International Journal of Clinical Science and Medical Research
ISSN(print): 2770-5803, ISSN(online): 2770-582X
Volume 06 Issue 11 November 2026
DOI: https://doi.org/10.55677/IJCSMR/V6I11-03/2026, Impact Factor: 8.005
Page No : 392-397



Diagnostic Value of D-dimers According to eGFR in Suspected Venous Thromboembolism

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ABSTRACT

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a potentially serious condition requiring rapid and accurate diagnosis. D-dimer testing plays a central role in the diagnostic strategy because of its high sensitivity and negative predictive value, particularly in patients with low or intermediate clinical probability. However, its low specificity may lead to unnecessary imaging. Chronic kidney disease represents a challenging clinical setting, as D-dimer levels increase progressively with declining estimated glomerular filtration rate (eGFR), independently of thromboembolic events. This renal function–related elevation may considerably reduce specificity and complicate the interpretation of D-dimer results, potentially increasing the use of contrast-enhanced imaging in a population already vulnerable to renal complications. Therefore, adjusting D-dimer interpretation according to eGFR may improve diagnostic performance and help optimize the diagnostic strategy.

Published Online: November 14, 2026

KEYWORDS:
D-dimer, renal impairment, estimated glomerular filtration rate (eGFR), venous thromboembolism, diagnostic performance.

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, is a common and potentially serious condition associated with significant morbidity and mortality. Its diagnosis relies on a strategy combining clinical pretest probability assessment, laboratory testing, and imaging, in order to optimize patient management while limiting unnecessary investigations.

D-dimer testing plays a central role in this diagnostic strategy. Owing to their excellent sensitivity, D-dimers allow the exclusion of VTE without imaging when the result is negative in patients with low or intermediate clinical probability. However, their low specificity represents a major limitation, particularly in certain populations where D-dimer levels are elevated in the absence of thrombosis, leading to excessive use of radiological investigations.

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Cite this Article: Chahbounia, M., Harrach, A., Mouslih, O., Bencharef, H., Oukkache, B. (2026). Diagnostic Value of D-dimers According to eGFR in Suspected Venous Thromboembolism. International Journal of Clinical Science and Medical Research, 6(11), 392-397. https://doi.org/10.55677/IJCSMR/V6I11-03/2026

Chronic kidney disease represents one of these complex clinical settings. Several studies have shown that a decrease in estimated glomerular filtration rate (eGFR) is associated with increased D-dimer levels, independently of any thromboembolic event. This elevation, unrelated to thrombosis, results in a significant decrease in test specificity, making its interpretation more challenging.

In clinical practice, this renal function–related limitation remains insufficiently considered by many clinicians. As a result, there is increased use of diagnostic imaging, particularly computed tomography pulmonary angiography (CTPA), sometimes performed unjustifiably. However, these investigations expose patients with renal impairment to additional risks, especially contrast-induced nephrotoxicity, potentially worsening already impaired kidney function.

In this context, adapting the interpretation of D-dimers according to eGFR appears to be a relevant approach to improve the diagnostic performance of the test and to rationalize management strategies. However, available data remain limited and sometimes conflicting regarding the actual impact of eGFR on the diagnostic value of D-dimers in suspected VTE.

The objective of this study was to evaluate the diagnostic value of D-dimers according to different eGFR categories in patients investigated for suspected venous thromboembolism,

and to assess the potential benefit of a renal function–adjusted interpretation in order to optimize the diagnostic strategy.

PATIENTS AND METHODS

We conducted a retrospective, observational, descriptive, and analytical study from January 2024 to June 2025 at the Hematology Laboratory of Ibn Rochd University Hospital in Casablanca, Morocco.

The study included patients followed in the nephrology department who were investigated for suspected venous thromboembolism. Patients with incomplete biological or radiological data were excluded.

Deep vein thrombosis (DVT) was confirmed by venous Doppler ultrasonography, while pulmonary embolism (PE) was diagnosed by computed tomography pulmonary angiography (CTPA).

D-dimer concentrations were measured by immunoturbidimetry using the Sysmex CN-3000 analyzer. Estimated glomerular filtration rate was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation.

Patients were divided into three groups according to eGFR:

- Group 1: eGFR ≥60 mL/min/1.73 m².
- Group 2: eGFR 30–59 mL/min/1.73 m².
- Group 3: eGFR <30 mL/min/1.73 m².

The conventional D-dimer threshold of 500 µg/L was assessed. Additional thresholds of 1,480 µg/L and 1,600 µg/L were explored in the different eGFR categories.

Statistical analysis was performed using R software. Quantitative variables were described using appropriate summary statistics. The diagnostic performance of D-dimers was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC), with 95% confidence intervals (CIs). Sensitivity and specificity were calculated for the selected thresholds, together with their exact binomial 95% CIs. A p-value <0.05 was considered statistically significant.

RESULTS

Study population and renal function distribution

A total of 126 patients investigated for suspected venous thromboembolism (VTE) were included in the study. VTE was confirmed in 51 patients, whereas no thromboembolic event was identified in the remaining 75 patients.

Regarding renal function, 64 patients (50.8%) had an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m², 43 (34.1%) had moderate renal impairment (eGFR 30–59 mL/min/1.73 m²), and 19 (15.1%) had severe renal impairment (eGFR <30 mL/min/1.73 m²).

Diagnostic performance of D-dimer according to renal function

Receiver operating characteristic (ROC) curve analysis was performed separately for each renal function category. The area under the curve (AUC) was 0.583 (95% confidence interval [CI]: 0.303–0.863) in patients with severe renal impairment, 0.879 (95% CI: 0.779–0.980) in those with moderate renal impairment, and 0.914 (95% CI: 0.842–0.985) in patients with eGFR ≥60 mL/min/1.73 m² (Figure 1).

Diagnostic performance at conventional and previously reported D-dimer thresholds

At the conventional threshold of 500 µg/L, sensitivity was 91.7% in patients with eGFR <30 mL/min/1.73 m² and 100% in both the moderate renal impairment and preserved renal function groups. Specificity was 14.3%, 20.8%, and 72.7%, respectively.

We subsequently evaluated higher thresholds previously reported in the literature for patients with impaired renal function [11–14].

At a threshold of 1,480 µg/L, corresponding to the range proposed for moderate renal impairment, specificity increased to 66.7% in patients with eGFR 30–59 mL/min/1.73 m², compared with 20.8% at the conventional threshold. Sensitivity was 89.5%.

At a threshold of 1,600 µg/L, evaluated in patients with severe renal impairment, specificity increased from .3% to 42.9%, while sensitivity decreased from 91.7% to 66.7%.

For comparison, in patients with preserved renal function (eGFR ≥60 mL/min/1.73 m²), the 1,480 and 1,600 µg/L thresholds yielded identical specificity values of 88.6%, with sensitivities of 70.0% and 65.0%, respectively.

The diagnostic performance of the different thresholds across renal function categories is summarized in Table 1.

Table 1. Diagnostic performance of D-dimer thresholds according to eGFR categories

eGFR category (mL/min/1.73 m²)	D-dimer threshold (µg/L)	Sensitivity (%)	Specificity (%)
eGFR <30	500	91.7	14. 3
	1,480	66.7	42.9
	1,600	66.7	42.9
eGFR 30–59	500	100.0	20.8
	1,480	89.5	66.7
	1,600	89.5	75.0
eGFR ≥60	500	100.0	72.7
	1,480	70.0	88.6
	1,600	65.0	88.6

Relationship between D-dimer concentrations and renal function

Correlation analysis demonstrated an inverse relationship between eGFR and plasma D-dimer concentrations, with higher concentrations observed as renal function declined (Figure 1). This relationship was observed in patients both with and without confirmed VTE. However, considerable overlap in D-dimer concentrations was observed between the two groups.

Distribution of D-dimer concentrations according to renal function

The distribution of D-dimer concentrations varied across eGFR categories (Figure 2). Higher concentrations and greater dispersion were observed in patients with reduced renal function, particularly those with moderate and severe renal impairment, compared with patients with preserved renal function.

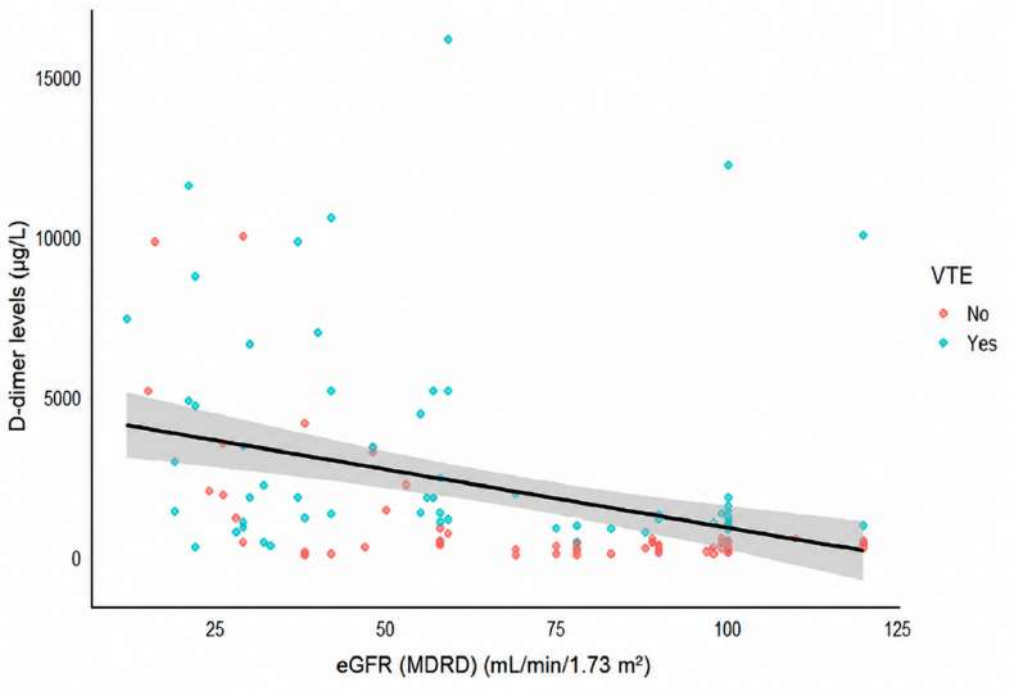


Figure 1. Correlation between D-dimer concentrations and eGFR according to thromboembolic status.

Scatter plot illustrating the inverse relationship between plasma D-dimer concentrations and estimated glomerular filtration rate (eGFR). Patients are categorized according to thromboembolic status (VTE = 0 or VTE = 1). The regression line and its 95% confidence interval illustrate the relationship between D-dimer levels and renal function.

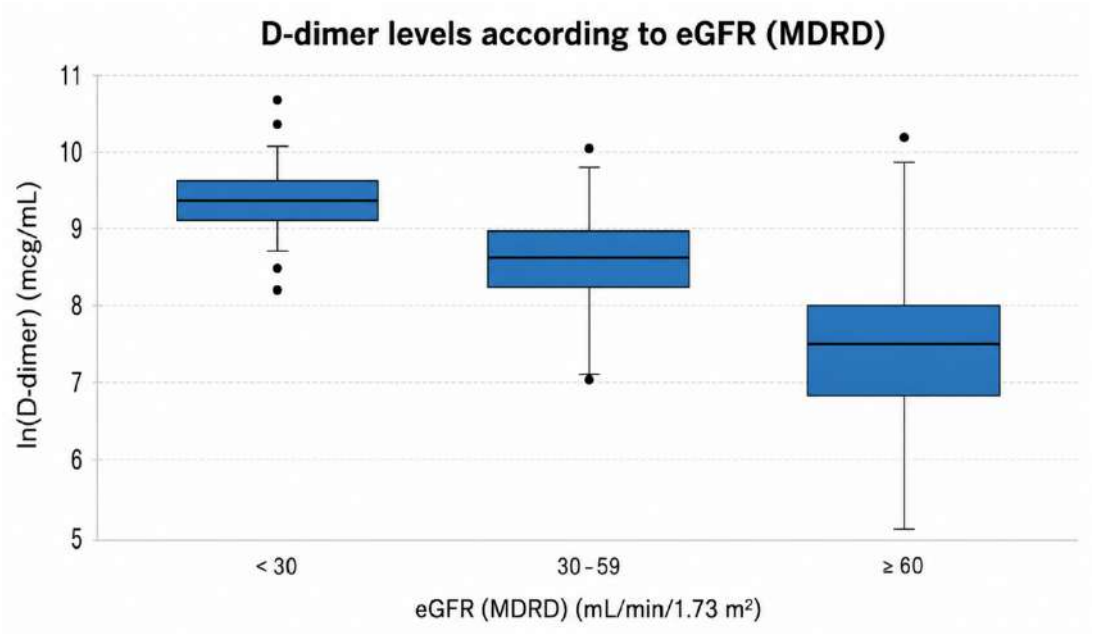


Figure 2. Distribution of D-dimer concentrations according to eGFR categories.

Boxplots showing the distribution of plasma D-dimer concentrations (expressed as natural logarithm) across the three eGFR categories (≥60, 30–59, and <30 mL/min/1.73 m²).

DISCUSSION

The interpretation of D-dimer levels in patients with suspected venous thromboembolism (VTE) and impaired renal function represents a major diagnostic challenge. Several studies have shown that renal dysfunction is associated with elevated D-dimer concentrations, even in the absence of confirmed thromboembolic events, primarily affecting test specificity while generally preserving high sensitivity [1–3]. This may limit the diagnostic efficiency of conventional algorithms based on the combination of clinical pretest probability and D-dimer testing.

The increase in D-dimer levels associated with renal impairment is likely multifactorial. Reduced estimated glomerular filtration rate (eGFR) may contribute to the accumulation of fibrin degradation products [4]. However, impaired renal clearance alone does not fully explain the elevation observed in patients with advanced kidney disease. Chronic kidney disease is characterized by a persistent systemic inflammatory state, with increased levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as C-reactive protein (CRP). This chronic inflammation may promote subclinical activation of coagulation and fibrinolysis, resulting in increased fibrin formation and consequently higher D-dimer concentrations [5,6]. Significant correlations between D-dimer levels and CRP have been reported in patients with severe renal impairment, suggesting a relationship between inflammation and hemostatic activation [7].

In addition, comorbidities frequently encountered in this population, such as infections, cardiovascular disease, diabetes, and malignancies, may independently contribute to elevated D-dimer levels in the absence of confirmed VTE [8]. Together, these factors may contribute to the reduced specificity of D-dimer testing in patients with renal impairment.

From a diagnostic standpoint, studies generally report that D-dimer testing retains high sensitivity and negative predictive value in patients with renal dysfunction [2,9]. In contrast, specificity tends to decrease with declining eGFR, resulting in more positive test results in patients without confirmed VTE and potentially increasing the need for imaging investigations.

This loss of specificity may have important clinical and economic consequences. It can lead to more frequent use of computed tomography pulmonary angiography (CTPA), with associated radiation exposure and potential risks related to iodinated contrast administration, particularly in patients with advanced renal impairment [10]. In this context, optimizing the interpretation of D-dimer results is clinically relevant.

Age is another major determinant of D-dimer concentrations. Aging is associated with progressively higher D-dimer levels and a physiological decline in eGFR. Consequently, age and renal function may act as interrelated determinants of D-dimer concentrations and should both be considered when interpreting results [6,9]. Age-adjusted D-dimer cut-offs have been shown to improve specificity while maintaining high sensitivity in older patients with suspected VTE and non-high clinical probability [11].

However, age adjustment may not fully account for elevated D-dimer levels in patients with moderate or severe renal impairment. In advanced stages of renal dysfunction (eGFR <30 mL/min/1.73 m²), systemic inflammation, as reflected by CRP levels, may play an important role [2,7]. This suggests that elevated D-dimer concentrations in these patients may reflect not only age-related changes but also the chronic inflammatory and procoagulant state associated with kidney disease.

To improve specificity, several studies have investigated renal function-adjusted D-dimer thresholds. Schefold et al. evaluated thresholds of 1,306 µg/L for moderate renal impairment and 1,663 µg/L for severe renal impairment [12]. More recently, Flueckiger et al. reported thresholds of 1,480 µg/L for patients with an eGFR of 30–59 mL/min/1.73 m² and 1,351 µg/L for those with an eGFR below 30 mL/min/1.73 m² [13]. These thresholds were evaluated in combination with clinical prediction rules to exclude pulmonary embolism. Although these findings support the potential value of renal function-adjusted D-dimer thresholds, their diagnostic performance and clinical applicability require further validation.

In our retrospective study, previously reported renal function-adjusted thresholds were evaluated in our population. Among patients with moderate renal impairment (eGFR 30–59 mL/min/1.73 m²), applying a threshold of 1,480 µg/L increased specificity from 20.8% to 66.7%, while sensitivity decreased from 100% to 89.5%.

In patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), a threshold of 1,600 µg/L increased specificity from .3% to 42.9%, accompanied by a reduction in sensitivity from 91.7% to 66.7%.

These findings indicate that higher D-dimer thresholds may improve specificity, but this benefit is accompanied by a reduction in sensitivity, particularly in patients with severe renal impairment. Furthermore, the limited discriminatory performance observed in this subgroup (AUC = 0.583; 95% CI: 0.303–0.863) warrants cautious interpretation. Therefore, our findings do not establish the clinical validity of these thresholds, and further studies involving larger independent populations are needed.

Elevated D-dimer concentrations in patients with renal impairment may partly reflect the use of conventional, non-adjusted cut-off values, in addition to the underlying inflammatory and procoagulant state associated with kidney disease. Although higher eGFR-based thresholds may improve specificity, this benefit must be balanced against a

potential reduction in sensitivity. Consequently, renal function-adjusted thresholds should be interpreted cautiously and cannot yet be considered validated diagnostic alternatives to conventional cut-offs.

To date, renal function-adjusted D-dimer thresholds have not been incorporated into established international diagnostic recommendations. Current approaches continue to emphasize the combination of clinical pretest probability and D-dimer testing, with age-adjusted thresholds as an option in appropriate patients [14–16]. In patients with severe renal impairment, alternative imaging approaches, such as ventilation–perfusion scintigraphy, may be considered when appropriate, although their availability may be limited [17].

In this context, the clinical biologist has an important role in informing clinicians about the limitations of D-dimer testing in patients with renal impairment and promoting an integrated interpretation that considers clinical context, age, and inflammatory status. Further prospective multicenter studies combining biological and clinical parameters are needed to establish safer and more effective diagnostic strategies in this population.

CONCLUSION

In patients with renal impairment, D-dimer sensitivity for excluding venous thromboembolism remains high, but specificity decreases significantly with declining eGFR. This elevation primarily reflects inappropriate standard thresholds rather than true thrombotic activity.

Adjusting D-dimer cut-off values according to eGFR improves specificity without compromising sensitivity, thereby reducing false positives and unnecessary imaging. However, D-dimer interpretation should always be integrated with pretest clinical probability, age, and inflammatory status, particularly in patients with severe renal impairment.

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