Association of Padua prediction score with in-hospital prognosis in COVID-19 patients

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Abstract

Background: Nearly 20% novel coronavirus disease 2019 (COVID-19) patients have abnormal coagulation function. Padua prediction score (PPS) is a validated tools for venous thromboembolism (VTE) risk assessment. However, its clinical value in COVID-19 patients evaluation was unclear.

Methods: We prospectively evaluated the VTE risk of COVID-19 patients using PPS. Demographic and clinical data were collected. Association of PPS with 28-days mortality was analyzed by multivariate logistic regression and Kaplan-Meier analysis.

Results: 274 continuous patients were enrolled, with total mortality of 17.2%. Patients in high PPS group, with significantly abnormal coagulation, have a higher levels of interleukin 6 (25.27 pg/ml vs.2.55 pg/ml, P<0.001), prophylactic anticoagulation rate (60.7% *vs*. 6.5%, *P*<0.001) and mortality (40.5% *vs*. 5.9%, *P*<0.001) as compared with that in low PPS group. Critical patients showed higher PPS (6 score *vs*. 2 score, *P*<0.001) than that in severe patients. Multivariate logistic regression revealed the independent risk factors of in-hospital mortality included high PPS (OR: 7.35, 95%CI: 3.08 - 16.01), increased interleukin-6 (OR: 11.79, 95%CI: 5.45 - 26.20) and elevated d-dimer (OR: 4.65, 95%CI: 1.15 - 12.15). Kaplan-Meier analysis indicated patients with higher PPS had a significant survival disadvantage. Prophylactic anticoagulation in higher PPS patients show a mild advantage of mortality but without statistical significance (37.1% *vs*. 45.7%, *P*=0.42) .

Conclusion: Higher PPS associated with in-hospital poor prognosis in COVID-19

patients. Prophylactic anticoagulation showed a mild advantage of mortality in COVID-19 patients with higher PPS, but it remain need further investigation.

Background

The 2019 novel coronavirus disease (COVID-19) has spread to more than 100 countries or regions since the outbreak in December 2019 in Wuhan, China. Recent study revealed that the potential risk factors of older age, high SOFA score, and elevated d-dimer greater could help to identify patients with poor prognosis at an early stage [1]. The inflammatory process, cytokine storm, and lung injury that are associated with COVID-19 can put patients at an increased risk of venous thromboembolism (VTE). Previous reports indicated that nearly 20% COVID-19 patients have abnormal coagulation function, and almost all severe or critical patients have coagulation disorders [2, 3]. In severe or critical COVID-19 patients, symptom of pulmonary thromboembolism (such as dyspnea or shortness of breath) might be covered by the respiratory symptom of COVID-19, which raised the risk of misdiagnosis.

Recent small scale investigations showed that the incidence of VTE for COVID-19 patients in ICU were 25% to 31% [4, 5]. But it is uncertain the total incidences of thrombotic events in COVID-19 patients. Update, no report evaluated the VTE risk in COVID-19 patients with different disease severity, especially outside of ICU.

Although VTE appeared to be associated with death [6-8], the role of prophylactic anticoagulation in COVID-19 patients is unknown. Preliminary data show that in patients with severe COVID-19, anticoagulant therapy appears to be associated with lower mortality in the subpopulation meeting sepsis-induced coagulopathy criteria or with markedly elevated d-dimer [3, 9]. However, another study suggested that routine chemical venous thromboembolism prophylaxis may be inadequate in preventing venous thromboembolism in severe COVID-19 patients [10].

In this prospectively study, we assessed VTE risk of COVID-19 patients using PPS and analyzed its relationship with in-hospital mortality. We also evaluated the prophylactic anticoagulation in COVID-19 patients.

Methods

Study design and participants

This study included 274 adult patients who were lab-confirmed with COVID-19, according to WHO interim guidance in Wuhan Tongji Hospital from February 09 to March 09, 2020. Exclusion criteria were bleeding, hospital stay <7 days, lack of

information of coagulation drugs, age <18 years. Severe and critically ill COVID-19 patients were identified by reviewing and analyzing admission logs and histories of all available electronic medical records and patient care resources by two physicians. All patients were diagnosed with COVID-19 using pharyngeal swabs or throat swab specimens obtained for nucleic acid of SARS-CoV-2 PCR detection.This study was approved by the institutional review boards at Wuhan Tongji Hospital and The First Affiliated Hospital of Soochow University. Due to the rapid emergence of this infectious disease, the requirement for written informed consent was waived by the Ethics Commission.

Severe form COVID-19 patients should meet any one of the following: 1. Shortness of breath, respiratory rate (RR) $\geq$ 30 breaths/minute; 2. SaO_2 or $SPO_2 \leq$ 93% on room air; 3. $PaO_2/FiO_2 \leq 300mmHg$. Critical form is defined as one or more of the following: 1. Respiratory failure with the requirement of mechanical ventilation; 2. Shock; 3. Combined other organs failure requiring monitoring and treatment in intensive care unit. The clinical classification of severe form were determined by two trained physicians via analyzing the data of all available electronic medical records and patient care resources.

Data collection

The demographic, clinical, laboratory and outcome data were collected from the electronic medical records using a standardized data collection form. The primary outcome was the in-hospital mortality after hospitalization. All data were checked by

two physicians. Routine blood examinations included complete blood count and coagulation profile. Anticoagulant treatment group was defined as receiving unfractionated heparin (UFH, 100-200 IU/kg/day) or low molecular weight heparin (enoxaparin 100IU/kg/day or nadroparin 86 IU/kg/d) for 7 days or longer [11]. PPS was performed by two physician with 24h after admission as previously reported [12].

Statistical analysis

Categorical or continuous variables were presented as n (%) or median respectively. We used the X^2 test or Mann-Whitney U test to compare differences between survivors and non-survivors where appropriate. Survival curves were plotted using the Kaplan-Meier method using the log-rank test. Multivariate logistic regression models were used to determine the independent risk factors for in-hospital mortality after hospitalization. Data were analyzed using SPSS 25.0. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of total COVID-19 patients

In this single retrospective cohort study, 274 consecutive patients were enrolled in this study, including 47 death. For all of patients, the median age was 62·0 years (50-71 years), ranging from 18 years to 87 years (Table 1). The most common comorbidity was hypertension (99/274, 36.1%), followed by diabetes (45/27, 16.4%)

and cardiac disease (44/274, 16.1%). Total mortality was 17.2% (47/274). The median

PPS was 2 (IQR: 2, 5) and the total prophylactic anticoagulation rate was 24.1%

(66/274).

Clinical features of COVID-19 patients with higher PPS or lower PPS

As shown in Table 1, patients in higher PPS group (PPS ≥4) was older (72.0ys vs.

56.6ys, $P<0.001$), have more comorbidities and a higher WBC count (7.62×10^9/L vs.

5.80×10^9/L, $P<0.001$), a lower lymphocytes count (0.75×10^9 /L vs. 1.54×10^9/L,

$P<0.001$) and platelet count (192×10^9/L vs. 238×10^9/L, $P<0.001$) than that in lower

PPS group (PPS <4). They also have a higher levels of inflammatory markers,

including hs-CRP (37.7mg/L vs. 3.2mg/L, $P<0.001$) and IL-6 (25.27pg/ml vs.

2.55pg/ml, $P<0.001$). Patients in higher PPS group have a significantly higher levels

of PT (14.5s vs. 13.3s, $P<0.001$), d-dimer (2.49μg/L vs. 0.36μg/L, $P<0.001$) and

fibrinogen (5.14g/L vs. 3.74g/L, $P<0.001$), but their APTT levels were similar to that

in lower PPS group (38.10s vs. 37.80s, $P=0.123$).

As PPS has been recommended as validated tools for VTE risk assessment, patients

with higher PPS in our study received a higher rate of prophylactic anticoagulation

(60.7% vs. 6.5%, $P<0.001$). It is not surprised that their mortality was significantly

higher than that in VTE low risk group (40.5% vs. 5.9%, $P<0.001$), as higher PPS

reflecting a more popular co-morbidity and disease severity index.

Clinical features of critical and severe COVID-19 patients

As shown in table 2, severe patients were older (60ys *vs.* 40ys, $P=0.007$), have a

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higher fibrinogen levels (4.01 g/L *vs.* 3.27 g/L, *P*=0.031) and a higher Padua score (4

score *vs.* 1 score, *P*<0.001) than that in moderate patients. Critical patients were older

than severe patients (74ys *vs.* 60ys, *P*<0.001), and have a significantly higher levels of

PT (15.35s *vs.* 13.30s, *P*<0.001), d-dimer (5.38 μg/L *vs.* 0.52 μg/L, *P*<0.001) and

fibrinogen (5.14 g/L *vs.* 4.01 g/L, *P*=0.004). The PPS in critical patients were both

higher than that in severe patients (6 score *vs.* 2 score, *P*<0.001).

Prophylactic anticoagulation in COVID-19 patients

The total prophylactic anticoagulation ratio was 24.1% (66/274, Table 1), all of

whom were severe or critical form patients. The prophylactic anticoagulation ratio in

critical patients were higher than that in severe patients (77.9% *vs.* 10.5%, *P*<0.001,

Figure 1A). As PPS has been recommended as validated tools for VTE risk

assessment, patients with higher PPS in our study received a higher rate of

prophylactic anticoagulation (60.7% vs. 6.5%, *P*<0.001, shown in Table 1). Next, we

analyzed the role of prophylactic anticoagulation in VTE high-risk subgroup patients

(PPS ≥4). After subgroup analysis in patients with higher PPS, we found that

prophylactic anticoagulation show a mild advantage of mortality (decreased 18.8%) in

patients with VTE high-risk, but without statistical significance (37.1% *vs.* 45.7%,

P=0.42, Figure 1B).

Association of Padua score with prognosis

Multivariate logistic regression analysis (Figure 1C) revealed that the independent

risk factors of 28-days outcome included age (OR: 1.18, 95%CI: 0.64 - 3.28), higher

PPS (OR: 7.35, 95%CI: 3.08 - 16.01),decreased lymphocytes (OR: 2.97, 95%CI: 0.84-9.18), increased interleukin-6 (OR: 11.79, 95%CI: 5.45 - 26.20) and elevated d-dimer (OR: 4.65, 95%CI: 1.15 - 12.15). Kaplan-Meier analysis indicated that patients with VTE low risk (Padua score <4) had a significant survival advantage (Figure 1D, log-rank P <0.01) as compared to patients with VTE high risk(Padua score $\geq$ 4).

Discussion

This study firstly evaluated PPS and prophylactic anticoagulation in COVID-19, which suggested that high PPS was associated with poor prognosis and as an independent risk factor of in-hospital mortality. Prophylactic anticoagulation showed a mild advantage of mortality in VTE high-risk COVID-19 patients, but without statistically significant difference. This remain need further evidence.

Infection is an independent risk factors for VTE and should be considered as potential indications for prophylaxis [13]. Observational reports showed that coagulation disorders existed in COVID-19 patients, especially in severe and critical cases. Actually, PPS has been recommended as validated tools for VTE risk assessment [10]. PPS can help discriminate between medical patients at high and low risk of VTE [14]. The adoption of adequate thromboprophylaxis in high-risk patients during hospitalization leads to longstanding protection against thromboembolic events with a low risk of bleeding. Usage of PPS for VTE risk assessment was associated with a

higher rate of appropriate thromboprophylaxis prescription and a reduced VTE incidence [15-16]. Moreover, PPS-guiding management could reduce unnecessary radiation exposure, such as CT pulmonary angiography, through the implementation of the score. Our study is the first observation about PPS and prognosis in COVID-19 patients. It showed the higher PPS in severe and critical patients and its association with short-term prognosis. It was consistent to previous reports. Some data suggest that a positive PPS, reflecting a more popular co-morbidity and disease severity index, associated with early mortality in internal medicine patients [17-18]. This revealed that PPS was one of the potential tool for the evaluation of early prognosis in COVID-19.

Pharmacological thromboprophylaxis can signifcantly reduce the risk of VTE in the medical patient [19]. However, the role of prophylactic anticoagulation in COVID-19 patients is unclear. Some studies revealed the potential benefit of anticoagulant treatment in severe COVID-19 patients with higher VTE risk [3, 9, 13]. But other report indicated that routine chemical prophylaxis was inadequate in preventing VTE in severe COVID-19 patients [10]. In our study, prophylactic anticoagulation showed a mild advantage of mortality in patients with VTE high-risk (decreased 18.8%), but without statistical significance. This result was opposite to the previous reports which suggesting the potential benefit of anticoagulant treatment in severe COVID-19 patients with higher VTE risk [3, 9, 13]. This might be due to two reasons. First of all, the enrolled patients and the epidemiological characteristics were different. Most of COVID-19 patient in our study were severe or critical form, with more comorbidities and higher mortality. The subjects enrolled in previous report have a proportion of

60.6% with underlying diseases, which was lower than that in our study (69.7%) [9]. The mortality of heparin users in previous report was also lower than that in our study (30.3% vs. 37.1%) [9]. Secondly, the prophylactic anticoagulation rate in our study in VTE high-risk COVID-19 patients was only 60.7%, which was far lower than tumor patients and critically ills [18, 21]. VTE assessment was inadequate due to the insufficient medical resources at the peak period of COVID-19 pandemic in Wuhan. The usage of prophylactic anticoagulation was limited. So, a larger scale trail or randomized controlled trial might provided more convincing evidence for the clinical value of prophylactic anticoagulation in COVID-19.

There were several limitations in this study. First, it is a retrospective and single-center study. More data and large samples were needed to confirm the results and correct the bias. Second, the VTE or pulmonary embolism (PE) incidence in whole patients was uncertain. Despite that, our report evaluated the VTE risk and the benefit of prophylactic anticoagulation in COVID-19 patients. We described the high-risk of VTE and low prophylactic anticoagulation rate in severe and critical COVID-19 patients.

In conclusion, this study revealed that severe and critical COVID-19 patients have a high risk of VTE and higher Padua Score, which was associated with poor prognosis. Prophylactic anticoagulation show a mild decrease of mortality in patients with VTE high risk. However, the prophylactic anticoagulation remain need improvement in COVID-19 patients with VTE high risk.

Acknowledgment

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Tables:

Table 1. Baseline features of COVID-19 patients with different VTE risk.

Characteristics	All patients (n=274)	High PPS (≥4 score) (n=89)	Low PPS(<4 score) (n=185)	P
Age, y	62 (50,71)	72.0 (63.5,80.0)	56.5 (43.0,66.0)	<0.001
Male sex	145 (52.9%)	56 (62.9%)	89 (48.1%)	0.007
Comorbidity				
Hypertension	99 (36.1%)	46 (51.7%)	53 (28.6%)	<0.001
Diabetes	45 (16.4%)	18 (20.2%)	27 (14.6%)	0.223
Cardiac disease [a]	44 (16.1%)	25 (28.1%)	19 (10.3%)	<0.001
COPD	8 (2.9%)	6 (6.7%)	2 (1.1%)	0.026
Lab findings on admission				
WBC count, ×10^9 /L	6.17 (4.86,7.90)	7.62 (5.86,9.67)	5.80 (4.51,7.16)	<0.001
Lymphocyte count, ×10^9 /L	1.30 (0.86,1.81)	0.75 (0.48,1.17)	1.54 (1.16,1.92)	<0.001
Platelet count, ×10^9 /L	232 (167.00,303.75)	192 (121,303)	238 (194.0,305.5)	0.001
Creatinine level, μmol/L	68.00 (57.00,80.00)	74 (62,101)	65.0 (55.5,76.0)	<0.001
ALT level, U/L	23.00 (15.00,40.50)	26.0 (16.5,45.0)	22.00 (14.25,39.00)	0.186
hs-CRP, mg/L	8.70 (1.60,61.00)	37.7 (33.40,119.28)	3.2 (1.1,11.6)	<0.001
IL-6, pg/ml	4.60 (1.67,22.73)	25.27 (10.99,63.54)	2.55 (1.50,5.04)	<0.001
Coagulation parameters				
PT, s	13.50 (12.95,14.30)	14.5 (13.9,16.1)	13.3 (12.8,13.7)	<0.001
APTT, s	37.90 (35.00,41.25)	38.10 (34.63,43.60)	37.80 (35.30,39.95)	0.123
D-dimer, μg/L	0.68 (0.26,1.94)	2.49 (1.27,17.02)	0.36 (0.22,0.80)	<0.001
Fibrinogen, g/L	4.13 (3.16,5.41)	5.14 (3.98,6.21)	3.74 (3.02,4.94)	<0.001
PPS at admission	2 (2,5)	5 (5,6)	2 (2,2)	<0.001

Prophylactic anticoagulan	66 (24.1%)	54 (60.7%)	12 (6.5%)	<0.001
In-hospital mortality	47 (17.2%)	36 (40.5%)	11 (5.9%)	<0.001

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

Abbreviations: PPS, Padua prediction score; WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; IL-6, interleukin-6.

[a] Includes congestive heart disease and coronary atherosclerotic heart disease.

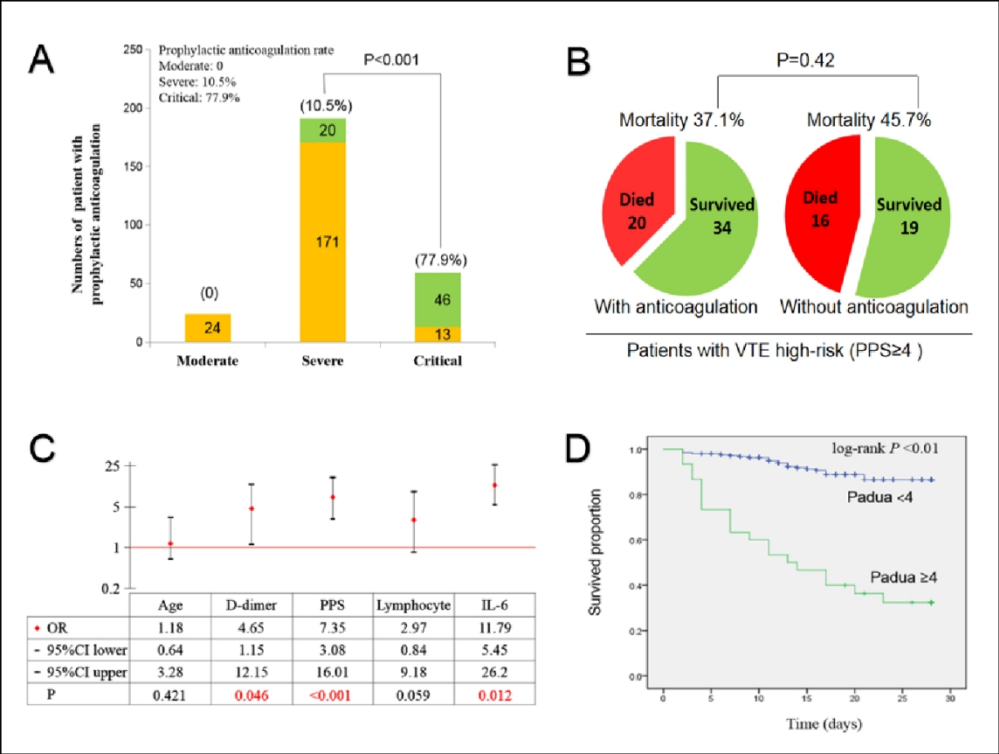**Table 2. Comparison of COVID-19 patients with different severity.**

Characteristics	Moderate (n=24)	Severe (n=191)	Critical (n=59)	P (moderate *vs.* Severe)	P (Severe *vs.* Critical)
Age, y	46.00 (37.00,56.75)	60.00 (47.75,69.00)	74.00 (64,80)	0.007	<0.001
Male sex	14 (58.3%)	93 (48.7%)	38 (64.4%)	0.374	0.008
Coagulation parameters					
at admission					
PT, s	13.35 (12.70,13.90)	13.30 (12.8,13.8)	15.35(14.08,16.45)	1.000	<0.001
APTT,s	37.10 (31.55,39.53)	37.8 (35.1,40.5)	39.10(36.05,43.70)	0.588	0.138
D-dimer, μg/L	0.28 (0.22,0.68)	0.52 (0.22,1.21)	5.38 (1.57,21.00)	0.177	<0.001
Fibrinogen, g/L	3.27 (2.30,4.08)	4.01 (3.18,5.28)	5.14 (3.94,6.45)	0.031	0.004
PPS at admission	1.00 (1.00,1.75)	2.00(2,3)	6.00 (5,6)	<0.001	<0.001
Prophylactic anticoagulation	0 (0%)	20 (10.5%)	46 (77.9%)	0.097	<0.001

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

Figure captions:

Figure 1: Relationship of PPS and prophylactic anticoagulation with in-hospital mortality in COVID-19. A: PPS and prophylactic anticoagulation in COVID-19 with different disease severity. B: Prophylactic anticoagulation show a mild decrease of mortality in VTE high-risk patients (PPS≥4). C: Multivariate logistic regression

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analysis of risk factors for 28-days mortality. D: Kaplan-Meier analysis of Overall

survival in COVID-19 patients by Padua score.

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