# Concentration and the value of D-dimer in the diagnosis of deep vein thrombosis

Concentración y valor del dímero D en el diagnóstico de trombosis venosa profunda

Phan Nguyen Thanh Van[1]* https://orcid.org/0000-0002-9018-9075

Nguyen Nhi De[2] https://orcid.org/0000-0003-4470-650X

Bui Dang Minh Tri[1] https://orcid.org/0000-0002-3729-3973

Tong Duc Minh[3] https://orcid.org/0000-0001-5449-0832

Nguyen Thi Ngoc Dung[4] https://orcid.org/0000-0001-8122-1515

Nguyen Hoang Trung[3] https://orcid.org/0000-0003-3527-7037

[1]Pham Ngoc Thach University of Medicine. Ho Chi Minh City, Vietnam.

[2]Gia Rai Medical Center. Laboratory Department. Baclieu, Vietnam.

[3]Vietnam Military Medical University. Department of Military Hygiene. Hanoi, Vietnam.

[4]Military Hospital 175. Ho Chi Minh City, Vietnam.

*Author for correspondence. Email: pnthanhvan@pnt.edu.vn

**ABSTRACT**

**Introduction:** Quantification of D-dimer levels is a valuable test in orienting the diagnosis of deep vein thrombosis.

**Objectives:** Determine D-dimer concentration and diagnostic value of D-dimer in patients with deep venous thrombosis.

**Methods:** A descriptive, uncontrolled study was performed in 260 elderly patients at risk of deep vein thrombosis. All patients underwent quantitative D-dimer assay.

**Results:** The D-dimer concentration of patients with deep venous thrombosis had a median of 3106.5 ng/ml and was about 1.5 times higher than that of patients without deep venous thrombosis. With a

threshold of D-dimer concentration of 500 ng/mL to determine deep venous thrombosis, the specificity of the method is low (16.51%), but the sensitivity is high (100%). And the positive predictive value is low (18.75%) but the negative predictive value is absolute (100%).

**Conclusion:** With a threshold of D-dimer concentration of 500 ng/mL to determine deep venous thrombosis, the specificity and positive predictive value of the method are low, but the sensitivity and negative predictive value are high.

**Keywords**: D-dimer concentration; D-dimer diagnostic value; deep vein thrombosis.


## RESUMEN

**Introducción:** La cuantificación de los niveles de dímero D es una prueba valiosa para orientar el diagnóstico de trombosis venosa profunda.

**Objetivos:** Determinar la concentración de dímero D y el valor diagnóstico del dímero D en pacientes con trombosis venosa profunda.

**Métodos:** Se realizó un estudio descriptivo, no controlado, en 260 pacientes ancianos con riesgo de trombosis venosa profunda. Todos los pacientes se sometieron a un ensayo cuantitativo de dímero D.

**Resultados:** La concentración de dímero D de los pacientes con trombosis venosa profunda tuvo una mediana de 3106,5 ng/mL y fue aproximadamente 1,5 veces mayor que la de los pacientes sin trombosis venosa profunda. Con un umbral de concentración de dímero D de 500 ng/mL, para determinar la trombosis venosa profunda, la especificidad del método es baja (16,51 %), pero la sensibilidad es alta (100 %). El valor predictivo positivo es bajo (18,75 %) pero el valor predictivo negativo es absoluto (100 %).

**Conclusión:** Con un umbral de concentración de dímero D de 500 ng/mL para determinar la trombosis venosa profunda, la especificidad y el valor predictivo positivo del método son bajos, pero la sensibilidad y el valor predictivo negativo son altos.

**Palabras clave:** concentración de dímero D; valor diagnóstico de dímero D; trombosis venosa profunda.

# INTRODUCTION

Deep venous thrombosis (DVT) is the leading cause of death in elderly inpatients. Venous thrombosis is a global burden with approximately 10 million cases occurring annually, making it the third leading vascular disease after acute myocardial infarction and stroke.[1]

Early diagnosis and treatment of deep venous thrombosis increases survival. In the past, contrast angiography was considered the gold standard in the diagnosis of deep venous thrombosis, but today this technique has been replaced by non- or less invasive techniques such as venography, magnetic resonance, CT scan, Doppler ultrasound, D-dimer, and others.[2,3] In particular, the concentration of D-dimer has a high sensitivity of 94-96% in most patients with deep venous thrombosis. In elderly and malignancies, sepsis, inflammation, chronic renal failure, surgery, trauma, severe burns, and pregnancy, the specificity is low, 42-52%. Therefore, a negative D-dimer result helps to rule out deep venous thrombosis, especially when there are few clinical symptoms to diagnose, and D-dimer results can change the requirements for testing and imaging studies to confirm the diagnosis of deep venous thrombosis.[2]

This study was conducted with the goal of determining the D-dimer concentration and diagnostic value of D-dimer in patients with deep venous thrombosis.

# METHODS

Elderly patients hospitalized for inpatient treatment and at risk for deep vein thrombosis, at Thong Nhat Hospital, Ho Chi Minh City, Vietnam, from November 2021 to August 2022 were included. Sample selection criteria were:

- Patients aged 60 years or older, hospitalized for inpatient treatment were at risk of deep venous thrombosis at the time of the study.
- The patient had a Wells score of 1-2 points.[4]
- Patient consented to participate in the study.

Research sample size: based on the average estimation formula, as follows:

$$n= Z^2_{(1-a/2)} \left(\frac{\sigma}{d}\right)^2$$

Where:

α is the probability of type I error, choose α = 0.05.

$Z^2_{(1-a/2)}$ is a normally distributed value, $Z^2_{(1-a/2)} = 1.96$.

Where d is the error of the estimate.

σ is the estimated standard deviation of the population. σ was calculated based on the research results of author *Kassim* et al.[5] with a sample size of 252 and σ = 1,065.

The error d chosen was approximately 15% either side (30% if 2-tailed) of the mean of the previous study, with μ=1.23(5) and d= 0.185.

Therefore, the minimum sample size for the study was 128. With expected 10% sample loss the required sample size for the study was 143. In fact, 260 patients were surveyed.

Research variables: Mean age, proportion of age groups (60-79), sex, medical condition at hospital admission (comorbidities), D-dimer concentration, D-dimer results, deep venous thrombosis status (diagnosed by Doppler ultrasound), and the parameters to calculate diagnostic values include: sensitivity, specificity, negative predictive value, positive predictive value.

Data analysis: data were analyzed using SPSS 22.0 software. D-dimer concentrations are reported as the median and interquartile range. D-dimer concentration was evaluated using threshold of 500 ng/mL in elderly patients compared with Doppler ultrasound results by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the prognosis of deep venous thrombosis. Area under

the curve ROC (AUC) was calculated based on sensitivity and specificity for D-dimer concentrations with 95% confidence interval (CI). Any value with p< 0.05 was considered to be statistically significant. Ethically, the patient's identity is kept confidential, used only for analysis as a group.

# RESULTS

The results of background characterization (table 1) showed that the median age of inpatients participating in the study was 79 years old; the age group 60-79 years accounted for more than 50%. In addition to the main disease of admittance to the hospital, all patients had comorbidities, of which up to 88.9% had hypertension, 45.8% diabetes, and 39.6% cardiovascular disease. About Wells score, most of the patients were at moderate risk (98.9%), and only a few high-risk patients (1.2%).The proportion of patients with deep venous thrombosis detected by Doppler ultrasound was 36 patients (13.85%).

**Table 1** - Characteristics of the study population (n= 260)

| Characteristics | Amount (n) | Percent (%) |
|---|---|---|
| Age* | 79 (69-85) | |
| Age groups | | |
| 60 – 79 | 137 | 52.7 |
| ≥ 80 | 123 | 47.3 |
| Sex | | |
| Male | 163 | 62.7 |
| Female | 97 | 37.3 |
| Comorbidity | | |
| No | - | - |
| Yes | 260 | 100.0 |
| Comorbidities | | |
| Diabetes | 119 | 45.8 |
| Blood pressure | 231 | 88.9 |
| Heart | 103 | 39.6 |
| Kidney failure | 43 | 16.5 |
| Injury | 30 | 11.5 |
| Chronic obstructive pulmonary disease | 54 | 20.8 |
| Other diseases | 240 | 92.3 |
| Wells | | |
| 1-2 point | 257 | 98.8 |
| ≥ 3 points | 3 | 1.2 |
| Deep venous thrombosis | | |
| Yes | 36 | 13.85 |
| No | 124 | 86.15 |

* Median (interquartile range).

The D-dimer concentration of patients with deep venous thrombosis had a median of 3106.5 ng/mL and was about 1.5 times higher than that of patients without deep venous thrombosis. In addition, all patients with deep venous thrombosis had a D-dimer limit above 500 ng/mL, in the group of patients without deep venous thrombosis, the D-dimer concentration was up to 8442.0 ng/mL.

**Table 2** - D-dimer concentrations in patients at risk of deep venous thrombosis (n= 260)

| Deep venous thrombosis | Characteristics | | D-dimer concentration (ng/ ml) | |
|---|---|---|---|---|
| | n | Ratio | Median (quartile) | Min - Max |
| Has deep venous thrombosis* | 36 | 13.85 | 3108.5 (1651.5-5196.0) | 553.0-9615.0 |
| No deep venous thrombosis* | 224 | 86.15 | 1344 (605.5-2718.5) | 147.0-8442.0 |
| Study population* | 260 | 100 | 1517 (712.5-2495.5) | 147.0-9106.0 |

* Median (interquartile range).

Research results in table 3 show that: Sensitivity: $Se = A/(A+ C) = 100\%$

Specificity: $Sp = D/(B+ D) = 18.75\%$

Negative predictive value: $NPV = D/(C+ D) = 100\%$

Positive predictive value: $PPV = A/(A+ B) = 16.51\%$

When compared with the diagnostic criteria of Doppler ultrasound, with a threshold of D-dimer concentration of 500 ng/mL, the specificity of the method is low (16.51%), but the sensitivity is high (100%), and the positive predictive value is low (18.75%) but the negative predictive value is absolute (100%).

**Table 3** - Sensitivity, specificity, negative predictive value, positive predictive value of D-dimer (threshold 500 ng/ml) according to Doppler ultrasound

| D-dimer concentration | Deep venous thrombosis (n= 260) | |
|---|---|---|
| | Yes (36) | No (224) |
| Increase (218) | 36 (A) | 182 (B) |
| Normal (42) | 0 (C) | 42 (D) |

The AUC curve against D-dimer concentration to predict deep venous thrombosis was 0.728 (Fig. 1).

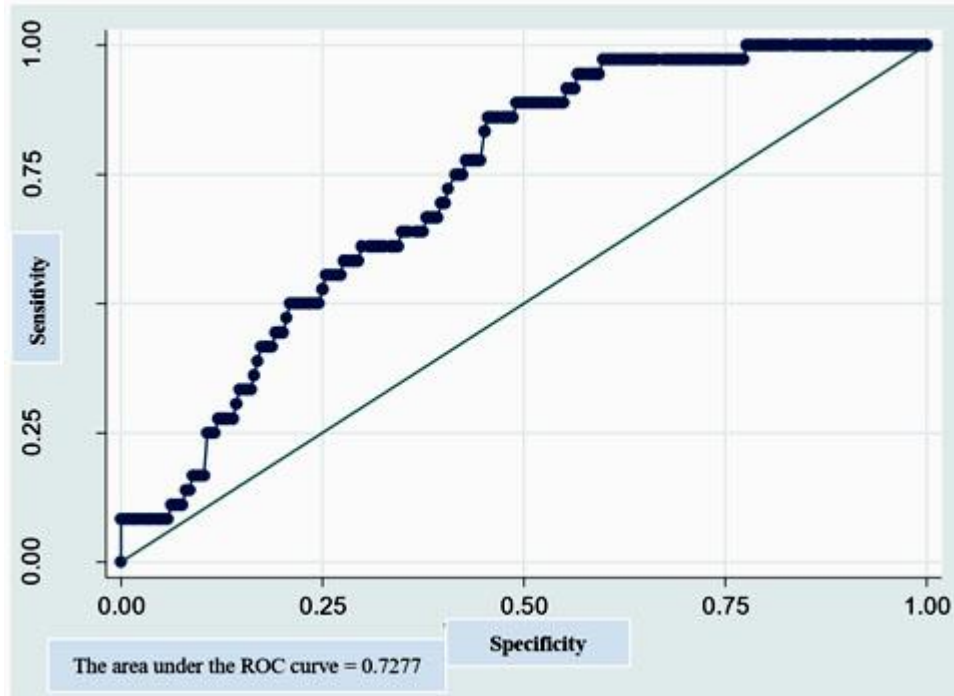The area under the ROC curve = 0.7277

**Fig. 1 -** ROC curve according to specificity, sensitivity of D-dimer concentration of deep venous thrombosis.

The results suggest that the cut-off point of D-dimer concentration was 1488, corresponding to a sensitivity of 86.11%, a specificity of 54.46% and the highest Youden index of 0.406.

**Table 4** - D-dimer cutoff value

| STT | D-dimer cut-off point | Sensitivity (%) | Specificity (%) | Youden index |
|-----|----------------------|-----------------|-----------------|--------------|
| 226 | 1488 | 0.8611 | 0.5446 | 0.406 |

# DISCUSSION

The study's results on age showed that inpatients participating in the study had a median age of 79 years. Age is also considered a risk factor for venous thromboembolism and increases with age.[6,7] The results of current study, similar to *Schoute*n et al.[8] shows that most of the participants are over 50 years old

(accounting for 68.1%).

Doctors use the Wells score to screen for the risk of deep venous thrombosis, and most studies have used it. In the study sample it accounted for most of the patients at average risk (98.9%) with 1-2 points. The results of the study by *Schouten* et al.[8] shows the rate with 47.1% of patients with Wells score ≤ 1. This difference can be explained because the author's sample differs from the current study.

The proportion of patients with DVT detected by Doppler ultrasound accounted for 13.85%. The results of current study are similar to those of *Wells* et al.[9] with the rate of DVT of 15.7%. In terms of DVT diagnostic methods, venography is still the "gold standard", but ultrasound is the most accurate noninvasive test for diagnosing DVT. It is is a common condition for which the clinical diagnosis is often unreliable due to infrequent classical findings of edema, warmth, erythema, and pain. Failure to identify and treat DVT can lead to devastating outcomes, including pulmonary embolism, superior vena cava syndrome and related complications, even death. Therefore, Doppler ultrasound was recommended to diagnose DVT in at-risk patients.

The study results also showed that the D-dimer concentration of patients with DVT (3108.5 ng/mL) was about 1.5 times higher than those without DVT (1344 ng/mL). In addition, all patients with DVT had D-dimer limits above 500 ng/mL. This result is consistent with many other studies, showing that the ratio of D-dimer concentration was very high in patients with a long-term hospital stay, especially in the group of elderly patients with DVT. The study by *Kassim* et al.[5] was performed on 252 elderly bedridden patients (> 65 years old). The results showed that patients who were found to have DVT on X-ray examination, had an average D-dimer result of 1980±1190 ng/mL. Meanwhile, on X-ray examination, patients without DVT had an average D-dimer result of 810±690 ng/mL. Similar to the MEDENOX 2 Multicenter Study by *Desjardins* et al.,[10] which randomized controlled trial was designed to evaluate outcomes in newly hospitalized patients over 40 years of age due to acute illness, and was considered to be at moderate risk of developing DVT. The study results show that the concentration of D-dimer in the group with DVT was 2250 ng/mL, and in the control group (without DVT) was 1170 ng/mL.[10]

In the diagnosis of DVT, a level of 500 ng/mL is considered the diagnostic threshold. The diagnostic threshold depends on many factors, but a level of 500 ng/mL is recommended for most D-dimer tests to diagnose DVT.[11] The results of current study showed that the sensitivity (100%), the negative predictive

value is absolute (100%), while the specificity (18.75%) and the positive predictive value are low (16.51%). A 100% sensitivity result means that a threshold of D-dimer concentration of 500 ng/mL predicts the risk of DVT in elderly inpatients, and will not miss any DVT patient. The negative predictive value of 100% means that for cases where the D-dimer concentration is less than 500 ng/mL, 100% will not have the disease. At the same time, when the specificity is 18.75%, it means that among people who do not have the disease, only 18.75% have an accurate negative result. The positive predictive value of 16.51% means that for cases where the D-dimer concentration is 500 ng/mL or higher, there can be 16.51% of patients without DVT. Thus, current research results with a threshold of D-dimer concentration of 500 ng/mL detected 100% of people with DVT and did not miss any case.

Compared with other studies, the predicted values were similar to current study; such as *Carrier et* al.[12] which used in combination, the Wells score and the threshold D-dimer 500 ng/mL to predict the risk of DVT. The results show high sensitivity in all patient groups (86.1% to 100%), resulting in a high negative predictive value of about 99%. However, the specificity was low, ranging from 54.7% to 79.4%, and the lowest results were found in older patients.[12] Similar was the results on retrospective study of *Kassim* et al.[5] performed on 252 patients (> 65 years old).

Another study by *Harper* et al.[13] looked at a 1000 ng/mL cut-off in a group of patients aged 60-80 years to increase the specificity of the D-dimer test. This study aimed to examine the effect of age on test specificity, and a cohort of 1897 patients with suspected venous thrombosis was analyzed separately. D-dimer-negative patients were discharged without further investigation. Patients with positive and clinically suspected thrombosis were further investigated. As a result, 165 cases of DVT or pulmonary embolism were identified. The specificity of the test decreases with age, from 70% in patients under 40 years of age, to less than 5% in patients over 80 years of age. In patients of 60-80 years of age, a threshold value of 1000 ng/mL increased the specificity of the test by 55% without loss of sensitivity.[13]

Using the usual threshold for D-dimer (500 ng/mL) is recommended by most manufacturers, and adopted by many laboratories and clinicians worldwide; however prone to false positives result in elderly patients. One possible solution is to raise the cut-off threshold to improve the specificity of the D-dimer test, without affecting its sensitivity. In elderly patients, D-dimer specificity is affected by increased D-dimer levels without any thrombotic disease, which increases false-positive results and increases the number of

patients who had an unnecessary X-ray examination. Developing a more accurate interpretation of D-dimer results will reduce the financial burden of unnecessary tests and ensure that diagnosis weren't missed, which can be fatal.[5] In summary, in the current study with a diagnostic threshold of 500 ng/mL, the quantitative D-dimer test was an accurate and effective method in diagnosing and excluding DVT in general medical patients, and patients with chronic obstructive pulmonary disease.

With 100% sensitivity and 100% negative predictive value, the current study results are consistent with the literature regarding the role of D-dimer in excluding the diagnosis of DVT. However, further studies are needed to consider other D-dimer thresholds for the elderly population, such as the age-dependent cut-off threshold (at age > 50), the limit of 750 ng/mL (at age ≥ 60 years) instead of usual cut-off value of 500 ng/mL (at all ages).

Research results show that the AUC, according to the D-dimer concentration is 0.728. The results suggested that the cut-off point of D-dimer concentration was 1488 ng/mL, corresponding to a sensitivity of 86.11%, a specificity of 54.46%.

Comparing this study with other studies, shows that the predictive value is also different. The cut-off value suggests that DVT in elderly patients is higher than in other studies. Specifically, according to the study of *Kassim* et al.,[5] it was found that when calculated over the entire study population, the AUC, according to D-dimer concentration in predicting DVT was AUC= 0.868 (95% CI: 0.825-0.911). At the same time, the cut-off D-dimer concentration suggesting DVT is 600 ng/mL. At this cut-off, there was a sensitivity of 97.8% and a specificity of 52.4%. However, the best results were when adjusted for age. Specifically, the suggested D-dimer score group is 600 ng/mL in the 65-70-year-old group, 900 ng/mL in the 71-80-year-old group, and only about 550 ng/mL in the over-80-year-old group. The corresponding AUC is 0.862 for the 65-70-year-old group, 0.902 for the 71-80-year-old group, and 0.835 for the over-80-year-old group.[5] Another study by *Prochaska* et al.[14] showed that the AUC for D-dimer concentrations in patients under 60 years of age in predicting venous thrombosis in the near future, was 0.842, and for predicting venous thrombosis in the long term was 0.674. In addition, for the group of patients from 60 years of age, the AUC of D-dimer concentration in predicting venous thrombosis in the near future was 0.865, and for predicting venous thrombosis in the long term was 0.622.

With a threshold of D-dimer concentration of 500 ng/mL to determine deep venous thrombosis, the

specificity and positive predictive value of the method were low, but the sensitivity and negative predictive value were high.

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## Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Authorship contribution

Conceptualization: *Phan Nguyen Thanh Van, Nguyen Nhi De.*

Data curation: *Nguyen Nhi De, Phan Nguyen Thanh Van, Bui Dang Minh Tri.*

Formal analysis: *Bui Dang Minh Tri, Tong Duc Minh, Nguyen Hoang Trung.*

Research: *Nguyen Nhi De, Phan Nguyen Thanh Van.*

Methodology: *Nguyen Nhi De, Phan Nguyen Thanh Van, Bui Dang Minh Tri, Tong Duc Minh, Nguyen Hoang Trung.*

Project administration: *Phan Nguyen Thanh Van, Nguyen Nhi De.*

Supervision: *Phan Nguyen Thanh Van, Bui Dang Minh Tri.*

Validation: *Phan Nguyen Thanh Van, Bui Dang Minh Tri, Tong Duc Minh, Nguyen Hoang Trung.*

Display: *Bui Dang Minh Tri, Phan Nguyen Thanh Van, Tong Duc Minh, Nguyen Hoang Trung, Nguyen Thi Ngoc Dung.*

Drafting - Revision and editing: *Phan Nguyen Thanh Van, Tong Duc Minh, Nguyen Hoang Trung, Bui Dang Minh Tri, Nguyen Thi Ngoc Dung.*