical parameters

This study involved extracting data from blood samples collected from the study population. A range of hematological and biochemical parameters were analyzed, including absolute eosinophil count, absolute monocyte count, absolute neutrophil count, absolute lymphocyte count, platelet count, mean platelet volume (MPV), D-dimer, fibrinogen, CRP, aPTT, sex, and age.

To assess the prognostic value of specific combinations of these parameters, several derived indices were calculated and evaluated. The Platelet-to-Lymphocyte Ratio (PLR) was determined by dividing the platelet count by the absolute lymphocyte count. The Neutrophil-to-Lymphocyte Ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, the Lymphocyte-to-Monocyte Ratio (LMR) was derived by dividing the absolute lymphocyte count by the absolute monocyte count.

Additionally, the Systemic Immune-Inflammation Index (SII) was calculated as (absolute neutrophil count × platelet count) / absolute lymphocyte count. The Fibrinogen-to-CRP Ratio (Fib/CRP) was obtained by dividing the fibrinogen level by the CRP level, while the Fibrinogen-to-Platelet Ratio (Fib/PLT) was calculated by dividing fibrinogen levels by platelet count. The Eosinophil-to-Lymphocyte Ratio (ELR) was also evaluated by dividing the absolute eosinophil count by the absolute lymphocyte count. Furthermore, the MPV-to-Platelet Ratio (MPV/PLT) was determined by dividing the MPV by the platelet count. Lastly, the D-dimer to aPTT Ratio was calculated as (D-dimer × 100) / aPTT.

These parameters and derived indices were analyzed to explore their potential associations with DVT within the study population.

Sample size calculations

The sample size was calculated based on the annual incidence rate of venous thrombosis, which is approximately 1 per 1,000 individuals in the adult population[12,13]. Assuming a 95% confidence level (Z = 1.96) and a margin of error of 5% (E = 0.05), the required sample size was estimated using the formula:

$$n = \frac{Z^2 \cdot P \cdot (1 - P)}{E^2}$$

The calculated sample size was 2. However, acknowledging the limitations associated with small sample sizes and the necessity of ensuring adequate statistical power for subgroup analyses, along with adjustments for missing or incomplete data, a larger sample size of 500 patients was targeted. Ultimately, the final analysis included 310 patients. This adjustment guarantees a robust evaluation of the relationship between inflammatory markers, hematological parameters, and the risk of DVT in the study population.

Statistical analysis

Missing data were imputed using the K-Nearest Neighbors (KNN) algorithm. To minimize potential biases from the order of the data, rows were shuffled, and the dataset was standardized. A K-Fold Cross-Validation framework was employed to ensure robustness and minimize overfitting. True values were visualized for evaluation.

To identify potential predictors of DVT, the cohort was stratified based on ultrasound (US) results into DVT-positive and DVT-negative groups. Logistic regression analysis was performed to identify markers associated with DVT. Variables were considered statistically significant if they had a likelihood ratio test (LRT) p-value < 0.05. For these significant variables, odds ratios (OR) and 95% confidence intervals (CI) were calculated. Markers with CIs including 1 were excluded from further analysis.

Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminatory power of selected variables. Variables with an area under the curve (AUC) exceeding 0.7 and p-values < 0.05 were retained for further investigation. Additionally, specificity was assessed for 100% sensitivity to ensure no cases of DVT were overlooked.

The Chi-square test was used to calculate the p-value with significance set at $p < 0.05$. All statistical analyses were conducted using Python (version 3.11; Python Software Foundation, Wilmington, DE, USA) with the following libraries: pandas, statsmodels.api, sklearn.metrics, roc_auc_score, scipy.stats, matplotlib.pyplot, KFold, mean_squared_error, KNNImputer, and StandardScaler. Missing data were handled using the KNN algorithm for imputation. The imputation process and visualization are provided in **Supplementary Figure 1**.

Ethical consideration

The study was approved by the Institutional Ethics Committee of Kaplan Medical Center, in accordance with the principles of the Declaration of Helsinki, under protocol number 0039-24-KMC, approved on 20 December 2019.

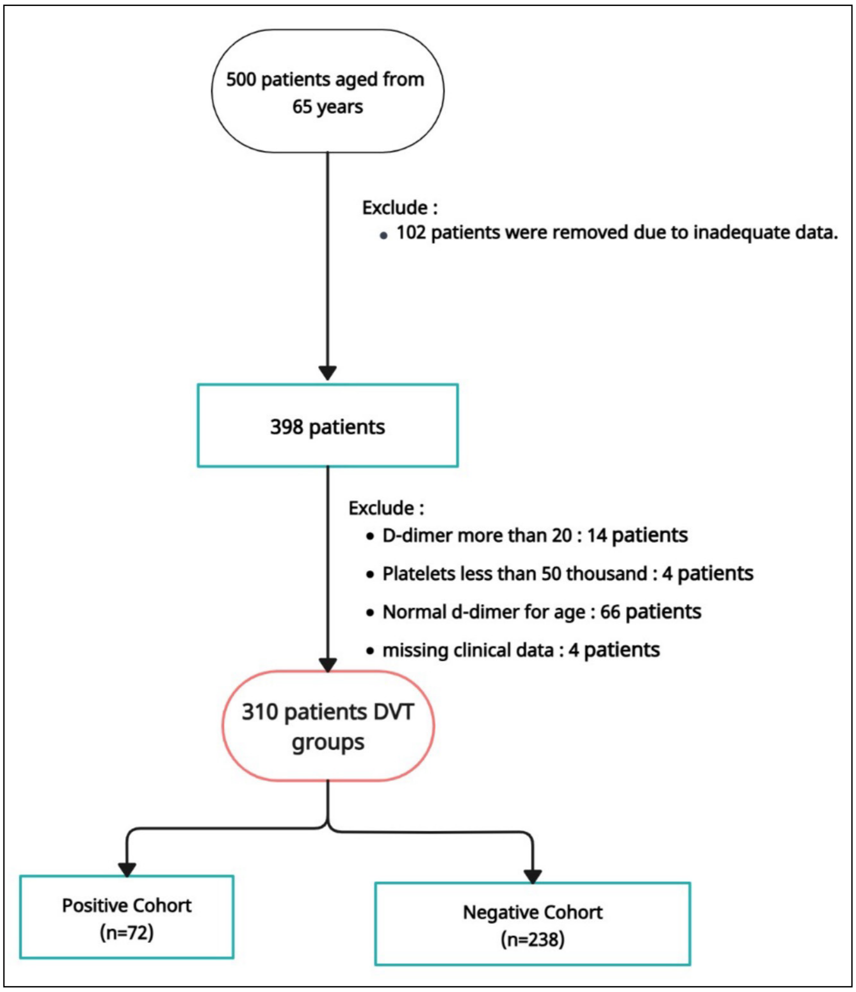


Figure 1. Flow chart of patient selection for the study.

RESULTS

During the study period, 500 patients aged 65 or older had a US for DVT; of them, only 310 were included. Patients were further divided into 23.23% positive and 76.77% negative for DVT (Figure 2). The mean age of the DVT and non-DVT group was 78.6 ± 9.1 years and 76.4 ± 4.65 years, respectively ($p < 0.01$) (Table I). There were 57% of women in the DVT group and 60% in the non-DVT group.

Table II presents that D-dimer is a significant predictor of DVT, with a p-value of less than 0.01 and an odds ratio of 1.33, indicating that each unit increase in D-dimer levels corresponds to a 33% increase in the odds of having DVT (CI for D-dimer: 1.21, 1.47).

Age is another significant variable, with a p-value of 0.037 and an odds ratio of 1.03, indicating that a one-year increase in age is associated with a 3% increase in the odds of DVT. The CI [1.00, 1.07] further reinforces its statistical significance.

Sodium levels are associated with DVT with a p-value of 0.039, presenting an odds ratio of 0.93. This suggests a potential negative correlation, indicating that higher sodium levels may protect against DVT; however, the confidence interval [0.86, 1.00] approaches the null value of 1, warranting careful consideration of this variable's significance.

Table I. Baseline characteristics of patients with and without deep vein thrombosis (DVT).

Variable	Positive DVT	Negative DVT	*p*-value
D-dimer	5.64 ± 3.74	2.52 ± 2.64	< 0.01
Fibrinogen	439.89 ± 121.08	431.83 ± 127.74	0.6229
MPV	8.44 ± 0.96	8.63 ± 1.02	0.1374
PLT	247.53 ± 86.79	248.38 ± 93.56	0.9423
NEUT ABS	6.08 ± 2.68	5.77 ± 3.07	0.4074
MONO ABS	0.33 ± 0.31	0.39 ± 0.35	0.1279
EOS ABS	0.47 ± 0.32	0.47 ± 0.34	0.9456
LYM ABS	1.64 ± 0.68	1.66 ± 0.89	0.8450
aPTT	24.46 ± 3.91	25.11 ± 3.55	0.2107
Sodium	138.03 ± 3.97	139.00 ± 3.28	0.0593
CRP	5.09 ± 7.03	3.69 ± 6.02	0.1258

MPV – mean platelet volume; PLT – platelets; NEUT ABS – absolute neutrophil count; MONO ABS – absolute monocyte count; EOS ABS – absolute eosinophil count; LYM ABS – absolute lymphocyte count; aPTT – activated partial thromboplastin time; CRP – C-reactive protein.

The Fib/CRP ratio, while showing a *p*-value of 0.01 and an odds ratio of 1.00, reveals a confidence interval of [0.99, 1.00] that includes 1, indicating that this variable lacks a significant association with DVT and was thus excluded from further assessment.

The D-dimer/aPTT ratio is significantly associated with DVT, evidenced by a *p*-value of less than 0.01 and an odds ratio of 1.07. The confidence interval [1.05, 1.10] does not include 1, affirming its importance in predicting DVT.

We excluded the variable if the value 1 was included in the 95% CI of the OR. We retained only D-dimer and D-dimer/aPTT ratio.

For D-dimer, achieving 100% sensitivity is possible with a threshold value of 0.89, but this comes with a specificity of only 0.11, indicating that while it is very good at identifying those who have the condition, it may also yield many false positives. The *p*-value is significant (less than 0.01), which supports the reliability of these results. Additionally, when seeking the optimal balance between sensitivity and specificity using the Youden Score, we obtained a score of 0.50, with an optimal threshold of 2.63. At this threshold, D-dimer showed a sensitivity of 0.78 and a specificity of 0.72, indicating it remains a reliable test for identifying DVT.

On the other hand, the Dd:aPTT ratio showed the best threshold of 3.99 for 100% sensitivity, but its specificity was lower at 0.22. Similar to D-dimer, this also indicates it is primarily useful in flagging potential cases of DVT, albeit with more false positives. The *p*-value here is also significant (less than 0.01). The Youden Score remains at 0.50, with an optimal threshold at 10.60, yielding a better sensitivity of 0.80 and a specificity of 0.70. As presented in Table III, the sensitivity and specificity analyses for D-dimer and D-dimer/aPTT ratio further support their diagnostic value in identifying DVT. Moreover, Figure 3 illustrates the ROC curve analysis comparing the predictive performance of these two parameters.

Table II. Variables associated with DVT diagnosis based on likelihood ratio test (LRT) from multivariate logistic regression.

Variable	*p*-value	Odds ratio (OR)	95% CI for OR
Age	0.037	1.03	[1.00, 1.07]
D-dimer	< 0.01	1.33	[1.21, 1.47]
Sodium	0.039	0.93	[0.86, 1.00]
Fib/CRP	0.01	1.00	[0.99, 1.00]
Dd:aPTT	< 0.01	1.07	[1.05, 1.10]

OR – odds ratio; CI – confidence interval; Fib/CRP – fibrinogen-to-C-reactive protein ratio; Dd:aPTT – D-dimer-to-activated partial thromboplastin time ratio.

DISCUSSION

In the current study, we aimed to elucidate the clinical and laboratory characteristics of patients

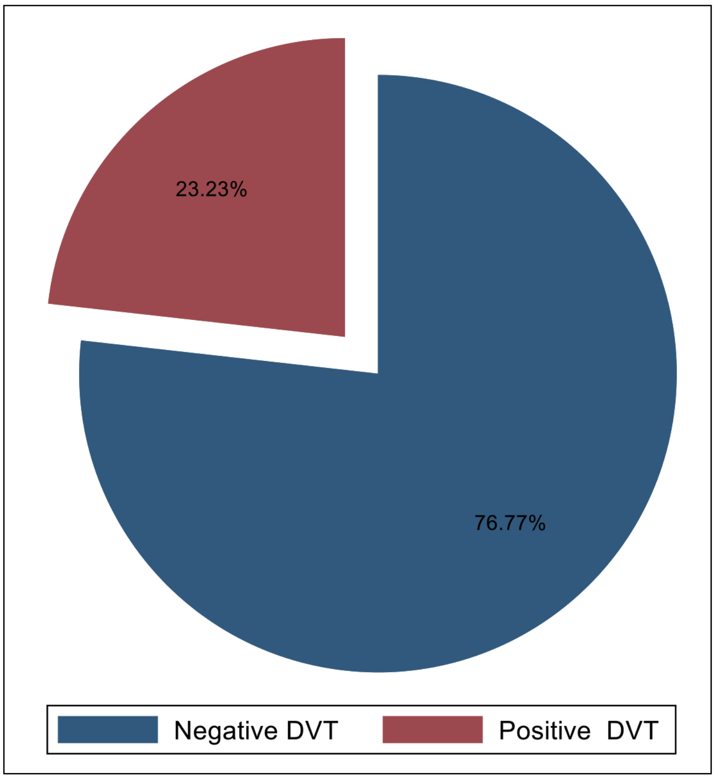


Figure 2. Pie chart for DVT groups.

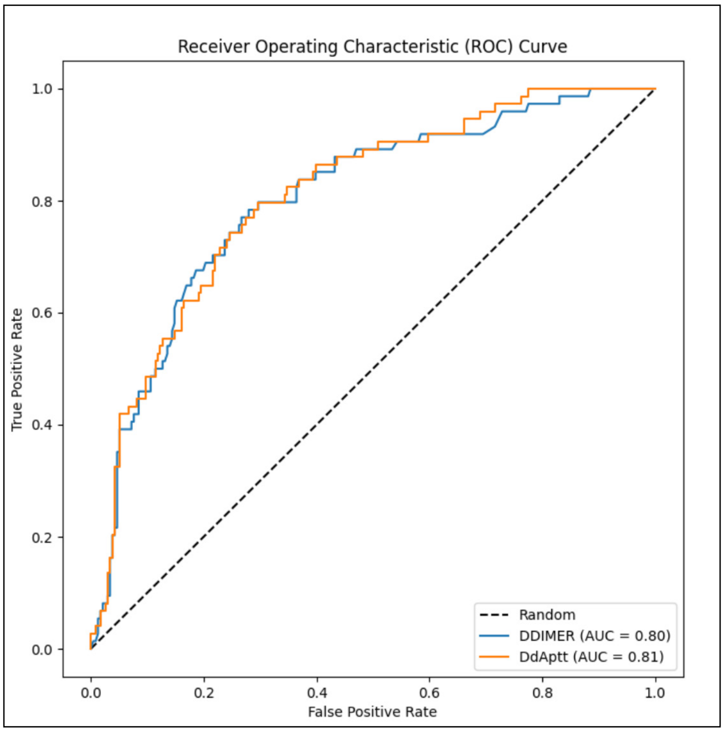


Figure 3. ROC curve analysis for D-dimer and D-dimer to aPTT ratio in predicting DVT.

aged 65 and older who underwent ultrasound for DVT. DVT is a significant health concern prevalent in older populations due to various intrinsic and extrinsic factors such as immobility, inflammation, and the increased presence of comorbidities. This demographic is particularly susceptible due to physiological changes associated with aging, which can decrease venous return and alter pro-coagulant and anti-coagulant systems. Our findings highlight the role of key hematological and biochemical markers, particularly D-dimer levels, in diagnosing DVT within this vulnerable group.

The univariate analysis revealed a stark contrast in D-dimer levels between the DVT group (5.64 ± 3.74 mg/L) and the control group (2.52 ± 2.64 mg/L), with a statistically significant *p*-value of less than 0.01. This finding is consistent with existing literature[14] that identifies D-dimer as a sensitive, though not specific, marker for thromboembolic disease. Elevated levels of D-dimer can reflect degradation products of cross-linked fibrin, indicating a greater likelihood of thrombus formation or resolution[15]. Therefore, D-dimer serves as a vital indicator in the assessment of suspected DVT cases. However, it is crucial to recognize that D-dimer's low specificity, demonstrated in our study by a specificity of only 11% at a sensitivity threshold of 100%, requires that clinicians exercise caution when interpreting elevated levels, particularly in elderly patients who may present with multiple differential diagnoses[16].

In our logistic regression analysis, age and biochemical markers like sodium and the Dd:aPTT ratio emerged as significant predictors of DVT. Of particular note, the Dd:aPTT ratio (OR: 1.07, 95% CI: 1.05-1.10) was retained in the final model, affirming its potential role in complementing D-dimer assessments to enhance diagnostic capabilities in clinical settings. The utility of the Dd:aPTT ratio further corroborates previous studies[17] that advocate for composite scoring systems integrating various biomarkers to aid in diagnosing thromboembolic events.

The D-dimer assay is commonly acknowledged as a crucial biomarker in the assessment of thromboembolic disorders; however, its sole use may exhibit limitations due to the non-specific elevation in various conditions. Age-adjusted D-dimer values increase the predictive accuracy for DVT,

Table III. Sensitivity and specificity analysis.

Column	Best threshold for sensitivity 100%	Specificity for sensitivity 100%	*p*-value	Youden score	Best threshold (Youden)	Best sensitivity (Youden)	Best specificity (Youden)
D-dimer	0.89	0.11	< 0.01	0.50	2.63	0.78	0.72
Dd:Aptt	3.99	0.22	< 0.01	0.50	10.60	0.80	0.70

especially in older populations, where age itself is a significant risk factor for venous thromboembolism[18,19]. Furthermore, the Dd:aPTT ratio offers a comprehensive measure that reflects both clotting activity and fibrinolysis, thereby improving the understanding of a patient's venous condition and thrombotic risk[20,21].

Notably, incorporating biochemical markers such as the Dd:aPTT ratio into diagnostic models is consistent with current research on novel DVT biomarkers. This approach emphasizes the importance of combining coagulation and inflammatory parameters to achieve a more accurate and comprehensive diagnostic assessment[22,23]. The interplay between these parameters reveals significant insights into hypercoagulable states and supports the implementation of composite scoring systems that may facilitate timely clinical interventions. Furthermore, the utility of integrating additional hematological markers in future studies could yield an even more robust predictive model that accounts for the complex interplay between various risk factors associated with DVT[24].

While our study identified significant associations between D-dimer levels and DVT, other hematological markers, such as fibrinogen and platelet count, failed to reach statistical significance. This implies that while inflammatory markers may play a role in the pathophysiological process, they do not necessarily correlate directly with the presence of DVT in the elderly population, warranting further exploration[25]. Additionally, the trend toward lower sodium levels in the DVT cohort, although not statistically significant, raises questions about underlying electrolyte disturbances related to comorbid conditions that could influence thrombotic risk[26].

Furthermore, the role of systemic inflammation in the development of DVT, primarily reflected through indicators such as platelets and leukocyte ratios, was also examined. The PLR, NLR, and LMR have been suggested as potential markers for thromboembolic risk, particularly in inflammatory states[27]. In our analysis, although the relationship between PLR and DVT showed promise, conclusive evidence was lacking, likely due to the specifics of our cohort, which was primarily composed of emergency department patients rather than post-surgical patients, where such ratios have been more robustly studied[28]. Thus, further examinations of these ratios are warranted, particularly in post-operative settings or among individuals with varying comorbidity profiles where inflammatory processes could significantly alter the risk of DVT.

Our findings reinforce the growing evidence that combining simple, routinely measured hematological and biochemical biomarkers can enhance the diagnostic specificity of DVT. Such integration not only facilitates earlier and more accurate detection but also aligns with current efforts to improve patient outcomes and quality of life through cost-effective, precision-driven approaches.

It is essential to assess the potential limitations of this study critically. A notable concern arises from the inclusion of patients undergoing treatment with newer oral anticoagulants (NOACs), which could bias the results by inherently lowering the risk of DVT[29]. The retrospective nature of this study and single-center design present challenges in generalizability and the robustness of correlations observed. Additionally, the exclusion criteria, while necessary to mitigate confounding factors, may have limited the range of hematological conditions assessed, affecting the statistical power of our findings[30]. Future multicenter, prospective cohorts integrating diverse populations and treatment modalities will be essential to validate the findings presented here and develop comprehensive diagnostic frameworks.

CONCLUSIONS

D-dimer remains a key diagnostic tool for suspected DVT in the elderly, despite limited specificity. The D-dimer/aPTT ratio offers added diagnostic value within the broader context of systemic inflammation. Future studies incorporating diverse populations and composite diagnostic models may enhance accuracy and improve DVT management in aging patients.

Authors' Contributions

Ramon Cohen and Elbirt Daniel contributed equally to the conception and design of the study. Shay Nemet and Alena Kirzhner were responsible for data collection and statistical analysis. Nizar Abu Hamdeh and Ameer Mahamid contributed to data interpretation and manuscript drafting. Tal Schiller provided clinical expertise and critical revision of the manuscript. Mohammad Alnees and Haitham Abu Khadija supervised the study, reviewed the methodology, and provided final approval of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study. No financial, personal, or institutional relationships could be perceived as influencing the research presented in this manuscript.

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Ethics Approval

The study was approved by the Institutional Ethics Committee of Kaplan Medical Center, in accordance with the principles outlined in the Declaration of Helsinki (protocol number 0039-24-KMC, approval date: December 20, 2019).

Informed Consent

Given the retrospective design, informed consent was waived by the Ethics Committee. Patient data were anonymized before analysis.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request and with approval from the Institutional Ethics Committee of Kaplan Medical Center.

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