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Superior Predictive Value of D-Dimer to the Padua Prediction Score for Venous Thromboembolism in Inpatients with AECOPD: A Multicenter Cohort Study

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On behalf of the MAGNET AECOPD Registry Investigators

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Background: The optimal tool for risk prediction of venous thromboembolism (VTE) in inpatients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is still unknown. This study aimed to evaluate whether D-dimer could predict the risk of VTE in inpatients with AECOPD compared to the Padua Prediction Score (PPS).

Methods: Inpatients with AECOPD were prospectively enrolled from seven medical centers in China between December 2018 and June 2020. On admission, D-dimer was detected, PPS was calculated for each patient, and the incidence of 2-month VTE was investigated. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of D-dimer and PPS on VTE development, and the best cut-off value for both methods was evaluated through the Youden index.

Results: Among the 4468 eligible patients with AECOPD, 90 patients (2.01%) developed VTE within 2 months after admission. The area under the receiver operating characteristic curves (AUCs) of D-dimer for predicting VTE were significantly higher than those of the PPS both in the overall cohort (0.724, 95% CI 0.672–0.776 vs 0.620, 95% CI 0.562–0.679; P<0.05) and the subgroup of patients without thromboprophylaxis (0.747, 95% CI 0.695–0.799 vs 0.640, 95% CI 0.582–0.698; P<0.05). By calculating the Youden Index, the best cut-off value of D-dimer was determined to be 0.96 mg/L with an AUC of 0.689, which was also significantly better than that of the PPS with the best cut-off value of 2 (AUC 0.581, P=0.007). After the combination of D-dimer with PPS, the AUC (0.621) failed to surpass D-dimer alone (P=0.104).

Conclusion: D-dimer has a superior predictive value for VTE over PPS in inpatients with AECOPD, which might be a better choice to guide thromboprophylaxis in inpatients with AECOPD due to its effectiveness and convenience.

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Introduction

It is estimated that the global prevalence of chronic obstructive pulmonary disease (COPD) is about 11.7%, with approximately three million deaths annually.[1] Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a vital cause of death among COPD patients and involves a rapid decline in health status and a longer hospitalization duration.[2] Venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, is a vital complication of AECOPD. The reported incidence of VTE ranges from 6.8% to 24.7%[3–6] in inpatients with AECOPD. COPD is a well-established independent risk factor for VTE, and the risk of VTE further increases during AECOPD.[6–8] In turn, the emergence of VTE in AECOPD patients is associated with an increased risk of adverse prognosis, including worsening medical conditions, longer hospital stay, and even unexpected death.[7–10]

Thromboprophylaxis could effectively reduce the risk of VTE in medical inpatients.[11–13] Although the prevalence of VTE in inpatients with AECOPD is higher than that in general medical inpatients, the use of thromboprophylaxis among this population is unsatisfactory. Additionally, as thromboprophylaxis has the risk of complications such as bleeding, it should be applied to an appropriate high-risk population to achieve the best risk–benefit ratio. This highlights the importance of identifying AECOPD patients at high risk of VTE who require thromboprophylaxis. For medical inpatients, the Padua Prediction Score (PPS) is reported as an effective tool to assess VTE risk in medical inpatients[14] and is also recommended by The American College of Chest Physicians guidelines for antithrombotic therapy and prevention of thrombosis 9th edition (ACCP-9).[15] However, some recent studies have shown poor performance of PPS in stratifying VTE risk in inpatients with some medical diseases,[1] and it has not been validated in inpatients with AECOPD until now.

D-dimer, as a soluble fibrin degradation product that results from the systematic degradation of vascular thrombi through the fibrinolytic mechanism, was first applied to the auxiliary diagnosis of VTE with a threshold of 0.5 mg/L.[16] D-dimer is an important reference index in VTE diagnosis, as it has a very high negative predictive value due to its high sensitivity. D-dimer could also be applied to VTE patients to further predict the risk of VTE recurrence.[17] In recent studies, D-dimer is also a predictor for thrombosis,[18–20] both in medical and surgical inpatients. Nevertheless, the cut-off value of 0.5 mg/L, which is widely used in the field of VTE diagnosis, has been proven unsuitable for the prediction of VTE.[1,21–23] To our knowledge, few studies have explored the value of D-dimer as a VTE predictor in inpatients with AECOPD. Hence, whether D-dimer could predict VTE occurrence and whether D-dimer combined with PPS could possibly optimize the prediction effect of PPS in inpatients with AECOPD remains to be studied.

The primary aim of this prospective multicenter study was to evaluate and compare the validity of the PPS and D-dimer in predicting the risk of VTE in inpatients with AECOPD. Furthermore, the best threshold of D-dimer and the predictive value of the combination of PPS and D-dimer were also investigated in this study.

Methods

Ethical Considerations

Our study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University and the institutional review boards of other six academic medical centers that participated. Written informed consent was obtained from all patients.

Patients and Study Design

Patient inclusion was based on the prospective, noninterventional, multicenter cohort study MAGNET AECOPD (MAnaGement aNd advErse ouTcomes in inpatients with acute exacerbation of COPD) Registry study in China. The major aims of this registry study were to investigate the management and adverse outcomes (including VTE, mortality, readmission, etc.) of inpatients with AECOPD and to establish and validate early warning models of these adverse outcomes. The original study enrolled consecutive adult inpatients diagnosed with AECOPD among seven major hospitals in China between September 2017 and July 2021, while

the current analysis adopted data from patients included from September 2018 to June 2020. The diagnosis of AECOPD was based on the following criteria: (1) a history of COPD, including (i) exposure to risk factors (eg, tobacco smoking, exposure to a specific environment); (ii) long-term dyspnea, chronic cough, or sputum production; (iii) postbronchodilator spirometry testing showing a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio less than 70%; and (2) an acute worsening of respiratory symptoms resulting in additional therapy. Patients were excluded from this analysis if they (1) were hospitalized for less than 3 days; (2) were diagnosed with VTE within 48 h after admission; and (3) failed to be followed up for 2 months.

Data Collection and the PPS

A standardized case report form was completed for every enrolled patient, including baseline demographics, comorbidities, risk factors for VTE, laboratory results, imaging findings, and treatments. In the MAGNET AECOPD Registry study, the enrolled individual received follow-up for 2 years by telephone, outpatient visits, or rehospitalization when necessary after 2, 3, 6, 9, 12, 18, and 24 months. The plasma D-dimer was measured by the latex-enhanced immunoturbidimetry (Sysmex, Kobe, Japan) (normal reference range for adults is less than 0.50 mg/L). D-dimer was detected and PPS was calculated for each included patient within 24 h of admission, and no additional direct intervention was performed.

The PPS is a recommended risk assessment model (RAM) for VTE in medical inpatients. In the PPS, the risk profile for VTE is calculated using 11 common risk factors for VTE. Each risk factor is weighted according to a point scale: (a) 1 point: age ≥70 years, heart and/or respiratory failure, obesity (BMI ≥30 kg/m^2), acute myocardial infarction and/or ischemic stroke, ongoing hormone therapy, acute infection and/or rheumatic disease; (b) 2 points: recent (≤1 month) trauma or surgery; (c) 3 points: history of VTE, long-term lying in bed, active malignant tumor, thrombotic tendency. According to the original RAM, a high risk of VTE is defined as a cumulative score ≥4, and a low risk is defined as a score <4.

Study Outcomes

The main outcome was symptomatic VTE, defined as DVT (proximal and/or distal), nonfatal and fatal pulmonary embolism during the 2-month follow-up after admission. All events were adjudicated by an independent committee. DVT was validated based on positive compression ultrasonography and/or contrast venography, and PE was validated based on positive CT pulmonary angiography (CTPA), ventilation-perfusion (V/Q) scanning and pulmonary angiography.

Statistical Analysis

All collected data were analyzed with SPSS 25.0 statistical software. The normally distributed data are expressed as the "mean ± standard deviation", and a *t* test was used for comparisons between two groups. The data with a skewed distribution are expressed as median values with interquartile ranges, and a nonparametric test was used for comparisons between two groups. Categorical data are expressed as percentages, and the chi-square test was used for comparisons between groups.

The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of D-dimer and PPS, and the best cut-off value for both methods was evaluated through the Youden index. The Youden index combines the importance of sensitivity (Sn) and specificity (Sp) and is calculated as Sn + Sp-1. To rule out the effects of thromboprophylaxis on the outcomes, we carried out an analysis in both the overall cohort and in the population not receiving thromboprophylaxis. In addition, the time course for the occurrence of VTE after admission in inpatients with AECOPD with different cut-off values according to the PPS and D-dimer was depicted as Kaplan–Meier curves. Group comparisons were made using the Log rank test. $P<0.05$ was considered statistically significant.

Results

Characteristics of the Study Population

Among the AECOPD patients enrolled in the registration study, patients were excluded for the following reasons: (1) hospitalization for less than 3 days (n = 156); (2) diagnosis of VTE within 48 h after admission (n = 66); and (3) loss to 2-month follow-up (n = 283). As a result, a total of 4468 patients with AECOPD were included, and 90 (2.01%) of them suffered from symptomatic VTE during the 2-month follow-up, including 79 confirmed isolated DVT, 6 confirmed isolated PE, and 5

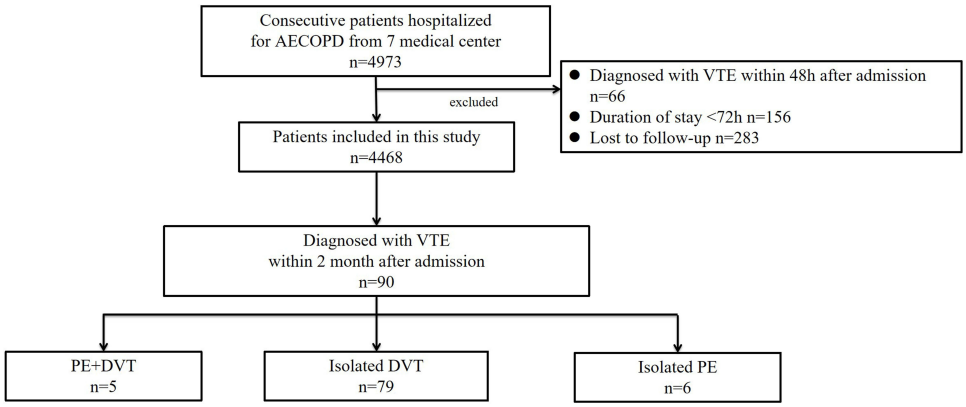

Figure 1 Flow chart of the study.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep venous thrombosis.

confirmed PE and DVT (Figure 1), with 3724 patients (83.3%) not receiving thromboprophylaxis. The median duration from admission to the diagnosis of VTE was 6.5 days (range: 3–59 days).

The characteristics of the included AECOPD patients are described in Table 1. The mean age of the VTE group was 75.99 ± 8.98 years, which was significantly higher than that of patients without VTE (71.77±10.27, P<0.001). Additionally, there were significant differences in the prevalence of age ≥70 y, BMI ≥30 kg/m^2, heart failure, chronic

Table 1 Characteristics of the Included AECOPD Patients

	Total (N=4468)	With VTE (N=90)	Without VTE (N=4378)	P value*
Baseline characteristics				
Age (years)	71.85±10.27	75.99±8.98	71.77±10.27	**<0.001**
Age ≥70 years	2641(59.1%)	67(74.4%)	2574(58.8%)	**0.003**
Male	3455(77.9%)	65(72.2%)	3390(78.1%)	0.186
History of smoking	3131(70.1%)	59(65.6%)	3072(70.2%)	0.344
BMI	21.74±4.18	22.17±4.61	21.73±7.17	0.449
BMI ≥30kg/m^2	93(3.3%)	5(9.1%)	88(3.2%)	**0.016**
Comorbidities				
Acute myocardial infarction	13(0.3%)	0(0%)	13(0.3%)	0.605
Heart failure	565(12.6%)	18(20.0%)	547(12.2%)	**0.034**
Pulmonary tuberculosis	188(4.2%)	5(5.6%)	183(4.2%)	0.520
Chronic pulmonary heart disease	1095(24.5%)	44(48.9%)	1051(24.0%)	**<0.001**
Interstitial lung disease	125(2.8%)	2(2.2%)	123(2.8%)	0.738
Pulmonary arterial hypertension	155(3.5%)	4(4.4%)	151(3.4%)	0.609
Pneumonia	1078(24.1%)	30(33.3%)	1048(23.9%)	**0.039**
Respiratory failure	385(8.6%)	7(7.8%)	378(8.6%)	0.774
Active cancer	171(3.8%)	5(5.6%)	166(3.8%)	0.338
Sepsis (<1 month)	16(0.4%)	2(2.2%)	14(0.3%)	**0.003**
Inflammatory bowel disease	4(0.1%)	0(0%)	4(0.1%)	0.774
Stroke (<1 month)	260(5.8%)	9(10.0%)	251(5.7%)	0.087
Rheumatological disorder	68(1.5%)	2(2.2%)	66(1.5%)	0.584
Varicose veins	38(0.9%)	3(3.3%)	35(0.8%)	**0.010**
Swollen legs (current)	791(17.7%)	42(46.7%)	749(17.1%)	**<0.001**
Reduced mobility	520(11.6%)	18(20.0%)	502(11.5%)	**0.012**
Recent (≤1 month) trauma	3(0.1%)	0(0%)	3(0.1%)	0.804
Recent (≤1 month) surgery	7(0.2%)	0(0%)	7(0.2%)	0.704
History of VTE	15(0.3%)	0(0%)	15(0.3%)	0.578

(*Continued*)

Table 1 (Continued).

	Total (N=4468)	With VTE (N=90)	Without VTE (N=4378)	P value*
Laboratory tests				
Hemoglobin (g/L)	122.93±32.18	117.73 ± 29.42	123.03 ± 32.23	0.122
Hematocrit (%)	0.40±0.07	0.38 ± 0.08	0.40 ± 0.07	**0.021**
White blood cell ($\times 10^3$ mm^{-3})	8.21±3.41	9.37± 4.04	8.18 ± 3.40	**0.009**
Platelet ($\times 10^3$ mm^{-3})	201.21±85.23	196.93± 93.02	201.30 ± 85.07	0.631
Fibrinogen (g/L)	4.18±2.41	4.93±8.35	4.15±2.12	0.391
Outcomes				
Mortality	80(1.8%)	10(11.1%)	70(1.6%)	**<0.001**
Length of stay (days)	9(7, 14)	15(11, 28.25)	9(7, 13)	**0.001**
Prediction factors				
D-dimer (mg/L)	1.64±3.15	4.63±7.46	1.58±2.97	**<0.001**
PPS	1(1, 2)	2(1, 3)	1(1, 2)	**<0.001**

Notes: *Those with P value <0.05 were highlighted using the bold font. Data are presented as the number of patients (%), mean±SD, median (interquartile range).
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; VTE, venous thromboembolism; BMI, body mass index; PPS, Padua Prediction Score.

pulmonary heart disease, pneumonia, sepsis (<1 month), varicose veins, swollen legs (current), and reduced mobility (all P<0.05), which were more frequently seen in patients with VTE. In terms of laboratory tests, patients with VTE had lower hematocrit and higher white blood cell counts. The mortality rate was higher and the length of hospital stay was longer in patients with VTE. As expected, the D-dimer and PPS scores on admission were both higher in patients with 2-month VTE than in patients without.

ROC Curve Analysis and Best Threshold for D-Dimer and PPS

The receiver operating curve (ROC) of D-dimer and PPS is depicted in Figure 2. The area under the ROC curve (AUC) of D-dimer for predicting VTE was significantly higher than that of the PPS both in the overall cohort (AUC 0.724, 95% CI 0.672–0.776 vs AUC 0.620, 95% CI 0.562–0.679; P<0.05) and the subgroup of patients without thromboprophylaxis (AUC 0.747, 95% CI 0.695–0.799 vs AUC 0.640, 95% CI 0.582–0.698; P<0.05). The best cut-off values of the D-dimer and PPS values were determined respectively in the overall cohort by calculating the Youden index, with the best cut-off values for the high-risk group defined as a D-dimer value ≥0.96 mg/L and PPS ≥2.

The AUCs of the different thresholds of D-dimer and PPS and the combination of the two in all patients and patients without thromboprophylaxis are shown in Table 2 and Supplemental Figure 1. In all patients, the original high-risk cut-off value of the PPS (PPS≥4) showed unacceptable discriminatory power in predicting VTE events (AUC=0.552, P=0.093, data not shown). The performance of PPS was still poor even when the cut-off was redefined as 2 (AUC=0.581) according to the best Youden index; the AUC of the combination of PPS≥2 and D-dimer≥0.96 mg/L was 0.621, which was not better than that of D-dimer≥0.96 mg/L alone (AUC=0.689, P=0.104 when the two AUCs were compared). Similarly, when analysis was performed among the patients without thromboprophylaxis, the predictive value of D-dimer≥0.96 mg/L alone was also the best among all the single methods (AUC=0.711 for D-dimer≥0.96 mg/L, P values all <0.05 when the AUCs of these methods were compared with the AUC of D-dimer≥0.96 mg/L alone respectively), and the AUC of the combination of PPS≥2 and D-dimer≥0.96 mg/L was not better than that of D-dimer≥0.96 mg/L alone either (P=0.074).

Incidence of VTE by Risk Levels of PPS and D-Dimer Cut-off Value

Based on different cut-off values of PPS, D-dimer and their combination, inpatients with AECOPD were divided into a high-risk group and a low-risk group. The incidence of VTE in different risk groups, sensitivity, specificity and Youden index of each prediction method are shown in Table 3. Among these risk prediction methods, the Youden index of

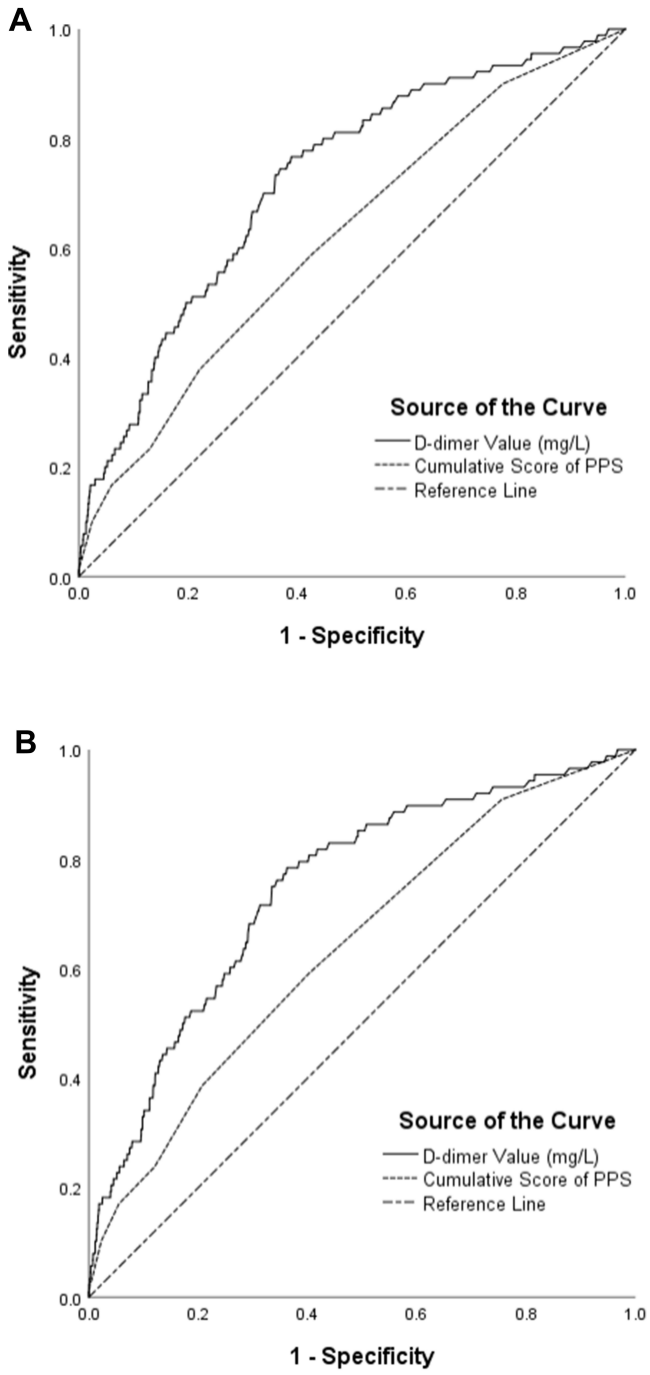

Figure 2 Receiver operating characteristic (ROC) curve of D-dimer and PPS in overall cohort (**A**) and patients without thromboprophylaxis (**B**).
Abbreviation: PPS, Padua Prediction Score.

D-dimer≥0.96 mg/L was the most satisfactory (Youden Index=0.3779, with sensitivity and specificity values of 76.67% and 61.12%, respectively), which suggests that D-dimer≥0.96 mg/L has the best risk prediction value.

Time-to-Event Analysis

The predictive value of different methods was further investigated by the time-to-event (acquired VTE) analysis in overall cohort and patients without thromboprophylaxis (Figure 3 and Supplemental Figure 2). Generally, all the methods could distinguish the risk of developing 2-month VTE in both populations (all P<0.05 by Log rank test), while it seems

Table 2 Area Under the ROC Curve According to the Different Methods

High-Risk Definition	All Patients (N=4468)	P value	Patients without Thromboprophylaxis (N=3724)	P value
PPS ≥4	0.552(0.488,0.615)	0.001	0.559(0.494,0.624)	0.001
PPS ≥2	0.581(0.522,0.640)	0.007	0.594(0.534,0.654)	0.004
D-dimer ≥0.5 mg/L	0.621(0.571,0.670)	0.065	0.631(0.582,0.681)	0.027
D-dimer ≥0.96 mg/L	**0.689(0.637,0.741)**	-	**0.711(0.660,0.762)**	-
PPS ≥2 and D-dimer ≥0.96 mg/L	0.621(0.558,0.684)	0.104	0.636(0.572,0.700)	0.074

Notes: The high-risk definition with best AUC was highlighted using bold font. Data are in AUC values (95% confidence interval). P values were from the comparisons of the AUCs of these methods with the AUCs of D-dimer≥0.96 mg/L alone.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; PPS, Padua Prediction Score.

Table 3 Predictive Reliability Indices of the Prediction Methods

High-Risk Definition	VTE Events in Low risk Group n (%)	VTE Events in High risk Group n (%)	Sensitivity(%) (95% CI)	Specificity(%) (95% CI)	Youden Index
D-dimer ≥0.5 mg/L	9(0.6%)	81(2.7%)	90.00(83.68, 96.32)	40.24(38.86, 41.63)	0.3024
D-dimer ≥0.96 mg/L	21(0.8%)	69(3.9%)	76.67(67.76, 85.57)	61.12(59.68, 62.57)	0.3779
PPS ≥4	69(1.8%)	21(3.6%)	23.33(14.43, 32.24)	87.00(86.01, 88.00)	0.1033
PPS ≥2	37(1.5%)	53(2.8%)	58.89(48.53, 69.25)	57.33(55.87, 58.80)	0.1622
PPS ≥2 and D-dimer ≥0.96 mg/L	49(1.4%)	41(4.2%)	45.56(35.07, 56.04)	78.58(77.36, 79.79)	0.2414

Abbreviations: VTE, venous thromboembolism; PPS, Padua Prediction Score; CI, confidence interval.

the cut-off value of 0.96 mg/L for D-dimer had better discriminatory power for the risk of 2-month VTE than the cut-off value of 0.5 mg/L in both populations. Furthermore, after combining the two best cutoff values of D-dimer and the PPS score, the predictive value was not superior to that of D-dimer≥0.96 mg/L alone (Figure 3C and Supplemental Figure 2C), which was identical in both populations.

Discussion

In most guideline recommendations, medical inpatients should receive thromboprophylaxis if they are assessed to have an increased risk of VTE unless they are at high risk of bleeding.[24] The risk of VTE is especially high in inpatients with AECOPD compared with general medical inpatients. However, thromboprophylaxis is underused in inpatients with AECOPD in clinical practice in the real world, especially in China, probably due to the lack of a proper tool to identify high-risk patients. In this prospective study, only 16.65% (744/4468) inpatients with AECOPD received thromboprophylaxis, which is lower than that reported in medical inpatients in western countries, where more than half of medical inpatients had received thromboprophylaxis during hospitalization.[25–27]

The incidence rate of VTE was 2.01% within 2 months of admission in the inpatients with AECOPD, which was lower than the previous studies, which stated a VTE prevalence of 6.8–16.0%,[6,28,29] with some studies focused on the prevalence of PE in this population, which was up to 25.8%.[3]

The relative low incidence of VTE in this study may attribute to 1) the strictly exclusion of VTE events acquired before hospitalization (a total of 66 patients diagnosed with VTE within 48 h after admission were excluded), 2) that asymptomatic VTE screening was not routinely launched in each inpatient, and 3) that thromboprophylaxis in a small number of patients (16.65%) had an impact on the incidence of VTE. Nevertheless, the prevalence of VTE is still higher than that in general medical inpatients, which was reported to be 0.25–1.1%.[30–33]

In this study, we aimed to discuss the predictive value of D-dimer and PPS for VTE after admission, which was not clearly revealed in the AECOPD population. PPS, as one of the widely used RAMs for VTE in medical inpatients, was

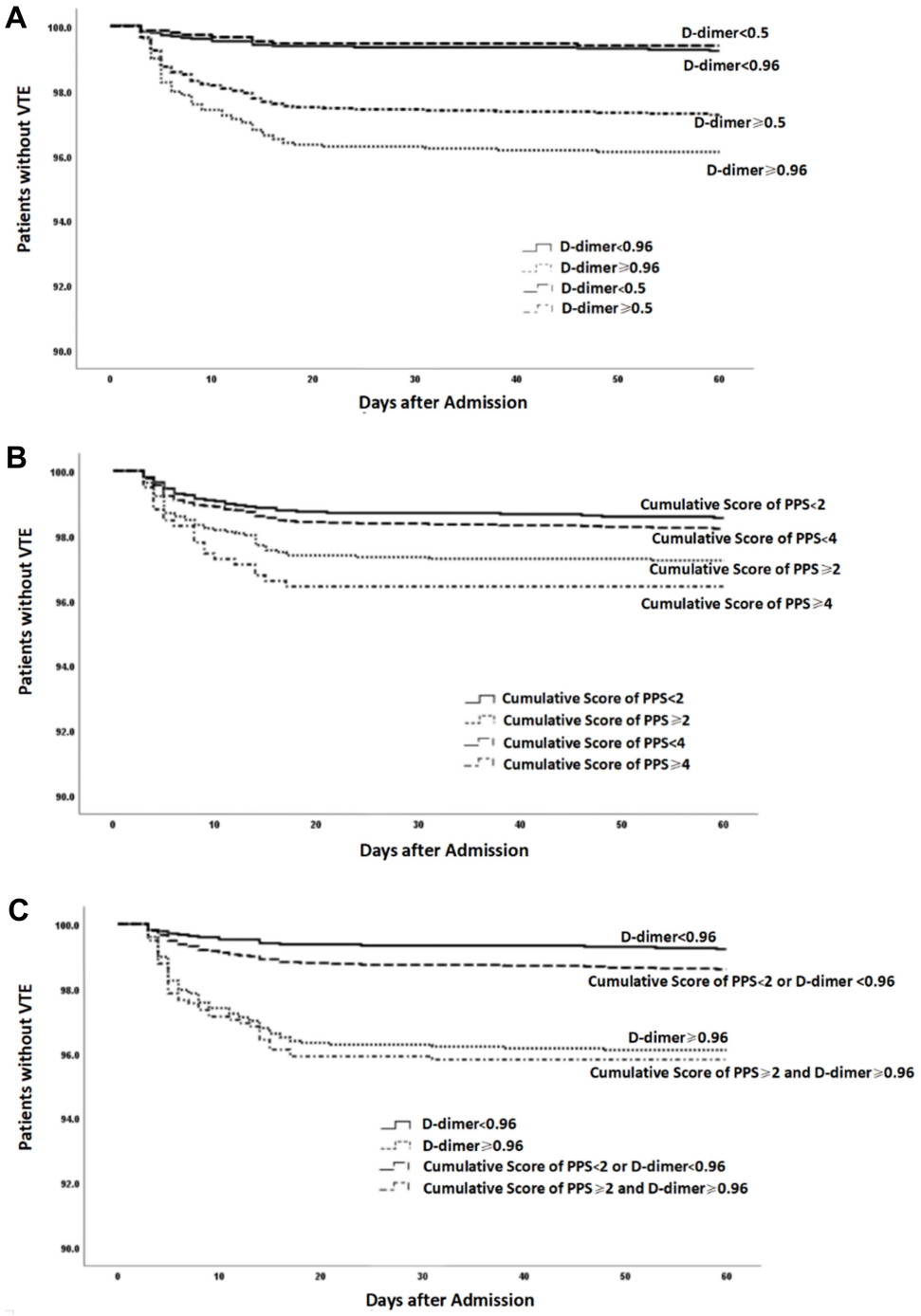

Figure 3 Kaplan–Meier estimates of the absence of VTE in low vs high-risk patients according to different cut-off values of D-dimer (mg/L) (**A**) and the PPS (**B**), and the combination of D-dimer (mg/L) and PPS (**C**) in overall cohort.
Abbreviations: VTE, venous thromboembolism; PPS, Padua Prediction Score.

first validated by Barbar et al in a prospective study, which indicated that PPS could help classify patients into high- and low-risk groups, and thromboprophylaxis in the high-risk group could help protect patients from VTE development.[14] However, the application of PPS in medical inpatients has not reached a consistent conclusion at present. Although PPS could differentiate patients into high- and low-risk groups, it was complained that less patients were classified into the high-risk group than other RAMs, and the sensitivity of PPS was low.[26,34] For populations with low VTE prevalence, such as medical inpatients with sepsis, PPS failed to detect high-risk patients.[35] In contrast, Luca et al reported that

thromboprophylaxis based on PPS risk levels could reduce health expenditure without sacrificing the aim of reducing VTE prevalence.[36] In this prospective study based on a large population of inpatients with AECOPD, the traditional threshold of PPS (4 points) showed poor performance in predicting the development of VTE in either the overall cohort (AUC was 0.552) or patients without thromboprophylaxis (AUC was 0.559). Although we revealed that PPS with a cut-off value of 2 could differentiate low- and high-risk patients, the AUC (0.581) was still unsatisfactory, which indicated that the PPS may be not applicable in inpatients with AECOPD.

D-dimer has an acknowledged negative diagnostic value of VTE with a threshold of 0.5mg/L. Furthermore, D-dimer is found to be an important indicator to predict the risk of VTE recurrence after discontinuation of anticoagulation therapy.[17,37] These evidences lay the foundation for the application of D-dimer in the VTE-related field. In recent years, the predictive value of D-dimer for VTE development among inpatients has emerged, which was first reported to be useful in predicting VTE onset in patients with cancer (with cut-off valued 1.44 mg/L).[1] In subsequent studies, the predictive value of D-dimer for VTE development has been validated in different populations. Interestingly, the threshold of D-dimer in predicting VTE onset is different in various diseases. Carles et al[22] defined 3 mg/L as the cut-off value of VTE prediction in COVID-19 inpatients, and it was the threshold for considering full-dose anticoagulation. Wen et al[23] determined D-dimer ≥5.50 mg/L as the predictive factor of VTE development during puerperium in women age 35 or older. Similar to the patients with cancer and women during puerperium, AECOPD patients are also in a prothrombotic state,[38,39] which could result in an upward trend of D-dimer in serum. To date, no D-dimer cut-off value for the prediction of VTE development in AECOPD patients has been reported. In this study, the most effective threshold of D-dimer was 0.96 mg/L, with a sensitivity and specificity of 76.67% and 61.12%, respectively, for predicting VTE. Although D-dimer≥0.50 mg/L, as the widely used threshold, had high sensitivity, which reached up to 90%, this cut-off value could hardly be used to identify patients who should receive thromboprophylaxis, as most of the patients would be in the high-risk group (as shown in this study, 2966/4468, 66.3%), which was mentioned as well in other studies.[20,23,40]

In this study, either PPS alone or the combination of PPS with D-dimer failed to beat D-dimer (with a cut-off value of 0.96 mg/L) only in predicting VTE in inpatients with AECOPD. In surgery patients, D-dimer also shows better predictive value than the traditional Caprini RAM[20] and could be incorporated into other RAMs to reach a better prediction effect.[40,41] The underlying mechanism of D-dimer for predicting VTE may be that it reflects the coagulation activity directly of the patients, while RAMs mainly consist of comorbidities. On the other hand, D-dimer could be easily obtained, as almost every patient receives a blood test on admission, and the simple value is more convenient and objective than scoring, which could be easily influenced by low obedience or information collection bias.

To our knowledge, this was the first large-scale multicenter study to validate and compare the predictive value of PPS and D-dimer in VTE development in inpatients with AECOPD. The prospective and consecutive inclusion of patients and complete 2-month follow-up data in our study ensured high data quality. Nevertheless, as mentioned previously, our study had limitations. First, VTE screening was not routinely carried out in inpatients with AECOPD, which resulted in a lower prevalence of VTE. However, we defined symptomatic VTE as the main outcome, and the clinical implications and the need for treatment of asymptomatic VTE remain controversial; additionally, in the patients who received VTE screening, a similar result was confirmed as in the overall cohort (data not shown). Second, the administration of thromboprophylaxis in the patients may affect the outcomes, but the order of thromboprophylaxis was to depend on the physicians' judgment and not on either of the D-dimer or PPS in this study, and the rate of prophylaxis was low. Thus, the potential effect might be negligible. More importantly, the exclusion of patients with thromboprophylaxis revealed similar results. Finally, the newly defined threshold of D-dimer had not been validated, and further investigation is required to validate the predictive effect of this D-dimer value on VTE development and prophylactic benefits in this population.

Conclusion

D-dimer could be an independent factor to predict VTE occurrence in inpatients with AECOPD with a threshold of 0.96 mg/L. The predictive value of D-dimer was found to be superior to PPS and the combination of both, which could hopefully provide new guidance for thromboprophylaxis in these patients in a convenient way. However, further studies

are still warranted to define and validate the best cut-off value of D-dimer in predicting VTE and confirm prophylactic benefits in a high-risk population defined by D-dimer.

Abbreviation

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AUC, area under the curve; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTPA, computed tomography pulmonary angiography; CI, confidence interval; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism.

Data Sharing Statement

The original data of this manuscript will not be shared in public.

Ethical Statement

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Ethics Committee on Biomedical Research, West China Hospital of Sichuan University. All adult participants provided written informed consent to participate in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. We appreciate the support and collaboration of the co-investigators participating in MAGNET AECOPD Registry study.

Guarantor Statement

Haixia Zhou is the guarantor of the whole content of the manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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