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Тромбоэмболические осложнения при заболевании COVID-19, коротко об изменениях в рекомендациях

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РЕЗЮМЕ

Роль коагулопатии при тяжелой новой коронавирусной инфекции еще предстоит выяснить. Механизмы коагулопатии можно суммировать по двум основным направлениям: пути, обусловленные воспалением, и пути, связанные со специфическими вирусами. Частота тромбоэмболических событий высока, при этом тромбоэмболия легочной артерии является наиболее частым тромбоэмболическим осложнением. Низкомолекулярный гепарин считается основным профилактическим и терапевтическим средством у пациентов с COVID-19. Лечение тромбоэмболических осложнений следует начинать без промедления во всех случаях с определенным или клинически подозреваемым диагнозом, подтвержденным или нет определенными диагностическими методами.

В обзоре рассмотрены: механизмы развития коагулопатии при COVID-19, в том числе связанные непосредственно с действием вируса; диагностическая значимость биохимических маркеров и тромбоэластографии; частота встречающихся тромбоэмболических событий; подходы к профилактике и лечению связанной с COVID-19 коагулопатией.

Ключевые слова: тромбоэмболизм, COVID-19, венозный тромбоз, коагулопатия, лечение коагулопатии

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Thromboembolic complications in COVID-19 disease, a brief update

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ABSTRACT

The role of coagulopathy in severe novel coronavirus infection remains to be clarified. Coagulopathy mechanisms can be summarised in two main pathways: inflammation-related and specific-virus related pathways. The incidence of thromboembolic events is high with pulmonary embolism being the most frequent thromboembolic complication. Low molecular weight heparin is considered the main prophylactic and therapeutic option in patients with COVID-19. Treatment of thromboembolic complications should be started without delay in all cases with certain or clinically suspected diagnosis, whether confirmed or not with specific diagnostic methods.

The article reviews the following: mechanisms of development of coagulopathy in COVID-19 including those directly related to the action of the virus, the diagnostic value of biochemical markers and thromboelastography, the incidence of thromboembolic events, and approaches to the prevention and treatment of COVID-19-associated coagulopathy.

Key words: thromboembolism, COVID-19, venous thrombosis, coagulopathy, coagulopathy treatment

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Patients with coronavirus infection are prone to developing thrombotic complications such as pulmonary embolism (PE), deep vein thrombosis (DVT) and arterial thrombosis. This review analyzes the complex mechanisms of COVID-19 (coronavirus disease 2019) infection-associated coagulopathy, summarizes the incidence of venous thromboembolic events (venous thromboembolism, VTE), and discusses prophylaxis issues and therapeutic interventions in critically ill patients with COVID-19 infection and venous thromboembolic disease.

Mechanisms of coagulation dysfunction in COVID-19

The activation of inflammation and coagulation pathways constitutes a key element of COVID-19 infection pathophysiology and clinical presentation. Initially, this response is appears to be part of the adaptive innate host defence mechanism in order to limit spread of the virus pathogen [1]. However, excessive activation of the inflammation and coagulation cascade is detrimental and shown to be associated with increased morbidity and mortality [52, 53]. In general, the three components of Virchow's triad, comprised of endothelial injury, stasis/low blood flow and hypercoagulable state, represent three major qualities in physiology that explain the higher risk of thrombosis in severe COVID-19 patients [54].

Different specific mechanisms are possibly involved in the pathogenesis of coagulation dysfunction in patients with SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) infection [17]. These mechanisms could be briefly summarized in the following two main pathways: 1) inflammatory reaction-related pathways, 2) specific virus-related pathways.

1. Inflammatory reaction induced pathway includes the following pathophysiologic features

a. Release of the acute phase mediators of systemic inflammatory response

Invasion of SARS-CoV-2 in the lung causes a damage of both epithelial and endothelial cells leading to high levels of pro-inflammatory cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α – TNFα) [56, 62]. The elevated levels of pro-inflammatory cytokines induced by coronavirus infection and the activation of the innate immune system constitute the so-called "cytokine release syndrome" and seem to be related to the most severe clinical manifestations of the disease [15, 33].

The enhanced cytokine production during virus infection stimulates procoagulant reactions, with increased tissue factor expression, a key initiator of the activation of coagulation cascade [6]. Proinflammatory cytokines such as interleukin (IL)-1β and IL-6 stimulate the expression of tissue factor on immune cells and initiates extrinsic coagulation cascade activation. Results from clinical trials in sepsis with drugs targeting these pathways, showed that IL-6 rather than TNF seems to be the most important mediator for cytokine-induced coagulation activation [20]. Interleukin-6 is a multifunctional cytokine that is associated with the synthesis of other coagulation factors such as fibrinogen and factor VIII [49, 50]. IL-6 is believed to be linked to vascular endothelial growth factor (VEGF) expression on endothelial cells, inducing endothelial damage through transcriptional control mechanisms and further accelerating the prothrombotic reactions [7].

Data suggest that complement cascade activation as well as other acute phase components of the systemic inflammatory response could also mediate thrombotic microvascular injury in COVID-19 patients [3, 20, 30].

b. Release of von Willebrand factor containing ultra-large multimers

COVID-19-related proinflammatory cytokines cause direct endothelial injury resulting in ultralarge von Willebrand factor multimers (ULVWF) release from endothelial storage, the overexpression of tissue factor (TF) and the activation of platelets and neutrophils [52, 56, 62]. VWF containing ultra-large multimers has been shown to have the highest binding affinity to platelets, thus facilitating rapid platelet accumulation to sites of vascular injury and exposed subendothelial structures such as collagen [44]. VWF containing ultra-large multimers is also believed to be connected to the activation of coagulation and subsequent hypercoagulability state via TF/FVIIa pathway [39].

c. Suppression of fibrinolytic system and increase of procoagulant factors

Dysregulation of the fibrinolytic system is closely associated with multiple pathologic conditions, including inflammation, infection and thrombosis. Virus infection provokes suppression of the fibrinolytic system due to the decreased activity of urokinase-type plasminogen activator and increased release of plasminogen activator inhibitor-1 (PAI-1), which is the main modulator of the fibrinolytic system. PAI-1 is synthesized in endothelial cells and stored in platelets. Thrombin generation provoked by inflammation additionally triggers the generation and release of PAI-1 from platelets leading to the supressed fibrinolysis and pathological fibrin deposition [13, 23]. Hypercoagulation is further exacerbated by an imbalance between increased levels and activity of procoagulant factors (FV, FVIII, fibrinogen) and normal natural coagulation inhibitors (antithrombin III and proteins C) [2, 11, 19, 32].

2. Virus-specific pathway of coagulopathy in COVID-19 includes the following features

a. Direct endothelial injury

There is evidence of direct invasion of endothelial cells by coronavirus, potentially leading to cell injury [22, 28, 58]. Experimental data demonstrated that coronacirus can directly infect engineered human blood vessel cell organoids and human kidney cell organoids [35]. Post-mortem analysis of the transplanted kidney by electron microscopy revealed viral inclusion structures in endothelial cells in severe cases of SARS-CoV-2 [58]. Additionally, the injured endothelial cells can actively participate in pre-coagulation reactions. The rapid viral replication within endothelial cells may induce massive endothelial cell apoptosis causing the activation of the endothelial cell-dependent pathway of coagulation [48]. Although platelets can augment thrombin formation by endothelial cell-dependent reactions, endothelial cells damage alone can lead to formation of a cell-associated fibrin clot. The infected endothelial cell could provide an additional substrate for coagulation cascade initiation leading to fibrin formation.

b. Activation of the renin-angiotensin system

In addition to procoagulant and anticoagulant pathways dysregulation, there are data regarding the key role of renin-angiotensin system angiotensin-I-converting enzyme 2 (ACE2) receptor in pathophysiology of SARS-CoV-2 [15]. Spike surface glycoprotein of the coronavirus binds ACE2, an integral membrane receptor expressed in many mammal cells, inducing the virus-mediated decrease in ACE2 expression and activation of the renin-angiotensin system (RAS). This mechanism could play an important role in enhancing platelet adhesion and aggregation and reducing fibrinolytic activity [31, 57].

In summary, the following four major factors accelerate thrombus formation in COVID-19 infection.

1. Release of proinflammatory cytokines, mediators of inflammation and von Willebrand factor containing ultra-large multimers leads to the activation of coagulation cascade.
2. Release of plasminogen activator inhibitor-1 provokes suppression of the fibrinolytic system.
3. Activation of the renin-angiotensin system promotes platelets activation and aggregation.
4. Endothelial damage induced by inflammation and directs virus invasion further accelerates thrombus formation.

Markers of coagulation in COVID-19 infection

The most typical findings in patients with COVID-19 and coagulopathy include an increased D-dimer concentration, a relatively modest decrease in platelet count, and a prolongation of prothrombin time. Based

on the experience from published literature, monitoring PT, D-dimer and fibrinogen levels, platelet count are suggested to be helpful in monitoring and determining prognosis in COVID-19 patients requiring hospital admission.

Using the available evidence, the expert panel of International Society on Thrombosis and Haemostasis (ISTH) suggests monitoring coagulopathy in patients with severe COVID-19 by measuring prothrombin time, platelet count, and D-dimer concentrations every 2–3 days [47, 54]. However, high fibrinogen and D-dimer levels is known to be associated both with the hypercoagulable and inflammatory states. It should be kept in mind that D-dimer levels could not accurately differentiate between the presence of thromboembolic events and high levels due to the critical illness state and activation of inflammatory reaction. Consequently, an increase in D-dimer level is not specific for venous thromboembolic events and is not sufficient to make the diagnosis of VTE [24].

Updated guidelines on antithrombotic therapy in patients with COVID-19 declared that in hospitalized patients with COVID-19, hematologic and coagulation parameters should be commonly measured, although there are currently insufficient data to guide management decisions [36].

There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the levels of their coagulation markers. Experts suggest the use of standard-of-care objective testing (i.e., CTPA (computed tomography pulmonary angiogram), V/Q (ventilation-perfusion) scan, MRI (magnetic resonance imaging) venography, Doppler ultrasonography) to diagnose VTE based on clinical index of suspicion. Routine screening for VTE using bedside Doppler ultrasonography of the lower extremities based on elevated D-dimer levels is not recommended [36, 47].

Thromboelastography findings in COVID-19 patients

Thromboelastography (TEG) is a point-of-care test designed to assess multiple aspects of overall clotting formation and dissolution in whole blood.

The most common thromboelastography (TEG) findings in patients with COVID-19 include shortened reaction time, indicating increased early thrombin burst, shortened clot formation time, indicating increased fibrin generation, increased maximum amplitude, consistent with greater clot strength, and reduced clot lysis at 30 minutes consistent with suppression of fibrinolysis [39].

A few recent studies have demonstrated the ability of thromboelastography to identify patients at increased risk for VTE in COVID-19 patients with conflicting results [37, 39, 45, 61]. A study of J. R. Mortus et al. [37] evaluated the association of thromboelastographic results with hypercoagulability among critically ill patients with coronavirus disease 2019. Ninety percent of patients demonstrated hypercoagulable TEG findings associated with high incidence of thrombotic events (62%). A hypercoagulable innate TEG MA yielded 100% sensitivity and 100% negative predictive value for the occurrence of multiple thromboses. N. Salem et al. [45] observed a lower rate of hypercoagulable state using thromboelastography in critically ill patients with COVID-19 (30.8%). Additionally, the authors did not find a significant association between hypercoagulable state and thrombotic events. A study of E. Yuriditsky et al. [61] showed a significant proportion of critically ill patients with coronavirus disease who demonstrated hypercoagulable thromboelastography profiles (50%). Thirty-one percent of patients admitted to an ICU had thromboembolic events, however, the authors did not observe any association between thromboelastography variables and thromboembolic events in this cohort of patients.

Further studies are necessary in order to conclude a causal association between the thromboelastography variables and the prevalence of thrombotic complications in patients with coronavirus disease.

Differential diagnosis of COVID-19 associated coagulopathy

Many patients with severe COVID-19 present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy. However, COVID-19-related systemic coagulopathy presents specific pattern, distinct from DIC and thrombotic microangiopathy [2, 9, 46]. In fact, most patients with COVID-19 would not be classified as having DIC according to the DIC score of the International Society on Thrombosis and Haemostasis [14, 15, 18, 59]. Table 1 summarizes the main differences of clinical and laboratory features in patients with COVID-19, DIC and thrombotic microangiopathy.

Incidence of thromboembolic events

Coagulation system changes associated with COVID-19 suggest the presence of a hypercoagulable state which, together with endothelial injury, increases the risk of thromboembolic complications [40, 53]. In critically ill patients, the incidence of thromboembolic complications ranges from 5% to 15%; initial cohort studies show that the incidence of thromboembolic complications in patients with COVID-19 is as high as 21–69% [16, 21, 27, 34, 38, 41]. A study of F. A. Klok et al. [16] evaluated the incidence of the composite outcome of symptomatic acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism in 184 ICU patients with proven COVID-19 pneumonia; all patients received at least standard doses thromboprophylaxis. The cumulative incidence of thrombotic complications in ICU patients with COVID-19 infections was remarkably high (31%, 95% CI 20–41). CTPA and/or ultrasonography confirmed VTE in 27% and arterial thrombotic events in 3.7%. PE was the most frequent thrombotic complication (81%). Age and coagulopathy, defined as spontaneous prolongation of

Таблица 1. **Клинико-лабораторные характеристики COVID-19, ДВС и тромботической микроангиопатии**
Table 1. **Clinical and laboratory characteristics of COVID-19, DIC and thrombotic microangiopathy**

Clinical and laboratory characteristics	COVID-19	DIC	Thrombotic microangiopathies
Platelets consumption	Rare, mild	Frequent, profound increase	Frequent, profound
Fibrinogen levels	Upper limits of normal	Decrease	Normal
D-dimer concentrations	Profound increase	Profound or mild increase	Mild increase
International normalized ratio (INR)	Mild increase	Profound increase	Normal/mild increase
PTT	Mild increase	Profound increase	Normal/mild increase
Plasminogen activators, (u-PA and t-PA)	Profound increase	Increase in early phase, decrease thereafter	Increase
PAI-1	Increase	Increase	Increase
Natural anticoagulants	Mild decrease	Profound decrease	Normal
Lactate dehydrogenase (LDH)	Mild increase	Mild increase	Profound increase
Ferritin concentrations	Profound increase	Frequent Increase	High concentrations
Ultra-large von Willebrand factor multimers	Increase	Increase	Profound increase
ADAMTS13 concentrations	No data	Decrease	Profound decrease (< 10%) in TTP
C-Reactive protein	Profound increase	Profound increase	Increase
Hemolysis	Rare	Rare	Frequent, profound
Schistocytes	Rare	Frequent	Frequent, profound
Hypercytokinaemia	Profound	Frequent	Rare
Bleeding complications	Rare	Frequent	Frequent

Abbreviations: **DIC:** disseminated Intravascular Coagulation, **INR:** international normalized ratio, **PTT:** partial thromboplastin time, **PAI-1:** plasminogen activator inhibitor-1, **ADAMTS13 zinc-protease:** a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, **TTP:** thrombotic thrombocytopenic purpura, **u-PA** and **t-PA**: plasminogen activators urokinase-type (u-PA) and tissue-type (t-PA)

the prothrombin time > 3 s or activated partial thromboplastin time > 5 s were independent predictors of thrombotic complications.

R.A. Trigonis et al. [55] analysed data of 45 intubated patients with COVID-19 who underwent ultrasound evaluation to identify DVT and revealed the overall incidence of DVT 19 of 45 patients (42.2%) with all noted findings being lower extremity DVT. The authors found that all patients with DVTs received prophylactic regimens consisting of both LMWH and unfractionated heparin and there was no relationship between different prophylactic anticoagulation treatment and diagnosis of DVT.

C. Lodigiani et al. [27] studied data of 388 consecutive symptomatic patients (16% requiring intensive care) with proven COVID-19 admitted to a university hospital in Milan, Italy. The primary outcome includes thromboembolic complication (venous thromboembolism, ischemic stroke, and acute coronary syndrome). Thromboprophylaxis was used in all of ICU patients and 75% of patients admitted to the general wards. Thromboembolic events occurred in 28 patients, corresponding to a cumulative rate of 21% (27.6% ICU, 6.6% general ward). Diagnosis of venous thromboembolism was confirmed in 36% of all patients tested with VTE imaging tests and pulmonary embolism was confirmed in 33% of patients who underwent CTPA.

P. Demelo-Rodríguez et al. in a prospective study including 156 consecutive patients hospitalized in non-intensive care units with diagnosis of COVID-19 pneumonia and D-dimer levels > 1,000 ng/ml, screened for asymptomatic DVT with compression ultrasound (CUS) [8]. Doppler imaging test was positive for DVT in 23 patients (14.7%), of whom seven patients (4.5%) had bilateral distal DVT. Patients with DVT had higher median D-dimer levels: 4,527 ng/ml vs 2,050 ng/ml; $p < 0.001$. D-dimer levels > 1,570 ng/ml were associated with asymptomatic DVT (OR 9.1; 95% CI 1.1–70.1).

A prospective cohort study, including patients referred to 4 intensive care units (ICUs) of a French tertiary hospital referred to a high number of patients with COVID-19 ARDS developing life-threatening thrombotic complications, essentially pulmonary embolisms (16.7%), despite the use of prophylactic or therapeutic anticoagulation treatment [11]. Comparison with non-COVID-19 ARDS patients ($n = 145$) showed that COVID-19 ARDS patients ($n = 77$) developed significantly more thrombotic complications, mainly pulmonary embolism (11.7 vs. 2.1%, $p < 0.008$).

A systematic review and meta-analysis of K. Boonyawat et al. [5] evaluated the incidence of incidence of venous thromboembolic events in patients with COVID-19. The authors analysed data from 36 studies and found that critically ill patients requiring ICU admission had a higher incidence of VTE (28%) than those in a non-ICU setting (10%), additionally studies that incorporated the screening protocols had higher incidence of venous thromboembolic events. The post hoc subgroup analysis revealed that studies from the Netherlands and France had a

higher pooled incidence of PE ranging from 17 to 27%, whereas the studies from Italy and UK reported lower incidence of PE, ranging from 3 to 7%. Among the imaging studies which reported PE events detected by CTPA or DVT detected by CUS, the incidences of PE and DVT were 26 and 33%, respectively. The differences between studies could be explained by several confounding factors, such as different diagnostic approach, divergences in performing imaging tests and CTPA. The indications for CTPA were varied between studies. Most studies performed CTPA based on clinical suspicion, whereas some studies based on a high D-dimer level or only in patients with DVT. Several studies did not mention performing CTPA or did not mention the indication for CTPA, which could underestimate the incidence of PE. In twelve studies with no leg compression ultrasound screening (CUS), the incidence of DVT was 6% (95% CI 4–9%), whereas in nine studies with CUS screening, the incidence of DVT was 32% (95% CI 18–45%).

Management of COVID-19 associated coagulopathy

Prophylactic anticoagulation

An early study of Tang et al. evaluated coagulation status, medications, and outcome in 449 patients with severe COVID-19, 99 of them receiving heparin (mainly with low molecular weight heparin) for prophylactic anticoagulation. Anticoagulant therapy appears to be associated with better prognosis in severe COVID-19 patients presenting coagulopathy, especially those with markedly elevated D-dimer (> 6-fold of upper limit of normal). Interestingly, the incidence of hemorrhagic complications in patients with COVID-19, even in those with severe coagulopathy, appear to be low [51].

In view of the hypercoagulable state of patients with severe COVID-19, and the potential increased risk of thrombosis, experts suggest that in all patients who require hospital admission with COVID-19 infection prophylactic treatment with low molecular weight heparin (LMWH) should be considered in the absence of any medical contraindications such as active bleeding and low platelet count (less than 25×10^9/L); while monitoring is advised in patients with severe impairment of renal function [47, 54].

Guidelines from the American College of Chest Physicians (ACCP) [36] suggest prophylaxis with LMWH or fondaparinux instead of unfractionated heparin or direct oral anticoagulants (DOACs) for all hospitalized patients with COVID-19 in the absence of contraindications. Once-daily injectable LMWH and fondaparinux, are preferred to unfractionated heparin (2–3 times per day), because of the lower exposure of clinicians to infected patients and lower incidence of heparin-induced thrombocytopenia. Additionally, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID-19 infection where proinflammatory cytokines are markedly raised [42].

If LMWH is not available, unfractionated heparin could be used, although this requires more frequent injections; an alternative is fondaparinux, but whether this drug has the postulated anti-inflammatory benefits of heparin is unclear and data on the use of fondaparinux are scarce. Additionally, concerns were raised about relatively longer half-life and reversibility of fondaparinux compared to LMWHs [36, 47].

Both LMWH and fondaparinux are preferred to direct oral anticoagulants (DOACs) because of possible interactions of DOACs with immunosuppressant, antiviral and other experimental drugs used for treatment of COVID-19 [36, 47].

It is still debated if the use of standard prophylactic anticoagulation dosing is sufficient in patients with increased disease severity as well as in patients requiring ICU admission, given the high VTE incidence despite standard thromboprophylaxis [4, 26, 29]. Although higher dose of LMWHs has been proposed for prophylaxis in critically ill patients with COVID-19, the experts suggest standard-dose LWMH based on the absence of clinical trial data on this issue [47]. The ACCP states that patients with severe COVID-19 might need higher-dose thromboprophylaxis than routinely given because of their hypercoagulable state [47]. However, experts highlight that benefit-to-risk ratio remains to be addressed in prospective trials, before adopting an aggressive anticoagulation approach.

The International Society on Thrombosis and Hemostasis (ISTH) [47] suggests that half-therapeutic-dose LMWH be considered for prophylaxis in high-risk patients with COVID-19, and that a higher dose be considered in patients with obesity; however, optimal prophylactic therapy remains unclear. Probably, a more aggressive thromboprophylaxis using LMWH or UFH could be considered on an individual basis, especially in patients with multiple risk factors for thromboembolism such as obesity, cancer, personal history of venous thromboembolism [25, 36].

Prophylactic anticoagulation in specific clinical scenarios

a. Genetic risk factors and prophylaxis in specific ethnic populations

Data suggest that the incidence of venous thromboembolism is higher in Caucasian population in comparison to Chinese population [12, 21, 43]. Conversely, risk of thromboembolic complications is higher in American-African population compare to Caucasian individuals [10, 60]. Because the evidence suggests that the prevalence and genetic risk factors of VTE vary significantly among ethnic populations, and the incidence of VTE in Asian populations is low (21–29 cases per 100,000 individuals per year), a higher dose of LMWH might be considered in non-Asian patients with severe COVID-19 [51].

b. Chronic anticoagulant or antiplatelet therapy

Hospitalized patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops, or other contraindications are present [36].

Therapeutic measures

Current guidelines suggest for hospitalized COVID-19 patients who experience sudden deterioration of pulmonary, cardiac, or neurological function, rapid increase of oxygenation requirements, rapid development of right heart failure, and/or shock in combination with high D-dimer levels, thromboembolic disease should be part of the differential diagnosis [36, 47].

In patients with COVID-19 and acute PE with cardiopulmonary deterioration (progressive increase in heart rate, decrease in systolic BP, increase in jugular venous pressure, worsening gas exchange, clinical signs of shock i.e. cold sweaty skin, reduced urine output, confusion, progressive right heart dysfunction on echocardiography, or increase in cardiac biomarkers) after initiation of anticoagulant therapy who have not yet developed hypotension and who have a low risk of bleeding, experts suggest systemic thrombolytic therapy in favour of no therapy [36].

In patients with a strong clinical suspicion of thromboembolic complications in whom no objective diagnosis can be obtained due to practical difficulties to perform the diagnostic tests in unstable patients, or due to the limited access to contrast-enhanced CT, therapeutic anticoagulation could be initiated, particularly in the absence of contraindications for anticoagulation treatment [36, 47].

Current recommendations on thromboprophylaxis and VTE treatment in hospitalized COVID-19 patients based on ACCM and ISTH guidelines [4, 36, 47] are presented in table 2.

***Таблица 2*. Текущие рекомендации по ведению ВТЭ у госпитализированных пациентов с COVID-19**

***Table 2*. Current recommendations on VTE management in hospitalized COVID-19 patients**

Recommendations	American College of Chest Physician (ACCP)	Committee of the International society on Thrombosis and Haemostasis (ISTH)
Prophylaxis, hospitalized, non-critically ill patients	Use of anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis (in the absence of a contraindication) ***(Suggestion)***	Use of anticoagulant thromboprophylaxis over no anticoagulant thromboprophylaxis (in the absence of contraindications)
Anticoagulant thromboprophylaxis, critically ill patients/ sick ICU hospitalized COVID-19 patients	Use of thromboprophylaxis over no anticoagulant thromboprophylaxis (in the absence of contraindications) ***(Recommendation)***	Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleeding risk
Choice of anticoagulant for thromboprophylaxis in critically ill or acutely ill hospitalized patients	Thromboprophylaxis with LMWH or fondaparinux over thromboprophylaxis with UFH. ***(Suggestion)*** Thromboprophylaxis with LMWH, fondaparinux or UFH over thromboprophylaxis with a DOAC ***(Recommendation)***	Thromboprophylaxis with either UFH or LMWH or fondaparinux over DOACs unless there are absolute contraindications
Prophylactic dose in critically ill or acutely ill hospitalized patients	Standard dose anticoagulant thromboprophylaxis over intermediate or increased weight-based dosing) or full treatment dosing, per existing guidelines ***(Recommendation)***	Thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH can also be considered in high risk patients. Patients with obesity should be considered for a 50% increase in the dose of thromboprophylaxis
Duration of VTE prophylaxis for hospitalized COVID-19 patients	No recommendations	Extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria. The duration of post-discharge thromboprophylaxis can be approximately 14 days at least. Either LMWH or a DOAC (i.e., rivaroxaban or betrixaban) can be used for extended duration thromboprophylaxis
Anticoagulant treatment, critically ill COVID-19 patients with proximal DVT or PE, anticoagulant drug choice	Use of parenteral over oral anticoagulant therapy. Use of LMWH or fondaparinux over UFH ***(Suggestion)***	LMWH in the inpatient setting and DOACs in the post-hospital discharge setting. A change of anticoagulant regimen (i.e., from prophylactic or intermediate dose to treatment dose regimen) can be considered in patients without established VTE but deteriorating pulmonary status or ARDS
Anticoagulant treatment, duration	Anticoagulation therapy for a minimum duration of three months for COVID 19 patients with proximal DVT or PE ***(Recommendation)***	The duration of treatment should be at least three months
Treatment, thrombolytic therapy	No systemic thrombolytic therapy in most patients with COVID-19 and acute, objectively confirmed PE not associated with hypotension ***(Recommendation)***	No recommendations
Treatment, thrombolytic therapy	Use of systemically administered thrombolytics over no such therapy in patients with COVID-19 and both acute, objectively confirmed PE and hypotension (systolic BP < 90 mm Hg) with cardiopulmonary deterioration or signs of shock due to PE, who are not at high risk of bleeding ***(Suggestion)***	No recommendations

Таблица 2. **Окончание**

Table 2. **Ending**

Recommendations	American College of Chest Physician (ACCP)	Committee of the International society on Thrombosis and Haemostasis (ISTH)
Thrombolysis in patients with high clinical suspicion and not obtainable imaging	Thrombolysis may be considered in select patients when cardiac arrest is suspected to be caused by PE and imaging is not obtainable ***(Suggestion)***	No recommendations

Abbreviations: **LMWH**: low-molecular-weight heparin; **UFH**: unfractionated heparin, **DOAC**: direct oral anticoagulant, **DVT**: deep venous thrombosis, **PE**: pulmonary Embolism

Conclusion

It is still challenging to establish the association between the perplexed concepts of COVID-19 induced immune response, inflammatory reaction, endothelial injury and coagulopathy. In practice, however, the high incidence, as well as the complex nature and severity of thrombotic events occurring in critically ill patients with COVID-19 disease emphasize the pivotal role of coagulation-targeted laboratory monitoring and therapeutic management.

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