Awareness and Prophylaxis of Venous Thromboembolism in Patients with COVID-19: A National Cross-Sectional Survey in Epidemic Era

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Aim: Patients with acute infectious diseases are at an increased risk of venous thromboembolism (VTE). Clinicians should be aware of the VTE risk in patients with COVID-19, many of whom present with severe coagulation disorders.

Method: We used an online platform to conduct a cross-sectional questionnaire survey among doctors in mainland China in March 2020. The questionnaire was designed to figure out the clinician's current awareness of VTE prevention and detection rates, as well as the current status of VTE prophylaxis in patients with COVID-19.

Results: We collected 1,636 replies, of which 1,579 were valid. Among these, 991 (63%) clinicians were involved directly in frontline treatment. Most of the clinicians (1,492, or 94%) thought it was necessary to assess the VTE risk in patients with COVID-19. However, only 234 (24%) clinicians performed appropriate assessment during the COVID-19 outbreak. For patients with mild/moderate COVID-19, 752 (76%) clinicians would prescribe exercise and water to prevent VTE. For patients with severe COVID-19, 448 (45%) clinicians would prescribe mechanical devices if the patient had a high bleeding risk, and 648 (65%) clinicians would choose LMWH as prophylaxis if the patient had a low bleeding risk. The VTE detection rate was not that high in both mild/moderate and severe patients.

Conclusion: Although most clinicians recommended prescribing VTE prophylaxis to patients with COVID-19, the practice still needs to be improved. A real-world registry to investigate the true incidence of VTE, and the effect of prescribing appropriate prophylaxis for patients with COVID-19, is necessary in the future.

Key words: Venous Thromboembolism, COVID-19, Survey

Abbreviations and Acronyms: ABG = Arterial Blood Gas, ARDS = Acute Respiratory Distress Syndrome, COVID-19 = Coronavirus Disease 2019, CTPA = Computed Tomography Pulmonary Angiography, CUS = Compression UltraSonography, DIC = Disseminated Intravascular Coagulation, IPC = Intermittent Pneumatic Compression, ISTH = International Society of Thrombosis and Haemostasis, LMWH = Low-Molecular-Weight Heparin, PE = Pulmonary Embolism, VTE = Venous Thromboembolism

Highlights

- Most clinicians supported prescribing VTE prophylaxis to patients with COVID-19.
- The practice of prescribing VTE prophylaxis for patients with COVID-19 should be improved in China.
- A registry study is needed to investigate VTE prophylaxis in patients with COVID-19.
- Clinical experience and standard education have a profound impact on the selection of VTE prophylaxis.

Introduction

From December 2019, a series of unexplained pneumonia cases occurred in the city of Wuhan, Hubei Province, China[1]. On February 11, 2020, the World Health Organization (WHO) officially named the disease Coronavirus Disease 2019 (COVID-19). Since December 2019, millions of people have been infected with COVID-19; hundreds of thousands have died from virus-related complications. COVID-19 has become a global crisis.

According to reports from frontline doctors treating patients with COVID-19, nearly 20% of the recorded patients have presented with coagulation disorders, and almost all the patients who were severely affected suffered from coagulation dysfunctions. The pathological findings support that microthrombosis can occur in most organs of the patients infected with COVID-19 [2, 3]. A prospective study from Germany performed autopsies on 12 patients who died of COVID-19. They found that the incidence rate of deep venous thrombosis was 58%, and pulmonary embolism (PE) was the direct cause of death in four patients[4]. As an acute systematic infectious disease, COVID-19 is a significant risk factor for venous thromboembolism (VTE)[5]. The risk of VTE further increases when the patient is experiencing complications due to immobilization, an active malignancy, or obesity, especially in elderly patients or those with an underlying disease[6]. Some studies have associated VTE and COVID-19 [7], which should not be considered a random event.

VTE is a fatal disease, and 55-60% of the cases are directly related to hospitalization[8]. However, it is preventable and treatable if identified early. Risk-adapted prophylaxis for the patients will reduce the incidence and mortality of hospital-associated VTE, which may also contribute to reduced mortality in patients with COVID-19.

On February 9, 2020, the China Pulmonary Thromboembolism Registry Study (CURES) network issued the "Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines" (hereafter referred to as the "Statement")[9]. The "Statement," attached in **Supplementary Table 1**, recommended to screen all patients with COVID-19 for VTE risk and prescribe appropriate prevention strategies for them. However, the current clinical practice is still uncertain, and the VTE detection rate in patients with COVID-19 remains unknown. Therefore, in this study, we designed a survey to understand clinicians' current of the VTE risks among patients with COVID-19, the status of prophylaxis, and the estimated VTE detection rate.

Methods

In March 2020, a cross-sectional questionnaire survey was designed for online use by the CURES network. **Supplementary Table 2** presents the English version. The survey was distributed to clinicians through the Tencent online platform (supported by the Tencent Customer Research and User Experience Design Center) between March 13-17, 2020, in mainland China. It was divided into three parts. The first part recorded the baseline information of the physicians, including the following nine demographic variables: gender, age, department, job title, level of the hospital, location of the licensed hospital, present location, whether they had made VTE diagnosis and treatment and whether they were involved in treating patients with COVID-19. The second part consisted of seven questions that focused on the participant's risk assessment awareness and their backing of the "Statement." The third part consisted of 17 questions regarding the risk assessment, prophylaxis strategies, and VTE diagnosis in patients with COVID-19, specifically targeting doctors involved in treating patients with COVID-19. All participants provided informed consent, and the Ethics Committee of the China-Japan Friendship Hospital approved the study.

We analyzed the survey data with descriptive sta-

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Table 1. Baseline information

Characteristics	Total, n (%) N=1,579 (%)	Whether directly involved in COVID-19 treatment		
		Yes n (%) (N=991)	No n (%) (N=588)	P
Age, years				
<31	262 (17)	124 (13)	138 (24)	<0.01
31-60	1307 (83)	860 (87)	447 (76)	<0.01
> 60	10 (1)	7 (1)	3 (1)	0.75
Sex				
Male	766 (49)	552 (56)	214 (36)	<0.01
Female	813 (52)	439 (44)	374 (64)	<0.01
Title				
Junior Residents	228 (14)	104 (11)	124 (21)	<0.01
Senior Resident	467 (30)	307 (31)	160 (27)	0.12
Attending or Deputy chief	709 (45)	505 (51)	204 (35)	<0.01
Other	175 (11)	75 (8)	100 (17)	<0.01
Departments				
PCCM	957 (61)	668 (67)	289 (49)	<0.01
Infectious diseases	61 (4)	58 (6)	3 (1)	<0.01
ICU or Emergency departments	80 (5)	55 (6)	25 (4)	0.29
Other medical departments	54 (3)	31 (3)	23 (4)	0.47
Other surgical departments	87 (6)	39 (4)	48 (8)	<0.01
Non-clinical departments	340 (22)	140 (14)	200 (34)	<0.01
Original hospital level				
Tertiary or teaching hospitals	1252 (79)	804 (81)	448 (76)	0.02
Primary or secondary hospitals	327 (21)	187 (19)	140 (24)	0.02
Current region				
Hubei province	578 (37)	578 (58)	0 (0)	<0.01
Other provinces	1001 (63)	413 (42)	588 (100)	<0.01
Experience with VTE treatments	1446 (92)	927 (94)	519 (88)	<0.01

COVID-19 = Coronavirus disease-2019; ICU = Intensive care unit; PCCM = Pulmonary and critical care medicine; VTE = Venous thromboembolism

tistics. Categorical data were presented as N (%), and continuous data were presented as means (with standard deviation, SD) or medians (with range). Additional subgroup analyses were performed between the physicians who were directly involved in treating patients with COVID-19 and those who were not. Frontline doctors were then further divided into two groups based on whether they worked in the Hubei Province or not. Fisher's exact test was used to compare quantitative data between subgroups. A P-value <0.05 was considered statistically significant. All statistical analysis was performed using the SPSS 26.0 software (IBM).

Results

The 1,636 clinicians participated in this questionnaire, among which 55 did not complete the questions and 2 filled in the forms incorrectly. As a result, 1,579 valid survey results used in the analysis, among which 991 (63%) were involved directly in the frontline treatment of patients with COVID-19 (Table 1). Most of the participants (83%) aged between 31-60 years. Of these participants, 51% were women, and 49% were men. Besides, 45% of participants were attending, or deputy chiefs and 61% of the participants were pulmonary and critical care medical doctors.

Many doctors around the country signed up to assist in the Hubei province, which was the major COVID-19 hotspot in China, to support the frontline healthcare effort. Most clinicians worked in tertiary or teaching hospitals (79%). Fig. 1 shows the distribution of participants, most of whom were from the provinces of Hubei (557), Shanxi (153), and Henan (106); 92% of the participants claimed that they had previous experience with the diagnosis and treatment of VTE.
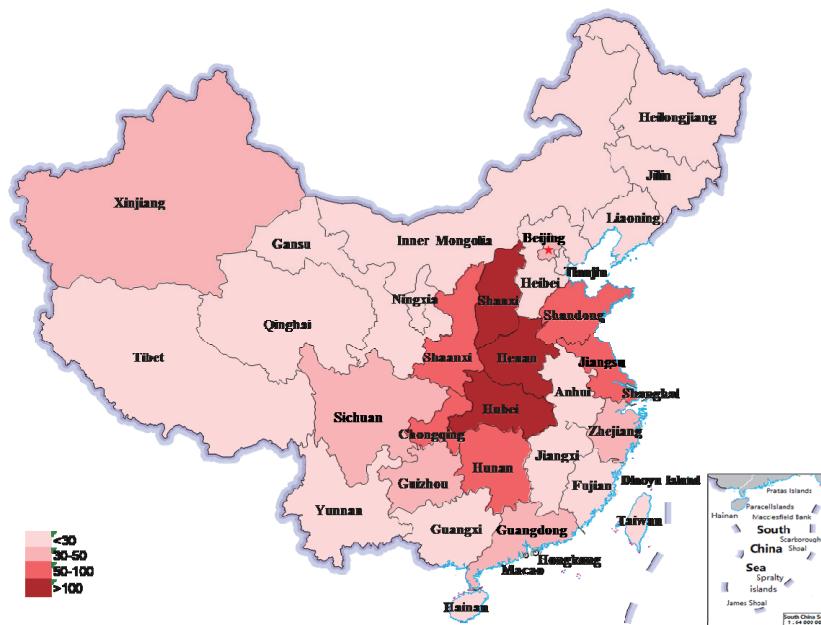
Fig. 1. The distribution of participants across various Chinese provinces

The figure shows that participants are mainly from the provinces of Hubei (557), Shanxi (153), and Henan (106).

Table 2. The percentage of severe/critically ill COVID-19 cases handled by frontline doctors participating in the survey

	< 10 cases			10-30 cases			30-50 cases			50 cases or more		
	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P
0-20%	102 (18)	276 (67)	<0.01	88 (15)	66 (16)	0.79	56 (10)	16 (4)	<0.01	104 (18)	9 (2)	<0.01
21%-40%	19 (3)	16 (4)	0.73	29 (5)	9 (2)	0.03	22 (4)	0 (0)	<0.01	46 (8)	3 (1)	<0.01
41%-60%	7 (1)	5 (1)	1.00	9 (2)	3 (1)	0.38	3 (1)	0 (0)	0.27	27 (5)	1 (0)	<0.01
61%-80%	3 (1)	1 (0)	0.65	8 (1)	0 (0)	0.02	3 (1)	1 (0)	0.65	18 (3)	2 (0)	<0.01
81%-100%	7 (1)	4 (1)	0.77	12 (2)	0 (0)	<0.01	3 (1)	0 (0)	0.27	12 (2)	1 (0)	0.01
Total	138 (24)	302 (73)	<0.01	146 (25)	78 (19)	0.02	87 (15)	17 (4)	<0.01	207 (36)	16 (4)	<0.01

COVID-19 = Coronavirus disease-2019

*Hubei province is the main hot spot in China during the pandemic. It consists of 12 cities, such as Wuhan, Huanggang and Xiaogan.

Of the 991 participating frontline workers, 23% treated more than 50 patients with COVID-19. Most of them were in Hubei Province (Hubei vs. outside Hubei: 36% vs. 4%, $P<0.01$) **(Table 2)**.

Regardless of whether they worked on the frontline or not, the vast majority of the participants (1492, or 94%) believed that patients with COVID-19 have an increased risk of suffering from VTE and VTE risk assessment is essential.

The top five VTE risk factors that the participants selected were immobilization (95%), advanced age (92%), underlying diseases (88%), concurrent infection (88%), and central venous catheterization (79%). However, the participants who were involved in treating patients with COVID-19 prioritized these factors differently. Frontline clinicians paid more attention to the risk factor of underlying diseases compared with non-frontline clinicians (frontline vs. non-frontline: 90% vs. 85%, $P<0.01$) **(Table 3)**. However, most non-frontline clinicians considered inserting a central venous catheter to be the most significant risk factor for VTE in patients with COVID-19 (frontline vs. non-frontline: 77% vs. 83%, $P=0.01$) **(Table 3)**. Among the frontline doctors, those enlisted outside Hubei Province linked more importance to risk factors such as dehydration and hypotension

Table 3. Awareness of the VTE risk factors among the participants

Risk factors	Total, n (%) (N=1579)	Whether directly involved in COVID-19 treatment			
		Yes n (%) (N=991)	No n (%) (N=588)	P	OR (95%CI)
Immobilization	1498 (95)	946 (95)	552 (94)	0.19	1.37 (0.874-2.152)
Advanced age	1454 (92)	917 (93)	537 (91)	0.39	1.18 (0.811-1.708)
Underlying diseases	1393 (88)	896 (90)	497 (85)	<0.01	1.73 (1.270-2.349)
Concurrent infection	1387 (88)	880 (89)	507 (86)	1.13	1.27 (0.932-1.721)
Central venous catheter	1253 (79)	767 (77)	486 (83)	0.01	0.72 (0.554-0.932)
Obesity	1212 (77)	764 (77)	448 (76)	0.71	1.05 (0.827-1.338)
Dehydration	1120 (71)	708 (71)	412 (70)	0.57	1.07 (0.854-1.337)
Hypotension or shock	1050 (66)	660 (67)	390 (66)	0.91	1.01 (0.816-1.256)
Mechanical ventilation	992 (63)	625 (63)	367 (62)	0.83	1.03 (0.883-1.270)

COVID-19 = Coronavirus disease-2019; VTE = Venous thromboembolism

Table 4. The status of the VTE preventive strategies for patients with COVID-19 followed by doctors directly involved in COVID-19 treatment

	Mild/moderate patients with COVID-19 with low VTE risk			Mild/moderate patients with COVID-19 with high VTE risk			Severe/critically ill patients with COVID-19 with low bleeding risk			Severe/critically ill patients with COVID-19 with high bleeding risk		
	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P	Hubei* n (%) (N=578)	Outside Hubei n (%) (N=413)	P
Exercise / drinking water	425 (74)	327 (79)	0.04	86 (15)	48 (12)	0.16	61 (11)	49 (12)	0.54	71 (12)	38 (9)	0.15
UFH	11 (2)	7 (2)	1.00	19 (3)	19 (5)	0.32	25 (4)	20 (5)	0.76	20 (3)	22 (5)	0.15
LMWH	102 (18)	37 (9)	<0.01	419 (72)	269 (65)	0.01	387 (67)	261 (63)	0.22	152 (26)	51 (12)	<0.01
NOAC	2 (0)	0 (0)	0.51	3 (1)	5 (2)	0.06	8 (1)	9 (2)	0.46	21 (4)	12 (3)	0.59
Fondaparinux	0 (0)	1 (0)	0.42	3 (1)	9 (2)	0.03	16 (3)	9 (2)	0.68	25 (4)	19 (5)	0.88
Mechanical prevention[1]	27 (5)	32 (8)	0.06	40 (7)	48 (12)	0.01	45 (8)	47 (11)	0.06	212 (37)	236 (57)	<0.01
Other	11 (2)	9 (2)	0.82	8 (1)	12 (3)	0.11	36 (6)	18 (4)	0.26	77 (13)	35 (8)	0.02

COVID-19 = Coronavirus disease-2019; LMWH= Low-molecular-weight heparin; sNOAC = New oral anticoagulant; UFH = Unfractionated heparin; VTE = Venous thromboembolism;
[1]: mechanical prevention includes intermittent pneumatic compression, graduated compression stockings, etc.
*Hubei province is the main hotspot in China during the pandemic. It consists of 12 cities, such as Wuhan, Huanggang and Xiaogan.

(Hubei vs. outside Hubei: 67% vs. 78%, P<0.01; 63% vs. 71%, P=0.01) **(Supplementary Table 3)**. We also found that compared with residents, senior doctors had a more thorough understanding of the VTE risk factors related to COVID-19, including the effects of dehydration, hypotension or shock, and mechanical ventilation (residents vs. attendings or deputy chiefs: 58% vs. 77%, P<0.01; 55% vs. 69%, P<0.01; 53% vs. 64%, P<0.01), while there was little difference among different levels of hospitals for VTE awareness **(Supplementary Table 4)**.

During our survey, we only asked the frontline workers (n=991) about implementing the VTE risk assessment. The results showed that a considerable proportion of the surveyed clinicians (76%) did not conduct the VTE risk assessment or completely follow the "Statement." The rate of correctly performed VTE risk assessment was significantly different between Hubei province and the rest of mainland China (9% vs. 15%, respectively, P<0.05).

Regarding the choice of treatment to prevent VTE in mild/moderate patients with COVID-19 with a low VTE risk, 76% of the clinicians would choose to prescribe exercise and water. (Hubei vs. outside Hubei: 74% vs. 79%, P=0.04). 69% of the clinicians would prescribe low-molecular-weight heparin (LMWH) for VTE prophylaxis in mild patients with COVID-19 who have a high VTE risk (Hubei vs. outside Hubei: 72% vs. 65%, P=0.01). **Table 4** shows these results.

For severely/critically ill patients with COVID-19 who have a low bleeding risk, 65% of the clinicians
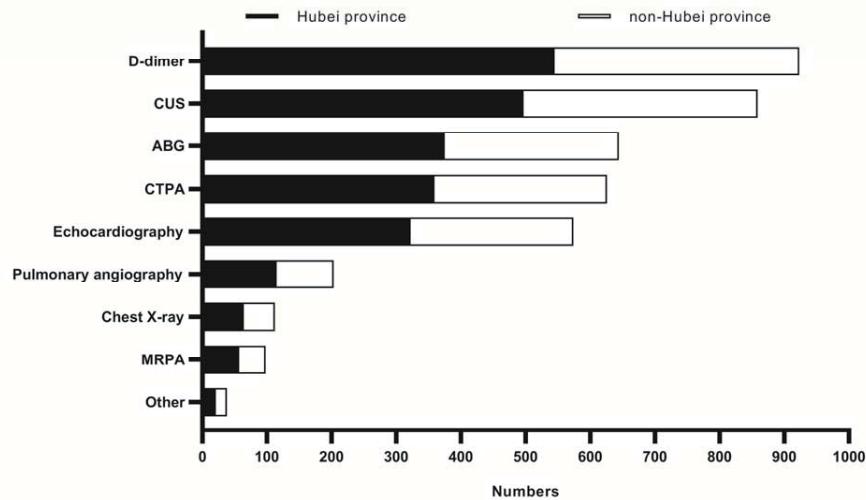
Fig. 2. The priority of the VTE diagnostic methods, according to doctors directly involved in COVID-19 treatment

The figure shows that the top five diagnostic methods are: D-dimer testing (93%), venous ultrasound of lower extremities (87%), arterial blood gas analysis (65%), CT pulmonary angiography (63%) and Echocardiography (58%). There is no significant difference between the results in Hubei Province and outside of it, which are both consistent with the overall trend.

would choose LMWH as prophylaxis. Fewer than half (45%) of the clinicians would choose mechanical devices for patients with high bleeding risk, 20% would still choose LMWH, while 11% would select exercise/drinking water as a treatment for patients with a high bleeding risk and severe COVID-19 symptoms. For the participants who worked in Hubei Province, only 37% would choose mechanical devices, 26% would choose LMWH, and 12% would choose exercise/drinking water as a treatment for patients with COVID-19 who had severe symptoms and high bleeding risk **(Table 4)**.

For severe/critically ill patients with low bleeding risk, the residents were more likely to prescribe unfractionated heparin (UFH), compared with senior doctors (residents vs. attendings or deputy chiefs: 9% vs. 4%, *P*=0.02) **(Supplementary Table 5)**. Doctors in tertiary hospitals tended to prescribe LMWH, compared with those in primary or secondary hospitals (tertiary or teaching hospitals vs. primary or secondary hospitals: 30% vs. 57%, *P*<0.01) **(Supplementary Table 6)**. For severe/critically ill patients who have a high bleeding risk **(Supplementary Table 7)**, senior doctors were more likely to choose mechanical prevention instead of prescribing LMWH (residents vs. attendings or deputy chiefs: 34% vs. 48%, *P*<0.01) **(Supplementary Table 5)**. There was no significant difference among different hospital levels **(Supplementary Table 6)**.

After a COVID-19 patient is cured and dis-charged from the hospital, 94% of the clinicians (Hubei vs. outside Hubei: 93% vs. 95%, *P*=0.275) claimed that they would assess the risk of VTE in the patient and take the appropriate preventive measures, which is consistent with the "Statement." If the clinicians believed that a discharged patient had a risk for VTE, 45% would choose to tell the patient to exercise/drink water, 35% would choose to prescribe rivaroxaban (Hubei vs. outside Hubei: 34% vs. 37%, *P*=0.46) and 7% would choose to use LMWH (Hubei vs. outside Hubei: 9% vs. 5%, *P*=0.04) **(Supplementary Fig. 1)**.

We asked the frontline clinicians about their choice of diagnostic methods for patients with COVID-19 suspected of having VTE. The top five preferred diagnostic methods were D-dimer (93%), compression ultrasonography (CUS) (87%), arterial blood gas (ABG) (65%), computed tomography pulmonary angiography (CTPA) (63%) and echocardiography (58%). No significant difference was observed between the clinicians working in Hubei Province and their peers in other provinces **(Fig. 2)**.

The survey included the detection rate of VTE in patients with COVID-19 handled by frontline doctors. We found that the detection rate of VTE was low in patients with COVID-19. Among patients with mild/moderate COVID-19, most clinicians (*n*=637, 68%) reported that they had never diagnosed a VTE event (Hubei vs. outside Hubei: 61% vs. 79%, *P*<0.05), while the vast majority (*n*=871, 93%) believed

that the VTE incidence was lower than 5% (Hubei vs. outside Hubei: 91% vs. 96%, $P < 0.01$). Similarly, more than half of the surveyed clinicians ($n = 433$, 51%) claimed that VTE did not occur when they provided healthcare to severely/critically ill patients with COVID-19 (Hubei vs. outside Hubei: 40% vs. 70%, $P < 0.05$). During the pandemic, the VTE detection rate in severe/critically ill patients with COVID-19 in Hubei was generally higher than that of outside Hubei (Hubei vs. outside Hubei: 60% vs. 30%, $P < 0.05$).

Among all the participants in this survey ($n = 1,579$), the majority of the involved clinicians ($n = 1,537$, 97%) believed that the "Statement" had clinical significance and could serve as a reference for clinical practice. Still, only 64% of them said they had read the "Statement" (either the full text or its interpretation). However, the number of frontline clinicians who had read the "Statement" was higher than that of non-frontline clinicians (frontline vs. non-frontline: 72% vs. 51%, $P < 0.05$).

Discussion

This study is the first survey to focus on VTE prophylaxis in patients with COVID-19 in mainland China. It shows the inadequate VTE prophylaxis during the COVID-19 pandemic and the existing gap between clinical work and evidence-based medicine. Most clinicians believe that patients with COVID-19 are at risk of VTE, and evaluating VTE risks is valuable for these patients. However, this was inconsistent with the real-world scenario, which showed a low VTE assessment and implementation rate of current VTE prevention measures, leading to a low VTE detection rate.

Over the past 10 years, Chinese clinicians' ability to diagnose and treat VTE has improved with the support of CURES. From 1997 to 2008, the hospital-associated VTE mortality rate decreased from 25.1% to 8.7%[10]. At the same time, the awareness of VTE among Chinese clinicians has increased[11]. The results of our study showed that Chinese clinicians demonstrate high awareness of VTE and generally believe that patients with COVID-19 are at risk of VTE. Meanwhile, it showed that there is little difference in VTE awareness among hospitals of different levels. This may indicate that our previous work can well promote the standardization of VTE diagnosis and treatment in China. However, our findings showed that most of the clinicians did not actually assess the VTE risk in patients with COVID-19, and the prophylaxis was not appropriately implemented, especially for the severe COVID-19 cases; this is partially due to the gap between the guidelines and clinical practice. Also, senior doctors or doctors working in tertiary or teaching hospitals were more likely to comply with the "Statement" and chose reasonable VTE prophylaxis. In other words, clinical experience and standard education have profound impacts on the selection of VTE prophylaxis. Intensive training will be needed to solve this problem in the future.

Another interesting finding from our survey was that frontline clinicians felt that underlying diseases represented the most concerning VTE risk factor, as opposed to the clinicians who were not involved in treating patients with COVID-19, who were mostly concerned about the central venous catheter. The reason for this may be that frontline doctors are treating many hospitalized patients with COVID-19, who are severely ill and mostly suffer from underlying diseases.

Coagulopathy is known to have occurred in the majority of patients who died of COVID-19. Multiple mechanisms are involved in this process, including endothelins and inflammatory biomarkers[12]. The SARS-Cov-2 virus binds to the host cells via the Angiotensin-Converting Enzyme 2 Receptor (ACE2R), which is universal in all major organs, especially the lungs, heart, veins, and arteries. ACE2Rs are expressed widely in endothelial cells, which can explain their susceptibility to thromboembolic events[12]. On the other hand, Inflammation may also increase thrombosis risk. Inflammation markers are elevated significantly in patients with COVID-19, which are related to poor prognosis. SARS-Cov-2 activates the inflammatory cells, such as macrophages. As inflammation worsens, the release of pro-inflammatory cytokines progresses into a cytokine storm, causing acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC)[13]. A histological examination of patients with COVID-19 showed prominent endotheliitis and accumulated inflammatory cells[14]. Endothelial cell infection and immune-mediated endotheliitis both play an important role in COVID-19 related coagulopathy.

Coagulation dysfunction may occur in severe cases of both COVID-19 and VTE. Recent studies have shown that severe COVID-19 cases often have major coagulation abnormalities, as the level of D-dimer is increased and significantly higher than that of mild/moderate patients. The level of fibrin degradation products (FDP) is also significantly increased. These levels are closely related to the mortality in patients with COVID-19 [15-17]. Besides, D-dimer is of great significance in the diagnosis and treatment guidelines of VTE. It has a high sensitivity in acute PE diagnosis (92-100%), and a high negative predictive value as well. Recent emerging evidence implies that D-dimer is also valuable for COVID-19

prognosis and risk stratification. According to the International Society of Thrombosis and Haemostasis (ISTH), a markedly increased D-dimer level is associated with high mortality in patients with COVID-19. When coagulation dysfunction occurs in patients with COVID-19 [18], it is unclear whether the elevation of D-dimer indicates VTE development. Therefore, clinicians may overlook the abnormality of D-dimer levels, resulting in a decreased detection rate of VTE.

With the continually improved understanding of COVID-19 related VTE, emerging evidence suggests that all hospitalized patients with COVID-19 (including non-critically ill patients) should receive prophylactic dose LMWH, unless they have contraindications (active bleeding and platelet count $<25 \times 10^9$ per liter) [19]. A case report showed that a patient with COVID-19 who was not admitted to hospital because of mild symptoms developed PE [20]. It seems that the hypercoagulable state may exist for a long time in the course of COVID-19. Venous thrombotic events can occur in both mild and severe COVID-19 cases, who should receive anticoagulant therapy. However, in our study, a substantial number of clinicians would prescribe exercise and water to prevent VTE in mild/moderate COVID-19 cases, which may not be enough for the prophylaxis.

Our results showed that the promotion of the "Statement" is still insufficient. Although almost all clinicians could recognize its necessity and clinical significance, only 64% of them said they had previously read it, and the percentage of non-frontline clinicians was even lower. When faced with suspected VTE patients, clinicians who had not read the "Statement" might rely on their previous potentially inappropriate clinical experience to choose diagnostic measures, which can decrease the prevention and detection rates of VTE.

During the pandemic, there are limitations on the various diagnostic measures for various reasons. Therefore, future research should consider new biomarkers to help clinicians in the decision-making process regarding the appropriate diagnosis and treatment for VTE apart from CTPA during the pandemic. For example, it may be necessary to closely monitor the changes in the D-dimer level, which is now addressed in the ISTH guidance. A recent study showed that dynamic changes in the D-dimer level are positively correlated with the severity and prognosis of COVID-19 [21, 22].

This study has certain limitations. First of all, this study is an observational cross-sectional study, and further research is needed to verify whether the changes in the D-dimer levels can assist in identifying VTE in patients with COVID-19. Also, this study was conducted through an online questionnaire, which may include the risk of response bias, thus having inaccurate and one-sided collected data. Finally, the sample size of this study is small and cannot represent the overall population.

Conclusion

Through this online survey, we have found that most clinicians are generally aware of VTE prophylaxis for patients with COVID-19 and that the clinical practice still needs to be improved. However, the diagnosis of VTE may still be missed due to the unspecific clinical characteristics of VTE and difficulty in using CTPA as a result of the highly contagious features of COVID-19. VTE risk assessment and prophylaxis measurements, especially in severe COVID-19 cases, should be taken as early as possible. Additionally, we should also look for other simple and feasible methods to assist in the diagnosis of VTE, which will contribute to reducing the mortality of COVID-19. A real-world registry study is needed to investigate the true incidence of VTE and the effect of appropriate prophylaxis for patients with COVID-19.

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Disclosure of Conflict of Interests

No conflicts of interest are involved in this manuscript.

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Supplementary Table 1. Prevention and treatment of venous thromboembolism associated with COVID-19 infection: a consensus statement before guidelines

Venous thromboembolism (VTE) risk assessment and bleeding risk assessment for COVID-19 patients

1. All severe and critically ill COVID-19 patients have a high risk of VTE, so prevention of VTE is strongly recommended in absence of contraindication.
2. For mild or moderate COVID-19 patients, it is recommended to determine the risk of VTE using PADUA or IMPROVE risk assessment models (RAM) for medical patients, CAPRINI RAM for surgical patients, leading to VTE prevention in high risk and moderate risk patients in absence of contraindications.
3. Dynamic and repeated risk assessment for VTE and/or bleeding risks should be conducted for COVID-19 patients involving underlying diseases, laboratory monitoring, concomitant medications and invasive procedures to adjust thromboprophylaxis strategy.

Prevention of VTE for severe or critically ill COVID-19 patients

4. In severe or critically ill COVID-19 patients at high risk of bleeding or with active bleeding contra-indicating temporarily pharmacological thromboprophylaxis, it is recommended to use IPC for VTE prevention
5. Pharmacological prevention with LMWH is recommended as first-line treatment in patients at low or moderate risk of bleeding and with no contraindication to antithrombotic drugs. In patients with severe renal impairment (creatinine clearance rate: <30 ml/min) it is recommended to use unfractionated heparin (UFH).

Prevention of VTE in mild and moderate COVID-19 patients

6. Mild and moderate COVID-19 patients isolated for medical treatment, especially those with fever and/or gastrointestinal symptoms (diarrhea and anorexia) should be rehydrated without delay.
7. Mild and moderate COVID-19 patients presenting acute medical diseases and assessed to have a high or moderate risk of VTE (PADUA or IMPROVE RAM), pharmacological prevention should be prescribed and LMWH is recommended as first-line treatment, in absence of contraindication.
8. Mild and moderate COVID-19 patients requiring surgical procedure or presenting traumatic conditions and assessed to have a high or moderate risk of VTE (CAPRINI RAM), pharmacological prevention should be prescribed and LMWH is recommended as first-line treatment, in absence of contraindication.
9. Mild and moderate COVID-19 patients perceived to have a persistent risk of VTE at the time of discharge, a prolonged out-patient VTE prophylaxis care should be considered with LMWH over DOAC use, caution due to potential drug-drug-interactions and/or frequent comorbidities.
10. Suspected mild and moderate COVID-19 patients should avoid sedentariness, dehydration, and should be encouraged to remain active with regular mobilization (ankle pump movements) and drinking appropriate volume of water during their isolation at home.

Diagnosis of VTE in COVID-19 patients

11. In case of DVT or PE suspicion, diagnosis should be primarily based on careful bedside clinical examinations and then objectively confirmed by imaging explorations (venous echo-doppler ultrasound, echocardiography and CTPA with mandatory clinical and protective conditions.
12. In COVID-19 patients suspected for VTE, or relevant examinations fail to be conducted due to restricted conditions, starting a curative anticoagulant parenteral treatment with LMWH as first-line treatment is recommended in absence of contraindication.

Supplementary Table 2. A survey on the current status of venous thromboembolism (VTE) prevention, treatment and management

Dear colleagues, the beginning of 2020 witnessed the outbreak and rapid spread of COVID-19 across the country. In this silent war, VTE becomes a hidden killer. This questionnaire is designed to better understand your cognition of COVID-19 complicated with VTE, improve the awareness of thrombosis prevention among healthcare providers and ensure the safety of patients.
Sponsors:
National Pulmonary Embolism and Deep Venous Thrombosis Prevention and Control Capacity Building Project Office
Pulmonary Embolism and Pulmonary Vascular Disease Group of the Chinese Thoracic Society
Pulmonary Embolism and Pulmonary Vascular Disease Working Committee of the Chinese Association of Chest Physicians
Objective: To evaluate the awareness and management status of frontline COVID-19 clinicians on the risk for VTE.
Participants: All clinicians (nationwide).
Content: VTE risk assessment methods, preventive measures, identification, diagnosis and treatment of VTE in COVID-19 patients.
This questionnaire should take you about 5 minutes to complete.

Part 1: Basic Information

1. Have you been directly involved in confirming COVID-19 cases during the pandemic?
   ☐ Yes ☐ No

2. Sex: ☐ Male ☐ Female

3. Age in years: ☐ <20 ☐ 21-25 ☐ 26-30 ☐ 31-35 ☐ 36-40 ☐ 41-45 ☐ 46-50 ☐ 51-55 ☐ 56-60 ☐ >60

4. Title: ☐ Attending or Deputy chief ☐ Senior Resident ☐ Junior Resident ☐ Other (Please specify):_____

5. Department: ☐ Pulmonary and Critical Care Medicine ☐ Infectious diseases ☐ ICU ☐ Cardiology ☐ Emergency ☐ Neurology ☐ Vascular Surgery ☐ General Surgery ☐ Orthopedics ☐ Other (Please specify): ____

6. Hospital level: ☐ Tertiary or teaching hospital ☐ Secondary hospital ☐ Primary hospital

7. Location of your hospital: ☐ A drop-down menu of provinces (and municipalities directly under the central government)

8. Where do you currently provide medical care for COVID-19 patients?
   ☐ A drop-down menu of provinces (and municipalities directly under the central government)

9. Have you had any clinical experience in diagnosing or treating patients with VTE?
   ☐ Rich experience ☐ Some experience
   ☐ Very little experience ☐ No experience

Part 2: For all participants

10. Do you think there are risk factors for VTE in COVID-19 patients?
    ☐ Yes ☐ Some patients do have risks (such as severe/critically ill patients) ☐ No

11. Which of the following factors do you think will increase the VTE risk in COVID-19 patients? (Multiple choice)
    ☐ Co-infection ☐ Dehydration ☐ Immobilization ☐ Obesity ☐ Old age ☐ Underlying diseases ☐ Mechanical ventilation ☐ Central venous catheter ☐ Hypotension or shock

12. Which COVID-19 patient group do you think needs VTE risk assessment?
    ☐ None ☐ Mild/moderate patients ☐ Severe/critically ill patients ☐ All COVID-19 patients

13. Do you think that it is of great clinical significance to actively carry out VTE risk assessment and prevention for COVID-19 patients?
    ☐ Yes ☐ No ☐ Not sure

14. Have you read the "Statement on Prevention and Control of Venous Thromboembolism Related to COVID-19 (Trial)"?
    ☐ I've read the original text
    ☐ I've not read the original text, but I've read an interpretation of it
    ☐ I've heard of it, but I haven't read the original text or an interpretation of it
    ☐ Never heard of it

15. Do you think the "Statement on Prevention and Control of Venous Thromboembolism Related to COVID-19 (Trial)" has a directive value for your clinical work?
    ☐ Not at all ☐ Very little ☐ Valuable ☐ Very Valuable

16. Does performing VTE risk assessment and prevention increase your workload of COVID-19 treatment?

    YES ├──┼──┼──┼──┼──┤ NO
        0 1 2 3 4 5

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

(Cont. Supplementary Table 2)

PART 3: Only for participants in the frontline

17. How many COVID-19 patients have your treated so far?
☐ <10 cases ☐ 10-30 cases ☐ 30-50 cases ☐ Over 50 cases

18. Among the COVID-19 patients you have treated, what is the proportion of severe/critically ill cases:
☐ 0-20% ☐ 21%-40% ☐ 41%-60% ☐ 61%-80% ☐ 81%-100%

19. Which VTE risk assessment model do you commonly use when treating COVID-19 patients?
☐ Padua score ☐ Caprini risk assessment model ☐ Rogers score ☐ Clinical experience assessment

20. Which VTE risk assessment model do you commonly use for COVID-19 patients who require surgical treatment or are experiencing trauma?
☐ Padua score ☐ Caprini risk assessment model ☐ Rogers score ☐ Clinical experience assessment

21. For COVID-19 patients with a risk for VTE, do you evaluate their bleeding risk?
☐ Yes ☐ Yes for some patients (such as severe/critically ill patients) ☐ No

22. Among the mild/moderate COVID-19 patients you have treated, what is the proportion of patients who have been diagnosed with VTE?
☐ None ☐ 1%-5% ☐ 6%-10% ☐ 11%-15% ☐ 16%-20% ☐ >20% ☐ Not involved in treating mild/moderate patients

23. Among the mild/moderate COVID-19 patients you have treated, what is the proportion of patients taking preventive measures for VTE?
☐ None ☐ 1%-10% ☐ 11%-20% ☐ 21%-30% ☐ Over 30%

24. For mild/moderate COVID-19 patients, if their VTE risk is low, which of the following options is your preferred preventive measure?
☐ Exercise/drinking water ☐ Unfractionated heparin ☐ LMWH ☐ NOAC ☐ Fondaparinux sodium
☐ Mechanical prevention (IPC, GCS, etc.) ☐ Other

25. For mild/moderate COVID-19 patients, if their VTE risk is high or medium-high, which of the following options is your preferred preventive measure?
☐ Exercise/drinking water ☐ Unfractionated heparin ☐ LMWH ☐ NOAC ☐ Fondaparinux sodium
☐ Mechanical prevention (IPC, GCS, etc.) ☐ Other

26. Among the severe/critically ill COVID-19 patients you have treated, what is the proportion of patients diagnosed with VTE?
☐ None ☐ 1%-5% ☐ 6%-10% ☐ 11%-15% ☐ 16%-20% ☐ >20% ☐ Not involved in treating severe/critically ill patients

27. Among the severe/critically ill COVID-19 patients you have treated, what is the proportion of patients taking preventive measures for VTE?
☐ None ☐ 1%-10% ☐ 11%-20% ☐ 21%-30% ☐ Over 30%

28. For severe/critically ill COVID-19 patients combined with a low bleeding risk, which of the following options is your preferred preventive measure?
☐ Exercise/drinking water ☐ Unfractionated heparin ☐ LMWH ☐ NOAC ☐ Fondaparinux sodium
☐ Mechanical prevention (IPC, GCS, etc.) ☐ Other

29. For severe/critically ill COVID-19 patients combined with a high bleeding risk, which of the following options is your preferred preventive measure?
☐ Exercise/drinking water ☐ Unfractionated heparin ☐ LMWH ☐ NOAC ☐ Fondaparinux sodium
☐ Mechanical prevention (IPC, GCS, etc.) ☐ Other

30. If COVID-19 patients suffer from thrombocytopenia or HIT while taking heparin, which of the following drugs do you usually use?
☐ Switch to mechanical prevention ☐ Argatroban ☐ Bivalirudin ☐ NOAC ☐ Fondaparinux sodium

31. When COVID-19 patients are cured and discharged from the hospital, do you assess their VTE risks and take follow-up preventive measures?
☐ Yes ☐ Yes for some patients (such as severe/critically ill patients) ☐ No

32. If VTE risks are assessed for COVID-19 patients who are cured and discharged from the hospital, which of the following preventive measures do you recommend?
☐ Exercise/Drinking water ☐ LMWH ☐ Rivaroxaban ☐ Mechanical prevention ☐ Other

33. For COVID-19 patients, which of the following tests do you prefer to use to assist in VTE diagnosis (multiple choice)?
☐ ABG ☐ D-dimer ☐ Echocardiography ☐ Chest X-ray ☐ CTPA ☐ MRPA ☐ CUS ☐ Pulmonary angiography
☐ Other (please specify):

Thank you again for your support and cooperation!
March 2020

Supplementary Table 3. The awareness of VTE risk factors among participating doctors directly involved in COVID-19 treatment

Risk factors	Total (N=991) n (%)	Whether enlisted in Hubei province		P	OR (95%CI)
		Yes (N=578) n (%)	No (N=413) n (%)		
Immobilization	946 (95)	551 (95)	395 (96)	0.88	0.930 (0.505-1.712)
Advanced age	917 (93)	536 (93)	381 (92)	0.81	1.072 (0.664-1.729)
Underlying diseases	896 (90)	526 (91)	370 (90)	0.51	1.176 (0.768-1.799)
Concurrent infection	880 (89)	516 (89)	364 (88)	0.61	1.120 (0.753-1.688)
Central venous catheter	767 (77)	435 (75)	332 (80)	0.06	0.742 (0.546-1.010)
Obesity	764 (77)	435 (75)	329 (80)	0.11	0.777 (0.572-1.054)
Dehydration	708 (71)	387 (67)	321 (78)	<0.01	0.581 (0.435-0.776)
Hypotension or shock	660 (67)	365 (63)	295 (71)	0.01	0.685 (0.522-0.900)
Mechanical ventilation	625 (63)	351 (61)	274 (66)	0.07	0.784 (0.603-1.021)

COVID-19 = Coronavirus disease-2019; VTE = Venous thromboembolism

Supplementary Table 4. The awareness of VTE risk factors among survey participants

Risk factors	Title				Hospital levels			
	Residents, n (%) (N=228)	Attendings or Deputy chiefs, n (%) (N=1176)	P	OR (95%CI)	Tertiary or teaching hospitals, n (%) (N=1252)	Primary or secondary hospitals, n (%) (N=327)	P	OR (95%CI)
Immobilization	218 (96)	1117 (95)	0.87	1.151 (0.580-2.286)	1190 (95)	308 (94)	0.57	1.184 (0.698-2.010)
Advanced age	211 (93)	1083 (92)	0.89	1.066 (0.623-1.744)	1150 (92)	304 (93)	0.57	0.853 (0.533-1.363)
Underlying diseases	194 (85)	1050 (89)	0.09	0.685 (0.455-1.030)	1108 (88)	285 (87)	0.50	1.134 (0.785-1.638)
Concurrent infection	193 (85)	1041 (89)	0.12	0.715 (0.478-1.069)	1100 (88)	287 (88)	1.00	1.009 (0.695-1.463)
Central venous catheter	171 (75)	957 (81)	0.03	0.687 (0.492-0.959)	994 (79)	259 (79)	0.94	1.012 (0.749-1.366)
Obesity	164 (72)	929 (79)	0.02	0.681 (0.494-0.939)	963 (77)	249 (76)	0.77	1.044 (0.784-1.390)
Dehydration	133 (58)	903 (77)	<0.01	0.423 (0.315-0.569)	883 (71)	237 (72)	0.54	0.909 (0.693-1.192)
Hypotension or shock	126 (55)	811 (69)	<0.01	0.556 (0.416-0.742)	836 (67)	214 (65)	0.65	1.061 (0.821-1.371)
Mechanical ventilation	120 (53)	751 (64)	<0.01	0.629 (0.472-0.837)	793 (63)	199 (61)	0.44	1.111 (0.865-1.427)

COVID-19 = Coronavirus disease-2019; VTE = Venous thromboembolism

Supplementary Table 5. The status of VTE preventive strategies for COVID-19 patients in doctors directly involved in COVID-19 treatment based on the doctor's title

	Mild/moderate COVID-19 patients with low VTE risk			Mild/moderate COVID-19 patients with high VTE risk			Severe/critically ill COVID-19 patients with low bleeding risk			Severe/critically ill COVID-19 patients with high bleeding risk		
	Residents, n (%) N=104	Attendings or Deputy chiefs, n (%) N=812	P	Residents, n (%) N=104	Attendings or Deputy chiefs, n (%) N=812	P	Residents, n (%) N=104	Attendings or Deputy chiefs, n (%) N=812	P	Residents, n (%) N=104	Attendings or Deputy chiefs, n (%) N=812	P
Exercise / drinking water	66 (63)	645 (79)	<0.01	13 (13)	106 (13)	0.87	12 (12)	85 (10)	0.74	12 (12)	85 (10)	0.74
UFH	4 (4)	11 (1)	0.06	4 (4)	32 (4)	0.96	9 (9)	31 (4)	0.02	3 (3)	36 (4)	0.46
LMWH	23 (22)	98 (12)	<0.01	78 (75)	569 (70)	0.30	65 (63)	544 (67)	0.36	30 (29)	148 (18)	0.01
NOAC	0 (0)	0 (0)	-	1 (1)	8 (1)	0.98	1 (1)	15 (2)	0.52	3 (3)	27 (3)	0.81
Fondaparinux	0 (0)	1 (0)	0.72	2 (2)	10 (1)	0.56	2 (2)	21 (3)	0.68	3 (3)	40 (5)	0.35
Mechanical prevention[1]	7 (7)	42 (5)	0.51	5 (5)	71 (9)	0.17	5 (5)	77 (9)	0.12	35 (34)	391 (48)	<0.01
Other	4 (4)	15 (2)	0.18	1 (1)	16 (2)	0.47	10 (10)	39 (5)	0.04	18 (17)	85 (10)	0.04

COVID-19 = Coronavirus disease-2019; LMWH = Low-molecular-weight heparin; NOAC = New oral anticoagulant; UFH = Unfractionated heparin; VTE = Venous thromboembolism; [1]: mechanical prevention includes intermittent pneumatic compression, graduated compression stockings, etc.

Supplementary Table 6. The status of VTE preventive strategies for COVID-19 patients in doctors directly involved in COVID-19 treatment based on the hospital's level

|	Mild/moderate COVID-19 patients with low VTE risk			Mild/moderate COVID-19 patients with high VTE risk			Severe/critically ill COVID-19 patients with low bleeding risk			Severe/critically ill COVID-19 patients with high bleeding risk		
	Tertiary or teaching hospitals N=804 (%)	Primary or secondary hospitals N=187 (%)	P	Tertiary or teaching hospitals N=804 (%)	Primary or secondary hospitals N=187 (%)	P	Tertiary or teaching hospitals N=804 (%)	Primary or secondary hospitals N=187 (%)	P	Tertiary or teaching hospitals N=804 (%)	Primary or secondary hospitals N=187 (%)	P
Exercise / drinking water	607 (34)	145 (78)	0.56	106 (6)	28 (15)	0.52	83 (5)	27 (14)	0.11	81 (10)	28 (15)	0.05
UFH	11 (1)	7 (4)	0.03	26 (1)	12 (6)	0.04	37 (2)	8 (4)	0.85	36 (4)	6 (3)	0.44
LMWH	113 (6)	26 (14)	0.96	570 (32)	118 (63)	0.04	542 (30)	106 (57)	<0.01	167 (21)	36 (19)	0.64
NOAC	2 (0)	0 (0)	0.49	9 (0)	2 (1)	0.95	14 (1)	3 (2)	0.90	27 (3)	6 (3)	0.92
Fondaparinux	1 (0)	0 (0)	0.63	12 (1)	0 (0)	0.09	21 (1)	4 (2)	0.71	34 (4)	10 (5)	0.50
Mechanical prevention[1]	52 (3)	7 (4)	0.16	66 (4)	22 (12)	0.12	68 (4)	24 (13)	0.06	372 (46)	76 (41)	0.16
Other	18 (1)	2 (1)	0.31	16 (1)	5 (3)	0.56	39 (2)	15 (8)	0.09	87 (11)	25 (13)	0.32

COVID-19 = Coronavirus disease-2019; LMWH= Low-molecular-weight heparin; NOAC = New oral anticoagulant; UFH = Unfractionated heparin; VTE = Venous thromboembolism; [1]: mechanical prevention includes intermittent pneumatic compression, graduated compression stockings, etc.

Supplementary Table 7. The definitions of high bleeding and low bleeding risks

① Bleeding risk factors for medical patients	
One of the following indicates high bleeding risks	Three or more of the following indicate high bleeding risks
• Active peptic ulcer • Previous bleeding (within the last three months) • Platelet count $<50 \times 10^9$/L	• Advanced age ($\geq$ 85 years) • Hepatic dysfunction (INR >1.5) • Severe renal insufficiency (GFR <30 ml·min^{-1}·m^{-2}) • Admitted to ICU/CCU • Central venous catheterization • Rheumatic diseases • Active cancer • Male

INR = International normalized ratio; GFR = Glomerular filtration rate; ICU = Intensive care unit; CCU = Cardiac care unit

② Bleeding risk factors for surgical patients	
Underlying conditions -related	Surgery-related
• Active bleeding • Previous bleeding (within the last three months) • Severe hepatic dysfunction or renal insufficiency • Platelet count $<50 \times 10^9$/L • Uncontrolled hypertension • Lumbar puncture / Intravertebral or epidural anesthesia • 4 h before surgery ~ 12 h after surgery • Concomitant use of anticoagulants, antiplatelet therapy or thrombolytics • Coagulation disorder • Active peptic ulcer • Known but untreated bleeding disorders	• Abdominal surgery: preoperative anemia/complex surgery (combined surgery, difficult separation or more than one anastomosis) • Pancreaticoduodenectomy: sepsis, pancreatic leak, surgical site bleeding • Hepatectomy: primary hepatocellular carcinoma, low preoperative hemoglobin and platelet counts • Cardiac surgery: longer extracorporeal circulation time • Thoracic surgery: pneumonectomy or total extended lung resection • Craniotomy, spine surgery, spinal trauma, free flap reconstruction surgery
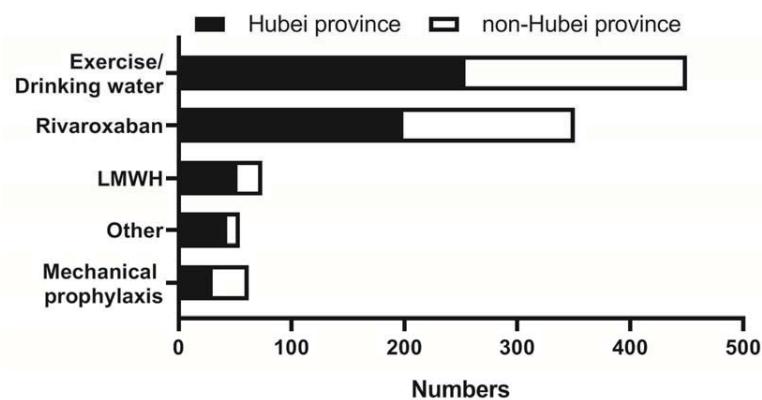
Supplementary Fig. 1. The preventive strategies for COVID-19 patients who have VTE risk on discharge

Most of the participants chose multi-activity/drinking water or rivaroxaban as the main strategies for outpatients to prevent VTE.
COVID-19 = Coronavirus disease-2019; VTE = Venous thromboembolism; LMWH = Low-molecular-weight heparin.