Comparison of Deep Vein Thrombosis Risks in Acute Respiratory Distress Syndrome Caused by COVID-19 and Bacterial Pneumonia: A Retrospective Cohort Study

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Abstract

Background: High incidence of deep vein thrombosis (DVT) has been observed in patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 and those by bacterial pneumonia. However, it is also important to differentiate between these two groups of patients.

Study Design and Methods: We performed a retrospective cohort study to investigate the difference of DVT between the two independent cohorts of ARDS and eventually enrolled 240 patients, 105 of whom with ARDS caused by COVID-19 and 135 by bacterial pneumonia. We analyzed demographics and clinical characteristics for patients with and without DVT in these two cohorts and explored the main differences and similarities between them.

Results: The 28-days incidence of DVT in COVID-19 cohort was higher than that in bacterial pneumonia cohort (57.1% vs 41.5%, P=0.016). Taking death as competitive risk, Fine-Gray test showed no significant difference in 28-day cumulative incidence of DVT between these two groups (P=0.220). Fine-Gray competing risk analysis showed an association between CK (creatine kinase isoenzyme)-MB levels, PaO2 (partial pressure of arterial oxygen)/FiO2 (fraction of inspired oxygen) ratios, D-dimer levels and DVT in COVID-19 cohort and an association between serum creatinine levels, IMV, and DVT in bacterial pneumonia cohort. The sensitivity and specificity of corresponding receiver operating characteristic curve originating from the combination of CK-MB levels, PaO2/FiO2 ratios and D-dimer levels ≥ 0.5 μg/mL was not inferior to those of the Padua prediction score and the Wells score for screening for DVT in COVID-19 cohort.

Conclusions: Compared with patients with ARDS caused by bacterial pneumonia, the incidence of DVT is higher by logistic model in patients with ARDS caused by COVID-19, and the risk factors for DVT are completely different. Our novel prediction model can aid early identifying patients with high risk for DVT.

Keywords: Acute Respiratory Distress Syndrome; Pneumonia, Bacterial; COVID-19; Deep Vein Thrombosis

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), constitute a major global burden of disease.[1] Coronavirus disease 2019 (COVID-19), like some other viruses, may also have significant impact on the hematopoietic and hemostatic systems resulting in thrombotic and bleeding complications.[2-5] Our previous study confirmed that infection of

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might result in an increased risk of VTE, especially the incidence of DVT increased rapidly in proportion to disease severity.[6] Then in another study we found that the incidence of DVT is extremely high in patients with ARDS and may be associated with adverse outcomes.[7]

However, the DVT risks in ARDS have not been compared between patients with COVID-19 and those with bacterial pneumonia. The aim of this study therefore was to compare the incidence and risks of DVT between patients with ARDS caused by COVID-19 and those by bacterial pneumonia, and to further test that the COVID-19 is an additional risk factor and provide some guidance for DVT in ARDS patients infected with COVID-19.[8]

Methods

Study Design and Population

This analysis was a retrospective cohort study. All of the COVID-19 subjects were confirmed by using results of laboratory tests and were hospitalized in West Branch of Union Hospital (affiliated with Tongji Medical College, Huazhong University of Science and Technology), Wuhan, China, one of the major designated referral and treatment hospitals for critically ill adult patients (≥18 years old) with COVID-19 from January 29, 2020, to February 29, 2020, in accordance with the World Health Organization's interim guidance. The bacterial pneumonia ARDS cases were from a single-center retrospective cohort study of patients (≥18 years old) at Beijing Chao-Yang Hospital, Beijing, China. All of the cases were confirmed by using laboratory test results, and corresponding patients were hospitalized from January 1, 2015, to June 30, 2021. All of the patients met the criteria of the Berlin definition for diagnosis of ARDS.[9]

The exclusion criteria include: active malignant tumor, cerebral stroke, acute myocardial infarction, serious trauma, major operation lasting longer than 45 minutes, fracture of lower limb, and joint replacement for hip or knee. Patients with a survival time less than 3 days and patients without lower extremity venous compression ultrasound data were also excluded.

The first ultrasound examination was performed within 1-3 days after the diagnosis of ARDS, and then the ultrasound examination was reexamined again according to the patient's condition. After intensive treatment, if the patient remained unstable because of conditions such as unexplained hypoxemia or cardiac insufficiency, he or she should be reexamined by ultrasound. If there was more than one ultrasound scan for a single patient, all the results were recorded. Patients were divided into a DVT and a non-DVT group according to the results of the venous compression ultrasound of the lower extremities. The flow chart is shown in Figure 1 (A, B).

The study was approved by the Union Hospital, affiliated with Tongji Medical College, Huazhong University of Science and Technology (2020-0197) and the ethics committees of the Beijing Chao-Yang Hospital (2020-ke-429), and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Clinical Data

We analyzed the medical records of the enrolled patients. Data, which included demographic information, clinical history, vital signs, laboratory findings, treatments, complications, and outcomes of the patients

during hospitalization, were collected and analyzed. We analyzed the survival rates of all patients within 28 days after a diagnosis of ARDS. For patients discharged within 28 days, we followed up by telephone concerning their survival status after discharge.

Ultrasound Assessment

Bedside ultrasound examinations were performed using a portable color ultrasound scanner (CX50, Philips Medical Systems, the Netherlands, equipped with an L12-3/S5-1 probe or EPIQ 7C, Philips Medical Systems, Andover, MA, equipped with an L12-5/S5-1 probe or a Mindray portable Ultrasound M9, GD, China, equipped with an L10-3 probe). The lower extremity venous compression ultrasound was obtained from the institution's Picture Archiving and Communication System. The levels of DVT included the bilateral common femoral, deep and superficial femoral veins, the popliteal veins, and the anterior tibial, posterior tibial, peroneal, and calf muscle veins.

Definitions

ARDS was defined according to the Berlin definition.[9] COVID-19 was diagnosed according to the Chinese Management Guideline for COVID-19 (version 6.0).[10] Bacterial pneumonia, including community-acquired pneumonia and hospital-acquired pneumonia, was diagnosed according to the Clinical Practice Guidelines of the Infectious Diseases Society of America and the America Thoracic Society.[11,12] A distal thrombosis was defined as a thrombosis in the veins of the calf muscle or in at least 1 branch of the 3 pairs of deep calf veins (anterior tibial vein, posterior tibial vein, or peroneal vein); a proximal thrombosis was defined as a thrombosis in the popliteal vein or above. The Padua prediction score was defined according to the Barbar model.[13] The Wells score for DVT was defined according to the Di Nisio model[1]. We applied the Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ score and the Sequential Organ Failure Assessment (SOFA) score to assess the severity of disease.[14,15]

Statistical Analyses

Categorical variables were described as number and percentage (%) and continuous variables, as mean, standard deviation, median, and interquartile range. The Shapiro-Wilk test was used to verify normality. Differences between the DVT and the non-DVT groups were assessed by a two-sample *t*-test for normally distributed continuous variables, the Mann-Whitney *U* test for non-normally distributed continuous variables, and the χ^2 or Fisher exact test for categorical variables. We took death as the competitive risk and plotted 28-day cumulative incidence curves (points estimates with 95% confidence interval [CI]) for COVID-19 and bacteria ARDS patients, and used Fine-Gray competitive risk model to explore the risk factors of DVT under COVID-19 and bacterial pneumonia subgroups respectively. The adjusted hazards ratio (HR) with 95% CI was reported. To further evaluate the observed differences in risk factors for DVT between COVID-19 and bacterial pneumonia, we utilized interaction terms between ARDS type and each risk factor. A receiver operating characteristic (ROC) analysis was performed to calculate the sensitivity and specificity of risk factors for screening for DVT. The comparison methods of diagnostic accuracy for

screening for DVT in the ARDS cohort caused by COVID-19 are as follows: Patients were split by generating random numbers to produce a training data set (n*0.7) and a validation data set (n*0.3). The area under receiver operating curves (ROC-AUCs) for different risk factors were compared using the method of DeLong et al.[16] In order to enhance the practicability of the prediction model, we drew a nomogram based on the predictors selected from COVID-19 ARDS population. Calibration was evaluated with calibration plots, which used the bootstrap method of 1000 resampling to show the relationship between the actually observed frequency and the prediction probability through a graph. In a well-calibrated model, the prediction should fall on a 45-degree diagonal. All statistical analyses were performed using the Statistical Analysis System, version 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed; $P < 0.05$ was considered statistically significant.

Results

A total of 240 patients with ARDS were enrolled in this study; 105 patients were considered to belong to the COVID-19 ARDS cohort and 135 patients to the bacterial pneumonia ARDS cohort. The flow chart is shown in Figure 1 (A, B).

Ultrasound scan for screening for DVT

Lower extremity venous compression ultrasound scanning was performed whenever feasible for 240 patients regardless of clinical symptoms of the lower limbs (Figure 1B), and the median number of ultrasound scans was 1 (range, 1-5). Eighty (80/240) developed DVT was found and the other 160 was a negative result at the first ultrasound scan. Subsequently, 75 patients underwent more than one ultrasound scans, for whom 36 developed DVT and 39 had no DVT with 2 (range, 2-5) ultrasound examinations. The interval from the diagnosis of ARDS to the occurrence of DVT in the 36 developed DVT group was 8 (3, 14) days, and the interval from the diagnosis of ARDS to the last ultrasound examination in the 39 non-DVT group was 10 (5, 16) days. There was no difference between the two groups ($P = 0.344$). Finally, of the 240 patients, 116 (48.3%) developed DVT, including 22 with proximal DVT and 94 with distal DVT, 77 of whom had muscular calf vein thrombosis only. The incidence of asymptomatic DVT was 94 (39.2%) including 15 (6.3%) proximal DVT and 79 (32.9%) distal DVT, of whom muscular calf vein thrombosis accounted for 67 (27.9%). For all the 240 patients, the interval from the diagnosis of ARDS to the occurrence of DVT in DVT group was 7 (4, 12) days, and the interval from the diagnosis of ARDS to the last ultrasound examination in non-DVT group was 8 (3, 14) days. There was no difference between the two groups ($P = 0.725$). Six patients were clinically suspected of having PE; 4 were further confirmed by computed tomography pulmonary angiography (CTPA) examination. (Table 1 and e-Table 1)

Demographic and clinical characteristics of patients in COVID-19 and Bacterial pneumonia ARDS cohorts

Of the 240 patients with ARDS, 105 were infected with COVID-19 (age [63.6 ± 13.1] years, male 60 [57.1%]), 135 with bacterial pneumonia (age [64.8 ± 15.1] years, male 101 [74.8%]). Compared with

patients with bacterial pneumonia, patients with COVID-19 had lesser underlying diseases (smoke, chronic respiratory disease, cerebral vascular disease, and chronic kidney disease) lower APACHE Ⅱ scores and lower SOFA scores ($P < 0.05$ for all). There was no difference in PaO_2/FiO_2 ratios between two groups ($P = 0.858$). More patients with COVID-19 received therapy of glucocorticoids, immunoglobulin, vasoactive drugs and VTE prophylaxis ($P < 0.05$ for all). There was significantly higher incidence of DVT (57.1% vs 41.5%; $P = 0.016$) and proximal DVT (15.2% vs 4.4%; $P = 0.004$) in patients with COVID-19 than those with bacterial pneumonia. (Table 1)

The 28-day cumulative incidence curves of DVT and 28-day cumulative death curves in COVID-19 and Bacterial pneumonia ARDS cohorts

Took death as competitive risk, the 28-day cumulative incidence rate (95% CI) of DVT in patients with ARDS caused by COVID-19 and by bacterial pneumonia were 85.3% (66.6 %, 92.3%) and 62.7 % (48.1 %, 72.0 %) respectively. There was no significant difference between the two groups ($P = 0.220$). (Figure 2)

Independent predictors of DVT in patients with ARDS caused by COVID-19 and Bacterial Pneumonia

Took death as competitive risk, we used Fine-Gray competitive risk model to explore the risk factors of DVT under COVID-19 and bacterial pneumonia subgroups respectively (Table 2). Of the 105 ARDS patients with COVID-19, the independent contributors to DVT were CKMB levels (HR, 1.014; $P = 0.003$), PaO_2/FiO_2 ratios (HR, 0.997; $P = 0.079$), and D-dimer levels (HR, 2.975; $P = 0.041$), whereas in the bacterial pneumonia ARDS group, DVT was independently associated with serum creatinine levels (HR, 0.951; $P = 0.040$) and IMV (HR, 2.750; $P = 0.004$). Serum creatinine levels were independently associated with DVT for bacterial pneumonia ARDS patients instead of COVID-19 ARDS patients, nevertheless, the interaction analysis displayed no significant difference between these two groups (test for interaction, $P = 0.090$; Figure 3). However, the incidence of DVT increased more significantly with rising CK-MB levels in patients with COVID-19 than those with bacterial pneumonia (test for interaction, $P = 0.027$; Figure 4).

Comparison of diagnostic accuracy for screening for DVT of different ROCs in ARDS cohort caused by COVID-19

We propose three new ways of combining forecasting models for screening for DVT based on the significant risk factors in patients with ARDS caused by COVID-19. The sensitivity and specificity of the corresponding ROC curves of the proposed models were not inferior to those of the Padua prediction score and the DVT Well score for screening for DVT (Figure 5 A - C).

Nomogram for screening for DVT of prediction variables

In order to increase the practicability of the prediction model, we draw a nomogram based on the selected predictors (Figure 6). There are three prediction variables. The corresponding points can be obtained by making a vertical line upward based on the value of each variable. The total points can be obtained by

adding the points of the three variables. The probability of survival (without DVT) in 5 days, 7 days and 14 days can be obtained by making a vertical line downward based on the total points.

Discussion

The investigations on the critically ill patients showed that different pathogenic types might account for the high prevalence of DVT.[17-19] Meanwhile, hypercoagulability appears to be a typical feature of patients with COVID-19.[20] However, no previous study has compared the DVT risks between the two groups of COVID-19 pneumonia patients and bacterial pneumonia patients. To our knowledge, this study is the first description of DVT difference and hospital mortality in ARDS patients with COVID-19 pneumonia vs Bacterial pneumonia.

In this retrospective cohort study, the 28-days incidence of DVT in the COVID-19 pneumonia patients with ARDS was higher than that in the bacterial pneumonia cohort (57.1% vs 41.5%). Several reasons probably account for the notably higher incidence of DVT in the COVID-19 pneumonia patients with ARDS. First, it is known that the coagulation pathway can be activated through the contact system and kallikrein/kinin system (KKS).[21] But it is worth recalling that the KKS is dysregulated by binding of SARS-CoV-2 to the angiotensin-converting enzyme II (ACE-2) receptor of vascular endothelium, this may be a more reasonable mechanism for the noted interaction between COVID-19 and DVT.[22,23] Second, coronavirus infections may be a trigger for VTE, and several pathogenetic mechanisms, which include endothelial dysfunction, characterized by increased levels of von Willebrand factor; systemic inflammation, by Toll-like receptor activation; and a hypercoagulable state, by tissue factor pathway activation.[24] Third, high plasma levels of proinflammatory cytokines were observed in the severe COVID-19.[25] The direct activation of the coagulation cascade by a cytokine storm is conceivable. Lastly, the immune-mediated damage according for the acute coronavirus infections may partially contribute.[26] Although it is worth noting that after taking death as competitive risk, Fine-Gray test showed no significant difference in the 28-day cumulative incidence of DVT between these two groups (P=0.220). The results showed that the value of the point estimation was different between these two groups. Meanwhile, the confidence intervals were wide. One reason could be the fact that our sample size was small, which may reduce the power of test.

Fine-Gray competing risk analysis in the bacterial pneumonia group showed that serum creatinine levels and IMV were associated with DVT, whereas there was a stronger association between CK-MB levels, PaO_2/FiO_2 ratios, D-dimer levels and DVT in COVID-19 group. To further figure out the observed differences in risk factors for DVT between COVID-19 and Bacteria, we utilized interaction terms between COVID status and each risk factor, which suggested that CKMB levels might be independent predictor of DVT in the COVID-19 group compared with bacterial pneumonia.

The incidence of DVT in the COVID-19 pneumonia patients with ARDS increased with the raising of the CK-MB levels. Notwithstanding the incomplete knowledge on its pathophysiology, the mainly suggested mechanisms are: heart and arterial vascular system injury due to increased oxygen demand

but in the context of hypoxemia triggered by cytokine storm and systemic immune response, which were most frequently encountered among patients with COVID-19 cases.[27-32] Likewise, it has been hypothesized that a direct viral toxicity through the interaction with ACE-2 receptors highly expressed by some pericytes.[29] So considering comprehensively above-mentioned factors, it is revealed that severe COVID-19 cases have elevated levels of biomarkers of cardiovascular system injury such as CK-MB. Meanwhile, it is indicated that CK-MB itself might be regarded as a predict marker of DVT. A thorough assessment should therefore be conducted in the follow-up of severe COVID-19 patients with ARDS and adequate measures should be managed to detect, diagnose, and treat VTE at their early stage, considering the high-risk of developing DVT.

We found that serum creatinine may modify the association between the COVID-19 and bacterial pneumonia group and the risk of DVT. The association was stronger among the ARDS patients with bacterial pneumonia. Contrary to findings from our research, some studies have demonstrated that renal impairment is independent risk factor for DVT.[33,34] It is worth noting that other studies have shown that LWMH may have different levels of bioaccumulation in the case of renal insufficiency.[35,36] So, we speculate that the same dose of LWMH may play a stronger role in the prevention of DVT because of renal insufficiency. The study by Cook *et al.* indicated that the incidence of DVT for patients with renal insufficiency in ICU who received dalteparin 5,000 IU once daily was 5.1%,[37] which was far lower than that in the overall population of critically ill patients who received prophylaxis recommended by the guidelines.[38,39] However, we did not find significant association between serum creatinine levels and DVT in patients with COVID-19 pneumonia. There are a number of factors, but one of the biggest reasons is that the patients with COVID-19 had lower serum creatinine levels, lower APACHE Ⅱ scores and lower SOFA scores compared with those with bacterial pneumonia, the protective effect on DVT of higher levels of serum creatinine was weakened obviously. Unfortunately, due to the retrospective nature of the study, on the one hand, the decrease of LWMH metabolism in patients with AKI and higher level of serum creatinine was based on the conjecture of clinical data analysis, on the other hand, we did not monitor the dynamic change of blood coagulation and detect the activities of plasma levels of coagulation/anticoagulation factors in patients with venous thromboembolism.

Multivariant analysis showed an association only among CK-MB levels, PaO_2/FiO_2 ratios, D-dimer levels $\geq$ 0.5 μg/mL, and DVT in COVID-19 cohort. Using a ROC analysis, a combination of the corresponding indicators mentioned above yielded a sensitivity of 66.7 % and a specificity of 82.4% for prediction for DVT in these hospitalized patients with COVID-19, and the AUC-ROC was 0.804. Statistical test showed that the prediction power of this model was significantly better than DVT Wells score in COVID-19 patients with ARDS. Although there was no significant difference in AUCs between the prediction models, the prediction sensitivity and specificity of the combined model were improved compared with Padua prediction score. This combined prediction model has also been identified to depict effectively for screening for DVT in this group by drawing a nomogram and its calibration curve. A possible reason for the superiority of this new prediction model is that the commonly used predictive scoring systems such as Padua score and Wells score apply to the general medical and surgical patients in hospital. As a

serious clinical pathophysiological syndrome with an overwhelming inflammatory response and coagulation abnormalities, ARDS caused by COVID-19 has unique clinical characteristics and serious complications.

The prognosis in ARDS patients with COVID-19 pneumonia analyses showed that DVT was associated with adverse outcomes compared with Bacteria ARDS cohort, including length of stay in hospital ($P < 0.001$). To validate the prognosis of DVT in these two cohorts, we further plotted 28-day cumulative incidence curves of DVT, with death as the competitive risk, and found that the mortality increased with rising incidence of DVT, especially in the COVID-19 cohort. The worse outcome in COVID-19 cohort may be a result of the inflammatory response to SARS-CoV-2 infection resulting in thrombo-inflammation and driving thrombosis.[40] Coagulation activation could also have been associated with a sustained inflammatory response.[41] In addition, there is a 50% chance for patients with untreated proximal DVT to develop symptomatic PE within 3 months.[42] PE might aggravate the hypoxemia of ARDS patients and then result in lower actuarial survival rates. If there was any clinical suspicion of PE, a CTPA would be considered and obtained, if possible. Unfortunately, due to the critical condition of ARDS patients, CTPA examination was restricted. We only underwent CTPA examination on 1 patient with highly suspected PE and 1 patient was diagnosed with PE in the COVID-19 cohort. By contrast, in the bacterial pneumonia cohort we had performed 5 CTPA examinations, and 3 patients was diagnosed with PE.
Using the figures given above, we may significantly underestimate the incidence of PE. The presence of PE associated with DVT may also be a cause of poor survival in patients with DVT. Although these findings are not surprising, given that our patient population represented older, severely ill patients at high risk for DVT, with other organ-related diseases, our data raised the question of screening for DVT, risk stratification, and potential VTE prophylaxis to improve outcomes in ARDS patients infected with COVID-19 and those infected with bacterial pneumonia.

This study has some limitations. First, this was a retrospective study that included data from two independent single-center cohorts, which may have resulted in selection bias. Second, our sample size was small, which may underestimate the influence on DVT of factors such as obesity, being bedridden, and the insertion of a central venous catheter. Third, due to the critical condition of patients with ARDS, CTPA examinations were restricted, which significantly underestimated the incidence of PE. Finally, the data from the bacterial pneumonia cohort originated from a 6-year span, whereas the data from the COVID-19 cohort originated from only a 1-month span, which may also have affected the study's results.

Conclusions

Compared with patients with ARDS caused by bacterial pneumonia, the incidence of DVT is higher by logistic model in patients with ARDS caused by COVID-19, and the risk factors for DVT are completely different. The prediction model based on the combination of CK-MB levels, PaO_2/FiO_2 ratios, and D-dimer levels has been identified effectively for screening for DVT in ARDS patients with COVID-19. Future studies investigating the correlation between DVT and COVID-19 should focus on the COVID-19 and its

implications for thrombosis and anticoagulation, which could provide more experience and evidence regarding COVID-19 treatment measures.

Abbreviations

ACE-2, angiotensin-converting enzyme II; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AUC, area under the curve; BUN, blood urea nitrogen; CI, confidence interval; CK, creatine kinase isoenzyme; COVID-19, coronavirus disease 2019; CTPA, computed tomography pulmonary angiography; CVC, central venous catheterization; DBIL, direct bilirubin; DVT, deep vein thrombosis; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; IQR, interquartile range; KKS, kallikrein/kinin system; LDH, lactate dehydrogenase; MV, mechanical ventilation; OR, odds ratio; PaO_2, partial pressure of arterial oxygen; PCT, procalcitonin; PE, pulmonary embolism; PT, prothrombin time; ROC, receiver operating characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TBIL, lower total bilirubin; VTE, venous thromboembolism; WBC, white blood cell.

Declarations

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Authors' contributions

NC and CJ designed the study, collected clinical data, analyzed the data, and wrote the manuscript. CY analyzed the data and wrote the manuscript. XF and LZ helped manage the research, performed the statistical analyses, and revised the paper. NC、CJ and CY contributed equally to this article and share first authorship. XF and LZ contributed equally to this article and share corresponding authorship. All authors read and approved the final manuscript.

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Availability of data and materials

All data analyzed during the study are presented in the main manuscript. The anonymous dataset is available from the corresponding author upon reasonable request.

Ethics and approval and consent to participate

This retrospective study involving human participants was approved by the Union Hospital, affiliated with Tongji Medical College, Huazhong University of Science and Technology (2020-0197) and the ethics committee of the Beijing Chao-Yang Hospital, Capital Medical University (2020-ke-429) and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic and clinical characteristics of patients with ARDS caused by COVID-19 and Bacterial pneumonia

Characteristic	Total (N = 240)	Bacterial pneumonia (N = 135)	COVID-19 (N = 105)	*P* value
Age, y	64.3 ± 14.2	64.8 ± 15.1	63.6 ± 13.1	0.522
Male	161 (67.1)	101 (74.8)	60 (57.1)	0.004
BMI, kg/m^2	23.6 ± 3.4	23.7 ± 3.9	23.6 ± 2.7	0.977
Bed time ≥ 3 days	189 (78.8)	117 (86.7)	72 (68.6)	0.001
Hospital stays, d	23 (13, 38)	18 (11, 29)	31 (18, 41)	< 0.001
ARDS to DVT or last US scan, d	7 (3, 13)	5 (2, 12)	10 (6, 14)	< 0.001
Median number of US scans	1 (1, 2)	1 (1, 2)	1 (1, 1)	< 0.001
DVT Wells score	1 (1, 2)	1 (1, 1)	1 (0, 2)	0.004
Padua prediction score	5 (5, 6)	5 (5, 6)	5 (4, 6)	0.171
APACHE II score	16 (12, 23)	22 (17, 27)	11 (11, 13)	< 0.001
SOFA score	5 (4, 10)	6 (4, 10)	4 (3, 12)	0.012
Underlying disease				
Smoke	84 (35.0)	76 (56.3)	8 (7.6)	< 0.001
Chronic respiratory disease	32 (13.3)	25 (18.5)	7 (6.7)	0.007
Hypertension	103 (42.9)	60 (44.4)	43 (41.0)	0.588
Coronary heart disease	39 (16.3)	24 (17.8)	15 (14.3)	0.467
Diabetes	54 (22.5)	33 (24.4)	21 (20.0)	0.413
Cerebral vascular disease	31 (12.9)	27 (20.0)	4 (3.8)	< 0.001
Chronic liver disease	5 (2.1)	2 (1.5)	3 (2.9)	0.656
Chronic kidney disease	16 (6.7)	13 (9.6)	3 (2.9)	0.037
Symptoms of onset				
Fever	222 (92.5)	128 (94.8)	94 (89.5)	0.123
Cough	188 (78.3)	114 (84.4)	74 (70.5)	0.009

Dyspnea	198 (82.5)	130 (96.3)	68 (64.8)	< 0.001
DVT symptoms	46 (19.2)	27 (20.0)	19 (18.1)	0.710
Edema of lower extremities	42 (17.5)	27 (20.0)	15 (14.3)	0.248
Leg pain	6 (2.5)	2 (1.5)	4 (3.8)	0.408
Arterial blood gas analysis				
PaO_2/FiO_2, mm Hg	135 (81, 195)	137 (80, 188)	130 (81, 197)	0.858
Hematologic and infection-related indices				
White blood cell count, $\times10^9$/L	10.9 (7.23, 16.0)	14.4 (10.1, 19.0)	8.1 (5.7, 10.9)	< 0.001
Neutrophil count, $\times10^9$/L	9.7 (5.9, 14.2)	12.8 (9.0, 17.3)	6.5 (4.2, 9.6)	< 0.001
Lymphocyte count, $\times10^9$/L	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	0.8 (0.5, 1.1)	0.528
Neutrophil-to-lymphocyte ratio	12.5 (7.1, 21.0)	15.1 (8.7, 23.7)	8.9 (4.7, 15.1)	< 0.001
Platelet count, $\times10^9$/L	190 (133, 263)	185 (115, 261)	190 (144, 270)	0.205
Hemoglobin, g/L	116 (99, 130)	112 (87, 130)	118 (108, 132)	0.021
C-reactive protein, mg/L	99.5 (51.8, 120.0)	120.0 (82.0,120.0)	58.0 (20.7, 99.5)	< 0.001
Serum procalcitonin, ng/L	0.8 (0.1, 4.2)	3.2 (1.2, 11.3)	0.1 (0.1, 0.4)	< 0.001
Biochemical test				
Total protein, g/L	57.6 (50.9, 63.2)	53.0 (47.0, 59.0)	60.8 (57.6, 65.3)	< 0.001
Albumin, g/L	26.3 (23.6, 29.9)	25.3 (23.0, 29.6)	27.3 (24.2, 30.2)	0.007
Aspartate aminotransferase, U/L	35.0 (25.5, 58.0)	40.8 (26.0, 71.7)	33.0 (24.0, 44.0)	0.008
Alanine aminotransferase, U/L	33.2 (19.6, 60.2)	29.7 (17.9, 58.8)	35.0 (26.0, 62.0)	0.101
Total bilirubin, μmol/L	14.2 (10.1, 20.3)	15.2 (10.7, 22.8)	13.6 (9.2, 17.0)	0.006
Direct bilirubin, μmol/L	4.8 (3.1, 7.3)	5.2 (3.3, 8.4)	4.5 (3.0, 6.2)	0.038

Lactate dehydrogenase, U/L	354.0 (234.3, 546.0)	350.0 (239.0, 624.8)	354.0 (224.0, 511.0)	0.360
Blood urea nitrogen, mmol/L	7.54 (4.80, 13.78)	10.21 (5.39, 17.42)	6.50 (4.21, 9.21)	< 0.001
Serum creatinine, μmol/L	73.5 (56.7, 125.8)	89.1 (62.4, 193.0)	64.3 (53.7, 75.5)	< 0.001
CK-MB, U/L	16.2 (10.8, 29.7)	16.2 (11.0, 26.9)	16.2 (10.0, 31.0)	0.812
Coagulation function				
D-dimer, μg/mL	1.8 (0.7, 4.6)	1.5 (0.6, 2.6)	2.8 (1.1, 8.0)	< 0.001
Prothrombin time, s	13.6 (12.60, 15.1)	13.5 (12.3, 15.2)	13.6 (12.7, 14.9)	0.193
Activated partial thromboplastin time, s	33.7 (29.7, 38.1)	32.1 (28.7, 35.7)	34.8 (32.5, 39.2)	< 0.001
DVT	116 (48.3)	56 (41.5)	60 (57.1)	0.016
Proximal DVT	22 (9.2)	6 (4.4)	16 (15.2)	0.004
Distal DVT	94 (39.2)	50 (37.0)	44 (41.9)	0.443
Muscular calf vein thrombosis only	77 (32.1)	38 (28.1)	39 (37.1)	0.139
Treatments				
Glucocorticoid therapy	90 (37.5)	40 (29.6)	50 (47.6)	0.004
Immunoglobulin therapy	56 (23.3)	3 (2.2)	53 (50.5)	< 0.001
CVC	82 (34.2)	45 (33.3)	37 (35.2)	0.758
CRRT	22 (9.2)	12 (8.9)	10 (9.5)	0.866
IMV	103 (42.9)	79 (58.5)	24 (22.9)	< 0.001
Sedative therapy	86 (35.8)	62 (45.9)	24 (22.9)	< 0.001
Vasoactive drugs	64 (26.7)	27 (20.0)	37 (35.2)	0.008
VTE prophylaxis	137 (57.1)	64 (47.4)	73 (69.5)	0.001
LMWH	117 (48.8)	55 (40.7)	62 (59.0)	0.005
LMWH + physical	80 (33.3)	40 (29.6)	40 (38.1)	0.168
Physical prophylaxis only	21 (8.8)	8 (5.9)	13 (12.4)	0.079

28-day mortality	73 (30.4)	46 (34.1)	27 (25.7)	0.163

Data are presented as mean ± SD, median (IQR), or n (%). *P* values comparing DVT and non-DVT groups were from a two-sample *t*-test, Mann-Whitney *U* test, χ^2 test, or Fisher exact test. $P < 0.05$ was considered statistically significant.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CK, creatine kinase isoenzyme; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; CVC, central venous catheterization; DVT, deep venous thrombosis; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; IQR, interquartile range; LMWH, low molecular weight heparin; PaO_2, partial pressure of arterial oxygen; PE, pulmonary embolism; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; US, ultrasound; VTE, venous thromboembolism.

Table 2 Predictors of DVT in patients with ARDS caused by COVID-19 and Bacterial pneumonia

Variable	Total ARDS (N = 240)		Bacterial Pneumonia (N = 135)		COVID-19 (N = 105)		*P* for Interaction With COVID-19 Status
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	
Age, per 10 years	1.165 (1.017, 1.334)	0.028	1.217 (0.991, 1.494)	0.061	1.015 (0.834, 1.236)	0.878	
Serum creatinine, per 10 μmol/L	0.955 (0.924, 0.987)	0.006	0.951 (0.907, 0.998)	0.040	0.988 (0.966, 1.010)	0.288	0.090
Serum procalcitonin, per 1 ng/L	1.001 (0.977, 1.025)	0.957	1.005 (0.975, 1.037)	0.734	1.316 (0.811, 2.134)	0.266	
CK-MB, per 1U/L	0.998 (0.994, 1.002)	0.328	0.994 (0.984, 1.004)	0.214	1.014 (1.005, 1.024)	0.003	0.027
PaO_2/FiO_2, per 1mmHg	0.996 (0.993, 0.999)	0.012	0.996 (0.991, 1.002)	0.166	0.997 (0.993, 1.000)	0.079	
D-dimer							
< 0.5 μg/mL	Reference		Reference				
≥ 0.5 μg/mL	1.911 (1.163, 3.139)	0.011	1.534 (0.768, 3.063)	0.225	2.975 (1.046, 8.464)	0.041	
IMV							
No	Reference		Reference				
Yes	1.676 (1.140, 2.464)	0.009	2.750 (1.389, 5.443)	0.004	0.823 (0.453, 1.497)	0.524	

Fine and Gray competing risk analysis was performed in the ARDS cohorts. The interactions of ARDS type (COVID-19 status) with age, serum creatinine level, serum procalcitonin level, CK-MB level, PaO_2/FiO_2, D-dimer level, and IMV were included in the analysis.

Abbreviations: ARDS, acute respiratory distress syndrome; CK, creatine kinase isoenzyme;

CI, confidence interval; COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; OR, odds ratio; PaO_2, partial pressure of arterial oxygen.

Figures

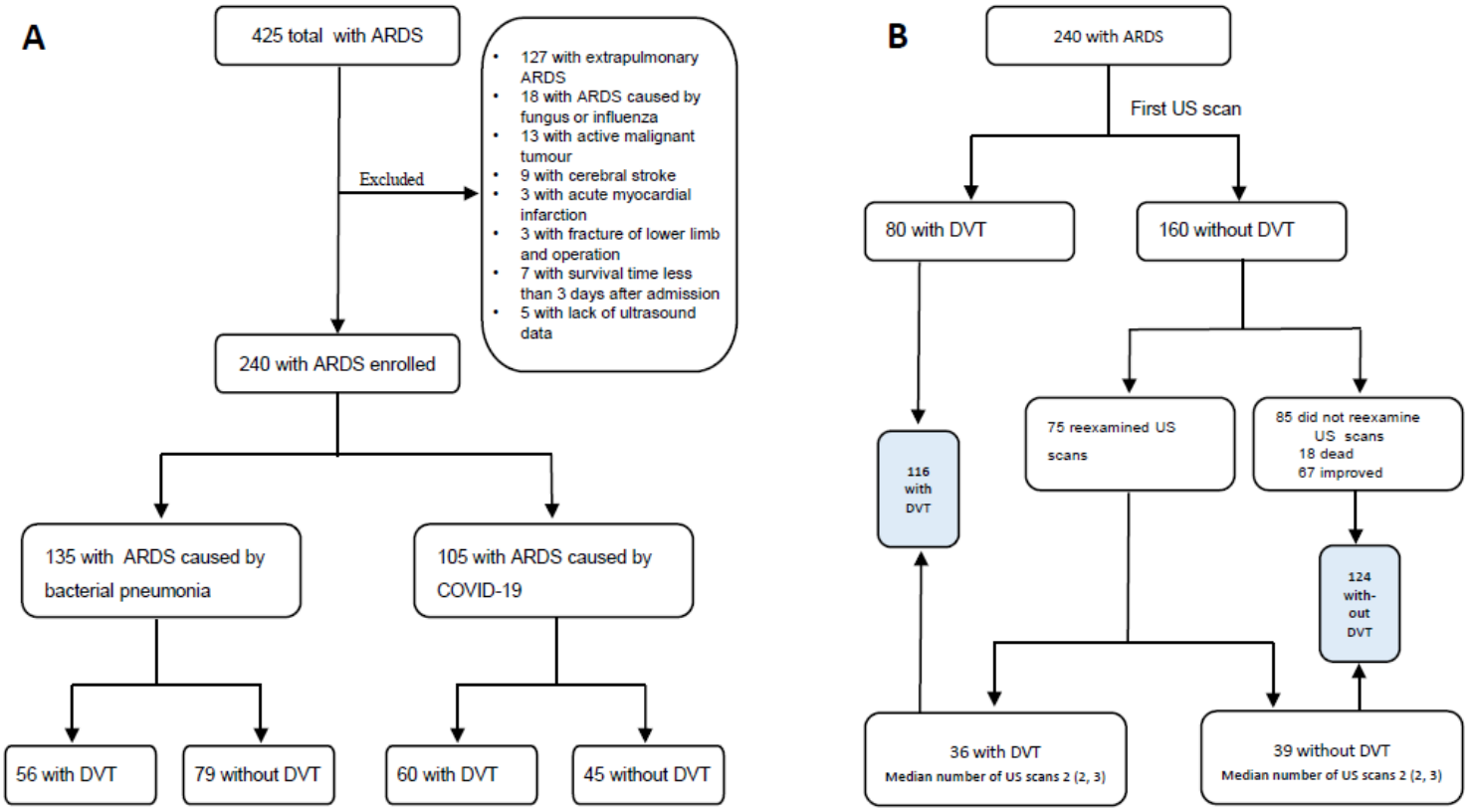

Figure 1

(A, B) Study flow chart.

A, flow chart for including patients; B, flow chart for screening for DVT.

The interval from the diagnosis of ARDS to the occurrence of DVT in the DVT group was 7 (4, 12) days, and the interval from the diagnosis of ARDS to the last ultrasound examination in the non-DVT group was 8 (3, 14) days. There were no differences between the two groups (P = 0.725).

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; US, ultrasound

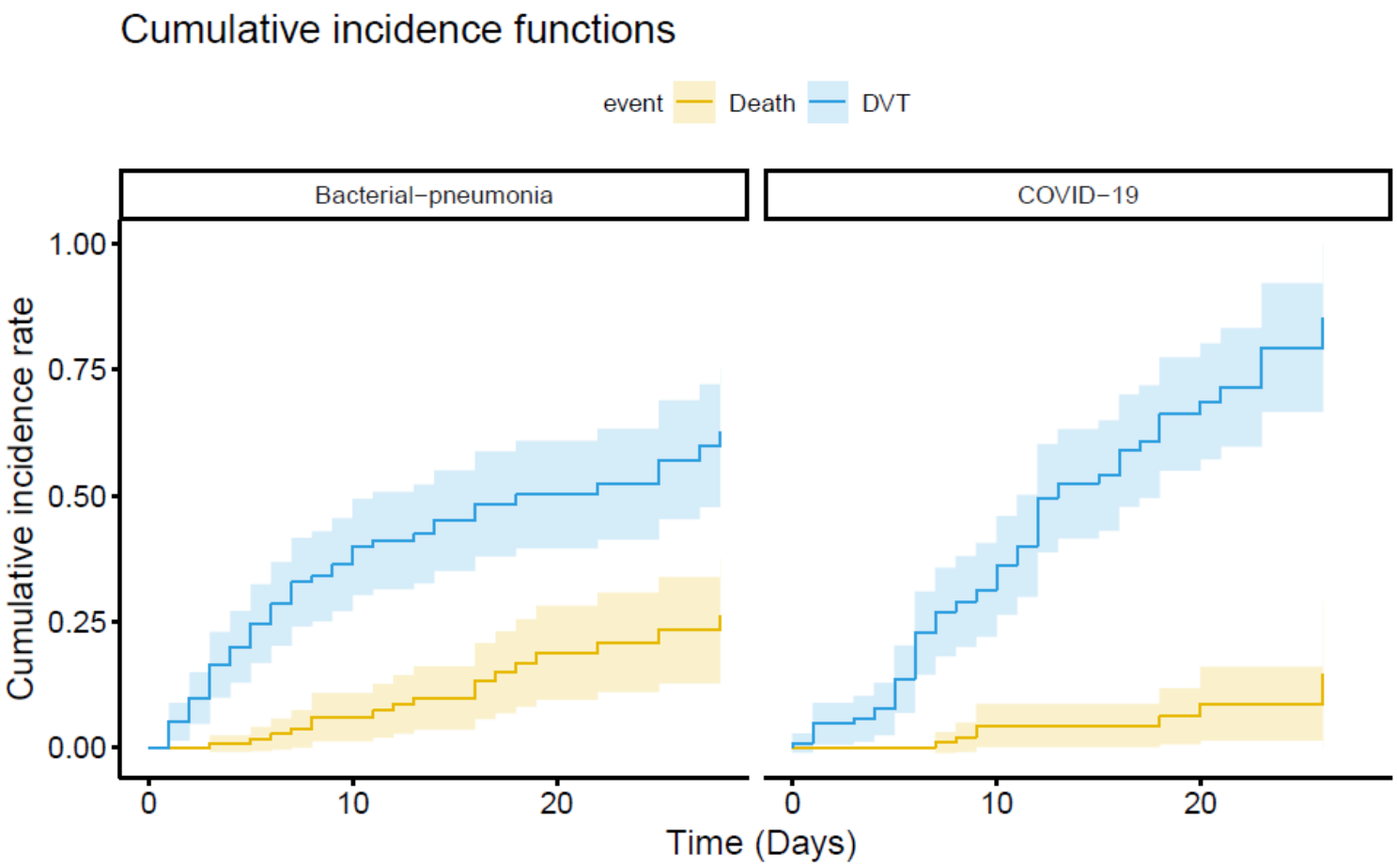

Figure 2

The 28-day cumulative incidence curves of DVT and 28-day cumulative death curves in COVID-19 and Bacterial pneumonia ARDS cohorts.

Took death as the competitive risk, Fine-Gray test showed no significant difference in the 28-day cumulative prevalence of DVT between COVID-19 ARDS and Bacterial pneumonia ARDS group (P = 0.220).

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis.

Figure 3

Prevalence of DVT decreased with serum creatinine levels in the Bacterial pneumonia ARDS group.

Serum creatinine levels were independently associated with DVT for Bacterial pneumonia ARDS patients (red line) instead of COVID-19 ARDS patients (green line), nevertheless, the interaction analysis displayed no significant difference between two groups (test for interaction, P = 0.090). Data are adjusted for age, serum PCT levels, CK-MB levels, D-dimer levels, PaO_2/FiO_2 ratios, and IMV.

Abbreviations: ARDS, acute respiratory distress syndrome; CK, creatine kinase isoenzyme; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; PaO_2, partial pressure of arterial oxygen; PCT, procalcitonin

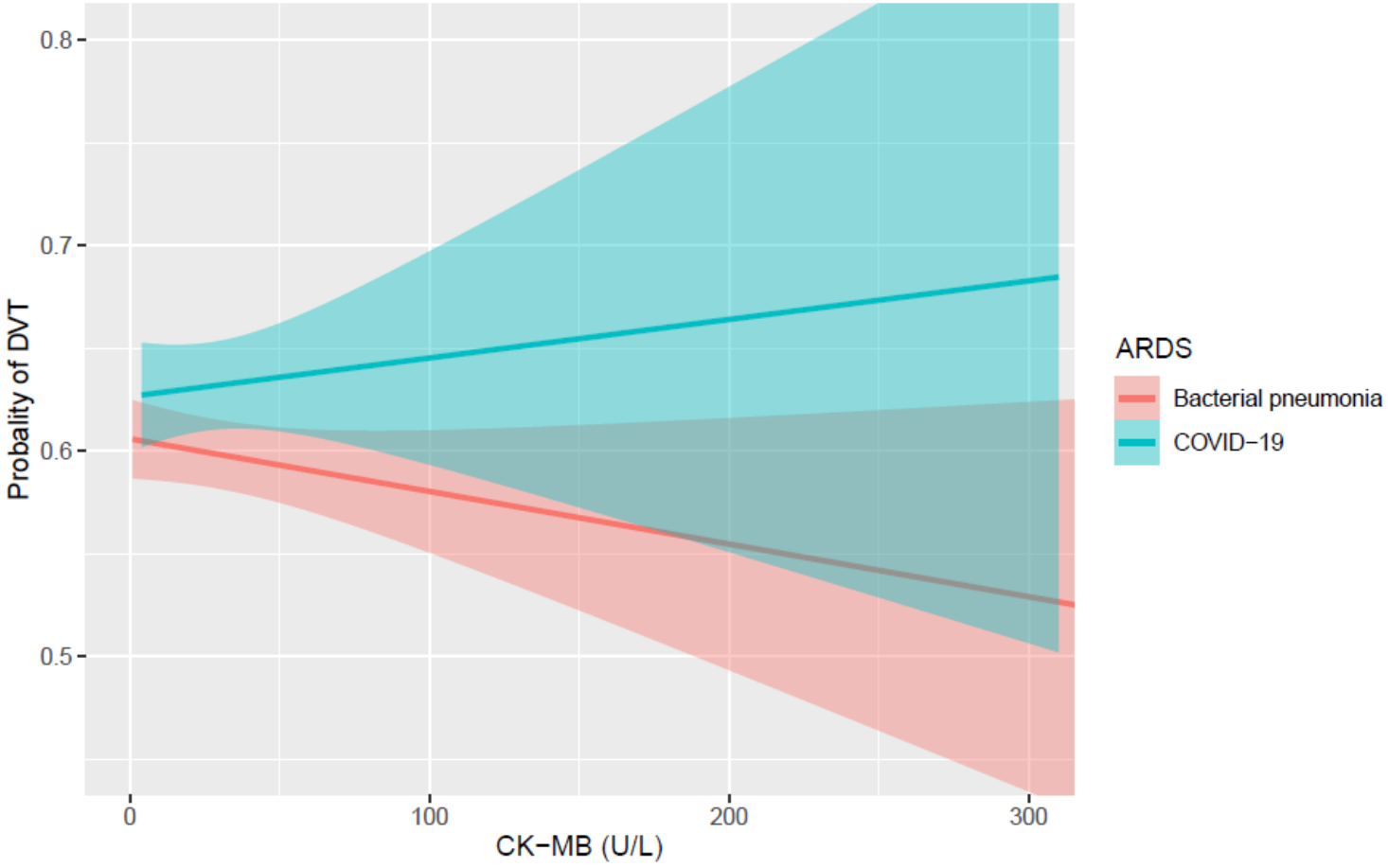

Figure 4

Prevalence of DVT increased with CK-MB levels only in the COVID-19 ARDS group.

The occurrence of DVT in COVID-19 ARDS group (green line) increased with rising CK-MB levels, whereas there was no association between DVT and CK-MB levels in Bacterial pneumonia ARDS group (red line; test for interaction, $P = 0.027$). Data are adjusted for age, serum creatinine levels, serum PCT levels, D-dimer levels, PaO_2/FiO_2 ratios, and IMV.

Abbreviations: ARDS, acute respiratory distress syndrome; CK, creatine kinase isoenzyme; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; PaO_2, partial pressure of arterial oxygen; PCT, procalcitonin

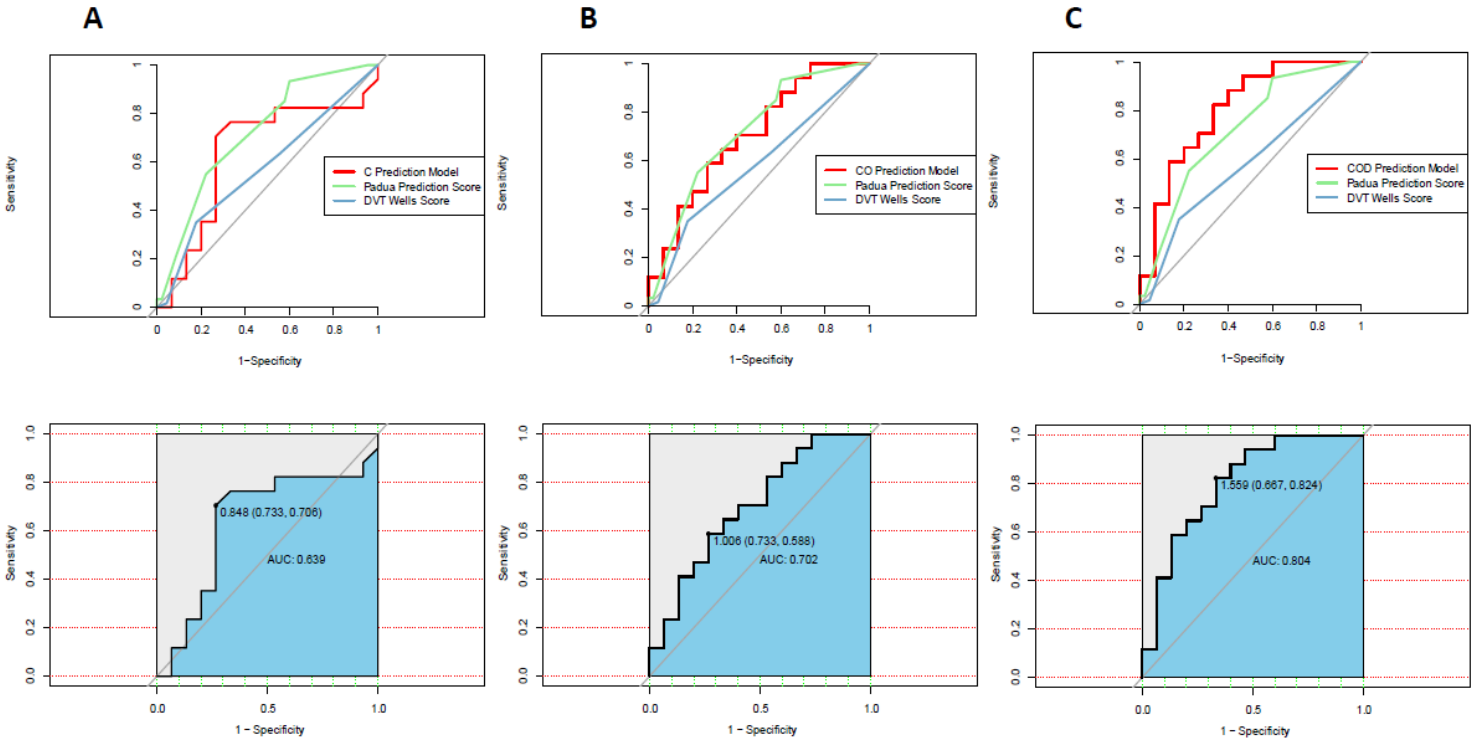

Figure 5

(A-C) Comparison of diagnostic accuracy for screening for DVT of different ROCs in ARDS cohort caused by COVID-19.

Patients were split by generating random numbers to produce a training data set (n*0.7) and a validation data set (n*0.3) in ARDS cohort caused by COVID-19.

A, the CK-MB level shows satisfactory forecasting ability for DVT (AUC = 0.639; 95% CI: 0.428 - 0.850; sensitivity: 70.6%; specificity: 73.3%) which has no significant difference compared with the DVT Wells score (AUC = 0.537; *P* = 0.587 for these two curves) and the Padua prediction score (AUC = 0.717; *P* = 0.515 for these two curves). B, the CO model including CK-MB and PaO_2/FiO_2 ratio shows satisfactory forecasting ability for DVT (AUC = 0.702; 95% CI: 0.516 - 0.887; sensitivity: 58.8%; specificity: 73.3%) which has no significant difference compared with the DVT Wells score (*P* = 0.242 for these two curves) and the Padua prediction score (*P* = 0.888 for these two curves). C, the COD model including CK-MB, PaO_2/FiO_2 ratio, and D-dimer level shows satisfactory forecasting ability for DVT (AUC = 0.803; 95% CI: 0.641 - 0.961; sensitivity: 66.7%; specificity: 82.4%) which significantly higher than that of the DVT Wells score (*P* = 0.020 for these two curves), and has no significant difference compared with the Padua prediction score (*P* = 0.363 for these two curves).

Abbreviations: CO = CK-MB + PaO_2/FiO_2 ratio; COD = CK-MB + PaO_2/FiO_2 ratio + D-dimer level; ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; CK, creatine kinase isoenzyme; DVT, deep vein thrombosis; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; ROC, receiver operating characteristic.

Figure 6

Nomogram for screening for DVT of prediction variables.

The nomogram was draw based on the selected three predictors. The corresponding points can be obtained by making a vertical line upward based on the value of each variable. The total points can be obtained by adding the points of the three variables. The probability of survival (without DVT) in 5 days, 7 days and 14 days can be obtained by making a vertical line downward based on the total points.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx
- SupplementaryFigure.pdf