Special article

Hematologic issues in COVID-19

Darintr Sosothikul and Phumin Chaweephisal

Pediatric Hemato-Oncology Unit, Department of Pediatrics, Faculty of Medicine, King Chulalongkorn Memorial Hospital

The novel coronavirus 2019 is now in the focus due to the pandemic spread causing morbidity and mortality to mankind. Since the first cluster cases of pneumonia with unknown etiology reported in Wuhan, China in late December 2019, the infectivity has risen resulting in a worldwide spread within three months so that the World Health Organization (WHO) had to declare COVID-19 as a global pandemic March 11, 2020. Most cases present mild symptoms including fever, cough and malaise while others present severe clinical features, acute respiratory distress syndrome (ARDS), along with hematological complications such as thrombosis and coagulopathy.

Thrombotic manifestations associated with COVID-19 infection

From clinical experience, several clotting events in central venous catheters have been noted. Some experience unusual thrombotic complications such as ischemic limbs, stroke and venous thrombo-embolism (VTE). Lower extremity deep vein thrombosis (DVT) has an incidence of approximately 25% without VTE prophylaxis[1]. Of 183 cases reported in Tongji Hospital, Wuhan Province, 71.4% of nonsurvivors met the International Society on Thrombosis and Hemostasis (ISTH)'s diagnostic criteria for disseminated intravascular coagulation (DIC) resulting in high mortality rates[2]. The median time of DIC status was 4 days. Significantly higher D-dimer, fibrin degradation product (FDP), and prothrombin time (PT) were observed in the nonsurvivors group as compared with those in the survivors group as shown in Table 1.

In another study[1], D-dimer was a good predictor of VTE. When D-dimer level is >1.5 μg/mL, patients have a risk of VTE showing a sensitivity of 85%, specificity of 88.5%, negative predictive value (NPV) of 94.7% and positive predictive value (PPV) of 70.8%. When low molecular weight heparin (LMWH) was initiated at a dose of 0.6 mg/kg every 12 hours, all patients demonstrated decreased D-dimer levels[4]. Mean D-dimer can be used not only to diagnose thrombosis but is valuable in predicting the effectiveness of anticoagulants. The thrombotic complications among 184 patients in intensive care units of three Dutch hospitals are shown in Table 2[5]. However, all patients received standard dose VTE prophylaxis using nadroparin.

Table 1 Clinical and laboratory parameters in survivors and nonsurvivors groups of COVID-19 infection[3].

Parameters	Normal range	Total (n = 183)	Survivors (n = 162)	Nonsurvivors (n = 21)	*p* values
Age (years)		54.1 ± 16.2	52.4 ± 15.6	64.0 ± 20.7	< 0.001
Underlying disease		75 (41.0%)	63 (38.9%)	12 (57.1%)	0.156
PT (sec)	11.5-14.5	13.7 (13.1-14.6)	13.6 (13.0-14.3)	15.5 (14.4-16.3)	< 0.001
APTT (sec)	29.0-42.0	41.6 (36.9-44.5)	41.2 (36.9-44.0)	44.8 (40.2-51.0)	0.096
Fibrinogen (g/L)	2.0-4.0	4.55 (3.66-5.17)	4.51 (3.65-5.09)	5.16 (3.74-5.69)	0.149
D-dimer (μg/mL)	< 0.50	0.66 (0.38-1.50)	0.61 (0.35-1.29)	2.12 (0.77-5.27)	< 0.001
FDP (μg/mL)	< 5.0	4.0 (4.0-4.9)	4.0 (4.0-4.3)	7.6 (4.0-23.4)	< 0.001
AT (%)	80-120	91 (83-97)	91 (84-97)	84 (78-90)	0.096

PTT, activated partial thromboplastin time; AT, antithrombin; FDP, fibrin degradation product; PT, prothrombin time

Table 2 Incidence of thrombosis in three Dutch hospitals[5]

Type of event	Numbers	Comments
Pulmonary embolism (PE)	25	18 cases with extensive PE, 7 cases with PE of subsegmental arteries
Other venous thromboembolic events	3	1 proximal deep-vein thrombosis of the leg, 2 cases of catheter related upper extremity thrombosis
Arterial thrombotic events	3	All ischemic strokes

PE, pulmonary embolism.

Still, thrombosis occurred as high as 31% (95%CI: 20-41%) and comprised imaging-confirmed VTE in 27% (95%CI: 17-37%) and arterial thrombosis in 3.7% of cases (95%CI: 0-8.2%). Pulmonary embolism (PE) was the most frequent thrombotic complication (81%). These data indicated that a dose higher than the prophylaxis may be required.

Pathogenesis of thrombosis and DIC associated with COVID-19 infection

Critically ill patients fulfilled all three criteria of Virchow's triad including reduced venous flow due to immobility, endothelial injury by direct invasion of the COVID-19 virus or central venous catheter use and prothrombotic changes.

Prothrombotic change by various components of hemostatic cascades was proposed[6]. Hyperfibrinogenemia is the major risk of thrombosis. Even though COVID-19 induced DIC, the fibrinogen in early stage still remained high indicating low consumption of fibrinogen, the hallmark sign in COVID-19. Elevated factor VIII is also caused by the inflammatory process and revealed many causes of infection including COVID-19. Increased circulating prothrombotic microparticles as a result of platelet and monocytes destruction, which is well known among septic patients, may also occur in COVID-19 cases. Activated neutrophils released Neutrophil Extracellular Traps (NETs), promoting hypercoagulability. Another elevated parameter is von Willebrand factor will also raise the concern to cause other events.

The pathophysiology of DIC is complex. The activation of vascular endothelium, platelets and leukocytes can induce the release of cytokines resulting in systemic thrombin dysregulation. The deposition of fibrin will subsequently thrombose and damage tissues, especially the microvascular tissues in the lung. The exaggeration will also inhibit fibrinolysis and impair anticoagulant mechanisms[2].

Interestingly, at the late stage of COVID-19 infection, the level of fibrin-related markers (D-dimer and FDP) are markedly elevated. Therefore, secondary hyperfibrinolysis occurs in this setting[3] and so with coagulopathy would replace the hypercoagulable state due to acute inflammatory the response process[7].

Different clinical manifestations of DIC, emerging in the late stage of COVID-19 infection, from others causes of DIC are described below.

1. Some laboratory data especially platelet count may not show compatibility with DIC even when a full-blown status is encountered. Because organ dysfunction is mainly limited in the lungs, this condition induces an increase in thrombopoietin level following pulmonary inflammation. In one study, only 21.6% of severe cases met the sepsis induced coagulopathy (SIC) criteria, consisting of platelet count, PT-INR, SOFA score, meaning cases that fulfilled the criteria for treatment are limited[8].

2. The ISTH for DIC score is not sensitive in the fibrinogen domain because the physiologic fibrinolysis terminated at the early stage but hyperfibrinolysis developed in the late stage of patients with COVID-19 infection.

3. Low anti-thrombin levels were reported and hyperfibrinogenemia might be apparent, both raising the concern that prophylactic dose of heparin or LMWH might be inadequate[9].

4. Despite VTE prophylaxis, the incidence of thrombosis remains high.

The autopsy findings in COVID-19 cases showed that thrombosis may be the key feature of pulmonary failure[10]. In eight of ten cases autopsied in Brazil, pulmonary histology revealed variable numbers of small fibrinous thrombi in small pulmonary arterioles. A large number of pulmonary megakaryocytes were observed in the pulmonary capillaries, indicating activation of the coagulation cascade together with increased megakaryocytes in glomeruli and superficial dermal vessels.

Another pathological study reported similar results. The biopsy of purpuric skin lesions of three proven severe COVID-19 cases with ARDS showed pauci-inflammatory thrombogenic vasculopathy[11]. In three cases, minimally invasive autopsies were attempted in multiple organs including the lungs, heart, kidneys, spleen, bone marrow, liver and others[12]. Monocyte and lymphocyte infiltration in the pulmonary vasculature were found with congestion along with hyaline thrombi of vessels. Necrosis of parenchymal cells and hyaline thrombus formation in small vessels were observed in multiple organs without evidence of infection. In contrast, one study failed to demonstrate the evidence of thrombosis[13]. The thrombosis in multiple organs was possibly due to local inflammation only or might imply a hypercoagulable status. Large study cohorts are necessary to prove that thrombotic evidence or other safer strategies should be explored because of safety concerns.

Management of thrombotic risk and bleeding episodes

The routine testing in a hematologic laboratory is indicated for all hospitalized COVID-19 cases in the USA and Europe. The tests include complete blood count (CBC), coagulation studies, fibrinogen, and D-dimer for thrombotic evaluation reasons. Further, we recommend testing all cases admission in Thailand. Repeated test is followed on a daily basis or less frequently as appropriate[14]. A specific diagnosis test for DVT and PE is considered when signs/symptoms are present.

The use of anticoagulant in severe cases has proven to have some benefits in multiple single institute trials. In all, 449 patients in Tongji Hospital had used anticoagulant treatment, mainly LMWH for 7 days or longer. No difference was observed in the 28-day mortality rate for user and nonuser groups (30.3 vs. 29%, $p = 0.910$). However, for subgroup analysis, when the severity is high enough (SIC score ≥ 4) or high D-dimer level (more than 6 fold of the upper normal limit), use of anticoagulants showed more significant improvement in the 28-day mortality rate in the user than in the nonuser group [(high severity) 40.4% vs. 64.2, $p = 0.029$ and (high D-dimer) 32.8 vs. 52.4%, $p = 0.017$]. Bleeding complications were unusual and commonly mild in prophylactic dosage. However, regarding D-dimer ≤ 1 upper limit of normal, the 28-day mortality rate was higher in the treatment group compared with that of the nontreatment group but without statistical significance (33.3 vs 9.7%, $p = 0.260$). Therefore, anticoagulants have an advantage only in some exclusively selected cases[9]. The recommendations for anticoagulant therapy in COVID-19 are summarized in Table 3.

American Society of Hematology (ASH) recommends all hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis, preferably LMWH or fondaparinux (over unfractionated heparin due to frequent contact risk), unless the risk of bleeding is higher. However, when anticoagulants are contra-indicated, mechanical thromboprophylaxis such as pneumatic compression devices may be needed. Combining medical and pharmacological methods is discouraged. The therapeutic role of

Table 3 Comparison of different guidelines in anticoagulant treatment among patients with COVID-19

	ASH[15]	ISTH[7]	ACC[16]
Evaluated risk of thrombo-embolism	-	All hospitalized patients	All hospitalized patients
Hospitalized			
- Prophylaxis dose	All cases	All immobilized and severely ill patients	All immobilized patients with respiratory failure, with comorbidities and those requiring intensive care
- Therapeutic dose without evidence of thrombosis	No adequate data		No adequate data
- Type of medication	LMWH, fondaparinux	LMWH, fondaparinux	LMWH
- Mechanical prophylaxis	Only with pharmacological contra-indication	All cases completely immobilized combined with pharmacologic method	Only when there is pharmacologic contra-indication
Postdischarge thromboprophylaxis	May consider DOACs	-	May consider (DOACs, LMWH)
Management of hemorrhage	-	Replacement therapy along with tranexamic acid	Same as ISTH

ACC, American College of Cardiology; ASH, American Society of Hematology; ISTH, International Society on Thrombosis and Hemostasis; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulants.

anticoagulants in cases without evidence of thrombosis remains unknown. When recurrent clotting occurs despite prophylactic therapy, increasing the intensity should be considered. Any acute medical illness carries an increasing risk for VTE for up to 90 days after discharge. Thus, despite inadequate data on postdischarge thromboprophylaxis, it can be prescribed using adjusted doses among individuals who are elderly, with comorbidities and with elevated D-dimer levels > 2 times the upper normal limit[15].

According to ISTH recommendations, the VTE risk must be assessed in all hospitalized patients. Pharmacological thromboprophylaxis should be given to all immobilized and severely ill patients, preferably LMWH or fondaparinux. All completely immobilized patients would benefit from pneumatic compression in addition to pharmacological thromboprophylaxis, differing from ASH recommendations. Mechanical thromboprophylaxis should be used alone when platelet level is less than 30×10^9/L. When sudden onset of desaturation or respiratory distress occurs, pulmonary VTE should be considered. Abnormal coagulopathy laboratory results do not require correction when no clinical bleeding is observed. However, when major bleeding is encountered, fresh frozen plasma, fibrinogen or platelet replacement therapy is indicated. Use of tranexamic acid is reasonable in major hemorrhages without increased thrombotic events if no DIC is present. Recombinant factor VII and prothrombin complex concentrate are not recommended[7].

According to the American College of Cardiology (ACC) recommendations, VTE risk stratification should be evaluated in all hospitalized patients. Multiple bleeding tools are proposed such as the Caprini, IMPROVE and Padua models. Hospitalized patients with respiratory failure and co-morbidities, immobilized or requiring intensive care, should receive pharmacological prophylaxis. According to WHO recommendation, LMWH and direct oral anticoagulants (DOACs) should be considered for postdischarge thromboprophylaxis because they can reduce the risk of VTE. However, they may increase bleeding events.

Extended prophylaxis for up to 45 days is indicated only among patients with high VTE risk (especially those with comorbidities and elevated D-dimer > 2 times the upper normal limit). The role of therapeutic dose VTE without thrombotic evidence remains unclear[16].

The effect of anticoagulants in potentiating anti-inflammatory effects to decrease mortality is also mentioned. The complex relationship between thrombosis and inflammation may have some correlation and depend on multiple mediators working at different levels of the vascular system. Endothelium injury may also release P selectin and VCAM-1 to induce migration of leukocytes, initiating inflammation. Thrombin may directly stimulate an inflammatory response on endothelial cells and platelets and further lead to increasing pro-inflammatory cytokines[17]. This effect can explain the beneficial effectiveness of anticoagulant therapy in severe COVID-19 cases.

In Thailand, no obviously thrombotic cases have been reported and anticoagulants are not widely used for prophylaxis. Genetics thrombophilia is less possible due to Chinese patients also presenting high incidence of DIC and VTE events. More clinical data are required for acceptance to perform VTE prophylaxis in Thai clinical practice guidelines.

DOACs are considered another option for patients receiving vitamin K antagonists. DOACs do not need laboratory monitoring in an individual with normal kidney function. However, current data did not prove that DOACs are safer than VKA in bleeding aspects and DOACs may have some drug interaction with anti-viral regimens[18].

Salvage therapy with fibrinolytic agents is now proposed as an expert opinion especially in massive pulmonary VTE cases. Other indication includes limb-threatening DVT, acute stroke or acute myocardial infarction[6]. Urgent thrombolysis with recombinant tissue plasminogen activator may be indicated as a last chance for survival[9] along with therapeutic LMWH but unfractionated heparin (UFH) is more preferred in this setting due to concerns in bleeding complications.

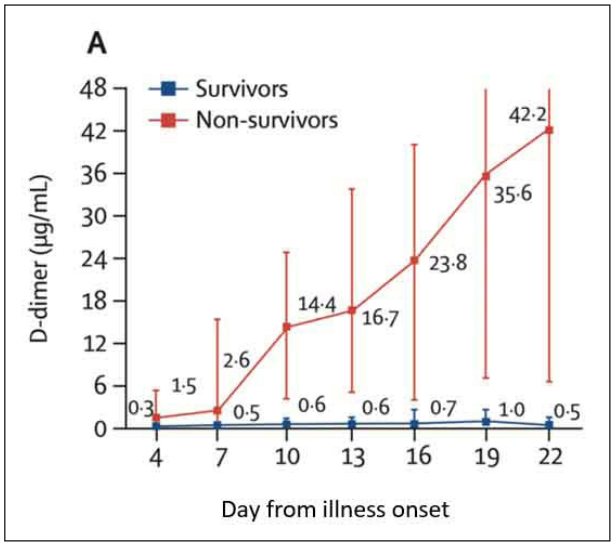

Figure 1 Serial D-dimer comparison between survivor and nonsurvivor groups[19]

Hematologic parameters to predict COVID-19 prognosis

Prognosis may depend on multiple factors such as age and underlying disease but hematologic parameters also predict the mortality as well. Multivariate analysis of 28-day mortality in severe COVID-19 showed D-dimer, PT and platelet count correlated with mortality rate[8]. Another study showed values to predict mortality included D-dimer level > 1 µg/mL, platelet count < 100 × 10^9/L, WBC count > 10 ×10^9/L, lymphocyte count < 0.8 ×10^9/L and PT ≥ 16 sec described in Table 4[19]. D-dimer rise as time progressed in a nonsurvivor group was observed compared with a steady level in the survivor group as shown in Figure 1.

Summary

Severe COVID-19 infection obviously manifests hypercoagulability in its early stages and later could transform to hemorrhage. The pathogenesis of the thrombosis may be due to the hypercoagulable state, vascular injury or immobilization. The DIC form in COVID-19

Table 4 Hematologic parameters and prediction of prognosis[19]

	Total (n = 191)	Survivor (n = 137)	Nonsurvivor (n = 54)	*p* value
White blood cell count, ($\times 10^9$/L)	6.2 (4.5-9.5)	5.2 (4.3-7.7)	9.8 (6.9-13.9)	< 0.0001
- < 4	32 (17%)	27 (20%)	5 (9%)	< 0.0001*
- 4-10	119 (62%)	95 (69%)	24 (44%)	-
- > 10	40 (21%)	15 (11%)	25 (46%)	-
Lymphocyte count ($\times 10^9$/L)	1.0 (0.6-1.3)	1.1 (0.8-1.5)	0.6 (0.5-0.8)	< 0.0001
- < 0.8	77 (40%)	36 (26%)	41 (76%)	< 0.0001
Hemoglobin (g/L)	128.0 (119.0-140.0)	128.0 (120.0-140.0)	126.0 (115.0-138.0)	0.30
- Anemia	29 (15%)	15 (11%)	14 (26%)	0.0094
Platelet count ($\times 10^9$/L)	206.0 (155.0-262.0)	220.0 (168.0-271.0)	165.5 (107.0-229.0)	< 0.0001
- < 100	13 (7%)	2 (1%)	11 (20%)	< 0.0001
Prothrombin time (sec.)	11.6 (10.6-13.0)	11.4 (10.4-12.6)	12.1 (11.2-13.7)	0.0004
- < 16	171/182 (94%)	124/128 (97%)	47 (87%)	0.016*
- ≥ 16	11/182 (6%)	4/128 (3%)	7 (13%)	-
D-dimer (μg/mL)	0.8 (0.4-3.2)	0.6 (0.3-1.0)	5.2 (1.5-21.1)	< 0.0001
- ≤ 0.5	55/172 (32%)	51/118 (43%)	4 (7%)	< 0.0001*
- > 0.5 to ≤ 1	45/172 (26%)	39/118 (33%)	6 (11%)	-
- > 1	72/172 (42%)	28/118 (24%)	44 (81%)	-
Serum ferritin (μg/L)	722.0 (377.2-1435.3)	503.2 (264.0-921.5)	1435.3 (728.9-2000.0)	< 0.0001
- > 300	102/128 (80%)	58/82 (71%)	44/46 (96%)	0.0008

has unique features including frequent normal platelet counts, low anti-thrombin levels and hyperfibrinogenemia with progression to hyperfibrinolysis. D-dimer level has greater advantage in predicting mortality and clotting status including pulmonary embolism and deep venous thrombosis. A prophylactic dose of anticoagulants is recommended in nearly all hospitalized patients especially those having prolonged immobility, respiratory failure or needing intensive care. LMWH or fondaparinux is preferred over heparin due to multiple contact risk. However, because a high incidence of thrombosis despite prophylactic regimen has been reported, the use of anticoagulants in therapeutics dose without evidence of thrombosis is proposed. Still, until now, studies to support this remain inadequate. Post discharge thromboprophylaxis may be considered among adults. All data at hand, should be reviewed and updated frequently as more studies emerge, so we can perceive the clinical entity of COVID-19's hematologic issues regarding hypercoagulability.

References

1. *Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020. doi:10.1111/jth.14830. [Epub ahead of print]*
2. *Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost. 2020;18:786-7.*
3. *Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-7.*
4. *Rezaie S. COVID-19: Thrombosis and Hemoglobin 2020 [cited 2020 April 9]. Available from: https://rebelem.com/covid-19-thrombosis-and-hemoglobin/.*
5. *Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020. Apr 10:S0049-3848(20)30120-1. doi:10.1016/j.thromres.2020.04.013. Epub ahead of print. PMID: 32291094; PMCID: PMC7146714.*
6. *Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A Report of Thromboelastography Findings and other Parameters of Hemostasis. J Thromb Haemost. 2020. Apr 17. doi:10.1111/jth.14850. [Epub ahead of print]*

7. *Hunt BR, A. McClintock, C. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19 International Society on Thrombosis and Haemostasis; 2020 [cited 2020 March 25]. Available from: https://thrombosisuk.org/covid-19-thrombosis.php.*
8. *Tang NB, H Chen, X Gong, J Li, D Sun, Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020. May;18:1094-9. doi:10.1111/jth.14817. Epub 2020 Apr 27.*
9. *Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A Comment. J Thromb Haemost. 2020. Apr 17. doi: 10.1111/jth.14860. [Epub ahead of print]*
10. *Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020. Apr 15. doi:10.1111/jth.14844. [Epub ahead of print]*
11. *Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020. Apr 15. pii: S1931-5244(20)30070-0. doi: 10.1016/j.trsl.2020.04.007. [Epub ahead of print]*
12. *Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. [A pathological report of three COVID-19 cases by minimally invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020;49:E009.*
13. *Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020. doi: https://doi.org/10.1016/j.kint.2020.04.003.*
14. *Cuker A, Peyvandi F. Coronavirus disease 2019 (COVID-19): Hypercoagulability 2020 [cited 2020 April 29]. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-hypercoagulability.*
15. *Kreuziger LL, A Garcia, D Cuker, A Cushman, M Connors, J. COVID-19 and VTE/Anticoagulation: Frequently Asked Questions American Society of Hematology; 2020 [cited 2020 April 17]. Version 2.1:[Available from: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation.*
16. *Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J Am Coll Cardiol. 2020. Apr 15:S0735-1097(20)35008-7. doi: 10.1016/j.jacc.2020.04.031. Epub ahead of print. PMID: 32311448; PMCID: PMC7164881.*
17. *Porterucha T, Libby P, Goldhaber S. More than an anticoagulant: Do heparins have direct anti-inflammatory effects? Thromb Haemost. 2017;117:437-44.*
18. *Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. DOACs and 'newer' haemophilia therapies in COVID-19. J Thromb Haemost. 2020. Apr 13. doi: 10.1111/jth.14841. [Epub ahead of print]*
19. *Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.*