CURRENT STATE OF THE PROBLEM OF VENOUS THROMBOEMBOLIC COMPLICATIONS ASSOCIATED WITH COVID-19

S.A. Fedorov[1*], *A.P. Medvedev*[1,2], *L.M. Tselousova*[3], *V.V. Pichugin*[1,2], *S.A. Zhurko*[1], *S. Kulkarni*[2], *D.I. Lashmanov*[1]

[1] Specialized cardiosurgical clinical hospital named after academician B. A. Korolev, 209 Vaneeva str., Nizhny Novgorod, 603950, Russia;
[2] Privolzhsky Research Medical University of the Ministry of Health of the Russian Federation, 10/1 Minin and Pozharsky square, Nizhny Novgorod, 603005, Russia;
[3] Nizhny Novgorod Regional Clinical Oncology Dispensary, 11/1 Delovaya str., Nizhny Novgorod, 603093, Russia.

[*] Corresponding author: sergfedorov1991@yandex.ru

Abstract. At present, it can be noted that COVID-19 is the most serious challenge to the international health care system in its recent history. Extremely high rates of morbidity and mortality dictate the need for a more detailed study of the pathogenetic aspects of the developing infectious catastrophe. Besides respiratory distress syndrome, systemic inflammatory response syndrome, COVID-19 is characterized by polyvalent disorders of the mechanisms of systemic hemostasis, which has reflected in an increase in the number of venous thromboembolic complications in the overall structure of morbidity and mortality. The given literature summarizes the information on COVID-associated coagulopathy and its effect on changes in the clinical and epidemiological characteristics of venous thromboembolic complications.

Keywords: COVID-19, SARS-CoV-2, venous thromboembolic complications, COVID-associated coagulopathy.

List of Abbreviations

PE – pulmonary embolism
W.H.O. – World Health Organization
ACE 2 – angiotensin converting enzyme 2
VTEC – venous thromboembolic complications

Coronavirus infection is an acute respiratory infection caused by the SARS-CoV-2 virus, which is one of 7 currently known species of viruses in the Coronoviride family. For the first time, the new type of virus was detected while analyzing an outbreak of SARS of an infectious nature in the city of Wuhan, (Hubei province, China) (CDC, 2019). This pathology was first mentioned by the World Health Organization (WHO) on December 31, 2019, and by February 11, 2020, the research group of the International Committee on Virus Systematization named this infectious agent the SARS-CoV-2 virus. There was a rapid spread of infection among the population of individually developed countries, by the end of January 2020 SARS-CoV-2 (2019-nCoV) was declared an emergency in the international health system (Gallegos, 2019; Atzrodt *et al.*, 2020). In early March, WHO gave the new infection the status of a pandemic (W.H.O., 2020). In addition to extremely high incidence rates, the pandemic is characterized by high mortality parameters, reaching an average of 10% and increasing in the group of elderly and senile patients, as well as among patients with an initially compromised state of the respiratory and cardiovascular systems (Goyal *et al.*, 2020; Lo *et al.*, 2020).

SARS-CoV-2 belongs to the single-stranded RNA-containing viruses of the Coronoviride family. Its distinctive morphological feature is the presence of specific glycoproteins or peplomers on its surface, the combination of which gives it the appearance of a crown when viewed in electron microscopy. It is the presence of these peplomers, or spike S – proteins that determines the tropism of the virus to the human body, mediated through interaction with the angiotensin converting enzyme 2 (ACE 2) receptor, according to the principle of enzyme – substrate interaction. Subsequently, the virus – contaminated cells begin to produce interferon gamma, as well as a number of specific chemokine ligands, which lead to excessive activation of macrophages and the development

of an un-controlled inflammatory response (Nicholls *et al.,* 2006). Unlike its predecessor, the SARS-CoV virus, it has a number of characteristics that determine its pathogenicity and virulence. In particular, it has a more compact 3D conformation of the binding domain, which facilitates its interaction with ACE 2. In addition, SARS-CoV-2 has a furin cleavage site located at the S1 / S2 border of the S-spike protein 12, which facilitates the penetration of the virus into the recipient's cell (Oudit *et al.,* 2009).

Disorders of the blood coagulation system occupy one of the key positions in the pathogenesis of coronavirus infection, being one of the main causes of death in the group of patients with a high morbid profile (Asakura & Ogawa, 2021; Dobesh & Trujillo, 2020). At the same time, it is not completely clear whether the developing coagulopathy is directly influenced by a viral agent, or is it secondary to the developing immune-inflammatory response (Zhang *et al.,* 2020). The fact is that, interaction with a viral agent leads to a distortion of the start of compensatory activation of coagulation, aimed at isolating the infectious origin, to a pathologically developing DIC, a syndrome that tends to a progressive course (Agbuduwe & Basu, 2020; Chan & Weitz, 2020). This is determined, on one hand, by the production of a whole spectrum of immune-inflammatory complexes with a pronounced pleiotropic effect by the host organism, including anti-inflammatory cytokines that activate the coagulation system. On the other hand, the activation of the vascular - thrombotic link of the hemostatic system due to the developing endothelial dysfunction, exactly like the procoagulant ability of SARS-CoV-2, also potentiates hypercoagulation, which together determines the development of consumption coagulopathy, with all the complications that follow from this. In a number of experimental studies aimed at studying the mechanisms of interaction of SARS-CoV-2 with the cells of the human body, it was noted that after the internalization of the virus into the cell, there is a decrease in ACE 2 on its surface. Initially, this phenomenon was explained as a compensatory physiological process aimed at reducing viral load and transmembrane diffusion in the epithelium of the respiratory tract. However, subsequent observations showed that a decrease in the concentration of ACE 2 determines the accumulation of angiotensin II and its excessive activity, including procoagulation (Oudit *et al.,* 2009).

Thus, the study by Kloka et al, based on the study of case histories of 184 resuscitated patients with confirmed coronavirus infection and severe bilateral pneumonia, demonstrated the role of venous thromboembolic complications (VTEC), as well as arterial thrombosis in more than 30% of deaths (Kloka *et al.,* 2020). It should be noted that the authors emphasize the dominant position of VTEC in the overall structure of mortality, which, according to their data, was more than 25% (Oudit *et al.,* 2009). Cui et all also reported the incidence of VTEC in 25% of the patients studied by him (Cui *et al.,* 2020).

The results of Poissy J. et al, demonstrated approximately comparable epidemiological parameters of VTEC in the group of patients receiving inpatient treatment in French clinics. According to their data, VTEC as a cause of death was up to 20% in a cohort of 100 patients. The authors note that the incidence of VTEC in the group of patients comparable in morbid profile, treated for a similar period of time 2019, has an almost three-fold nature of growth, namely 20% versus 6.1% (Poissy *et al.,* 2020).

A retrospective analysis of the results of resuscitation treatment of 80 patients with severe coronavirus pneumonia in China determined the incidence of VTEC up to 25%, which fully coincides with the data of European studies presented above (Cui *et al.,* 2020). The reliability of the data obtained is confirmed by the results of pathological - anatomical studies, which is opposed to ordinary clinical practice, when the frequency of pathomorphological findings of VTEC is several times higher than the frequency of intravital diagnoses (Oudit *et al.,* 2009; Cui *et al.,* 2020). However, microthrombi in the pulmonary arterial bed, verified on sectional material, demonstrated a fundamental pathogenetic difference between COVID-associated coagulopathy and the classical mechanisms of their formation, which only warms up

the interest of researchers (Dolhnikoff *et al.*, 2020).

Today, many questions remain, for example, whether COVID-19 is the direct etiological factor of these, often fatal complications, or they develop as the infectious process progresses and are characteristic of any infection proceeding to a severe scenario. The role and causes of these disorders, their real frequency, despite the large number of works and publications, remains the substrate of heated discussions, the tension of which is not inferior only to the intensity that arises when discussing the issues of therapy and prevention of VTEC in coronavirus infection. It is the relevance of this issue that prompted our literary review (O'Driscoll *et al.*, 2021).

Currently, it is known that coronavirus enters the human body via ACE 2, which is a membrane protein and is widely present in the vascular endothelium and cells of the respiratory tract (Bikdeli *et al.*, 2020). According to Menachery V. D. et al, this histological feature makes them the most vulnerable to COVID-19 (Menachery *et al.*, 2015; Marchand-Senécal *et al.*, 2020). Pathomorphological studies of patients with COVID-19 showed a diffuse lesion of the lung parenchyma, manifested by edema of the alveoli, the phenomena of exudative inflammation, the formation of hyaline membranes, followed by hyperplasia of type II pneumocytes, which is typical for most acute respiratory viral infections (Xu *et al.*, 2020). However, in comparison with other acute respiratory viral infections, patients with COVID-19 have a delayed onset of respiratory distress syndrome, which is characterized by high respiratory compliance and a high shunt fraction (Zhang *et al.*, 2020). In addition, the work of Hamming et all showed a high frequency of ACE 2 expression in the endothelial lining of venous and arterial vessels, as well as in the thickness of their smooth muscle cells, which determines the pathogenetic basis of the formation of arterial and venous thrombosis (Hamming *et al.*, 2004).

Initially, a qualitative assessment of the condition of patients with coronavirus infection revealed that certain disorders of hemostasis occur in 20% of patients, first of all, talking about changes in the concentration of D – dimer and fibrinogen degradation products (Alsharif & Qurashi, 2021; Hamming *et al.*, 2004; Gómez-Mesa *et al.*, 2021). The pathogenetic justification for this phenomenon is the fact that an acute inflammatory reaction caused by viral intervention has a pronounced multicomponent effect on the parameters of the hemostasis and fibrinolysis system. On the one hand, there is a decrease in the concentration of C - protein and antithrombin circulating in the blood plasma, which directly or indirectly leads to an increase in the concentration of the plasminogen activator inhibitor 1, which in turn determines the blocking of fibrinolysis processes and the activation of hypercoagulation processes (Xu *et al.*, 2020; Hamming *et al.*, 2004; Iba *et al.*, 2020). Among the mechanisms of thrombus formation, the phenomenon of systemic hypoxemia should be noted, which is most pronounced in patients requiring supportive oxygen therapy. Thus, a decrease in the partial tension of oxygen and hypercapnia has a stimulating effect on transcription factors inducible to hypoxia, the target genes of which determine the production of a number of chemical compounds with procoagulant properties (Gupta *et al.*, 2019).

In addition, the patient's native somatic status is an extremely important, but often escaping the attention of researchers, risk factor for the development of VTEC in the considered group of patients. Severe intoxication and dehydration caused by physical cooling of terminal patients, as well as concomitant digestive disorders in the form of diarrhea, determine violations of the water and electrolyte balance, lead to dominant hemoconcentration and the formation of micro- and macrothrombosis (Tang *et al.*, 2020).

Another extremely important risk factor for the development of VTEC is a long-term immobilization regime due to the severity of the developing primary pathology, and aggravated by the addition of a secondary infection (bacterial or fungal), obesity, and concomitant comorbid pathology (Menachery *et al.*, 2015; Zhang *et al.*, 2020). It is this postulate of Virchow's triad that acquires one of the key positions in relation

to terminal patients being treated in the ICU, as well as among elderly and senile patients (Chen *et al.*, 2020; Santos-Sánchez *et al.*, 2020).

The leading link in the pathogenesis of severe forms of COVID-19 is the so-called «cytokine storm», mediated by the excessive release of pro-inflammatory mediators in response to an inadequately strong response of the immune system (Colling & Kanthi, 2020). The latter determine the formation of a vicious pathological circle, in which the initial immuno-inflammatory complexes determine damage to the endothelial lining of the vascular wall, which determines the release of even more inflammatory mediators, as well as the activation of the vascular-platelet link of the hemostasis system, due to the exposure of collagen and elastin molecules, which determine progression of hypercoagulability (Huang *et al.*, 2020). It is the damage to the endothelial lining, both primary and secondary, that many researchers attribute to the role of a trigger of the developing cytokine «storm» (Mucha *et al.*, 2020). Namely, damage to a cell in the human body causes the production of a tissue factor, which acts as an initiator of the initiation of hypercoagulation processes, mediated through interaction with factor VII in blood plasma (Witkowski *et al.*, 2016). Subsequently, the progression of the inflammatory process determines the production of tumor necrosis factor, which, along with viral endotoxin, leads to the closure of the vicious circle of the developing infectious process (Witkowski *et al.*, 2016). A characteristic feature of the considered «cytokine storm», in addition to the excessive production of immunoinflammatory mediators (Il-1, Il-1, tumor necrosis factor, etc.), is the suppression of the T – cell link of immunity, in the form of a decrease in the number of T – lymphocytes and discoordination of T – cellular regulatory mechanisms, as well as an increase in the number of circulating neutrophils and activated monocytes. A similar regulatory imbalance between humoral and cellular immunity often occurs in sepsis, which, in addition to impaired adaptive T-cell immunity, is characterized by a pronounced systemic inflammatory reaction syndrome with symptoms of damage to the endothelial lining of the vascular wall and internal organs (Cao, 2020). One of the distinctive characteristics of the new coronavirus infection is the low expression of interferon types 1 and III against the background of increased production of Il-6 and pro-inflammatory chemokines. SARS-CoV-2 generates a unique gene signature enriched for cell death and leukocyte activation, including transcripts such as IL1A, CCL2, CCL8 and CCL11. A significant increase in CXCL9 and CXCL16 (chemoattractants of T or natural killer (NK) cells, respectively), CCL8 and CCL2 (which attract monocytes and/or macrophages) and CXCL8 (classical chemoattractant of neutrophils) suggests that the presence of these cells may be the main driving force of the characteristic pathology observed in patients with COVID-19 (Blanco-Melo *et al.*, 2020). Given this pathogenetic feature, a number of authors postulate that the terminal stage of COVID-19 is nothing more than a variant of viral sepsis, which, unlike other infectious nosologies, has a tendency not to hypo- but to hypercoagulation (Iba *et al.*, 2020). It is the endothelial dysfunction that progresses at the height of the «cytokine storm» that a number of authors give priority when considering the issues of COVID-associated coagulopathy, and the level of blood-soluble thrombomodulin is assigned the role of a predictor of an unfavorable outcome (Goshua *et al.*, 2020; Katneni *et al.*, 2020). The Goshua G. et al. study included 68 patients with confirmed SARS-CoV-2 – associated pneumonia. At the same time, 48 patients were in the ICU on artificial lung ventilation (ALV), the remaining 20 patients received inpatient treatment and were on supportive oxygen therapy. Research results demonstrated an increase in the level of D-dimer, thrombin – antithrombin, von Willebrand factor in all the patients under consideration. However, in the group of patients in the ICU, these indicators were significantly higher ($P < 0.001$). Plasma plasminogen activator was increased in 96% of the subjects. In addition, a number of researchers suggest that progressive endothelial dysfunction determines the activation of the compliment system with developing thrombotic microangiopathy, similar to microangiopathy as-

sociated with he-molytic uremic syndrome (Goshua *et al.*, 2020; Lippi *et al.*, 2019). Studying changes in the parameters of the hemostasis, the researchers found that an increase in the level of soluble thrombomodulin correlates with patient survival, namely, exceeding the threshold value (3.26 ng/ml) is associated with death (p = 0.0087) (Guan *et al.*, 2019). The most persistent disorders in the hemostasis in the group of patients with COVID-19 are manifested in thrombocytopenia, and an increase in the level of D-dimer, which is directly proportional to the clinical outcome of the disease, as well as the need and duration of mechanical ventilation (Fogarty *et al.*, 2020). The first data on the predictive value of the D-dimer level were published by Chinese researchers. Thus, the authors observed an increase in its level > > 0.5 mg / l in 46–63% of the studied patients (Guan *et al.*, 2019). In another study, it was noted that the level of D-dimer > 1 mg / l is associated with an 18-fold increase in the risk of death (Zhou *et al.*, 2020; Gao *et al.*, 2020). Thus, in the study by Tang N et all, the results of treatment of 183 patients with COVID-19 were analyzed. In the general group of patients, 21 deaths were recorded, which amounted to about 12%. Among the dead patients, significantly higher levels of D-dimer and fibrin degradation products were noted (3.5 versus 1.9), an increase in prothrombin time by 14% ($p <$ < 0.0001). In addition, more than 70% of patients who died met the criteria of the International Society of Thrombosis and Hemostasis for DIC, compared with only 0.6% of surviving patients (Tang *et al.*, 2020). At the same time, coagulopathy associated with COVID-19 has clear differences both from the classic DIC syndrome and from sepsis. These include: low consumption of platelets and blood plasma coagulation factors (primarily fibrinogen), an extremely low percentage of hemorrhagic complications, as well as involvement of the pulmonary microvasculature in the primary pathological process, with the development of «pulmonary microvascular angiopathy» (Fogarty *et al.*, 2020).

It should be noted that the use of hormonal drugs, immunoglobulins in terms of the pathogenetic treatment regimen, as well as catheterization of the central veins and artificial ventilation of the lungs, which are integral attributes of patients in an extremely difficult clinical situation, potentiate the activation of the vascular-platelet link of the hemostatic system and increase the risks of development VTEC (Huang *et al.*, 2020). Obviously, severe forms of the disease are much more often complicated by VTEC, and pulmonary embolism (PE) in particular. In one of the European studies, which included the experience of treating more than 180 patients with confirmed coronavirus infection, it was found that the diagnosis of PE was verified in more than 13% of patients. At the same time, all patients with COVID-19 proceeded in a severe form (Klok *et al.*, 2020). In addition, a number of authors note that the phenomena of cardiovascular failure and pulmonary hypertension, acting both as a premorbid background and as a complication of coronavirus infection, should also be considered as factors causing the development of the BODY in COVID-19 (Driggin *et al.*, 2020). So, according to a number of authors, markers of myocardial damage (Troponin T and I) is a factor in the development of unfavorable complications. According to the observations of other researchers, the accumulation of cardioselective enzymes requires a more detailed diagnosis and can be observed both in nonspecific myocardial damage, renal pathology, contributing to the violation of their excretion in the urine, and also be a qualitative sign of acute right ventricular failure in PE (Januzzi, 2020). The authors declare a similar tactical approach in relation to the prognostic significance of natriuretic peptide (Cao, 2020). Shi et al in their study proved that the presence of pathology of the cardiovascular system, primarily coronary heart disease, postinfarction cardiosclerosis, atherosclerotic lesions of the main arteries, at the time of COVID-19 disease significantly increases the risks of VTEC (Shi *et al.*, 2020).

An extremely important point is the difficulty of the initial diagnosis of VTEC, in particular PE, occurring against the background of COVID-19. A similar situation is determined by masking the classic manifestations of PE un-

der the symptoms of respiratory failure caused by viral pneumonia (Langer *et al.,* 2020). In turn, the maximum concentration of clinicians on the respiratory status of patients determines their lack of attention to the signs of deep vein thrombosis (DVT) (Sodhi *et al.,* 2018). Thus, the results of treatment of patients with new coronavirus infection at the University Hospital of Amsterdam showed that VTEC occurred in more than 22% of cases. Moreover, in 7.1% of cases, they were accidental findings during the screening follow-up examination, within the framework of standards of treatment of highly morbid patients in ICU conditions (Chi *et al.*, 2020). However, the authors of this study made an important note that screening for DVT was performed in only 28% of the subjects, and with regard to verification of PE only for strict indications, which allows us to speak of higher epidemiological characteristics in terms of the total number of patients (n = 199) (Gibson *et al.*, 2017). In one of the first reports from China, which cited the experience of treating patients with COVID-19 in the absence of routinely used thromboprophylaxis, the number of verified DVTs was 25% (Cohen *et al.,* 2016). In turn, the material of colleagues from the 3 largest anti-cavid hospitals in Amsterdam demonstrates the incidence of VTEC in 37% developing against the background of heparin prophylaxis (Chi *et al.,* 2020). Moreover, PE was found in more than 80% of the cases under consideration (Chi *et al.,* 2020).

It should be noted that in a number of studies based on the experience of performing pathomorphological studies, there was a quantitative discrepancy between the diagnoses of PE and DVT (Gibson *et al.,* 2017; Thachil *et al.,* 2020; Zhao *et al.*, 2021). Many researchers emphasize the fact that COVID-associated VTECs have pathognomonic anatomical localization. Namely, the thrombotic process in patients with COVID-19 usually has a distal localization, in the area of bifurcation of small venous tributaries, which determines an increase in the relative frequency of development of thrombosis of the sural veins and peripheral forms of PE in the general structure of VTEC (Chi *et al.,* 2020; Gibson *et al.*, 2017). In addition, in a number of works, the idea of the prevalence of Thromboembolism of pulmonary artery in situ in the structure of VTEC is expressed. A similar situation is determined by the fact that in more than 70% of patients with PE, the source of thromboembolic substrate formation was not found, and PE was of a diffuse peripheral nature, reminiscent of the type of ascending secondary thrombosis when analyzing materials of X-ray contrast research methods (Cohen *et al.*, 2016).

Thus, an analysis of modern literature demonstrates a close relationship between the gaining momentum of COVID-associated pneumonia and multifaceted mechanisms of disruption of coagulation processes. Despite the large number of works highlighting certain aspects of the diagnosis and treatment of COVID-19, the pathogenetic basis of the developing infectious process has not been fully understood (Becker, 2020).

The extremely high epidemiological data of VTEC presented in the review are only «relatively» reliable, since the use of instrumental verification methods, in most percent of the studies, was associated only with the manifestation of obvious clinical signs of a developing thromboembolic process. Therefore, an extremely important point in the treatment strategy for patients with COVID-19 many researchers consider the mandatory routine use of duplex scanning of the arteries and veins of the lower extremities, transthoracic echocardiography, as well as the use of rating scales for the risk of VTEC among patients who are both inpatient and in ICU. Performing MSCT – angiography is an important screening method of examination in the group of patients in the ICU, and also requires a revision of the issue and the expansion of indications for MSCT – angiography among general inpatients. A deeper study of the risk of thromboembolic complications associated with COVID-19 will allow optimizing diagnostic algorithms for managing interested patients, and will also provide answers to the questions of choosing a strategy for the prevention and treatment of VTEC (Aryal *et al.,* 2020). The expediency of this approach is determined not so much by the high epidemiological values of VTEC, but also by completely

different pathogenetic mechanisms of development, which ultimately determines the difficulty of early verification of the true diagnosis (Marietta *et al.*, 2020).

Financing: the study was not sponsored. Conflict of interests: the authors declare that they have no conflicts of interest.

References

AGBUDUWE C. & BASU S. (2020): Haematological manifestations of COVID-19: From cytopenia to coagulopathy. *Eur J Haematol.* **105**(5), 540–546. doi: 10.1111/ejh.13491.

ALSHARIF W. & QURASHI A. (2021): Effectiveness of COVID-19 diagnosis and management tools: A review. *Radiography (Lond)* **27**(2), 682–687. doi: 10.1016/j.radi.2020.09.010.

ARYAL M.R., GOSAIN R., DONATO A., PATHAK R., BHATT V.R. ET AL. (2020): Venous Thromboembolism in COVID-19: Towards an Ideal Approach to Thromboprophylaxis, Screening, and Treatment. *Curr Cardiol Rep.* **22**(7), 52. doi: 10.1007/s11886-020-01327-9.

ASAKURA H. & OGAWA H. (2021): COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol.* **113**(1), 45–57. doi: 10.1007/s12185-020-03029-y.

ATZRODT C.L., MAKNOJIA I., MCCARTHY R.D.P. ET AL. (2020): A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. *FEBS J.* **287**(17), 3633–3650. doi: 10.1111/febs.15375.

BECKER R.C. (2020): COVID-19 update: Covid-19-associated coagulopathy. *J Thromb Thrombolysis*. **50**(1), 54–67. doi: 10.1007/s11239-020-02134-3.

BIKDELI B., MADHAVAN M.V., JIMENEZ D. ET AL. (2020): COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. *JACC* **75**(23), 2950–2973. doi:10.1016/j.jacc.2020.04.031.

BLANCO-MELO D., NILSSON-PAYANT B.E., LIU W.C., UHL S., HOAGLAND D. ET AL. (2020): Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell.* **181**(5), 1036–1045.e9. doi: 10.1016/j.cell.2020.04.026.

CAO X. (2020): COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*. **20**(5), 269–270. doi: 10.1038/s41577-020-0308-3.

CDC (2019): Novel Coronavirus, Wuhan, China. CDC. Available at *https://www.cdc.gov/coronavirus/2019-ncov/about/index.html*. Accessed on January 26, 2020.

CHAN N.C. & WEITZ J.I. (2020): COVID-19 coagulopathy, thrombosis, and bleeding. *Blood* **136**(4), 381–383. doi: 10.1182/blood.2020007335.

CHEN N., ZHOU M., DONG X. ET AL. (2020): Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* **395**(10223), 507–513.

CHI G., LEE J.J., JAMIL A., GUNNAM V., NAJAFI H., MEMARMONTAZERIN S., SHOJAEI F. & MARSZALEK J. (2020): Venous Thromboembolism among Hospitalized Patients with COVID-19 Undergoing Thromboprophylaxis: A Systematic Review and Meta-Analysis. *J Clin Med.* **9**(8), E2489. doi: 10.3390/jcm9082489.

COLLING M.E. & KANTHI Y. (2020): COVID-19-associated coagulopathy: An exploration of mechanisms. *Vasc Med.* **25**(5), 471–478. doi: 10.1177/1358863X20932640.

COHEN A.T., HARRINGTON R.A., GOLDHABER S.Z. ET AL. (2016): Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. *N Engl J Med.* **375**, 534–544. doi:10.1056/NEJMoa1601747.

CUI S., CHEN S., LI X., LIU S. & WANG F. (2020): Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J ThrombHaemost.* doi:10.1111/jth.14830.

CUI S., CHEN S., LI X., LIU S. & WANG F. (2020): Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J ThrombHaemost*. **18**(6), 1421–1424. doi:10.1111/JTH.14830.

DOBESH P.P. & TRUJILLO T.C. (2020): Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID-19. *Pharmacotherapy* **40**(11), 1130–1151. doi: 10.1002/phar.2465.

DOLHNIKOFF M., DUARTE-NETO A.N., MONTEIRO R.A.A ET AL. (2020): Pathological evidence of pulmonary thrombotic phenomena in severe COVID19. *J ThrombHaemost*. **18**(6), 1517–1519. doi:10.1111/JTH.14844.

DRIGGIN E., MADHAVAN M.V., BIKDELI B., CHUICH T., LARACY J., BONDI-ZOCCAI G. ET AL. (2020): Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J AmCollCardiol.* **75**(18), 2352–2371. doi: 10.1016/j.jacc.2020.03.031.

FOGARTY H., TOWNSEND L., CHEALLAIGH C.N., BERGIN C., MARTIN-LOECHES I., BROWNE P. ET AL. (2020): COVID-19 coagulopathy in caucasian patients. *Br J Haematol*. **189**(6), 1044–1049 doi: 10.1111/bjh.16749.

GALLEGOS A. (2020): WHO Declares Public Health Emergency for Novel Coronavirus. *Medscape Medical News*. Available at https://www.medscape.com/viewarticle/924596. Accessed on January 30, 2020.

GAO Y., LI T., HAN M. ET AL. (2020): Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol* **92**(7), 791–796.

GIBSON C.M., SPYROPOULOS A.C., COHEN A.T. ET AL. (2017): The IMPROVEDD VTE Risk Score: Incorporation of D-Dimer into the IMPROVE Score to Improve Venous Thromboembolism Risk Stratification. *TH Open* **1**, e56-e65. doi:10.1055/s-0037-1603929.

GÓMEZ-MESA J.E., GALINDO-CORAL S., MONTES M.C. & MUÑOZ MARTIN A.J. (2021): Thrombosis and Coagulopathy in COVID-19. *Curr Probl Cardiol.* **46**(3), 100742. doi: 10.1016/j.cpcardiol.2020.100742.

GOSHUA G., PINE A.B., MEIZLISH M.L., CHANG C.H., ZHANG H., BAHEL P., BALUHA A., BAR N., BONA R.D., BURNS A.J., DELA CRUZ C.S., DUMONT A., HALENE S., HWA J., KOFF J., MENNINGER H., NEPARIDZE N., PRICE C., SINER J.M., TORMEY C., RINDER H.M., CHUN H.J. & LEE A.I. (2020): Endotheliopathy is essential in COVID-19 associated coagulopathy. *Lancet Haematol.* **7**(8), e575–e582.

GOYAL P., CHOI J.J., PINHEIRO L.C., SCHENCK E.J., CHEN R., JABRI A. ET AL. (2020): Clinical characteristics of Covid-19 in New York City. *N Engl J Med*. **382**, 2372-4. doi: 10.1056/NEJMc2010419.

GUAN W., NI Z., HU Y. ET AL. (2019): Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. **2020**, 1–13.

GUPTA N., ZHAO Y.Y. & EVANS C.E. (2019): The stimulation of thrombosis by hypoxia. *Thromb Res.* **181**, 77–83. [PMID: 31376606] doi:10.1016/j.thromres.2019.07.013.

HAMMING I., TIMENS W., BULTHUIS M., LELY A., NAVIS G. & VAN GOOR H. (2004): Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A firststepinunderstanding SARS pathogenesis. *J Pathol.* **203**, 631–637.

HUANG C., WANG Y., LI X. ET AL. (2020): Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**(10223), 497–506.

IBA T., LEVY J.H., LEVI M. & THACHIL J. (2020): Coagulopathy in COVID-19. *J ThrombHaemost.* **18**(9), 2103–2109. doi: 10.1111/jth.14975.

IBA T., LEVY J.H., CONNORS J.M., WARKENTIN T.E., THACHIL J. & LEVI M. (2020): The unique characteristics of COVID-19 coagulopathy. *Crit Care* **24**(1), 360. doi: 10.1186/s13054-020-03077-0.

JANUZZI J.L. Jr. (2020): Troponin and BNP use in COVID-19. *Cardiology Magazine. Available at:* https://www.acc.org/latest-in cardiology/articles/2020/03/18/15/25/troponin-and-bnp-use-in-covid19. Accessed on April 7, 2020.

KATNENI U.K., ALEXAKI A., HUNT R.C., SCHILLER T., DICUCCIO M. ET AL. (2020): Coagulopathy and Thrombosis as a Result of Severe COVID-19 Infection: A Microvascular Focus. *Thromb Haemost.* **120**(12), 1668–1679. doi: 10.1055/s-0040-1715841.

KLOKA F.A., KRUIPB M.J.H.A., VAN DER MEERC N.J.M. ET AL. (2020): Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. doi:10.1016/j.thromres.2020.04.013

KLOK F.A. ET AL. (2020): Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thrombosis research*. **191**, 148–150. doi: 10.1016/j.thromres.2020.04.041.

LANGER F., KLUGE S., KLAMROTH R. & OLDENBURG J. (2020): Coagulopathy in COVID-19 and Its Implication for Safe and Efficacious Thromboprophylaxis. *Hamostaseologie*. **40**(3), 264–269. doi: 10.1055/a-1178-3551.

LIPPI G., PLEBANI M. & HENRY B.M. (2020): Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *ClinChim Acta* **506**, 145–148.

LO M.W., KEMPER C. & WOODRUFF T.M. (2020): COVID-19: Complement, Coagulation, and Collateral Damage. *J Immunol.* **205**(6), 1488–1495. doi: 10.4049/jimmunol.2000644.

MARCHAND-SENÉCAL X., KOZAK R., MUBAREKA S., SALT N., GUBBAY J.B. ET AL. (2020): Diagnosis and Management of First Case of COVID-19 in Canada: Lessons Applied From SARS-CoV-1. *Clin Infect Dis.* **71**(16), 2207–2210. doi: 10.1093/cid/ciaa227.

MARIETTA M., AGENO W., ARTONI A., DE CANDIA E., GRESELE P. ET AL. (2020): COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus.* **18**(3), 167–169. doi: 10.2450/2020.0083-20.

MENACHERY V.D., YOUNT B.L., DEBBINK K., AGNIHOTHRAM S., GRALINSKI L.E., PLANTE J.A. ET AL. (2015): A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat. Med.* **21**(12), 1508–1513. doi: 10.1038/nm.3985.

MUCHA S.R., DUGAR S., MCCRAE K., JOSEPH D., BARTHOLOMEW J. ET AL. (2020): Coagulopathy in COVID-19: Manifestations and management. *Cleve Clin J Med.* **87**(8), 461–468. doi: 10.3949/ccjm.87a.ccc024.

NICHOLLS J.M., BUTANY J., POON L.L., CHAN K.H., BEH S.L., POUTANEN S. ET AL. (2006): Time course and cellular localization of SARS-CoV nucleoprotein and RNA in lungs from fatal cases of SARS. *PLoS Med*. **3,** e27. doi: 10.1371/journal.pmed.0030027.

O'DRISCOLL M., RIBEIRO DOS SANTOS G., WANG L., CUMMINGS D.A.T, AZMAN A.S. ET AL. (2021): Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* **590**(7844), 140–145. doi: 10.1038/s41586-020-2918-0.

OUDIT G.Y., KASSIRI Z., JIANG C., LIU P.P., POUTANEN S.M., PENNINGER J.M. & BUTANY J. (2009): SARS coronavirus modulation of myocardial ACE-2 expression and inflammation in patients with SARS. *Eur J ClinInvestig.* **39**, 618–625.

POISSY J., GOUTAY J., CAPLAN M. ET AL. (2020): Pulmonary Embolism in COVID19 Patients: Awareness of an Increased Prevalence. *Circulation.* doi:10.1161/CIRCULATIONAHA.120.047430.

SANTOS-SÁNCHEZ N.F. & SALAS-CORONADO R. (2020): Origin, structural characteristics, prevention measures, diagnosis and potential drugs to prevent and COVID-19. *Medwave* **20**(8), e8037. doi: 10.5867/medwave.2020.08.8037.

SHI S., QIN M., SHEN B., CAI Y., LIU T., YANG F., GONG W., LIU X., LIANG J., ZHAO O., HUANG H., YANG B. & HUANG C. (2020): Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* **126**(12), 1671–1681. doi:10.1001/jamacardio.2020.0950.

SCHÜNEMANN H.J., CUSHMAN M., BURNETT A.E. ET AL. (2018): American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *BloodAdv.* **2**(22), 3198–3225.

SODHI C.P., WOHLFORD-LENANE C., YAMAGUCHI Y., PRINDLE T., FULTON W.B., WANG S. ET AL. (2018): Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *Am J PhysiolLungCellMolPhysiol.* **314**(1), 17–31. doi: 10.1152/ajplung.00498.2016.

THACHIL J., TANG N., GANDO S., FALANGA A., CATTANEO M. ET AL. (2020): ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost.* **18**(5), 1023-1026. doi: 10.1111/jth.14810.

TANG N., LI D., WANG X. & SUN Z. (2020): Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J ThrombHaemost.* **18**(04), 844–847.

THE NEW YORK TIMES (2020): Coronavirus Live Updates: W.H.O. Declares Pandemic as Number of Infected Countries Grows. *The New York Times. Available at https://www.nytimes.com/2020/03/11/world/coronavirus-news.html#link-682e5b06*. March 11, 2020; Accessed on March 11, 2020. https://coronavirus-monitor.ru/?fb.

XU Z., SHI L. & WANG Y. (2020): Pathologic findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respiratory Med.* **8**, 420–422.

WITKOWSKI M., LANDMESSER U. & RAUCH U. (2016): Tissue factor as a link between inflammation and coagulation. *Trends Cardiovasc Med*. **26**, 297–303.

ZHANG H., ZHOU P. & WEI Y. (2020): Histopathologic changes and SARS-Cov-2 immunostaining in the lung of a patient with COVID-19. *Ann Intern Med.* **172**(9), 629–632. doi: 10.7326/M20-0533.

ZHANG X., YANG X., JIAO H. & LIU X. (2020): Coagulopathy in patients with COVID-19: a systematic review and meta-analysis. *Aging (Albany NY)* **12**(24), 24535–24551. doi: 10.18632/aging.104138.

ZHAO X., LI Y., GE Y., SHI Y., LV P. ET AL. (2021): Evaluation of Nutrition Risk and Its Association with Mortality Risk in Severely and Critically Ill COVID-19 Patients. *JPEN J Parenter Enteral Nutr.* **45**(1), 32–42. doi: 10.1002/jpen.1953.

ZHOU F., YU T., DU R. ET AL. (2020): Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* **395**(10229), 1054–1062.