REVIEW ARTICLE

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Unreliability of d-dimers in diagnosis of venous thromboembolism – comprehensive literature review

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Abstract

Introduction and Objective. D-dimers are mainly used in daily clinical practice to exclude venous thromboembolism (VTE); however, in a significant number of measurements, a positive D-dimer result does not confirm it, which is emphasized in the review. In addition, this parameter is often overused and its results misinterpreted.

Review Methods. A review and analysis of the most up-to-date literature (using the PubMed and Scopus databases, with over 90% of the works being no older than 8 years) consisting solely of English-language original and review papers addressing the topic of D-dimer testing in daily clinical practice.

Brief description of the state of knowledge. Based on the literature review, it has been noted that D-dimers often produce false-positive results, which often leads to unjustified implementation of imaging diagnostics, which exposes the patient to ionizing radiation, contrast agents, administration of fibrinolytic drugs, as well as generating unnecessary costs. Modifying the D-dimer cut-off point in older patients and those with risk factors for VTE maintain negative predictive value (NPV) and specificity; however, there is still a large percentage of patients without VTE despite a positive D-dimer result.

Summary. In the analyzed studies that included both the standard cut-off point and modified reference ranges for D-dimers based on age and likelihood of venous thromboembolism, a high percentage of patients with false-positive results were obtained, with limited specificity and positive predictive value (PPV).

Key words

venous thromboembolism, pulmonary embolism, false positive results, d-dimer

INTRODUCTION

D-dimers are a product of the breakdown of fibrin, which is formed from fibrinogen and is responsible for the final formation of a blood clot. As a laboratory marker, it is used mainly to exclude or raise suspicion of VTE, which includes pulmonary embolism (PE) and deep vein thrombosis (DVT). In patients under 50 years of age, the upper limit of the reference range is 500 µg/L [1–3], while in patients over 50, the rule is applied: age in years x 10 = reference range in µg/L, which is due to the physiological fact of an increase in D-dimer levels with age [4–8]. In order to optimize management, the Wells and Geneva clinical rules are used to assess the pre-test probability of VTE [6, 9], but they are not always regularly used by practicing physicians [10, 11]. Based on the assessment of the pre-test probability in patients with low to moderate risk, a thromboembolic episode can be excluded using D-dimers [4]; however, it should be noted that a positive D-dimer result does not always indicate PE or DVT in a patient due to its limited specificity. This leads to attempts to introduce modifications to the D-dimer reference range, including the afore-mentioned variable reference range >50 years old, as well as a higher cut-off point in the low-risk patient group [3,9]. Many clinicians overly rely on D-dimer measurements and inappropriately conduct often unnecessary and potentially harmful imaging diagnostic by directing patients to undergo such tests [1–3, 9,12, 13].

The significant increase in the availability of computed tomography in recent years has contributed to over-use of this diagnostic method [6, 10, 11, 14, 15], and especially observed in emergency departments where clinically insignificant diagnoses are often obtained, and the diagnostic process is prolonged [12, 15–19]. This exposes the patient to ionizing radiation, contrast administration, or even administration of fibrinolytic drugs, all of which are possible to avoid. [10, 20]. It should be remembered that a D-dimer value above the reference range is observed in many cases without the presence of VTE. Examples of clinical situations may include post-operative state, neoplastic process, inflammatory processes, vascular diseases, such as coronary heart disease or stroke, as well as pregnancy and auto-immune diseases [21–24]. More extensive awareness of the factors influencing the presence of false-positive D-dimer results in the absence

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of venous thromboembolic disease can have a positive impact on decision-making by the medical staff in uncertain situations.

OBJECTIVE AND REVIEW METHODS

The aim was to review the current literature, both review and original articles, exclusively in the English language (PubMed, Scopus database – with over 90% of the articles being no older than eight years), covering the issue of the usefulness of D-dimer measurement in daily clinical practice. This includes the analysis of numerous patient groups and various clinical situations in which elevated values of this parameter can be observed. The review attempts to emphasize how often false-positive D-dimer results in modern practice directly expose low-risk patients to unnecessary diagnostics, including exposure to ionizing radiation, contrast in pulmonary artery CT angiography, as well as expose medical facilities to generating avoidable costs and prolong the time of medical services for other patients.

VTE DIAGNOSIS – PRE-TEST PROBABILITY ASSESSMENT

In the case of a patient suspected of VTE, the probability of the disease should be assessed. Over the years, various classifications have been attempted in the literature to assist in the diagnosis of venous thromboembolic disease. However, the Wells score and the Geneva score are among the most reliable in daily clinical practice today [5, 21].

Shortness of breath, chest pain, and sometimes loss of consciousness, are among the most common symptoms accompanying patients with pulmonary embolism; however, there are many patients with such symptom profiles in the emergency department [13,16].

Standard D-dimer threshold. In 2021, Vögeli et al. [4] conducted a single-centre cohort study of 3,301 patients (the TRIAGE project 03.2013 – 10.2016) who were eligible for D-dimer measurement. The mean age was 63 years, and many of the subjects had multiple comorbidities, including cardiovascular disease, diabetes, chronic kidney disease, and a history of cancer. 203 (6.1%) were confirmed to have pulmonary embolism or deep vein thrombosis, while 3,098 (93.9%) had confirmed absence of thromboembolic disease. Among the 203 patients with confirmed VTE, 2 (0.99%) had D-dimer levels <500 μg/L, resulting in a NPV of 99.9% (95% CI 99.5–100%) and sensitivity of 99% (95% CI 96.5–99.9%). In the group of patients without VTE, 1,570/3,098 (50.7%) had a D-dimer level >500μg/L L, resulting in a PPV of 11.4% (95% CI 10–13%) and a specificity of 49.3% (95% CI 47.5–51.1%). Subsequently, 2 subgroups were distinguished from the group in which VTE was excluded: n=1,528 (D-dimer <500 μg/L) and n=1,570 (D-dimer >500 μg/L). It was found that the group with D-dimer levels above the reference value included older patients (OR increased by 1.04 for each year, 95% CI 1.04–1.05; p<0.001), those with chronic heart failure (OR 2.79, 95% CI 1.77–4.40; p<0.001), or a history of cancer (OR 2.60, 95% CI 1.57–4.31; p<0.001).

Innocenti et al.[13] conducted an extensive literature review on the objective assessment of the usefulness of D-dimer measurement in the emergency department. One of the studies analyzed was an article by Lippi et al., which collected D-dimer results evaluated in the emergency department in 1,647 patients to rule out thromboembolic disease. The most common diagnosis among patients with elevated D-dimer levels was infection (n=257, 15.6%), with n=200 (12.1%) confirmed cases of thromboembolic disease.

The study conducted by Glober et al. [25] included 3,523 patients (2012–2016) who presented to the emergency department and were selected for D-dimer measurement, based on initial assessment of the probability of VTE, taking into account clinical presentation and predisposing factors. 2,253 patients had a positive D-dimer result, while the remaining 1,270 had a result below the standard cut-off. Subsequently, 3,501 patients were referred for CT angiography of the pulmonary arteries and 1,56 for ventilation/perfusion scintigraphy (some for both tests). In the group of patients with elevated D-dimer levels, pulmonary embolism (PE) was confirmed in 198 out of 2,253 cases (8.78% true positive rate), while the remaining 1,895 cases (84.1%) were false positives. In the group with negative D-dimer results, 9 out of 1,270 cases (0.7%) were false negatives, with PE confirmed on imaging. Six out of the 9 false negative cases had a history of thromboembolic disease and were taking anticoagulant medication. The study showed a sensitivity of 95.7% (95% CI, 91–98%) and a specificity of 40.0% (95% CI, 38–42%) for D-dimer measurements.

Table 1. Wells and revised Geneva score for PE

Wells score		Revised Geneva Score	
HR >100	1,5p	Age > 65	1p
Haemoptysis	1p	HR >95	5p
Cancer	1p	HR 75-94	3p
Previous PE or DVT	1,5p	Previous PE or DVT	3p
Recent surgery or immobilization	1,5p	Unilateral leg pain	3p
Clinical signs of DVT	3p	Unilateral leg oedema	4p
Alternative diagnosis less likely than PE	3p	Haemoptysis	2p
=<4 (low probability of PE) >6 (high probability of PE)		Active cancer	2p
		Surgery or fracture in the last 4 weeks	2p
		=<3 (*low* probability of PE) >11 (*high* probability of PE)	

PE- pulmonary embolism; DVT - deep vein thrombosis; HR - heart rate

In their 2021 study, Salehi et al. **[26]** collected data on the number of CT angiography of the pulmonary arteries performed in large emergency departments between 1 January 1, 2016 – 31 December 2017. They found that PE was confirmed in 292 out of 2,811 cases (10.4%). D-dimer measurements were performed in 1,847 out of 2,811 cases (65.7%), where 1,504 out of 1,847 (81.4%) had results above the reference range, and 343 were negative. In the group with elevated D-dimer levels, PE was confirmed on CT angiography in only 173 out of 1,504 patients (11.5%). In the group with 'negative' D-dimer results, 10 out of 343 cases had confirmed PE (false-negative results), some of whom had a history of thromboembolic disease and were on anticoagulant therapy. 964 out of 2,811 (34.3%) CT angiography studies were performed in patients without prior D-dimer testing, and interestingly, when compared to CT angiography studies preceded by D-dimer testing, there was no statistically significant difference in the confirmation of PE between the 2 groups (9.9% vs. 11.3%; p=0.26).

The study conducted by Francis et al. [27] evaluated 3,586 patients from the emergency departments of 23 centers, including 17 in the USA and 6 in Europe, for the presence of VTE (1752 for DVT and 1,834 for PE). Among the patients evaluated for DVT, 710 (40.5%) were male – mean age 53.1 (+-16.2 years), and elevated D-dimer levels were observed in 1,009/1,752, with 743 D-dimer levels <500 μg/L. DVT was confirmed in 191/1,752 (10.9%) patients overall. In the group with D-dimer levels >500 μg/L, DVT was confirmed in 173/1,009 (17.1%) patients. False-negative results were observed in 18/743 patients with negative D-dimer results, including 9/18 with distal DVT and a previous history of thromboembolic disease. Among the patients evaluated for PE, 676 (36.9%) were male – mean age 47.4 (+-15.8 years), elevated D-dimer levels (>500 μg/L) were observed in 872/1,834 patients, and D-dimer levels <500 μg/L were observed in 962/1,834 patients. PE was confirmed in 108/1,834 (5.9%) patients, including 105/872 (12.0%) in the group with elevated D-dimer levels. Three patients (0.3%) were diagnosed with PE, despite having normal D-dimer levels. The researchers attempted to analyze the probability of thromboembolic disease at higher D-dimer values and found that higher D-dimer levels indicated a significant increase in the percentage (positive predictive value) of confirmed VTE. In the group of patients with D-dimer levels >3,999 μg/L who underwent evaluation for DVT, DVT was confirmed in 71/142 patients (50.0%; 95% CI 51.7, 26.9–99.2), while in the group evaluated for PE, PE was confirmed in 55/107 patients (51.4%; 95% CI 221.5, 65.2–753.0) with D-dimer levels >3,999 μg/L.

Adjusted D-dimer threshold. Relying solely on D-dimer measurement and the standard cutoff point of <500 μg/L in older patients with risk factors for thromboembolic

Table 2. Summarized results with standard D-dimer threshold

Title of publication	Authors and year of publication	Study population	Patients with D-dimers >500 μg/L	Patients with D-dimers <500 μg/L	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Diagnostic and prognostic value of the D-dimer test in emergency department patients: secondary analysis of an observational study	Vögeli A, Ghasemi M, Gregoriano C, et al. (2019)	3301 patients, 203 with confirmed VT	1771/ 3301 patients: 201/1771= 11,4% (**confirmed VTE, true-positive**) 1570/1771= 88,6% (**excluded VTE, false-positive**)	1530/3301 patients: 2/1530 = 0,1% (**confirmed VTE, false-negative**) 1528/1530= 99,9% (**excluded VTE, true-negative**)	99.9	49,3	99,9	11,4
Use of the d-dimer for Detecting Pulmonary Embolism in the Emergency Department	Glober N, Tainter CR, Brennan J, et al. (2018)	3523 patients, 207 with confirmed PE	2253/3523 patients: 198/2253=8,8% (**confirmed PE, true-positive**) 1895/2253=84,1% (**excluded PE, false-positive**)	1270/3523 patients: 9/1270=0,7% (**confirmed PE, false-negative**) 1261/1270=99,2% (**excluded PE, true-negative**)	95,6	40,0	99,2	9,5
Utilization of serum D-dimer assays prior to computed tomography pulmonary angiography scans in the diagnosis of pulmonary embolism among emergency department physicians: a retrospective observational study.	Salehi L, Phalpher P, Yu H, et al. (2021)	2811 patients (1847 D-dimer measurements), 292 with confirmed PE.	1504/1847 patients: 173/1504=11,5% (**confirmed PE, true-positive**) 1331/1504=88,5% (**excluded PE, false-positive**)	343/1847 patients: 10/343=2,9% (**confirmed PE, false-negative**) 333/343=97,1% (**excluded PE, true-negative**)	94,5	20,0	97,1	11,5
Highly Elevated Quantitative D-Dimer Assay Values Increase the Likelihood of Venous Thromboembolism	Francis S, Limkakeng A, Zheng H, et al. (2019)	3586 patients, 299 with confirmed VTE (PE and DVT)	1881/3586 patients: 278/1881=14,8% (**confirmed VTE, true-positive**) 1603/1881=85,2% (**excluded VTE, false-positive**)	1705/3586 patients: 21/1705=1,2% (**confirmed VTE, false-negative**) 1684/1705=98,8% (**excluded VTE, true-negative**)	93,0	51,2	98,7	14,8

NPV - negative predictive value; PPV - positive predictive value; VTE - venous thromboembolism; PE -pulmonary embolism.

disease may contribute to more diagnostic errors. Therefore, numerous studies are being conducted to implement modified and individualized D-dimer cutoff points depending on the clinical situation.

Currently, there are two popular strategies that modify the D-dimer norm level: 1) age in years x 10 µg/L in patients >50-years-old (age-adjusted threshold – AAT), and 2) variable cutoff depending on the clinical pretest probability, which is <1000 µg/L in the low-risk patient group, and in the case of intermediate-risk patient group as standard <500 µg/L (clinical probability-adjusted threshold – CPAT) [2, 3, 28]. The aim is to maintain the highest sensitivity and negative predictive value, as well as the greatest specificity in patient groups where there is the highest chance of diagnostic error. Unfortunately, despite this, a high percentage of patients still have positive D-dimer results in the absence of VTE (many false-positive results).

Age-adjusted D-dimer threshold. The study conducted by De Pooter et al. [23] included 747 patients: 193 low-risk, 451 intermediate-risk, and 103 high-risk patients, who were not evaluated for D-dimer levels and were excluded from further analysis. Among the remaining patients (n=644), there were 260 men and 384 women (median age – 59.0), and venous thromboembolism (VTE) was confirmed in 88/644 (13.7%). In all patients with VTE and 299/556 without VTE, D-dimer levels were >500µg/L. The standard cut-off point was compared, which yielded a sensitivity of 100% (95% CI=95.9–100), specificity – 46.2% (95% CI=42.0–50.5), NPV – 100% (95% CI=98.6–100), and PPV – 22.7 (95% CI=18.7–27.2). However, the use of AAT resulted in an increase in specificity to 58.1% (95% CI=53.9–62.2) and PPV to 27.2 (95% CI=22.4–32.4), with a simultaneous decrease in sensitivity to 98.9% (95% CI=93.8–100) and NPV to 99.7 (95% CI=98.3–100).

Riva et al. [29] conducted the PALLADIO study in which 1,162 patients with suspected DVT were enrolled, 697 women (60%) and 465 men (40%) – median age 66. Using AAT, 632/1,162 (54%) of D-dimer levels were negative, and 530/1,162 (46%) had D-dimer levels above the cut-off point. The final diagnostic accuracy for VTE using an age-adjusted D-dimer cut-off point (95% CI) was a sensitivity of 89.5% (95% CI=84.7–93.3%), specificity – 65.1% (95% CI=61.9–68.2%), NPV – 96.3% (95% CI=94.5–97.6), and PPV – 38.1% (95% CI=33.9–42.4%).

In 2016, Sharp et al. [30] evaluated 31,094 emergency department patients, with data collected from 2008 – 2013, aged over 50 years (mean age 65): 18,967/31,094 (61%) women. They compared the standard cut-off point which resulted in (95% CI): sensitivity – 98.0% (96.4–84.2), specificity – 54.4% (53.9–55.0), NPV – 99.9% (99.9–100), and PPV – 3.4% (3.2–3.8). However, after taking into account the age-adjusted D-dimer cut-off, there was a noticeable decrease in sensitivity – 92.9% (95% CI=90.3–95.0), and a relative increase in specificity – 63.9% (95% CI=63.4–64.5), NPV – 99.8% (95% CI=99.8–99.9), and PPV – 4.1% (95% CI=3.7–4.5).

Flores et al. [31] conducted a study on 362 patients who presented to the emergency department with suspected pulmonary embolism (PE). Among the patients, 98 (27%) were confirmed to have PE. Using AAT, the study found that 96 out of 98 patients with confirmed PE had positive D-dimer results, while 142 out of 264 patients (53.8%) without PE had elevated D-dimer levels (false-positive result). The study reported a sensitivity of 97.9% (95%CI=92.1–99.6), specificity – 46.2% (95%CI=40.1–52.4), NPV – 98.3% (95%CI=93.7–99.7), and PPV – 40.3% (95%CI=34.1–46.8).

Clinical probability-adjusted D-dimer threshold. The study conducted by Kearon et al. [2] included 2,017 patients from emergency departments, with a mean age of 52 years (66.2% women). Of these, 1,752/2,017 (86.9%) were classified as low probability, 218/2,017 as intermediate probability, and 47 as high probability, for whom D-dimer was not measured. The CPAT was applied, with a cutoff of <1,000 in the low-risk group and <500 in the intermediate-risk group. In the low-risk and intermediate-risk groups combined, a negative D-dimer result (true negative result) was obtained in 1,325/1,970 (67.3%) patients without thromboembolic disease, while the remaining 645/1,970 had a positive result. False positive results were observed in 515/645 (79.8%) cases of patients without VTE.

The study by Sharif et al. [28] included 1,075 patients (data collected 2013–2015), with an average age of 48, of whom 69.6% (748/1,075) were women, and 6.8% had a current malignancy. Of these, 1,017/1,075 (94.6%) were classified as low probability, and confirmed PE was observed in 3.7% (31/1,017). According to the CPAT, D-dimer levels were negative in 859/1,017 (84.5%), with an NPV of 99.1% (95% CI 98.3–99.5) and 8 false negative results confirmed as VTE.

Table 3. Summarized results with age-adjusted D-dimer threshold (AAT)

Title of publication	Author(s) and year of publication	D-dimer age-adjusted value (10 µg/L x patient's age)			
		Sensitivity (%)	*Specificity (%)*	*NPV (%)*	*PPV (%)*
Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in patients with non-high pre-test probability: Clinical performance and cost-effectiveness analysis	De Pooter N, Brionne-François M, et al. (2021)	98.9 (95% CI=93.8-100)	58.1 (95%) CI=53.9-62.2)	99.7 (95%) CI=98.3-100)	27.2 (95%) CI=22.4-32.4)
Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm.	Riva N, Camporese G, Iotti M, et al. (2018)	8.,5 (95% CI=84.7-93.3%)	65.1 (95%) CI=61.9-68.2%	96.3(95%) CI=94.5-97.6)	38.1(95%) CI=33.9-42.4%
An Age-Adjusted D-dimer Threshold for Emergency Department Patients With Suspected Pulmonary Embolus: Accuracy and Clinical Implications.	Sharp AL, Vinson DR, Alamshaw F, et al. (2016)	92.9(95%CI=90.3-95.0)	63.9(95% CI=63.4-64.5)	99.8 (95%CI=99.8-99.9)	4.1(95% CI=3.7-4.5)
Clinical usefulness and safety of age-adjusted D-dimer cut-off levels to exclude pulmonary embolism: a retrospective analysis.	Flores J, García de Tena J, Galipienzo J, et al. (2015)	97.9 (95%CI=92.1-99.6)	46.2 (95%CI=40.1-52.4)	98.3 (95%CI=93.7-99.7)	40.3 (95% CI=34.1-46.8)

NPV-negative predictive value; PPV-positive predictive value

Table 4. Summarized results with clinical probability-adjusted D-dimer threshold (CPAT)

Title of publication	Authors of publication	Study population	Patients with a low C-PTP		Patients with a moderate C-PTP		False-positive D-dimer results in total
			Negative level of D-dimers (<1000 µg/L)	*Positive level of D-dimers (≥ 1000 µg/L)*	*Negative level of D-dimers (<500 µg/L)*	*Positive level of D-dimers (≥ 500 µg/L)*	
Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability.	Kearon C, de Wit K, Parpia S, et al. (2019)	In total 2017 patients with suspected PE	1752/2017 (86,9%) 87 with confirmed PE		218/2017 (10,8%) 43 with confirmed PE		515/645 (79,8%)
			1285/1752 (73,3%)	467/1752 (26,7%) 87/467 (18,6% - **confirmed PE**) 380/467 (81,4% - **excluded PE**)	40/218 (18,3%)	178/218 (81,6%) 43/178 (24,2% -**confirmed PE**) 135/178 (75,8% - **excluded PE**)	
Comparison of the age-adjusted and clinical probability-adjusted D-dimer to exclude pulmonary embolism in the emergency department	Sharif S, Eventov M, Kearon C, et al. (2019)	In total 1075 patients with suspected VTE	1017/1075 (94,6%) 31 with confirmed PE		58/1075 (5,4%) 7 with confirmed PE		164/194 (84,5%)
			859/1017 (84,5%) with 8 VTE confirmed	158/1017 (15,5%) 23/158 (14,6% - **confirmed VTE**) 135/158 (85,4% - **excluded VTE**)	22/58 (37,9%)	36/58 (62,0%) 7/36(19,4 - **confirmed VTE**) 29/36(80,6% - **excluded VTE**)	
Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism.	Sharif S, Eventov M, Kearon C, et al. (2019)	In total 1649 patients with suspected VTE	1034/1649 (62,7%) 46 with confirmed VTE		615/1649 (37,3%) 63 with confirmed VTE		618/724 (85,3%)
			724/1034 (70,0%) with 2 VTE confirmed	310/1034 (30,0%) 44/310 (14,2% - **confirmed VTE**) 266/310 (85,8% - **excluded VTE**)	201/615 (32,7%) with 1 VTE confirmed	414/615 (67,3%) 62/414 (15,0% - **confirmed VTE)** 352/414 (85,0% - **excluded VTE**)	

C-PTP - clinical pre-test probability; VTE - venous thromboembolism; PE - pulmonary embolism

In the group with a positive D-dimer result, 135/158 (85.4%) were ruled out for thromboembolic disease (false positive results). 58/1,075 (5.4%) were intermediate-risk patients, among whom 7/58 (12.1%) were confirmed for PE. Using the CPAT, negative D-dimer results were observed in 22/58 (37.9%), resulting in an NPV of 100% (95% CI 81.5–100.0). In the group with elevated D-dimer levels, 29/36 (80.5%) were not confirmed for thromboembolic disease (false positive results).

Takach Lapner et al. [3] enrolled 1,649 patients in their study, with a mean age of 58 years, including 1,034 in the low probability group (46/1034 – 4.4% confirmed VTE) and 615 in the intermediate probability group (63/615 – 10.2% confirmed VTE). In the low probability group, using the CPAT strategy, negative D-dimer results were obtained in 724/1,034 (70.0%) patients, with an NPV of 99.7% (95% Cl 98.9–99.9) and 2 false-negative results confirmed as VTE. 266/310 patients with positive D-dimer results were excluded from having thromboembolic disease – false-positive results. In the intermediate probability group, negative D-dimer results were obtained in 201/615 (32.7%) using CPAT, with an NPV of 99.5% (95% Cl 97.2–99.9), and one false-negative result confirmed as VTE. 352/414 (85.0%) patients with D-dimer levels above the normal range were found not to have thromboembolic disease – false-positive results.

DISCUSSION

The measurement of D-dimers is a laboratory parameter commonly used that allows for the exclusion of VTE with high probability; however, a positive D-dimer result does not definitively confirm it [4]. There are many factors such as comorbidities or age [25,26] that significantly affect the increase of D-dimers above the norm, but without the presence of thromboembolic disease [4]. Physicians in their daily clinical practice should approach this parameter with more prudence and a more detailed analysis of the clinical state, in order not to prolong the diagnostic and therapeutic process for every patient with a D-dimer level above the upper limit. A high frequency of subsequent imaging tests, mainly pulmonary CT angiography in low-risk patients, is common practice worldwide, and has been described in many published studies [6, 10, 11, 14, 15, 32, 33]. Many unnecessary imaging tests can be avoided by paying greater attention to the overall clinical picture of individual patients [34, 35]. The impact of ionizing radiation and contrast agents on patients undergoing pulmonary angio-CT should not be underestimated, and it should be mentioned that this generates unnecessary costs for hospitals and prolongs waiting times for patients in emergency departments [12,17,18, 25, 36]. In some cases, it is necessary to consider the validity of excessive reliance on D-dimer results in elderly patients, particularly in the presence of risk factors for VTE.

CONCLUSIONS

The impact of age and many clinical conditions undoubtedly affects the specificity of D-dimer measurement and reduces its usefulness. Strategies that modify cut-off thresholds are helpful in reducing false-positive results in older and burdened patients, but still, a significant proportion of patients receive positive D-dimer results without thromboembolic disease and undergo prolonged, potentially harmful diagnostics. Establishing a clear position on the interpretation of D-dimer results, especially in cases where the result is above the upper limit, requires further analysis and more studies.

REFERENCES

1. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv. 2018;2(22):3226–3256. doi:10.1182/bloodadvances.2018024828
2. Kearon C, de Wit K, Parpia S, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. N Engl J Med. 2019;381(22):2125–2134. doi:10.1056/NEJMoa1909159
3. Takach Lapner S, Julian JA, Linkins LA, Bates S, Kearon C. Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism. Thromb Haemost. 2017;117(10):1937–1943. doi:10.1160/TH17-03-0182
4. Vögeli A, Ghasemi M, Gregoriano C, et al. Diagnostic and prognostic value of the D-dimer test in emergency department patients: secondary analysis of an observational study. Clin Chem Lab Med. 2019;57(11):1730–1736. doi:10.1515/cclm-2019-0391
5. Corrigan D, Prucnal C, Kabrhel C. Pulmonary embolism: the diagnosis, risk-stratification, treatment and disposition of emergency department patients. Clin Exp Emerg Med. 2016;3(3):117–125. Published 2016 Sep 30. doi:10.15441/ceem.16.146
6. Sendama W, Musgrave KM. Decision-Making with D-Dimer in the Diagnosis of Pulmonary Embolism. Am J Med. 2018;131(12):1438–1443. doi:10.1016/j.amjmed.2018.08.006
7. Pawelec G, Goldeck D, Derhovanessian E. Inflammation, ageing and chronic disease. Curr Opin Immunol. 2014;29:23–28. doi:10.1016/J.COI.2014.03.007
8. Farm M, Siddiqui AJ, Onelöv L, et al. Age-adjusted D-dimer cut-off leads to more efficient diagnosis of venous thromboembolism in the emergency department: a comparison of four assays. J Thromb Haemost. 2018;16:866–875.
9. van Es N, van der Hulle T, Büller HR, et al. Is stand-alone D-dimer testing safe to rule out acute pulmonary embolism?. J Thromb Haemost. 2017;15(2):323–328. doi:10.1111/jth.13574
10. Hsu N, Soo Hoo GW. Underuse of Clinical Decision Rules and d-Dimer in Suspected Pulmonary Embolism: A Nationwide Survey of the Veterans Administration Healthcare System. J Am Coll Radiol. 2020;17(3):405–411. doi:10.1016/j.jacr.2019.10.001
11. Soo Hoo GW, Tsai E, Vazirani S, Li Z, Barack BM, Wu CC. Long-Term Experience With a Mandatory Clinical Decision Rule and Mandatory d-Dimer in the Evaluation of Suspected Pulmonary Embolism. J Am Coll Radiol. 2018;15(12):1673–1680. doi:10.1016/j.jacr.2018.04.031
12. Pernod G, Caterino J, Maignan M, et al. D-Dimer Use and Pulmonary Embolism Diagnosis in Emergency Units: Why Is There Such a Difference in Pulmonary Embolism Prevalence between the United States of America and Countries Outside USA?. PLoS One. 2017;12(1):e0169268. Published 2017 Jan 13. doi:10.1371/journal.pone.0169268
13. Innocenti F, Lazzari C, Ricci F, Paolucci E, Agishev I, Pini R. D-Dimer Tests in the Emergency Department: Current Insights. Open Access Emerg Med. 2021;13:465–479. Published 2021 Nov 11. doi:10.2147/OAEM.S238696
14. Eskandari A, Narayanasamy S, Ward C, Priya S, Aggarwal T, Elam J, Nagpal P. Prevalence and significance of incidental findings on computed tomography pulmonary angiograms: A retrospective cohort study. Am J Emerg Med. 2022 Apr;54:232–237. doi: 10.1016/j.ajem.2022.01.064. Epub 2022 Feb 3. PMID: 35182917.
15. Venkatesh AK, Agha L, Abaluck J, Rothenberg C, Kabrhel C, Raja AS. Trends and Variation in the Utilization and Diagnostic Yield of Chest Imaging for Medicare Patients With Suspected Pulmonary Embolism in the Emergency Department. AJR Am J Roentgenol. 2018;210(3):572–577. doi:10.2214/AJR.17.18586
16. Woo YP, Thien F. Ruling out low- and moderate-risk probability pulmonary emboli without radiological imaging: appraisal of a clinical prediction algorithm after implementation and revision with higher D-dimer thresholds. Intern Med J. 2016;46(7):787–792. doi:10.1111/imj.13092
17. Chong J, Lee TC, Attarian A, et al. Association of Lower Diagnostic Yield With High Users of CT Pulmonary Angiogram. JAMA Intern Med. 2018;178(3):412–413. doi:10.1001/jamainternmed.2017.7552
18. Kline JA, Garrett JS, Sarmiento EJ, Strachan CC, Courtney DM. Over-Testing for Suspected Pulmonary Embolism in American Emergency Departments: The Continuing Epidemic. Circ Cardiovasc Qual Outcomes. 2020;13(1):e005753. doi:10.1161/CIRCOUTCOMES.119.005753
19. Anjum O, Bleeker H, Ohle R. Computed tomography for suspected pulmonary embolism results in a large number of non-significant incidental findings and follow-up investigations. Emerg Radiol. 2019;26(1):29–35. doi:10.1007/s10140-018-1641-8
20. Smith-Bindman R, Miglioretti DL, Johnson E, et al. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996–2010. JAMA 2012;307:2400–9.
21. Linkins LA, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. Int J Lab Hematol. 2017;39 Suppl 1:98–103. doi:10.1111/ijlh.12665
22. Folsom AR, Gottesman RF, Appiah D, Shahar E, Mosley TH. Plasma d-Dimer and Incident Ischemic Stroke and Coronary Heart Disease: The Atherosclerosis Risk in Communities Study. Stroke. 2016;47(1):18–23. doi:10.1161/STROKEAHA.115.011035
23. De Pooter N, Brionne-François M, Smahi M, Abecassis L, Toulon P. Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in patients with non-high pre-test probability: Clinical performance and cost-effectiveness analysis. J Thromb Haemost. 2021;19(5):1271–1282. doi:10.1111/jth.15278
24. Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. J Am Coll Cardiol. 2017;70:2411–2420.
25. Glober N, Tainter CR, Brennan J, et al. Use of the d-dimer for Detecting Pulmonary Embolism in the Emergency Department. J Emerg Med. 2018;54(5):585–592. doi:10.1016/j.jemermed.2018.01.032
26. Salehi L, Phalpher P, Yu H, et al. Utilization of serum D-dimer assays prior to computed tomography pulmonary angiography scans in the diagnosis of pulmonary embolism among emergency department physicians: a retrospective observational study. BMC Emerg Med. 2021;21(1):10. Published 2021 Jan 19. doi:10.1186/s12873-021-00401-x
27. Francis S, Limkakeng A, Zheng H, et al. Highly Elevated Quantitative D-Dimer Assay Values Increase the Likelihood of Venous Thromboembolism. TH Open. 2019;3(1):e2-e9. Published 2019 Jan 7. doi:10.1055/s-0038-1677029
28. Sharif S, Eventov M, Kearon C, et al. Comparison of the age-adjusted and clinical probability-adjusted D-dimer to exclude pulmonary embolism in the ED. Am J Emerg Med. 2019;37(5):845–850. doi:10.1016/j.ajem.2018.07.053
29. Riva N, Camporese G, Iotti M, et al. Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm. J Thromb Haemost. 2018;16(2):271–278. doi:10.1111/jth.13905
30. Sharp AL, Vinson DR, Alamshaw F, Handler J, Gould MK. An Age-Adjusted D-dimer Threshold for Emergency Department Patients With Suspected Pulmonary Embolus: Accuracy and Clinical Implications. Ann Emerg Med. 2016;67(2):249–257. doi:10.1016/j.annemergmed.2015.07.026
31. Flores J, García de Tena J, Galipienzo J, et al. Clinical usefulness and safety of an age-adjusted D-dimer cutoff levels to exclude pulmonary embolism: a retrospective analysis. Intern Emerg Med. 2016;11(1):69–75. doi:10.1007/s11739-015-1306-5
32. Booker MT, Johnson JO. Optimizing CT Pulmonary Angiogram Utilization in a Community Emergency Department: A Pre- and Postintervention Study. J Am Coll Radiol. 2017;14(1):65–71. doi:10.1016/j.jacr.2016.08.007
33. Alhassan S, Sayf AA, Arsene C, Krayem H. Suboptimal implementation of diagnostic algorithms and overuse of computed tomography-pulmonary angiography in patients with suspected pulmonary embolism. Ann Thorac Med. 2016;11(4):254–260. doi:10.4103/1817-1737.191875
34. Singh B, Mommer SK, Erwin PJ, Mascarenhas SS, Parsaik AK. Pulmonary embolism rule-out criteria (PERC) in pulmonary embolism— revisited: a systematic review and meta-analysis. Emerg Med J. 2013;30:701–6.
35. Bozarth AL, Bajaj N,Wessling MR, Keffer D, Jallu S, Salzman GA. Evaluation of the pulmonary embolism rule-out criteria in a retrospective cohort at an urban academic hospital. Am J Emerg Med. 2015;33:483–7.
36. Brody AS, Guillerman RP. Don't let radiation scare trump patient care: 10 ways you can harm your patients by fear of radiationinduced cancer from diagnostic imaging. Thorax. 2014;69:782–4.