The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

Optimization Of Methods For The Prevention Of Pulmonary Embolism

Nodirbek Yakubov
Assistant, Department Of Oncology And Medical Radiology, Andijan State Medical Institute, Andijan, Uzbekistan

Nataliya Dadamyants
Ph.D., Senior Researcher, Republican Scientific Center For Emergency Medical Aid, Head Of Department Of Ultrasound Diagnostics, Tashkent, Uzbekistan

Dilfuzahon Mamarasulova
Md, Associate Professor, Head Of The Department Of Oncology And Medical Radiology, Andijan State Medical Institute, Andijan, Uzbekistan

ABSTRACT

This review examines changes in the hemostatic system parameters in patients with COVID-19 and analyzes their practical significance. The article discusses modern approaches to the prevention and treatment of thrombotic/thromboembolic complications in COVID-19.

KEYWORDS

Thrombosis, hemostasis, antithrombotic therapy, heparin, COVID-19.

INTRODUCTION

Coronavirus infection (COVID-19), an acute infectious disease caused by the SARS-CoV-2 virus, is characterized by activation of the hemostasis system, which in the most severe cases can lead to the development of consumption coagulopathy. At present, it remains unclear whether COVID-19 is the direct cause of these disorders or they arise as the infectious process progresses [1]. In COVID-19, the incidence of asymptomatic and clinically pronounced thrombotic/thromboembolic complications (TEC) remains unclear, which is largely due to the difficulties of their diagnosis (problems of instrumental examination of patients lying on their stomach, the desire to limit the involvement of additional equipment and personnel). At the same time, according to some reports, the frequency of venous and

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

arterial thrombosis in severely ill COVID-19 patients is quite high. Thus, in 184 patients with pneumonia with COVID-19, who was in intensive care units of 3 hospitals in Denmark, 13% of whom died, symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, myocardial infarction, or arterial thromboembolism noted in 31% of cases [2]. At the same time, objectively confirmed venous feasibility studies prevailed (27%, in the majority PE), while the incidence of arterial thrombosis was only 3.7%. According to a single-center retrospective study in China in patients with severe pneumonia with COVID-19, who was in the intensive care unit (n = 81), the incidence of venous thrombosis of the lower extremities was 25% [3]. When analyzing 107 patients with pneumonia with CODID-19, who were consecutively admitted to the intensive care unit in Lille (France), the detection rate of PE was 20.6% and was much higher than in patients of similar severity for the same period of 2019 (6.1%) [4]. During autopsies, microthrombi in small vessels of the lungs in the absence of a feasibility study has also been described [5, 6]. The role and causes of these disorders (specific effects of viral infection, inflammation, progressive coagulopathy) are being actively discussed.

The state of the hemostasis system in patients with COVID-19 Among the changes in indicators characterizing the state of the hemostasis system and associated with the severity of the disease and its prognosis, COVID-19 indicates an increase in the level of D-dimer in the blood, an increase in prothrombin time, as well as thrombin and activated partial thromboplastin time (APTT). Initially, there may be an increase in the concentration of fibrinogen; then, as the disorder progresses, the levels of fibrinogen and antithrombin in the blood decrease. Thrombocytopenia is also associated with the severity and prognosis of the disease, but it is rarely severe [7, 8].

One of the factors contributing to the activation of the blood coagulation system is an increase in the concentration of pro-inflammatory cytokines, which fits into the concept of the relationship between inflammation and thrombosis (the so-called "immunothrombosis"). Published data on 3 critically ill COVID-19 patients with multiple cerebral infarctions, who had high blood levels of antiphospholipid antibodies (anticardiolipin IgA in combination with anti-β2-glycoprotein 1 immunoglobulins A and G), which is believed to be most likely a consequence of severe inflammation, and can occur in any severe infection [9]. There is a hypothesis about the leading role of immunothrombosis with damage to lung microvessels in the progression of respiratory failure in COVID-19 [10].

Changes in indicators characterizing the state of the hemostasis system and their prognostic value were assessed in a retrospective study on 183 patients with confirmed COVID-19 who were consistently admitted to Tongji University Hospital in Wuhan (China). Of these, 11.5% died [11]. During hospitalization, the later deceased had higher D-dimer values than the survivors (median 2.12 vs 0.61 μg / ml; p <0.001), fibrin degradation products (median 7.6 vs 4.0 μg / ml; p <0.001) and prothrombin time (median 15.5 vs 13.6 sec; p <0.001). At the same time, in patients with an unfavorable outcome, these indicators continued to increase in the future, while in survivors they changed little, rarely and slightly exceeding the upper limit of the norm (0.5 μg / ml for D-dimer and 14.5 sec for prothrombin time).

MATERIALS AND METHODS OF RESEARCH

In a retrospective study of electronic medical records of 499 patients with severe manifestations of COVID-19 who were subsequently admitted to the same Tongji University Hospital in Wuhan, an increased

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

level of D-dimer along with age, an increase in prothrombin time and a lower concentration of platelets in blood was an independent predictor of death in the next 28 days. [12].

A similar result was obtained in a retrospective study of patients with COVID-19 admitted to a respiratory hospital in Wuhan (n = 191), 54 of whom died in hospital [13]. D-dimer levels at hospital admission exceeding 1 μg / ml were an independent predictor of death (relative risk (RR) 18.42 at 95% confidence intervals (CI): 2.64 - 128.55) along with age and the sum of points on the SOFA (Sequential Organ Failure Assessment) scale. At the same time, in deceased patients, it gradually increased, sometimes to a very high level, while in survivors it changed little and rarely exceeded the upper limit of the norm.

According to a retrospective analysis of electronic records from 260 outpatient offices and 4 emergency hospitals in New York, an independent risk factor for the severity of the disease to critical (the need to stay in an intensive care unit, mechanical ventilation, death or transfer to a hospice) in 4103 patients with confirmed COVID-19 along with blood oxygen saturation <88%, ferritin levels> 2500 ng/ml and C-reactive protein> 200 mg / L was a D-dimer level> 2500 ng/ml (RR 6.9 at 95% CI: 3.2-15.2) [14].

RESULTS AND DISCUSSION

In general, it is believed that of the studied indicators characterizing the state of the hemostasis system, D-dimer is the most attractive as a marker of severity and unfavorable prognosis in COVID-19 - its definition is widely available and standardized, and the differences between the groups of living and dead are well expressed [7]. The prothrombin time also has a prognostic value, however, during hospitalization, its changes in patients with a poor prognosis are not as pronounced as in the D-dimer, and, in general, slightly exceed the upper limit of the norm.

Experts of the International Society for Thrombosis and Hemostasis recommend that during hospitalization, determine the level of D-dimer in the blood, prothrombin time, fibrinogen concentration and perform a detailed general blood test, including the level of platelets, followed by regular monitoring of these indicators (daily or more often with a pronounced increase in D-dimer, increased prothrombin time, blood platelet level <100 × 109 / L, fibrinogen level <2.0 g / L), so as not to miss an aggravation of the disease and the development of severe consumption coagulopathy, when intensification of COVID-19 treatment may be required and/or the introduction of blood components [7]. At the same time, it is proposed to consider the level of D-dimer in the blood as expressed as 3-4 times higher than the upper limit of the norm and to classify such patients as candidates for hospitalization even in the absence of other severe manifestations of COVID-19. In addition, it is emphasized that the prothrombin time and prothrombin ratio cannot be replaced by an international normalized ratio, which does not capture the relatively small changes that occur with COVID-19, and also that the clinical interpretation of these indicators should take into account all other possible reasons for their changes (for example, progression of liver disease, use of anticoagulants). At the same time, not all medical organizations insist on such frequent monitoring of hemostatic system parameters - for example, in the algorithms of Massachusetts General Hospital, daily determination of these parameters is recommended only in the intensive care unit or when the level of D-dimer in the blood is> 1000 ng / ml [15]. It is known that an increase in the concentration of D-dimer in the blood indicates the activation of the processes of thrombus formation and fibrinolysis, but does not always indicate the presence of a thrombus. Thus, in a one-center retrospective study in China in 81

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19
IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

patients with severe pneumonia with COVID-19 who were in the intensive care unit, the D-dimer level> 1500 ng / ml had a sensitivity of 85.0%, a specificity of 88.5%, and a predictive the value of a negative result is 94.7% in relation to the detection of venous thrombosis of the lower extremities (for the level of D-dimer> 3000 ng/ml these indicators were 76.9%, 94.2%, and 92.5%, respectively) [3]. Given the undesirability of additional instrumental examinations in patients with COVID-19 without strict indications, most specialists now believe that routine screening for venous feasibility studies in asymptomatic patients with very high D-dimer levels should not be performed (68% of 46 members voted for this) international working group of experts [1]).

To assess the nature of disorders of the hemostasis system in patients with COVID-19, it was proposed to use two scales that are widely used in sepsis [16]. Obviously, the first of them - the scale of coagulopathy caused by sepsis - characterizes the activation of blood coagulation processes and indicates that stage of the process when there is still no pronounced coagulopathy of consumption. There is evidence that this scale can be used to select patients with COVID-19 who benefit most from anticoagulant use. Thus, in a retrospective study of electronic case histories of 499 patients with severe manifestations of COVID-19 who were sequentially admitted to Tongji University Hospital in Wuhan (China), it turned out that patients who received mainly prophylactic doses of heparin (mainly enoxaparin 40-60 mg / days, less often unfractionated heparin (UFH) 10,000-1500 U / day for at least 7 days), 28-day mortality is lower in cases when the sum of points on the sepsis-induced coagulopathy scale was ≥4 or there was a marked increase in the level of D-dimer in the blood (> 6 times the upper limit of normal) [12]. The presence of obvious disseminated intravascular coagulation (DIC) indicates the development of consumption coagulopathy, when the replacement of the missing components of the blood coagulation system may be required. The occurrence of ICE is associated with a poor prognosis. Thus, in the study cited above, 183 patients with confirmed COVID-19 during hospitalization had ICS in 71.4% of the deceased, and only 0.6% of those discharged from the hospital [11].

Prevention and treatment of feasibility studies in patients with COVID-19 It is obvious that since COVID-19 is an acute infection, approaches to the prevention of venous feasibility studies developed for patients hospitalized with acute non-surgical diseases can be extended to this disease.

After the publication of the results of randomized placebo-controlled trials ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study), MEDENOX (Prevention of Venous Thromboembolism in Medical Patients With Enoxaparin) and PRE-VENT (Prevention of Recurrent Venous Thromboembolism) by 2008, it became obvious that in a non-surgical hospital, patients hospitalized with severe heart failure, a lung disease with severe respiratory failure, including chronic obstructive pulmonary disease and pneumonia, as well as with a combination of severe limitation of mobility with large factors, need to prevent venous feasibility studies risk of venous thrombosis - DVT of the lower extremities / PE in history, active malignant neoplasm, sepsis, acute neurological disease with impaired mobility of the lower extremities, intestinal inflammation [17-20].

In the future, when deciding on the advisability of prevention, it was recommended to use the risk stratification scales, in particular, the validated Padua scale [21, 22]. Obviously, COVID-19 patients hospitalized with pneumonia have at least 2 points on this scale, and with an additional restriction of the motor regime, they fall into the category of venous feasibility studies in need of prevention. There are other scales for assessing the risk of venous

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

feasibility studies in patients hospitalized with nonsurgical diseases, including a well-validated scale based on the analysis of the IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) database [23]. In a subsequent large randomized controlled trial, APEX (Acute Medically III VTE Prevention With Extended Duration Betrixaban Study), it was shown that an increased level of D-dimer can be used to select patients in need of prevention of venous TEO: as it turned out, patients hospitalized with the acute non-surgical disease (heart failure, respiratory failure, infection, rheumatic disease, or ischemic stroke) and those with elevated D-dimer levels (at least 2 times the upper limit of normal) benefit from prolonged use of anticoagulants to prevent venous TEO [24].

Based on the database of this study, a modified IMPROVE scale - IMPROVED - was proposed, in which the level of D-dimer in the hospital was added (as a risk factor for venous thrombosis) [25]. It is characteristic that according to this scale, patients hospitalized with COVID-19 and having an increased level of D-dimer in the blood immediately fall into the group of increased risk of a venous feasibility study.

CONCLUSION

Thus, based on the totality of accumulated facts, most patients hospitalized with COVID-19 meet the criteria for a high risk of venous feasibility studies and need their prevention. The group of experts of the International Society for Thrombosis and Hemostasis believes that the use of anticoagulants for the prevention of venous feasibility study should be in all patients hospitalized with COVID-19 [7]. In addition, in the most severe cases (sepsis-induced coagulopathy score ≥4 or blood D-dimer level> 6 times the upper limit of normal), heparin can be expected to reduce mortality [12]. At the same time, another international group of experts proposes a more conservative approach, when in patients hospitalized with COVID-19, the risk of a venous feasibility study (for example, according to the Padua or IMPROVE scale) should first be determined and only after that a decision should be made about the appropriateness of prevention [1] However, they also recommend starting the prophylactic administration of heparin immediately in patients with respiratory failure or concomitant diseases (for example, malignant neoplasm, heart failure), as well as those who are bedridden or need intensive care. Obviously, this position is closer to the recommendations of the American College of Thoracic Physicians [20, 21].

In general, it is recommended to give preference to low molecular weight heparins (LMWH), primarily to reduce the number of subcutaneous injections in a patient with COVID-19 [1, 7, 15].

There is no single point of view on the doses of heparin in patients hospitalized with COVID-19 [1, 26]. Most tend to use standard prophylactic doses, but a number of experts prefer higher (intermediate or therapeutic) doses; according to the vote of 46 members of the international working group of experts, 31.6% voted for the use of intermediate doses in patients without DIC, 5.2% for therapeutic doses [1]. It is characteristic that in the above-mentioned study of 184 patients with pneumonia with COVID-19 in the intensive care unit, who were predominantly diagnosed with DVT and / or pulmonary embolism with symptoms, all received at least a prophylactic dose of LMWH [2]. However, upon closer examination, it becomes obvious that it was, apparently, often lower than that recommended for the prevention of venous thrombosis in high-risk nonsurgical patients. So, initially in 2 out of 3 hospitals, it was 2850 IU (0.3 ml) 1 time/day. for patients weighing <100 kg and only in one of the higher doses were used in this category of patients (5700 U - 0.6 ml - 1 time/day). Thus, the results of this study do not support the need for increased doses of LMWH.

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

It is believed that there are few contraindications for starting the use of prophylactic doses of heparin - this is ongoing bleeding and the level of platelets in the blood <25 × 109 / L, and when using LMWH or fondaparinux sodium - also severe renal failure [1, 7, 15]. At the same time, experts from the International Society for Thrombosis and Hemostasis emphasize that increased prothrombin time and APTT are no contraindications [7]. If anticoagulants are contraindicated, it is suggested to use intermittent pneumatic compression of the lower extremities for the prevention of DVT [1].

The recommended duration of prophylaxis of venous feasibility studies with anticoagulants in hospitalized nonsurgical patients is from 6 to 21 days, until the restoration of motor activity or discharge [21]. Extending it up to 45 days. after discharge, it is suggested to consider patients with persistent risk factors who do not have a high risk of bleeding [1]. Evidence of the effectiveness of this approach in nonsurgical patients (not with COVID-19) takes place for prophylactic doses of enoxaparin, as well as direct oral anticoagulants betrixaban and rivaroxaban, but none of them is registered in the Russian Federation for prolonged prophylaxis of DVT / PE [24, 27, 28]. There is also no data on the advisability of preventing DVT of the lower extremities in patients with mild manifestations of COVID-19 when treated at home. The international group of experts does not exclude this possibility for patients with the highest risk of venous TEO (in particular, severely limited mobility, history of DVT / PE, active malignant neoplasm) [1].

Obviously, with the identified feasibility study (DVT, PE, acute coronary syndrome with intracoronary thrombosis, etc.), one should switch to therapeutic doses of heparin. If there are no contraindications, it is suggested to give preference to LMWH, since this will avoid intravenous infusion and frequent blood sampling for the selection of the UFH dose [1, 15]. In addition, as the severity of COVID-19 increases, APTT rises. Accordingly, this indicator is difficult to use for the selection of the dose of UFH and the only way out is to regularly assess anti-Xa activity.

In patients with heparin-induced immune thrombocytopenia, a history of subcutaneous fondaparinux sodium or intravenous infusion of bivalirudin may be considered. At the same time, it is known that, unlike heparin preparations, fondaparinux sodium does not reduce the level of platelets in the blood. At the same time, it is most likely devoid of the potentially beneficial pleiotropic, primarily anti-inflammatory, effects inherent in heparin [26].

LMWH and fondaparinux sodium is contraindicated in severe renal failure - the threshold values for creatinine clearance / glomerular filtration rate differ for different drugs. In addition, they act for a long time and it is impossible to quickly eliminate their effect (the antidote of LMWH, protamine sulfate, only partially eliminates its effect, fondaparinux sodium has no antidote). Therefore, these drugs are not recommended for use in patients with rapidly changing renal function [15]. With severe renal failure, UFH may be used. In addition, a more controlled intravenous infusion of UFH, which has a shorter duration and has a complete antidote, appears to be preferable in cases where invasive interventions are required.

The proposed doses of heparin preparations are presented in Table 4. At present, it is not clear whether prophylactic doses of parenteral anticoagulants should be reduced in patients with renal insufficiency, low body weight, and increased in severe obesity [26]. Due to the lack of clinical trials, routine increases in prophylactic doses of anticoagulants in obesity are not recommended. At the same time, it was noted that 20 out of 22 patients with pneumonia with COVID-19 and PE in the intensive care unit of Lille (France) received standard preventive doses of heparin, and the

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

authors point out the widespread prevalence of obesity among hospital admissions [4]. It is possible that in difficult cases when choosing a prophylactic dose of heparin for obesity, it is worth considering the presence of other risk factors for venous feasibility studies (including an increased level of D-dimer), as well as monitoring anti-Xa activity in the blood.

Among other remaining uncertainties is whether the use of a higher than a prophylactic dose of heparin should be considered when the level of D-dimer in the blood is very high (for example, 6-8 times the upper limit of the norm), as well as in patients who need more intense respiratory support / in the development of acute respiratory distress syndrome [26].

When DIC occurs without overt bleeding, it is usually recommended to use a prophylactic dose of UFH or LMWH and emphasize that there is insufficient evidence to support the routine use of higher doses. In patients who have received therapeutic doses of an anticoagulant at the time of the development of DIC, it is proposed to reduce the intensity of anticoagulation, unless the danger of thrombosis is too great. In general, the decision to change the dose of heparin or to cancel it in a given clinical situation should be strictly individual, taking into account the indications for the use of anticoagulants on the one hand and the risk of bleeding on the other. However, there is no single point of view. Thus, of the 46 members of the international working group of experts, 29.7% voted for the use of intermediate doses of heparin in hospitalized patients with moderate and severe manifestations of COVID-19 in combination with suspected or confirmed DIC that do not have obvious bleeding, and 16 voted for therapeutic doses. 2% and 62% voted for the reduction of the therapeutic dose of anticoagulants in patients who did not have acute indications for it [1].

If a patient with mild manifestations of COVID-19 is already using oral anticoagulants for other indications (atrial fibrillation, previous venous feasibility studies, mechanical prosthetic heart valves, etc.), it is reasonable to continue taking them. However, if the condition worsens and/or the possibility of using drugs for the treatment of COVID-19 that interact undesirably with oral anticoagulants is not excluded, it is advisable to switch to therapeutic doses of heparin (preferably LMWH). There is also a recommendation to switch to therapeutic doses of heparin drugs in all patients hospitalized with COVID-19 [15].

If the use of antiplatelet agents is necessary, it is reasonable to prefer drugs without unacceptable drug interactions for the treatment of COVID-19 in a particular patient [1]. Obviously, the decision on the possibility of using antiplatelet agents and the composition of antiplatelet therapy should be made individually, taking into account the risk of coronary thrombosis and bleeding in a particular patient. In particular, it is not recommended to refuse double antiplatelet therapy in patients with the recent acute coronary syndrome, as well as in the first 3 months. after coronary stenting [1]. According to an international group of experts, if DIC occurs, all long-acting antiplatelet agents should be canceled, and if this is unacceptable, then in the absence of obvious bleeding, it is reasonable to continue double antiplatelet therapy with a blood platelet level of ≥50 × 109 / L, switch to monotherapy at a level of 25 × 109 / L to <50 × 109 / L and discontinue antiplatelet agents at a level of <25 × 109 / L (depending on the circumstances, the threshold values may be either higher or lower than those indicated) [1]. From the point of view of the risk of bleeding as part of dual antiplatelet therapy, clopidogrel is attractive, but when taking lopinavir/ritonavir its use becomes undesirable; It is believed that the combination of

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286
OCLC - 1121105510

lopinavir/ritonavir with clopidogrel or ticagrelor is not excluded when using modern methods for assessing the functional activity of platelets for P2Y12 receptor blockers, however, the effectiveness of this approach, as well as the target values of residual functional platelet reactivity, are not clear [1].

In case of coagulopathy of consumption and absence of bleeding, it is recommended to maintain the level of platelets> 20 × 109 / L, fibrinogen> 1.5-2.0 g / L, and in case of bleeding - the level of platelets> 50 × 109 / L, fibrinogen> 1.5-2, 0 g / l, prothrombin ratio <1.5 due to the introduction of missing blood components [1, 7].

There is a hypothesis that in patients with severe respiratory distress syndrome, intravenous administration of low doses of fibrinolytic may be useful to combat microcirculation disorders due to the formation of fibrin-rich microthrombi in the lung vessels [29]. The experience of long-term intravenous administration of low doses of tissue plasminogen activator (25 mg for 2 hours, then another 25 mg for 22 hours with the cessation of UFH infusion at this time) in 3 such patients indicates the possibility of a temporary decrease in respiratory disorders during infusion in the absence of bleeding [30]. However, it is obvious that there is still no sufficient reason to propose these scientific experiments for widespread use. In addition, it is possible that heparin may be beneficial in patients with respiratory distress syndrome. According to a meta-analysis of 9 studies, including a total of 465 patients with acute lung injury / respiratory distress syndrome (before the onset of the COVID-19 pandemic), adding LMWH to standard treatment reduced 7-day mortality (RR 0.52 at 95% CI: 0, 31-0.87), 28-day mortality (RR0.63 at 95% CI: 0.41-0.96), decreased APTT (median differences -1.1 sec at 95% CI: -1.97 to -0.23) and increased the PaO2 / FiO2 ratio (median difference 74.48 at 95% CI: 52.18-96.78) [31]. At the same time, the most pronounced positive effect on oxygenation was exerted by LMWH doses of ≥5000 IU / day, which is slightly higher than the usual prophylactic ones.

Accounting for drug interactions is an essential component of antithrombotic therapy in COVID-19. Data on the clinical significance of antithrombotic drug-drug interactions for the treatment of COVID-19 are presented in tables published by the University of Liverpool's Drug Interactions Group [32] and discussed in documents prepared by international expert groups [1, 33].

ACKOWLEDGMENT

Thrombosis activation and, less commonly, thrombotic/thromboembolic complications are an important element in the pathogenesis of COVID-19. Their severity is associated with the severity of the manifestations of COVID-19 and its prognosis. Much in the prevention and treatment of feasibility studies for COVID-19 remains unclear. The choice of treatment methods for a particular patient remains the priority of the attending physicians, who are currently acting on the basis of previously known facts, the considerations of the expert community, the rapidly accumulating data on the results of the use of various interventions for COVID-19 and their own experience.

It should also be borne in mind that at the time of this writing, a number of cited documents were posted on the Internet before their official peer review and the decision to publish them in the relevant scientific journal.

REFERENCES

1. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or

Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286

OCLC - 1121105510

Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. JACC. 2020. doi:10.1016/j.jacc.2020.04.031.

2. Kloka FA, Kruipb MJHA, van der Meerc NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020. doi:10.1016/j.thromres.2020.04.013.
3. 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.
4. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in COVID- 19 Patients: Awareness of an Increased Prevalence. Circulation. 2020. doi:10.1161/CIRCULATIONAHA.120.047430.
5. Dolhnikoff M, Duarte-Neto AN, Monteiro RAA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID- 19. J Thromb Haemost. 2020. doi:10.1111/JTH.14844.
6. Carsana L, Sonzogni A, Nasr A. Pulmonary post-mortem findings in a large series of COVID-19 cases from Northern Italy. doi:10.1101/2020.04.19.20054262 https://www.medrxiv.org/cont ent/10.1101/2020.04.19.20054262v1.
7. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020. doi:10.1111/jth.14810.
8. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta- analysis. Clin Chim Acta. 2020. doi:10.1016/j.cca.2020.03.022.
9. Zhang Y, Xiao M, Zhang S. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med. 2020. doi:10.1056/NEJMc2007575.
10. Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-
11. 19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc. 2020. [Epub ahead of print].
12. 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.doi:10.1111/jth.14768.
13. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020. doi:10.1111/ JTH.14817.
14. Zhou F, Yu T, Du R, 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. doi:10.1016/S0140- 6736(20)30566-3.
15. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City. doi:10.1101/2020.04.08.2005 7794. https://www.medrxiv.org/content/10.1101/2020 .04.08.20 057794v1.
16. Massachusetts General Hospital. Hematology Issues during COVID-19. Version 7.0, 4/14/2020. https://www.massgeneral. org/assets/MGH/pdf/news/coronavirus/gui dance-from-mass- general-hematology.pdf.
17. Iba T, Levy JH, Warkentin TE, et al. the Scientific and Standardiza- tion Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis. Diagnosis and ma-nagement of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17:1989-94. doi:10.1111/jth.14578.
18. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous

thromboembolism in acutely ill medical patients. N Engl J Med. 1999;341:793-800.

19. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomized placebo-controlled trial. BMJ. 2006;332:325-9. doi:10.1136/bmj.38733.466748.7C.
20. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo- controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110:874-9. doi:10.1161/01.CIR.0000138928.83266.24.
21. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of Venous Thromboembolism. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:381S-453S. doi:10.1378/chest.08-0656.
22. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in Nonsurgical Patients. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(suppl):e195S-e226S. doi:10.1378/chest.11-2296.
23. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8:2450-7. doi:10.1111/j.1538-7836.2010.04044.x.
24. Spyropoulos AC, Anderson FA, FitzGerald G, et al., for the IMPROVE Investigators. Predictive and Associative Models to Identify Hospitalized Medical Patients at Risk for VTE. Chest. 2011;140:706-14. doi:10.1378/chest.10-1944.
25. Cohen AT, Harrington RA, Goldhaber SZ, et al., for the APEX Investigators. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med. 2016;375:534-44. doi:10.1056/NEJMoa1601747.
26. Gibson CM, Spyropoulos AC, Cohen AT, et al. The IMPROVEDD VTE Risk Score: Incorporation of D-Dimer into the IMPROVE Score to Improve Venous Thromboembolism Risk Stratification. TH Open. 2017;1:e56-e65. doi:10.1055/s-0037-1603929.
27. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020. doi:10.1111/JTH.14821.
28. Hull RD, Schellong SM, Tapson VF, et al., for the EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study. Extended- Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility. A Randomized Trial. Ann Intern Med. 2010;153:8-18. doi:10.7326/0003-4819- 153-1-201007060-00004.
29. Spyropoulos AC, Ageno W, Albers GW, et al., for the MARINER Investigators. Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness. Engl J Med. 2018;379:1118-27. doi:10.1056/NEJMoa1805090.
30. Moore HB, Barrett CD, Moore EE, et al. Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS)? J Trauma and Acute Care Surgery. 2020. doi:10.1097/ TA.0000000000002694.
31. Wang J, Hajizadeh N, Moore EE, et al. Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series. J Thromb Haemost. 2020. doi:10.1111/JTH.14828.
32. Li J, Li Y, Yang B, et al. Low-molecular-weight heparin treatment for acute lung injury/acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2018;11:414-22.
33. Liverpool Drug Interaction Group. Interactions with Experimental COVID-19 Therapies. https://www.covid19-druginteractions.org.

Published: October 31, 2020 | **Pages:** 122-132
Doi: https://doi.org/10.37547/TAJMSPR/Volume02Issue10-19

IMPACT FACTOR
2020: 5. 286

OCLC - 1121105510

34. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. Last updated on 21 April 2020. https://www.escardio.org/Education/COVID-19-and-Cardiology/ ESC-COVID-19-Guidance.