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Research article

Low D-dimer in acute coronary syndrome and heart failure: Screening for large vessel diseases in patients with chest symptoms

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ABSTRACT

Background: Distinguishing between large-vessel diseases such as acute aortic syndrome (AAS) and pulmonary embolism (PE), and non-large-vessel diseases, such as acute coronary syndrome (ACS), heart failure (HF), and neurogenic diseases, in patients presenting with chest symptoms remains a challenge, which can result in a significant number of misdiagnoses. Simultaneously distinguishing both AAS and PE is essential because large-vessel diseases require angio-computed tomography (CT) during initial presentation whereas, non-large-vessel diseases do not. This study aimed to determine the optimal method for differentiating between large-vessel and non-large-vessel diseases using D-dimer, troponin I, and pretest probability scores.

Methods: From the 11683 patients who presented with chest symptoms including chest pain, discomfort, or dyspnea, this retrospective observational study included 1817 patients who had complete data for essential biomarkers; 105 with AAS, 139 with PE, 1093 with ACS, 451 with HF, and 83 with neurogenic diseases.

Results: D-dimer, D-dimer/troponin I ratio (DT ratio), and troponin I results distinguished the 2 groups: D-dimer (>2.38 μg/mL), AUC 0.935; DT ratio, AUC 0.827; and troponin I, AUC 0.653. For predicting AAS, the performances of D-dimer level and aortic dissection detection risk score (ADD-RS) were AUCs of 0.915 ($p < 0.0001$) and 0.67 ($p = 0.0004$), respectively; for predicting PE, the AUCs of D-dimer level and modified Wells score were 0.95 ($p = 0.0001$) and 0.857 ($p < 0.0001$), respectively.

Conclusions: The D-dimer levels proved to be a crucial discriminator for identifying AAS and PE, even when compared with the ADD-RS and modified Wells scores. Moderately elevated D-dimer levels suggest the need to consider AAS and PE diagnoses via angio-CT for patients with chest symptoms.

1. Introduction

Physicians suspect various conditions and diseases when patients present to the emergency department with chest symptoms including chest pain, discomfort, and dyspnea. Some can be easily determined with laboratory results, chest radiography, and electrocardiography. However, despite these tools, distinguishing certain diseases such as acute coronary syndrome (ACS), heart failure (HF), pulmonary embolism (PE), and acute aortic syndrome (AAS) remains challenging. The most common diseases and conditions of

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patients admitted to the emergency department with chest symptoms should be distinguished [1]. Angio-computed tomography (CT) is imperative for a definite diagnosis of large-vessel diseases, such as PE and AAS; however, it is not necessary for determining non-large-vessel diseases, such as ACS, HF, and neurogenic disease. Discriminating large-vessel diseases from non-large-vessel diseases is essential to correctly diagnose patients with chest symptoms during the clinical process and ensure the appropriate use of angio-CT.

The prevalence and mortality of the main diseases in patients with chest pain have been reported in a previous study: non-specific pain, 46 % (mortality 0.5 %); ACS, 14.9 % (mortality 10.4 %); pneumonia, 3.3 % (mortality 3.9 %); PE, 0.7 % (mortality 3.2 %); and AAS, 0.2 % (mortality 22.2 %) [1]. The incidence and mortality of myocardial infarction, HF, PE, and AAS are 200 cases(1-month mortality 8 %) [2], 320 cases(1 to 2-month mortality 19.3 %) [3], 60–120 cases (3-month mortality 20 %) [4], and 3–16 cases (1-month mortality 47%–49 % in Type A AAS, 13 % in Type B), respectively, per 100,000 patient-years [2].

To date, no studies have distinguished between more common and severe diseases, such as AAS, PE, ACS, HF, and neurogenic disease, in patients presenting with only chest symptoms. Since ACS and HF are common and significant, they are usually suspected first in patients with chest symptoms, which can lead to missed diagnoses of large-vessel diseases. Even when large-vessel diseases are suspected, the efficiency of diagnosis is only 2.5 % for patients suspected of having AAS and underwent angio-CT [5], and only 13.6 % of those suspected of having PE who underwent angio-CT [6]. It is necessary to consider PE and AAS, along with ACS, HF, and neurogenic diseases, which are not initially well-differentiated in patients with chest symptoms. Differentiating large-vessel diseases is particularly critical because of their relatively high mortality and decision-making regarding angio-CT.

Current guidelines recommend using the PE rule-out criteria (PERC) score, gestalt probability, YEARS criteria, and Wells score for

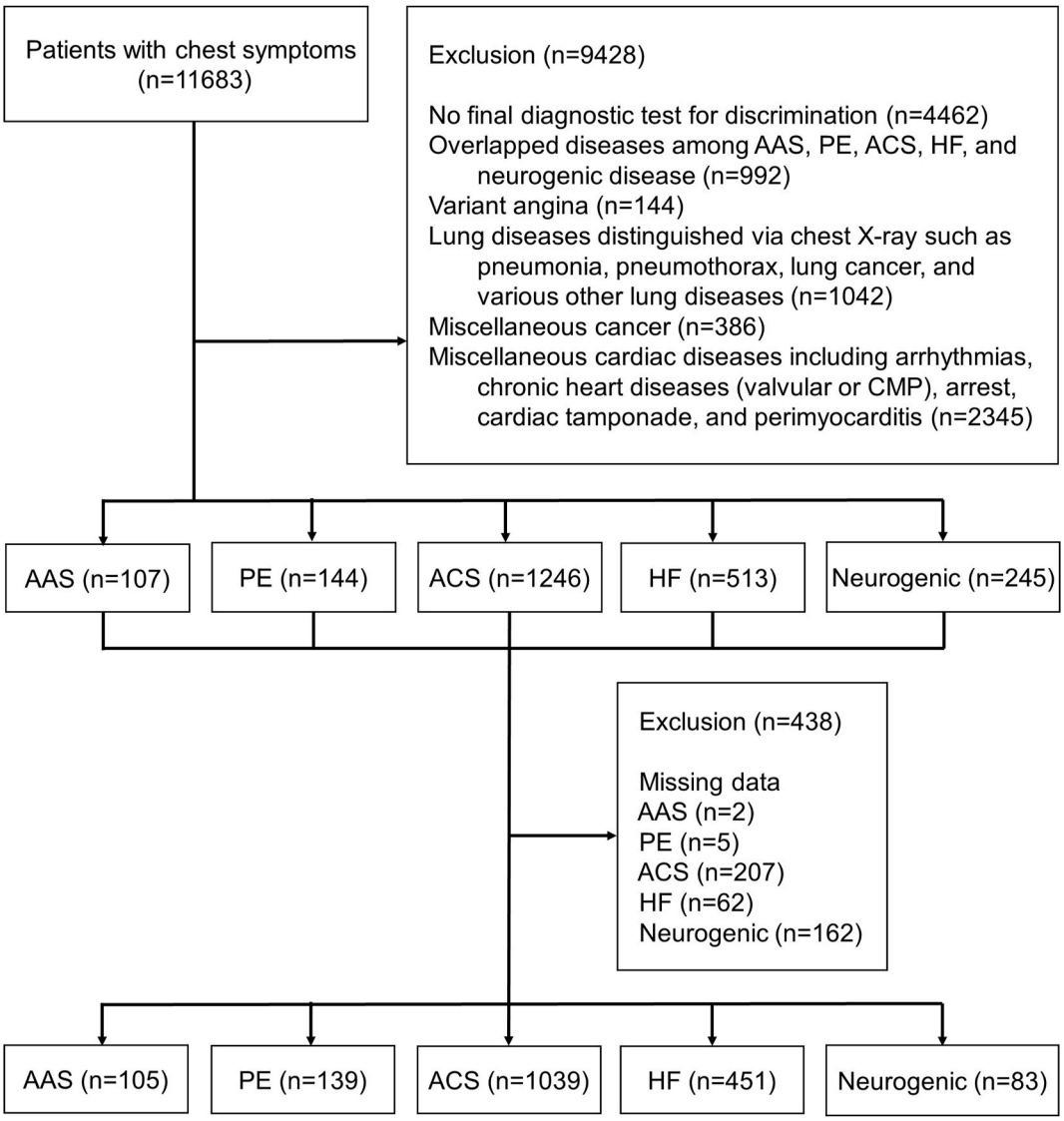

Fig. 1. Flow sheet.

differentiating PE and the aortic dissection detection risk score (ADD-RS) along with D-dimer level for differentiating AAS [4,7]. However, whether these differential tools are effective in patients with concurrent PE or AAS remains uncertain. There have been case-control studies differentiating between PE and non-ST elevation myocardial infarction (NSTEMI) and between AAS and NSTEMI using both D-dimer and troponin I results [8,9], yet observational studies have shown that discriminating large-vessel diseases from non-large-vessel diseases such as HF and unstable angina using troponin I levels can be challenging [10,11]. Two studies attempted to discriminate between large-vessel diseases and non-large-vessel diseases in various symptomatic patients; 1 study included only 279 patients, 6 with AAS and 5 with PE [12], and the other only analyzed patients with elevated D-dimer levels, among whom 22 had AAS [13]. Moreover, these studies included a variety of diseases that could elevate D-dimer levels in their control group. For patients with chest symptoms including those both AAS and PE, a discriminative strategy is required in practical clinical scenarios.

This study compared and evaluated common and severe diseases, including PE and AAS, using discriminative tools such as troponin I, D-dimer, and pre-test probability scores of patients who presented with chest symptoms. In addition, preventive strategies were explored to avoid overlooking large-vessel diseases in practical clinical scenarios.

2. Methods

2.1. Study design and patient selection

This retrospective observational cohort study was conducted at a tertiary care university teaching hospital, designated as a regional heart center, from January 2014 to December 2022. The hospital's ethics committee approved the study protocol (DAUHIRB-23-017). The requirement for written informed consent was waived due to the retrospective nature of the study, and all data were anonymized. We enrolled 11683 patients aged >18 years who had AAS, PE, ACS, HF, and neurogenic diseases and presented with acute chest symptoms, including chest pain, chest discomfort, and dyspnea. Enhanced chest CT or angio-CT was used to diagnose AAS and PE (large-vessel diseases); coronary angiography and echocardiography were used to diagnose ACS and HF (non-large-vessel diseases). Neurogenic diseases included mild diseases and conditions, such as non-specific pain, chest wall pain, hyperventilation, and neurosis, that showed no specific abnormal findings on coronary angiography and echocardiography.

The patients excluded comprised 4462 with ACS, HF, or neurogenic disease who did not undergo coronary angiography and echocardiography (to ensure diagnostic accuracy for ACS, HF, and neurogenic disease); 992 with overlapping diseases among AAS, PE, ACS, HF, and neurogenic disease; 144 with ACS presenting as variant angina; 1042 with conditions readily diagnosed by chest

Biomarker	Modified Wells score	Aortic dissection detection risk score
Troponin I	Clinical signs and symptoms of DVT	Marfan syndrome
D-dimer	No alternative diagnosis	Family history of aortic disease
	Heart rate >100 beats/min	Known aortic valve disease
	Immobilization ≥3 days or surgery in the previous 4 weeks	Recent aortic manipulation
	Previous DVT or PE	Known thoracic aortic aneurysm
	Hemoptysis	Sudden onset pain (chest, abdomen, back)
	Malignancy with active treatment in the past 6 months or under palliative care	Severe pain intensity
		Ripping / Tearing pain
		Pulse deficit or SBP differential >20 mmHg
		Focal neurological deficit + Pain
		New aortic requrgitation Murmur + Pain
		Hypotension

Fig. 2. Biomarker and pretest probability scores.

radiography, such as pneumonia, pneumothorax, lung cancer, and various other lung diseases; 386 patients with other cancers; 2345 patients with other cardiac conditions including arrhythmias, chronic heart diseases (valvular or cardiomyopathy), cardiac arrest, cardiac tamponade, and perimyocarditis; and 438 patients with missing data for D-dimer and troponin I. Patients who had inflammation, infection, cancer, or conditions that could elevate D-dimer level, were excluded.

Thus, our cohort included 1817 patients who underwent acute management for AAS (105), PE (139), ACS (1039), HF (451), and neurogenic disease (83) (Fig. 1).

2.2. Clinical data acquisition

Baseline characteristics including age, sex, height, weight, the nature of chest symptoms, history of alcohol and tobacco use, previous aortic disease, aortic valve disease, vital signs, and O_2 saturation at initial presentation were collected. Biomarkers were obtained from blood samples within 1 h of admission. The modified Wells score (Fig. 2), ADD-RS (Fig. 2), and the national early warning score (NEWS) were derived from the nurse records and medical charts at the time of admission by referencing previous medical records. The specific attributes of chest pain, characterized as severe, sharp, tearing, migrating pain, accompanying back pain, and any focal neurological deficit or pain, were assessed. History of aortic disease included conditions such as aortic aneurysm, coarctation of the aorta, aortic dissection, intramural hematoma, penetrating aortic ulcer, and previous surgery for aortic disease. D-dimer levels were measured using an immunoturbidimetric assay with a Sysmex CS-5100 System (Siemens Healthcare Diagnostics, Erlangen, Germany), with a reference level of <0.5 μg/mL. Troponin I levels were determined using a chemiluminescent microparticle immunoassay for the quantitative determination of cardiac troponin I on an ARCHITECT i2000SR (Abbott Diagnostics, Lake Forest, IL, USA). The reference level for high-sensitivity troponin I was <0.034 ng/mL. This level can vary with changes in the reagents used; thus, the same reagent was consistently used in our hospital. The 99th percentile upper reference limit for high-sensitivity troponin I can vary between sexes; however, the reference levels suggested by the device company were typically employed.

2.3. Statistical analyses

Continuous variables were presented as medians with interquartile ranges and were analyzed using the Mann–Whitney *U* test for non-parametric distributions. Categorical variables were compared using the Fisher's exact test. A multivariable binary logistic regression analysis was conducted to determine the adjusted odds ratios (ORs) for the selected predictors, allowing for significant covariates. Multicollinearity was not observed. The modified Wells score, ADD-RS, and NEWS had missing data for 19, 20, and 1 patients, respectively. A receiver operating characteristic (ROC) curve analysis was performed to ascertain the sensitivity, specificity, positive and negative likelihood ratios, and area under the ROC curve (AUC). The risks associated with large-vessel diseases were quantified as ORs in relation to D-dimer and troponin I levels using cubic spline models with 95 % confidence intervals.

Table 1
Baseline characteristics.

	AAS (n = 105)	PE (n = 139)	ACS (n = 1039)	HF (n = 451)	Neurogenic (n = 83)	*P*
	Large vessel disease		Non-large vessel disease			
Age, years	69 (55, 79)	72 (58, 79)	64 (54, 73)	78 (69, 84)	68 (58, 77)	0.608
Male, n (%)	53 (50.5)	50 (36)	800 (77)	212 (47)	40 (48.2)	<0.001
BMI, kg/m^2	23.9 (21.8, 26)	24.7 (22.6, 27.7)	24 (22.3, 26.1)	22.9 (20.8, 25.5)	22.6 (20.9, 26)	0.035
SBP, mmHg	130 (105, 150)	120 (100, 140)	130 (110, 150)	130 (110, 150)	130 (110, 150)	<0.001
DBP, mmHg	80 (60, 90)	80 (60, 90)	80 (70, 90)	80 (70, 90)	80 (70, 90)	0.002
HR, rate/min	76 (62, 90)	92 (82, 106)	78 (67, 89)	90 (78, 108)	84 (71, 102)	0.001
RR, rate/min	20 (20, 20)	20 (20, 24)	20 (20, 20)	20 (20, 25)	20 (20, 20)	0.174
BT, °C	36.5 (36.4, 36.6)	36.5 (36.2, 36.8)	36.5 (36.2, 36.6)	36.5 (36.2, 36.7)	36.4 (36.1, 36.6)	0.015
SpO_2, %	98 (95, 99)	94 (90, 97)	98 (96, 98)	95 (92, 98)	97 (95, 98)	<0.001
DM, n (%)	4 (3.8)	30 (21.6)	350 (33.7)	221 (49)	25 (30.1)	<0.001
HT, n (%)	38 (36.2)	74 (53.2)	565 (54.4)	314 (69.6)	44 (53)	0.7
Alcohol, n (%)	19 (33.9)	31 (22.3)	388 (37.3)	67 (14.9)	22 (26.5)	0.185
Smoking, n (%)	18 (32.1)	17 (12.2)	409 (39.4)	55 (12.2)	17 (20.5)	<0.001
TnI, ng/mL	0.009 (0.003, 0.023)	0.045 (0.01, 0.202)	0.16 (0.02, 1.67)	0.034 (0.016, 0.09)	0.006 (0.001, 0.147)	<0.001
D-dimer, μg/mL	8.4 (3, 22)	7.8 (4.8, 11)	0.4 (0.27, 0.8)	1.7 (0.9, 3.1)	0.6 (0.4, 1)	<0.001
Modified Wells	0 (0, 0)	3 (1.5, 4.5)	0 (0, 0)	0 (0, 1.5)	0 (0, 1.5)	<0.001
ADD-RS	1 (1, 1.5)	0 (0, 0)	1 (1, 1)	0 (0, 0)	0 (0, 0)	0.001
TA-AD, n (%)	78 (74.3)					
NEWS	2 (0, 4)	4 (2, 7)	1 (0, 3)	4 (2, 6)	2 (0, 5)	<0.001

AAS, acute aortic syndrome; PE, pulmonary embolism; ACS, acute coronary syndrome; HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BT, body temperature; SpO2, peripheral oxygen saturation; DM, diabetes mellitus; HT, hypertension; TnI, troponin I; ADD-RS, Aortic Dissection Detection Risk Score; TA-AD, type A-aortic dissection; NEWS, National Early Warning Score. A positive alcohol or smoking history was noted for patients exhibiting a persistent habit over the past three months.

3. Results

Baseline characteristics revealed no significant differences in age across groups; however, the ACS group had the highest proportion of males (77 %) and the highest rate of smoking (39.4 %). The PE group had the highest median body mass index (24.7 kg/m^2), the lowest initial blood pressure (120/80 mmHg), the highest heart rate (92 beats/min), and the lowest oxygen saturation (94 %). The NEWS was also elevated in the PE group, suggesting more severe clinical presentations in these patients (Table 1). The mean value of the modified Wells score was $\leq$4 in all subgroups, and that of the ADD-RS was <1, except for the AAS group. The modified Wells score was highest for patients with PE, whereas the ADD-RS was highest in patients with AAS. The median level of troponin I was significantly higher in the ACS group at 0.16 ng/mL, and the median D-dimer level was markedly elevated in the groups with AAS and PE, at 8.4 μg/mL and 7.8 μg/mL, respectively (Table 1). The median D-dimer levels of patients with large-vessel disease were much higher than those of patients with non-large-vessel disease (Fig. 3A). The median troponin I level was highest in the ACS group and lowest in the AAS and neurogenic groups (Fig. 3B). The D-dimer/troponin I ratio (DT ratio) was lower in ACS, HF, and neurogenic groups (Fig. 3C). The multivariate analysis of essential variables allowed for significant covariates such as oxygen saturation, smoking status,

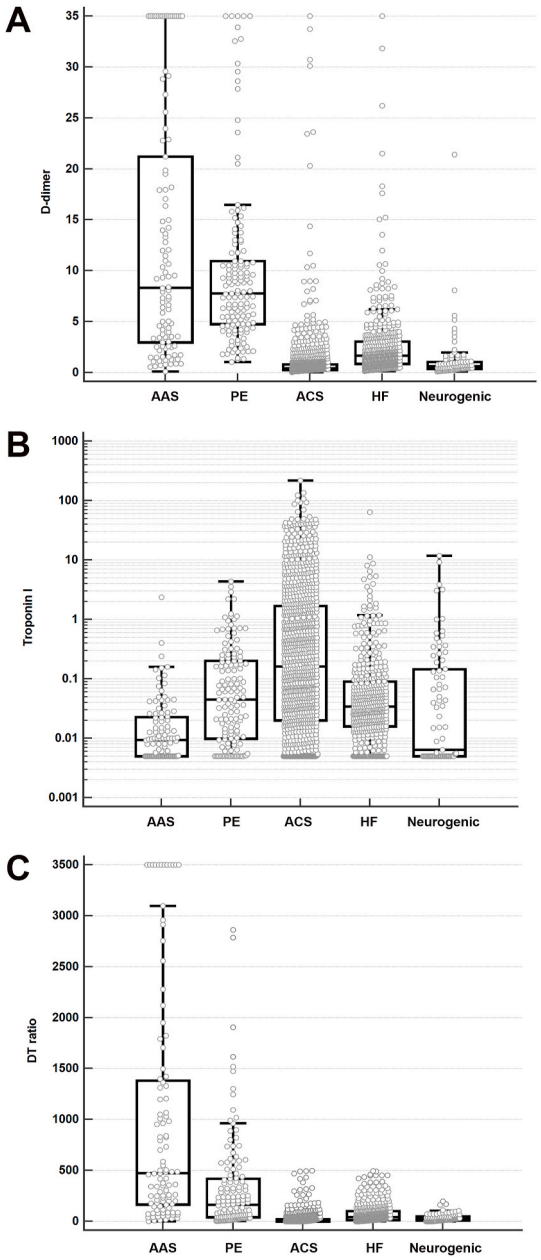

Fig. 3. Comparison of median values and inter-quartile ranges. A: D-dimer, B: Troponin I, C: D-dimer to troponin I ratio.

and ADD-RS. D-dimer was identified as the best predictor of large-vessel disease, with an odds ratio of 4.438 ($p < 0.001$) (Table 2). When comparing the predictive capabilities of D-dimer, the DT ratio, and troponin I, the AUC values were 0.935, 0.827, and 0.653, respectively (Fig. 4A). A D-dimer >0.5 μg/mL and an age-adjusted D-dimer as a rule-out criterion yielded AUCs of 0.722 and 0.77, respectively. D-dimer >0.55 μg/mL demonstrated a sensitivity of 100 % and a specificity of 47.9 %. None of patients with large-vessel disease had a D-dimer level <0.55 μg/mL, and age-adjusted D-dimer missed 1 patient with intramural hematoma in the infrarenal abdominal aorta. As a rule-in criterion, a D-dimer >2.38 μg/mL had the best performance with a sensitivity of 86.83 % and a specificity of 85.13 % (Table 3). The risk associated with D-dimer for predicting large-vessel diseases increased progressively, whereas the risk associated with troponin I had a trend towards an exponential decrease (Fig. 4B and C). Additionally, we compared the performances of D-dimer levels and pretest probability scores via a subgroup analysis. The ADD-RS had limited performance for predicting AAS, PE, and large-vessel diseases, with AUC values of 0.67, 0.702, and 0.559, respectively (Fig. 5A, B, and 5C). The modified Wells score was appropriate for predicting PE, with an AUC of 0.857; however, it was less effective for predicting AAS and large-vessel diseases, with AUCs of 0.527 and 0.71, respectively (Fig. 5A, B, and 5C). D-dimer demonstrated superior predictive power for AAS, PE, and large-vessel diseases, with AUC values of 0.915, 0.95, and 0.936, respectively (Fig. 5A, B, and 5C), compared to both the modified Wells score and ADD-RS.

4. Discussion

D-dimer exhibited a higher predictive capability for large-vessel diseases than troponin I or the DT ratio. Additionally, the D-dimer level was more accurate in predicting large-vessel diseases than both the modified Wells score and ADD-RS. Moderately elevated D-dimer levels were efficient in predicting large-vessel disease as a rule-in criterion, whereas normal D dimer levels served as a rule-out criterion. ACS and HF were associated with lower D-dimer levels; however, the levels in AAS and PE were higher.

Research on D-dimer levels is commonly conducted in patients with patients who have a wide range of symptoms. In patients presenting with various symptoms including chest pain, abdominal pain, back pain, syncope, or signs or symptoms of perfusion deficit, the use of D-dimer <0.5 μg/mL and ADD-RS ≤1 provided a method to rule out AAS with a sensitivity of 98.8 % and specificity of 57.3 % [7]. Conversely, for AAS rule-in criteria, such as ADD-RS > 1 combined with D-dimer >2 μg/mL, an AUC of 0.929 was exhibited in patients presenting with a variety of symptoms [14]. Similar results were observed for PE. For patients presenting with dyspnea and pleuritic pain, utilizing D-dimer levels <0.5 μg/mL along with a modified Wells score ≤4 served as criteria to exclude PE; however, only 32 % of patients met these rule-out criteria [15]. Conversely, employing a Wells score >4 alone as a rule-in criterion for predicting PE yielded a less impressive AUC of 0.744 [16]. The role of D-dimer as a rule-in criterion has not been extensively explored, and although most predictive tools for large-vessel diseases have been researched predominantly as rule-out criteria, higher D-dimer cut-off levels may offer substantial promise as a rule-in criterion. For patients with chief complaints including syncope, abdominal pain, back pain, and chest symptoms, D-dimer has proven to be an excellent discriminative tool for large-vessel diseases [12,13].

In patients presenting to the emergency department with diverse symptoms, physicians consider a broader spectrum of conditions; however, for those presenting with only chest symptoms, the evaluation can focus on several critical diseases, including ACS, HF, PE, AAS, and neurogenic diseases. In this narrow perspective, patients presenting with chest pain/discomfort and dyspnea are initially suspected of having ACS or HF, which often leads to missed diagnoses of large-vessel diseases. Therefore, distinguishing large-vessel diseases in patients with chest symptoms is crucial.

Therefore, the role of D-dimers in cohorts with both AAS and PE should be reviewed. Several studies have reported higher average D-dimer levels as a rule-out criterion for large-vessel diseases compared to ACS, HF, or other control groups [17,18]. However, D-dimer as a rule-in criterion has only been analyzed in a few studies, and the cut-off levels varied. In a study including 22 AAS and 193 PE patients, a D-dimer level above 4.6 μg/mL yielded an AUC of 0.906 [13]. Our research demonstrated accurate predictions of large-vessel diseases with lower cut-off levels. The elevated cut-off level observed in this study may be attributed to the inclusion of patients with infections, lung diseases, bleeding, and cancer because D-dimer levels are known to increase in conditions such as pregnancy, inflammation, malignancy, and post-surgery [19]. In another study with a small dataset (6 patients with AAS and 5 patients with PE), a D-dimer level above 5 μg/mL effectively discriminated large-vessel diseases from HF and ACS with high discriminative power of AUCs 0.981 and 0.96, respectively [12]. In this cohort, which included 279 patients, 160 were categorized as having unknown etiologies other than cardiovascular disease, which may have included conditions that elevate D-dimer levels. Another study of 40 patients with AAS reported that a cut-off level of D-dimer above 2 μg/mL can accurately distinguish aortic dissection, similar to the cut-off level in our findings [14]. Although the control group, which included patients with uncomplicated aortic aneurysms, PE, and

Table 2
Significant parameters for predicting both AAS and PE that CT angiography is required.

	β	Odds ratio	*P* value	95 % CI
Male	0.87	2.386	<0.001	1.496–3.805
DM	1.303	3.679	<0.001	2.052–6.594
D-dimer	1.49	4.438	<0.001	3.416–5.766
Modified Wells	1.327	3.771	<0.001	3.013–4.72
NEWS	−0.389	0.678	0.004	0.522–0.88

The analyzed variables were standardized and the result was allowed for significant covariates such as SpO_2, smoking, troponin I and aortic dissection detection risk score. Blood pressure and heart rate were excluded in analysis as being included in the risk scores.

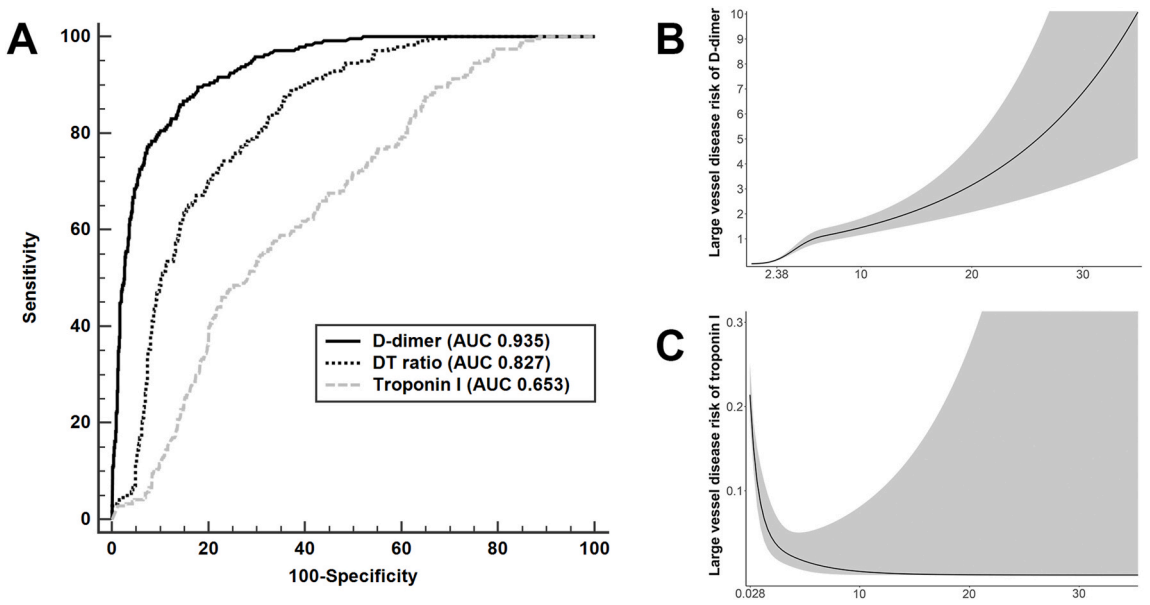

Fig. 4. Performances of D-dimer, troponin I, and D-dimer to troponin I ratio for predicting large-vessel diseases and risk curves using cubic spline models. A: ROC curves, B: Risk changes of D-dimer for large-vessel diseases, C: Risk changes of troponin I for large-vessel diseases. The likelihood of large-vessel diseases according to D-dimer and troponin I levels is depicted.

Table 3
Predictive accuracy of D-dimer, troponin I, DT ratio, modified Wells score and ADD-RS for predicting large vessel disease.

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
D-dimer	2.38	86.83	85.13	47.4	97.7	0.935
Troponin I	0.028	15.77	88.25	17	87.2	0.653
DT ratio	0.03	87.55	63.98	27.1	97.1	0.827
Modified Wells score	2.5	44.2	99.49	92.5	92.6	0.71
ADD-RS	0	56.95	58.58	16.3	90.6	0.56

DT ratio denotes D-dimer/troponin I ratio; ADD-RS, aortic dissection detection risk score; PPV, positive predictive value; NPV, negative predictive value.

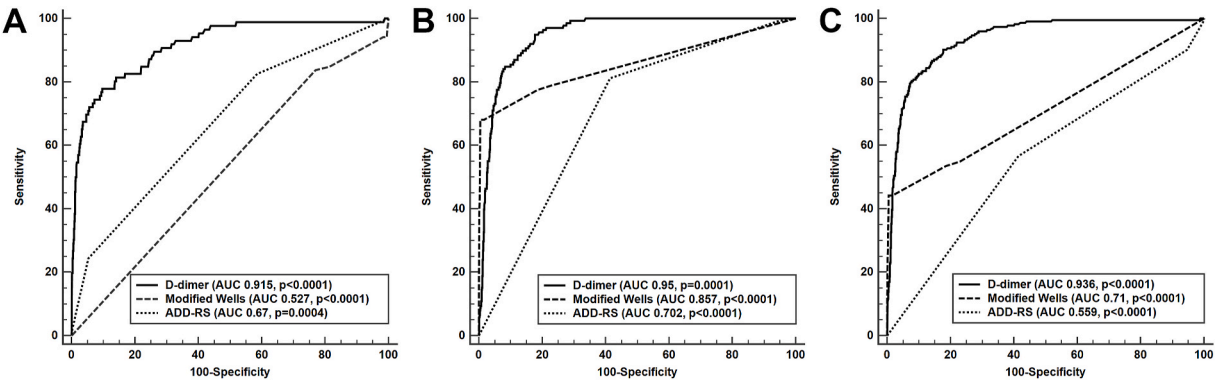

Fig. 5. Performances of D-dimer levels and pretest probability scores. A: Tools for predicting acute aortic syndrome, B: Tools for predicting pulmonary embolism, C: Tools for predicting large-vessel diseases.

pneumonia, was compared with the AAS group, notably the cutoff level was lower than in our results. This discrepancy may be attributed to the relatively small number of conditions known to elevate D-dimer levels in the control group. A study differentiating 87 of 220 patients with aortic dissection proposed a cut-off D-dimer level >1.6 μg/mL as a rule-in criterion [20]; although the control group included 5 patients with PE and 45 with uncertain diagnoses, thus the cut-off level of D-dimer was likely lower due to the inclusion of 83 patients with ACS in the control group of 133 patients. The D-dimer cut-off levels would be higher if a study group

included a larger proportion of patients with conditions such as pregnancy, inflammation/infection, cancer, and post-operative status, all of which can elevate D-dimer levels. Further studies are required to establish D-dimer cut-off levels for distinguishing large-vessel diseases within each group known to exhibit elevated D-dimer levels.

In our results, the D-dimer <0.55 μg/mL criterion excluded 754 of 1817 patients, which excluded all patients with large-vessel diseases. Patients with D-dimer <0.55 μg/mL as a rule-out criterion was more effective than a D-dimer level <0.5 μg/mL or an age-adjusted D-dimer. However, 8 patients with AAS and with a D-dimer <0.5 μg/mL were observed in a prospective study [7]. This study clinically diagnosed 804 of 1850 patients by case adjudication after a 14-day clinical follow-up without CT, transesophageal echocardiography, angiography, or magnetic resonance angiography. A definitive diagnosis using the gold standard should be determined, and the details of patients with AAS and with normal D-dimer levels should be further explored. In discriminating AAS, the integration of ADD-RS and D-dimer may demonstrate greater performance as both rule-out and rule-in criteria (D-dimer >2 μg/mL) compared to D-dimer alone [7,14]. In a PE cohort, 1 patient with D-dimer <0.5 μg/mL was observed in a retrospective study [21]. In this study, the integration of a modified Wells score ≤4 and D-dimer <0.5 μg/mL as rule-out criteria enhanced the predictive performance. However, the integration of a Wells score >4 and D-dimer >0.5 μg/mL as rule-in criteria did not improve the predictive ability [22]. There are pretest probability scores for either AAS or PE; however, no scores exist that simultaneously test for both AAS and PE. Clinical pretest probability scores for suspected AAS and PE are required for patients with chest symptoms.

In patients with chest symptoms, the initial suspicion often focuses on ACS and HF. Although AAS and PE are infrequent, missing them poses a high risk of mortality. In clinical practice, it is crucial to consider these life-threatening conditions along with the most prevalent neurogenic diseases, especially because angio-CT is not routinely performed for non-large-vessel diseases. Current evidence suggests that D-dimer >1.6–4.6 μg/mL, varying according to a patient's comorbidity, may indicate large-vessel diseases. Our meticulously planned study recommended conducting angio-CT when D-dimer exceeds 2.38 μg/mL. However, it is important to note that this D-dimer level serves as a reference, and efforts should be made to avoid missing large-vessel diseases by incorporating various pretest probability scores and clinical data.

One of the strengths of our study is that it included a suitable number of patients with large-vessel disease (105 with AAS and 139 with PE), whereas previous studies lacked sufficient populations of patients with either AAS or PE. The final diagnoses of all diseases were meticulously established. Patients with neurogenic diseases accompanied by cardiovascular diseases were excluded. ACS, HF, and neurogenic disease were accurately distinguished using coronary angiography and echocardiography. In addition, we excluded patients with conditions that could elevated D-dimer levels, such as pneumonia and lung cancer. The significance of our study was demonstrating the role of D-dimer in differentiating important but difficult-to-diagnose diseases among patients who presented with chest symptoms, and in reducing the overuse of angio-CT in patients suspected of having ACS and HF. Therefore, a prospective study is required for a more robust investigation involving more accurate prospective data, such as blood sampling at a specified time after the onset of chest symptoms and scoring the risks. A large-scale study of specific disease groups with increased D-dimer levels is also needed. Elaborate research on D-dimer levels as a rule-in criterion for predicting large-vessel diseases in patients with chest symptoms is warranted.

5. Limitations

This study has several limitations that must be addressed. First, conditions known to increase D-dimer levels, including pregnancy, bleeding/trauma, infection/inflammation, and cancer, were excluded. The D-dimer threshold for distinguishing large-vessel diseases should be evaluated within each disease category. For example, if a patient with cancer is admitted to the emergency department with chest pain, the cut-off level for distinguishing large-vessel disease may be 4.6 μg/mL [13]. Second, this was a retrospective, single-center study, and external validation was not conducted. The D-dimer cut-off level identified in our results for discriminating between common diseases in patients with chest symptoms should undergo prospective validation. Third, a selection bias may have occurred because of the exclusion of a significant number of patients. Fourth, this study did not compare other pretest probability scores, including the modified Geneva score and PERC, nor did it evaluate the combined performance of D-dimer levels and pretest probability scores. Finally, the onset of chest symptoms might have varied among our patient groups, which could influence the biomarker levels although blood samples were collected within 1 h of admission.

6. Conclusions

Distinguishing large-vessel diseases using D-dimer in patients with chest symptoms was more efficient than DT ratio, troponin I, and pretest probability scores. When a patient presents with chest symptoms, it is common to encounter a clinical scenario that necessitates the consideration of both AAS and PE, leading to contemplation about performing angio-CT. In such situations, the utilization of D-dimer levels, along with clinical data and pretest probability scores, can be clinically beneficial. Moderately elevated D-dimer levels can serve as a rule-in criterion, whereas normal D-dimer levels can be considered as a rule-out criterion. To enhance its efficacy as a predictive tool, further studies are required to develop new pretest probability scores that can simultaneously predict ACS and PE in patients presenting with chest symptoms, incorporating D-dimer results, a combination of specific symptoms, and previous history of large-vessel disease. The cut-off level for D-dimer may be higher with conditions such as pregnancy, trauma/surgery, infection/inflammation, and cancer.

Financial disclosure and conflicts of interest

The authors declare that they have no conflict of interest.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Min Joon Seo: Writing – review & editing, Resources, Investigation, Data curation. **Jae Hoon Lee:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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