

Does Preprocedural Age-Adjusted D-dimer Testing Have Any Advantage Before Percutaneous Pain Intervention for Detecting Potential Thrombovascular Events in Older Adults?

Hüseyin Utku YILDIRIM

drutkuyil@gmail.com

Karadeniz Technical University

Erdem Nail DUMAN

Karadeniz Technical University

Mert AKBAŞ

Akdeniz University Hospital

Esra KOÇ

Akdeniz University

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Abstract

Background: Venous Thromboembolism (VTE) is a serious reason of morbidity and mortality in elderly adults. Ordinary pre-procedural scanning can simplify beforetime detection of asymptomatic or subclinical Thrombovascular Events. Age-Adjusted D-dimer Testing (AADT) may aid in identifying Potential Thrombovascular Events (PTVE) in patients established for Percutaneous Interventional Pain Procedures (PIPP).

Objective: The aim of this study was to evaluate the relationship between age- adjusted d-dimer testing value and potential thrombovascular events in preparation for percutaneous interventional pain procedures.

Study Design: A retrospective study

Setting: This retrospective study included 131 patients over 18 years of age who underwent d-dimer testing for percutaneous interventional pain management.

Methods: We conducted a retrospective study of patients aged 18 years and older who underwent transforaminal epidural steroid injection, interlaminar epidural steroid injection, caudal epidural steroid injection, cervical epidural steroid injection, facet median branch radiofrequency therapy, or ganglion impar block for lumbar disc herniation, cervical disc herniation, or coccydynia between May 2022 and February 2023 and underwent pre-intervention laboratory evaluations (including D-dimer testing). Data collected included demographic variables (age, sex, occupation), reason for admission, pain scores, comorbid systemic diseases, presence of thromboembolic symptoms, history of venous thrombosis, anticoagulant use, smoking and alcohol use, obesity, COVID-19 infection history and timing, vaccination status, vaccine type, date of last vaccination, laboratory parameters (D-dimer, fibrinogen, platelet count, leukocyte count, hemoglobin level, renal and liver function tests), respiratory symptoms, presence of Homans' sign, specialist consultations, details of initiated anticoagulant therapy (if any), type of PIPP, hospital admission, intensive care unit (ICU) admission, and need for mechanical ventilation. Patients were also contacted by telephone six months after their procedure date to assess mortality outcomes. Statistical analyses used Mann-Whitney U tests, chi-square tests, and post-hoc analyses with Bonferroni correction.

Results: Of 143 patients scanned, 131 (mean age 64.2 ± 14.0 years) were added in the study. Higher age-adjusted D-dimer values were significantly correlated with elderly age ($p=0.00014$), greater comorbidity burden ($p=0.0025$), and the presence of PTVE ($p<0.000001$). No significant correlation was peered with COVID-19 vaccination status or number of vaccine doses.

Conclusion: AADT can be utilized as a cost-effective noninvasive monitoring tool to determine PTVE in patients more than 60 years of age, with two or more comorbidities, and who are planned for PIPP, especially if the value is high up $1.66 \mu\text{g/mL}$.

Limitations: Limitations of this study include the relatively small sample size and the retrospective study design.

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular event after myocardial infarction and cerebrovascular disease. In the general population, its incidence is estimated at 1.24 per 1000 patient-years (1, 2). VTE incidence increases sharply with age, occurring approximately eight times more frequently in those over 80 compared to individuals under 50. VTE is associated with considerable morbidity and mortality, with reported 30-day and one-year mortality rates of 10.6% and 23%, respectively (1). Given its increasing incidence and mortality with age, VTE represents a significant public health concern, particularly in countries with aging populations.

The impliment of scoring systems such as the Geneva and Wells scores in VTE algorithms is advocated (3). Patients with a high clinical probability should undergo imaging tests, while the Age-Adjusted D-dimer Test (AADT) is suggested for patients with a low or intermediate probability. A normal value succesfully excludes VTE in these patients. However, a high AADT should be supported by imaging (4). These suggestion highlight the value of AADT, particularly in asymptomatic patients or those with low clinical suspicion.

- dimer is a fibrin corruption product discharged during the deterioration of fibrin clots by plasmin. It is called "D-dimer" because it comprises the two D fragment in fibrin. Technics for evaluating D-dimer levels include latex agglutination, enzyme-linked immunosorbent assay (ELISA), enzyme-linked fluorescence assay (ELFA), immunofiltration, immunoturbidimetry, and whole blood agglutination tests. These methods vary in sensitivity, specificity, and time to result. The ELISA test provides results in 2–4 hours and has 94% sensitivity and 53% specificity. The ELFA test provides results in 35 minutes with 96% sensitivity and 46% specificity, while immunoturbidimetric tests provide results in 15 minutes with 93% sensitivity and 53% specificity (5). At our institution, the immunoturbidimetric method is choosed due to its quikness and acceptable diagnostic performance. The cutoff value for a positive D-dimer test in persons under 50 years of age is 0.5 µg/mL. In persons over 50 years of age, the age-adjusted cutoff value is computed by multiplying age by 10 (5) and projects physiological increments by aging. Further, some studies propose that an increment in serum AADT may be connected with the seriously of PTVE (6, 7).

The objective of this retrospective study is to check records of patients tested for D-dimer and fibrinogen in our clinic between May 1, 2022, and February 1, 2023, to spesify risk factors correlated with highed AADT levels and to appraise these patients for possible vascular pathologies as a DVE and PE. In light of incremented cardiovascular and Thrombovascular Events incoming the COVID-19 pandemic, we propound that routine AADT in at-risk patients represents a cost-effective strategy to facilitate early diagnosis and improve patient outcomes.

Methods

Study Design and Settings

The Algology Clinic within the University Hospital has been providing outpatient examinations and interventional procedures since 1998. Patients are assessed monthly by rotating anesthesia residents under the supervision of faculty specializing in algology. Patients scheduled for PIPP at our clinic are invited for pre-procedural evaluation five days in advance if on anticoagulant therapy, and two days in advance if not. During these visits, routine blood tests are performed. If abnormal results are detected, patients are referred to the appropriate specialties for further evaluation and consultation prior to the procedure. Patients with elevated AADT values are referred to the Department of Cardiovascular Surgery if deep vein thrombosis (DVT) is suspected, to the Department of Cardiology if a cardiovascular event is suspected, and to the Department of Pulmonary Medicine if pulmonary embolism (PE) is suspected. For patients diagnosed PTVE after specialist evaluation, early anticoagulant therapy is initiated, the planned PIPP is postponed, and treatment is coordinated with a multidisciplinary approach. Once anticoagulation can be safely discontinued, these patients are rescheduled for their PIPP.

Participants

Study Inclusion Criteria:

1. Patients presenting to the Algology outpatient clinic
2. Adult patients over 18 years of age

Study Exclusion Criteria:

1. Patients under 18 years of age
2. Patients previously diagnosed with thromboembolism
3. 4. Patients with elevated AADT values in previous examinations
4. 5. Pregnancy
5. 6. Patients with hematoma
6. 7. Patients with hematological diseases
7. 8. Presence of congestive heart failure, liver or kidney failure
8. 9. Presence of active malignancy
9. 10. Presence of active infection

After obtaining ethical approval from the Scientific Research Ethics Committee of the Faculty of Medicine, Karadeniz Technical University, Trabzon, Türkiye (Protocol No. 2022/236; approval date: 10 March 2023), we conducted a retrospective review of the medical records of all patients scheduled for PIPP between May 1, 2022, and February 1, 2023. Data collected included demographic variables (age, sex, occupation), reason for admission, pain scores, comorbid systemic diseases, presence of

thromboembolic symptoms, history of venous thrombosis, anticoagulant use, smoking and alcohol use, obesity, COVID-19 infection history and timing, vaccination status, vaccine type, date of last vaccination, laboratory parameters (D-dimer, fibrinogen, platelet count, leukocyte count, hemoglobin level, renal and liver function tests), respiratory symptoms, presence of Homans' sign, specialist consultations, details of initiated anticoagulant therapy (if any), type of PIPP, hospital admission, intensive care unit (ICU) admission, and need for mechanical ventilation. Patients were also contacted by telephone six months after their procedure date to assess mortality outcomes.

Outcome Measures

The primary analyse was the relation between elevated AADT and the presence of PTVE. Secondary analyses appraised relations between AADT values and age group, sex, number of comorbidities, history of COVID-19 infection, and vaccination status (including number of doses and vaccine type). Furthermore, we also defined a potential D-dimer cutoff value for predicting PTVE.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Version 26.0.

Descriptive statistics were presented as mean $\pm$ standard deviation (SD) for continuous variables and frequency/percentage for categorical variables. Normality of continuous variables was assessed with the Shapiro-Wilk test.

Group comparisons were performed using the Mann–Whitney U test for non-normally distributed continuous variables and the chi-square test for categorical variables. Bonferroni correction was applied for post hoc pairwise comparisons where appropriate. A p-value of < 0.05 was considered statistically significant.

Results

A total of 131 patients who met the inclusion criteria were included in the final analysis. The mean age of the study population was 64.2 ± 14.0 years (range: 18–89). For analysis, age was categorized into eight groups (18–20, 20–30, 30–40, 40–50, 50–60, 60–70, 70–80, and 80 + years) (Table 1). A significant association was observed between age group vs elevated AADT level ($\chi^2 = 23.30$, $p = 0.0015$), age group ve PTVE ($\chi^2 = 31.14$, $p < 0.00006$) with older age groups demonstrating a higher prevalence of elevated values (Table 2).

Table 1
Association AADT with age groups

Age Group	Normal AADT (%)	High AADT(%)	n
18–20	100.0	0.0	1
20–30	100.0	0.0	1
30–40	83.3	16.7	6
40–50	100.0	0.0	10
50–60	72.0	28.0	25
60–70	61.0	39.0	41
70–80	60.6	39.4	33
80+	14.3	85.7	14

Table 2
Age Group Analysis

Analysis	Test	P value
Age Group vs. AADT	$\chi^2 = 23.30$	0.0015
Age Group vs. PTVE	$\chi^2 = 31.14$	< 0.00006

There was no significant difference in gender distribution between groups (Female/Male in elevated D-dimer: 39/11 vs. normal D-dimer: 53/28; $\chi^2 = 1.77$, $p = 0.183$). Patients with elevated AADT levels also had a significantly higher number of comorbid conditions (median = 2.0, SD = 1.29) compared with those with normal levels (median = 1.0, SD = 1.16; $U = 2647.0$, $p = 0.0025$) (Table 3).

Table 3
Association Between AADT and Patient Characteristics

Variable	Normal AADT	High AADT	Test	P value
Gender (F/M)	53/28	39/11	$\chi^2 = 1.77$	0.183
Comorbidities (median $\pm$ SD)	1.0 $\pm$ 1.16	2.0 $\pm$ 1.29	$U = 2647.0$	0.0025
PTVE	0	17	$\chi^2 = 28.71$	< 0.000001

There was a strong association between PTVE and elevated AADT levels. All patients with PTVE ($n = 17$) had elevated AADT level (100%), whereas only 28.9% of patients without PTVE exhibited elevated levels ($\chi^2 = 28.71$, $p < 0.000001$)(Table 3).

The median AADT level was higher in the PTVE-positive group (median = 1.24 µg/mL; IQR: 1.02–1.80) compared to the PTVE-negative group (median = 1.10 µg/mL; IQR: 0.88–1.33). The mean AADT levels were 2.24 ± 2.74 µg/mL in the PTVE-positive group (n = 17) and 1.21 ± 0.54 µg/mL in the PTVE-negative group (n = 33). Although the difference approached statistical significance, it did not reach conventional thresholds (Mann–Whitney U = 369.0; p = 0.071) (Table 4, Fig. 1). Receiver Operating Characteristic (ROC) analysis was performed to evaluate the discriminative ability of D-dimer levels for predicting PTVE positivity. The area under the ROC curve (AUC) was 0.658, indicating modest discriminative power. The optimal cutoff value for D-dimer, determined using Youden’s J statistic, was identified as 1.66 µg/mL (Fig. 2).

Table 4
Association Between PTVE and AADT level

Group	n	Median AADT	IQR	Mean AADT	P value
PTVE +	17	1,24 µg/mL	1.02–1.80	2.24 ± 2.74	U = 369.0; p = 0.071
PTVE -	33	1,1 µg/mL	0.88–1.33	1.21 ± 0.54	

Regarding COVID-19 history, there was no significant association between prior infection and elevated D-dimer levels (COVID-19 positive: 19/55 [34.5%] elevated vs. COVID-19 negative: 31/76 [40.8%]; $\chi^2 = 0.30$, p = 0.587). Similarly, PTVE status did not differ significantly according to COVID-19 history ($\chi^2 = 1.93$, p = 0.165)(Table 5). Analysis of vaccination status also revealed no significant association between vaccine type and D-dimer elevation. Patients who had received at least one COVID-19 vaccine dose had similar rates of elevated D-dimer compared to unvaccinated individuals (Vaccinated: 43/112 [38.4%] vs. Unvaccinated: 7/19 [36.8%]; $\chi^2 = 0.0$, p = 1.0). Additionally, there was no significant difference in the total number of vaccine doses between the elevated and normal D-dimer groups (median = 3.0 doses in both; U = 1897.0, p = 0.530), nor did PTVE status differ by number of doses received (U = 1037.0, p = 0.631) (Table 5).

Table 5
Association of COVID-19 and Vaccination vs AADT and PTVE

Analysis	Test	P value
COVID-19 vs. AADT	$\chi^2 = 0.30$	0.587
COVID-19 vs. PTVE	$\chi^2 = 1.93$	0.165
Vaccinated (Yes/No) vs. AADT	$\chi^2 = 0.0$	1.0
Number of Vaccines vs. AADT	U = 1897.0	0.530
Number of Vaccines vs. PTVE	U = 1037.0	0.631

When stratified by vaccine type, no significant associations were observed between inactivated vaccine status and D-dimer elevation ($\chi^2 = 1.81$, $p = 0.405$) or PTVE occurrence ($\chi^2 = 1.74$, $p = 0.419$). Similarly, active vaccine status was not associated with D-dimer elevation ($\chi^2 = 0.0$, $p = 1.0$) or PTVE occurrence ($\chi^2 = 0.16$, $p = 0.687$) (Table 6). Finally, analysis of the four vaccination categories (Inactivated + Active, Only Inactivated, Only Active, Neither) revealed no significant differences in D-dimer levels ($\chi^2 = 0.31$, $p = 0.958$) or PTVE status ($\chi^2 = 2.75$, $p = 0.432$) (Table 7).

Table 6
Association with Inactivated and Active Vaccine Types
vs AADT and PTVE

Analysis	Test	P value
Inactivated Vaccine vs. AADT	$\chi^2 = 1.81$	0.405
Inactivated Vaccine vs. PTVE	$\chi^2 = 1.74$	0.419
Active Vaccine vs. AADT	$\chi^2 = 0.0$	1.0
Active Vaccine vs. PTVE	$\chi^2 = 0.16$	0.687

Table 7
Vaccine Group vs. AADT and PTVE

Analysis	Test	P value
Vaccine Group vs. AADT	$\chi^2 = 0.31$	0.958
Vaccine Group vs. PTVE	$\chi^2 = 2.75$	0.432

Discussion

Following reports of thrombovascular events after COVID-19 infection and vaccination, our clinic began performing routine D-dimer and fibrinogen testing in May 2022. Interestingly, two of the first five patients screened had significantly elevated AADT levels and were diagnosed with pulmonary embolism despite mild respiratory symptoms. These patients were initially admitted to the Department of Pulmonary Medicine ward then transferred to the intensive care unit on the second day and discharged with recovery after receiving noninvasive ventilation and anticoagulation therapy. After numerous patients had their PIPPs canceled due to similar issues, a work-action plan was implemented based on AADT results and patient symptoms. This study is a product of this work-action plan

Our analysis disclosed a statistically significant between elevated d-dimer levels and older age, as well as a higher burden of comorbidities. We sighted that patients with elevated d-dimer values were significantly older, with a median age of 69.5 years compared to 61.0 years in those with normal d-dimer. These findings align with existing literature demonstrating that d-dimer levels naturally increase with age, underscoring the value of age-adjusted cutoff value in maintaining diagnostic accuracy. The higher prevalence of elevated D-dimer in older age groups suggests that D-dimer elevations may be related to

factors more common in older age, such as greater chronic disease burden, systemic inflammation, and vascular pathology. Analysis by age group revealed a significant increase in the prevalence of high AADT associated with a positive PTVE status in older age groups, indicating that older patients are at higher risk for incident thrombovascular events detected by this screening. The rate of high AADT was 39% in the 60–70 age group, 39.4% in the 70–80 age group, and 85.7% in those over 80 years of age. This reason was considered the basis for routine D-dimer testing before PIPP in patients over 60 years of age.

AADT threshold values are known to be adequate to exclude pulmonary embolism when used with a non-high clinical probability (8). It has also been noticed that AADT is useful in excluding venous thromboembolism and acute aortic dissection in both cancer and non-cancer patients, and is also useful in making determinations with at least a moderate differential diagnosis in these diseases (9). However, studies on the use of AADT value as a marker for determining possible PTVE in asymptomatic or subclinical patients are few and inadequate. All patients diagnosed with potential thrombovascular events (PTVE) in this study had elevated AADT values, indicating high sensitivity but limited specificity of this marker in preprocedural screening. Because this indicated the need for a cutoff value, ROC analysis was performed, and the optimal threshold was selected based on Youden's J statistic. The optimal cutoff value for AADT was determined to be 1.66 µg/mL. This threshold demonstrated the best balance between sensitivity and specificity for distinguishing between PTVE-positive and PTVE-negative patients in this cohort.

Comorbidity burden was also significantly associated with elevated AADT. Importantly, AADT levels were associated with elevated and PTVE in all patients with vascular conditions such as hypertension and coronary artery disease, suggesting a potential role for this test in determining subclinical thrombotic risk in this subgroup. This requires clarification of the PTVE diagnosis in our study. Excluding a patient diagnosed with lung cancer who was excluded from the study, the diagnoses identified in our study were: deep vein thrombosis (4 patients), peripheral artery disease (1 patient), pulmonary embolism (5 patients), idiopathic alveolar hemorrhage (1 patient), and idiopathic pericardial effusion (6 patients). The etiologies of pericardial effusion are diverse (infectious, neoplastic, autoimmune, metabolic, and drug-related) (10). It is important to note that in clinical practice, determining the exact cause of pericardial effusion is often difficult, and most cases are ultimately labeled idiopathic (11, 12). Investigating the etiology of idiopathic pericardial effusion is costly, risky, and unnecessary except in emergency situations. Therefore, our patients with idiopathic alveolar hemorrhage and pericardial effusion were evaluated in the PTVE class because there were no underlying metabolic, infectious, autoimmune or neoplastic causes.

Studies have reported increased AADT and fibrinogen elevations in the early stages of COVID-19 disease and after vaccination (13–15). Although cases of pericardial effusion, venous thromboembolism and pulmonary embolism with elevated AADT levels due to COVID-19 infection or vaccination have been reported in the literature (16–20), our study found no significant association between elevated AADT levels and a history of COVID-19 infection, vaccination status, or the number or type of vaccine doses. This contradicts previous concerns about prothrombotic risks from COVID-19 and supports the safety

profile of vaccination in this context. Additionally, it is thought that it may be valuable in excluding thrombovascular pathologies due to vaccination or previous COVID history in patients diagnosed with PVTE in our study.

Finally, among patients over 60 years of age with two or more comorbidities, the detection rate of PTVE was statistically significantly higher, particularly when AADT levels exceeded 1.66 µg/mL. These findings suggest that preprocedural AADT screening may be particularly valuable in this demographic group, as a simple, noninvasive method to identify patients who may need further diagnostic imaging or risk stratification.

Conclusion

AADT is a simple, widely available, and noninvasive screening tool that can help determine the risk of incidental, asymptomatic, or subclinical thrombovascular events in elderly patients undergoing interventional procedures or surgery. Our findings support its routine use, particularly in patients over 60 years of age with multiple comorbidities such as coronary artery disease and hypertension. Incorporating AADT into preprocedural protocols may improve patient safety and improve perioperative management by providing early detection of incidental thrombovascular events. Furthermore, studies with larger patient series may clarify AADT cut off value and facilitate preprocedural imaging diagnosis in these patients.

Overall, these results demonstrate a strong association between increased age, comorbidity burden, and PTVE with elevated AADT levels, while indicating that COVID-19 infection history or vaccination status did not significantly affect D-dimer levels or thromboembolic risk. These findings underscore the importance of considering patient age and comorbidities when interpreting elevated AADT results, while also supporting the safety profile of COVID-19 vaccination with respect to thromboembolic risk. We believe that more prospective studies with larger patient numbers can yield more beneficial results in predicting Potential Thrombovascular Events in patients undergoing Percutaneous Interventional Pain Procedures.

Declarations

Ethics Approval and Consent to Participate: This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Scientific Research Ethics Committee of the Faculty of Medicine, Karadeniz Technical University, Trabzon, Türkiye (Protocol No. 2022/236; approval date: 10 March 2023).

As this was a retrospective study based on previously collected clinical records, the Scientific Research Ethics Committee of the Faculty of Medicine, Karadeniz Technical University, determined that informed consent from individual participants was not required.

Human Ethics and Consent to Participate declarations: Not applicable.

Consent for Publication: Not applicable.

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Competing Interests: The authors declare that they have no competing interests.

Study Design: A Retrospective Study

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Figures

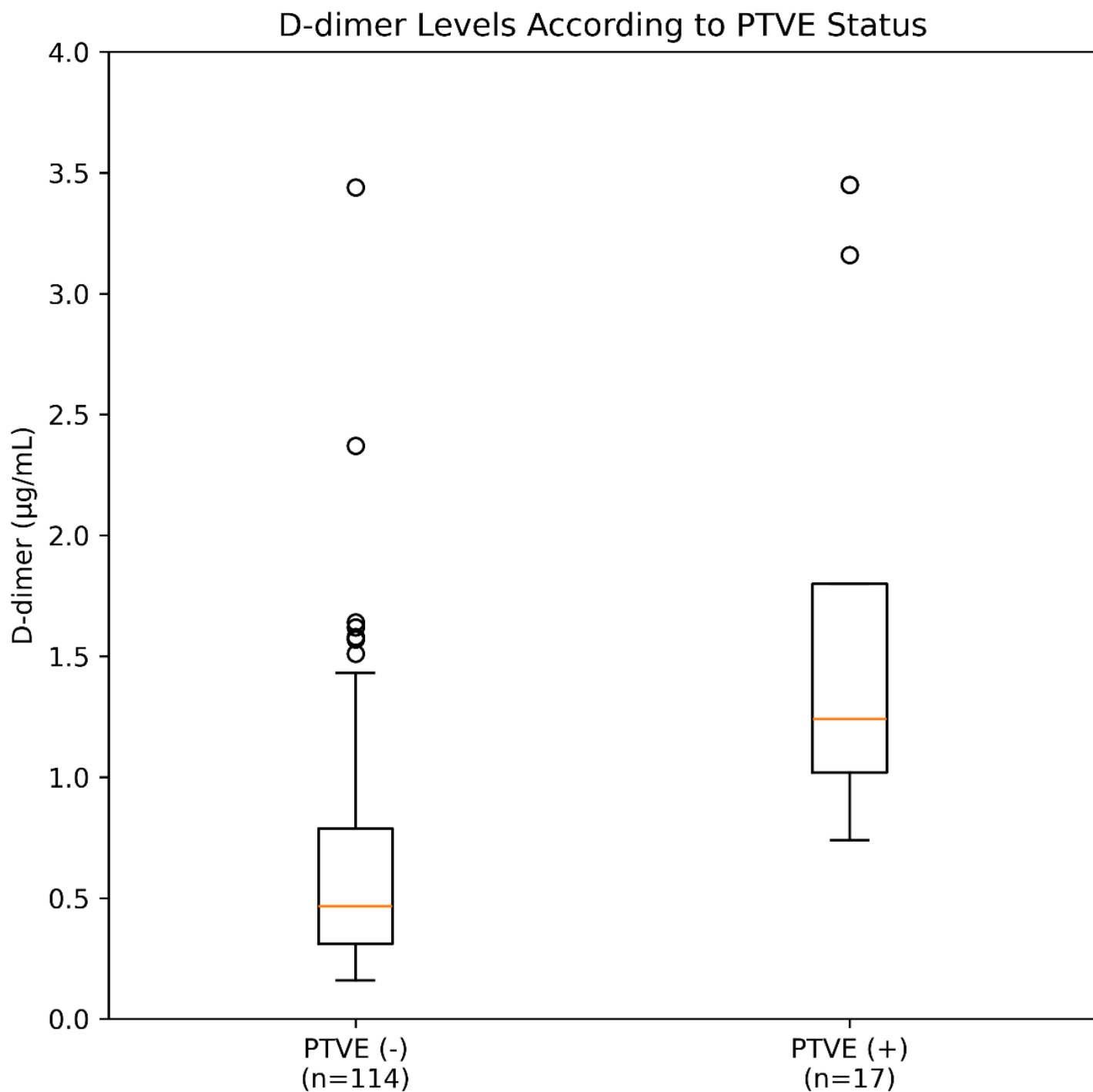


Figure 1

Boxplot demonstrating the distribution of D-dimer levels in PTEE-positive and PTEE-negative patients. The y-axis was limited to 0–4 $\mu\text{g/mL}$ to improve visualization of the central distribution.

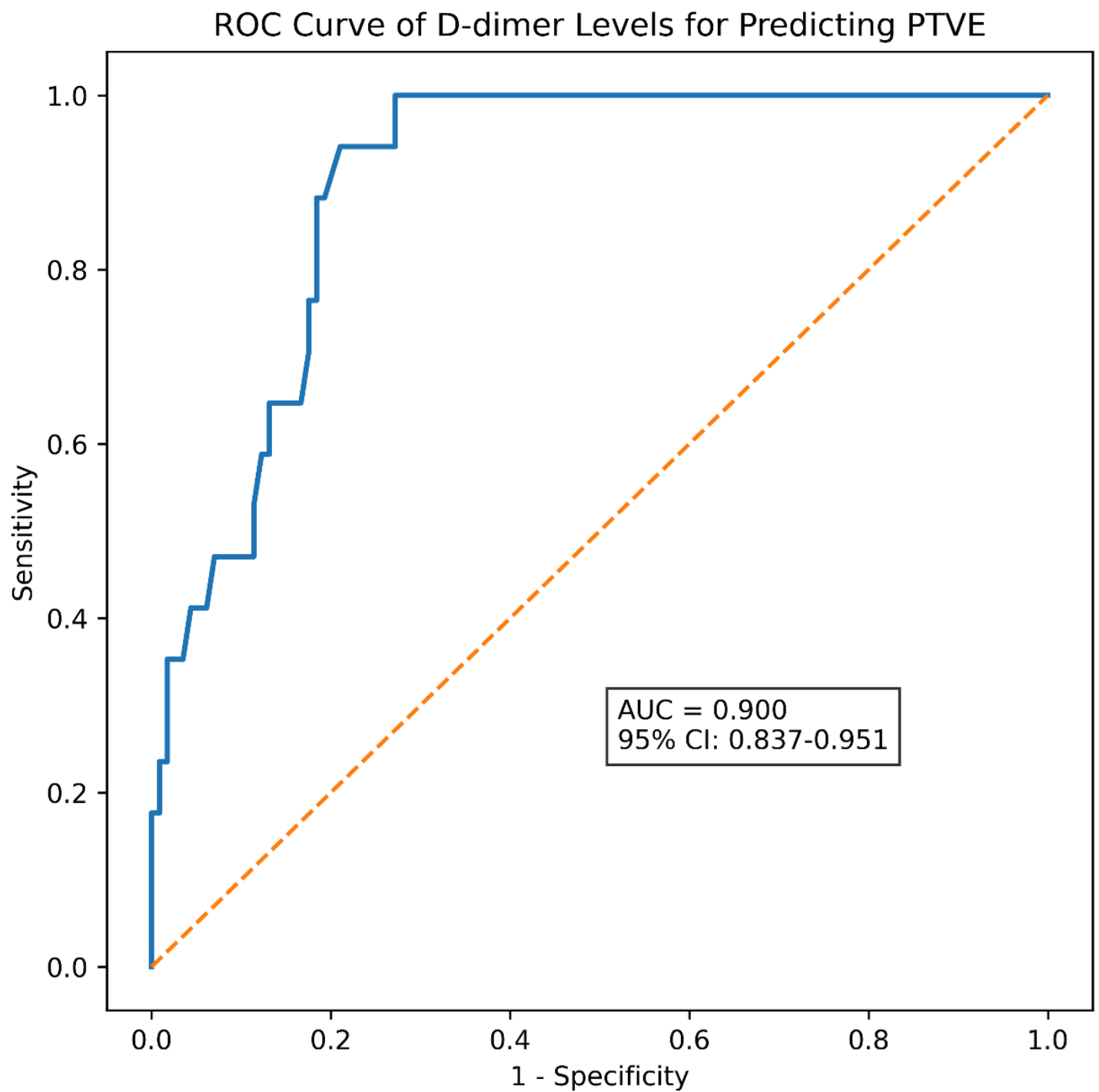


Figure 2

Receiver operating characteristic (ROC) curve of preprocedural D-dimer levels for predicting potential thrombovascular events (PTVE). The area under the curve was 0.900 (95% CI: 0.837–0.951).