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Breaking the Rules of Respiratory Diseases: Reviewing the Current Perspectives Regarding Thrombotic Conditions Associated with SARS-CoV-2 Infection

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Abstract

Many epidemiologic parameters of the viral infection are still being determined with precision, as the disease continues to spread - from the transmissibility, to the latent and infectious period, to the symptomatic case rate, to the case fatality proportion. Meanwhile, this virus has already broken many of the rules thought to apply to coronavirus-associated respiratory infection. The thrombotic pathology of COVID-19 and associated ischemic stroke risk is one of the most curious examples of this rule-breaking. In this editorial, we summarize the early findings of the COVID-19 pandemic with regard to thrombotic conditions and ischemic stroke in particular, and how these may be explained by the interwoven inflammatory mechanisms and coagulopathic cascade of viral infection.

Questions have surfaced about the potential mechanisms and the degree to which thrombotic events like ischemic stroke have resulted from the COVID-19 disease. Unique features of the interaction between SARS-CoV-2 and its cellular receptor protein Angiotensin-Converting Enzyme 2 may illustrate why COVID-19 patients with mild symptoms experience large vessel occlusions.

In lieu of a debate, there is a possible middle path that ties these mechanisms all together. Coagulation and inflammation reactions of the immune system are complementary and interrelated, but may also operate independently. Hypothetically, these two systems (inflammatory and coagulopathic) are not just overlapping, but synergistic in their biochemical pathways and therefore in their influence on clinical outcomes of patients infected with SARS-CoV-2.

Keywords: SARS-CoV-2 Infection; Coagulopathic Cascade; Thrombotic Conditions

Introduction

Beginning in late 2019 an outbreak of a novel coronavirus, named SARS-CoV-2, began spreading across the planet. Viral infection commonly leads to a disease referred to as COVID-19 (COrona VIrus Disease 2019). Many epidemiologic parameters of the viral infection are still being determined with precision, as the disease continues to spread - from the transmissibility, to the latent and infectious period, to the symptomatic case rate, to the case fatality proportion. Meanwhile, this virus has already broken many of the rules thought to apply to coronavirus-associated respiratory infection. The thrombotic pathology of COVID-19 and associated ischemic stroke risk is one of the most curious examples of this rule-breaking.

There seems to be an added element to the thrombotic risk of COVID-19 progression, which is showing up in the early case reports and observational studies of hospitalized patients. Previous respiratory infections such as influenzas

and coronaviruses (SARS, MERS) have been linked to elevated risk of ischemic strokes, through the exacerbation of natural inflammation responses to infection. However there seems to be an additional degree of prothrombotic activity in COVID-19, resulting in a unique etiologic profile of ischemic stroke that is unusual for other respiratory infections. Strokes are also presenting as the chief complaint, without or in the presence of only mild symptoms from infection. This pro-thrombotic activity of SARS-CoV-2 has led to aggressive treatment protocols with anticoagulation, in addition to the antiviral and anti-inflammatory treatments more consistent with past coronavirus outbreaks.

At this point, there are multiple mechanisms that have been theoretically linked to this procoagulant state. At its core, COVID-19 is not just a respiratory disease. It is a disease of the endothelium and the vascular system, evidently far more than previous coronavirus respiratory diseases. For example, studies estimate that 40% of COVID-19 deaths are related to cardiovascular complications [1]. The unique range of possible clinical manifestations is theorized to be driven by the unique viral and molecular pathology of SARS-CoV-2.

The unique clinical features may be related to the antigenic evolution of the virus protein structure since the last outbreak. This change has cleavage of the spike glycoprotein on SARS-CoV-2 by the Furin protease to prime binding with the Angiotensin-Converting Enzyme 2 (ACE2) receptor. This Furin-driven proteolytic cleavage was absent from the SARS-CoV virus [2]. It has been proposed that this distinction in pathology may be a reason SARS-CoV-2 infects a greater number and wider distribution of cells throughout the human body. ACE2 receptors are critical regulators of the renin-angiotensin system in the body and many of the systems that are uniquely impacted by COVID-19 are linked by the ACE2 receptor distribution throughout the body's renin-angiotensin system [3,4].

In this editorial, we summarize the early findings of the COVID-19 pandemic with regard to thrombotic conditions and ischemic stroke in particular, and how these may be explained by the interwoven inflammatory mechanisms and coagulopathic cascade of viral infection.

Stroke Risk in Covid-19

Questions have surfaced about the potential mechanisms and the degree to which thrombotic events like ischemic stroke have resulted from the COVID-19 disease. A few retrospective cohort studies have attempted to estimate the magnitude of the issue in various ways [5-9].

In a sample of 214 hospitalized COVID-19 patients in Wuhan, China, 78 (36.4%) showed some type of broadly-defined neurological manifestation. Of these, five patients (2.3%) experienced an ischemic stroke and one had a spontaneous intracranial hemorrhage. This study compared cases of severe infection (n=88) according to American Thoracic Society guidelines to those with non-severe infection (n=126)[5]. Of the ischemic strokes, 4 (4.5%) occurred in severe cases and 1 (0.8%) occurred in those with non-severe illness [5]. In addition, the authors of the study made the case that cerebrovascular injuries and some of the other neurological manifestations could be due to direct infection of the nervous system itself. Another study of 191 cases in two hospitals in Wuhan described the prognostic ability of inflammation, documented through elevated D Dimer values (present in 90% of the sample), in predicting mortality [6]. In addition, the study pointed to inflammatory cytokine responses to infection, subsequent effects on vascular endothelium structure and function resulting in plaque rupture, as well as hemodynamic impacts such as the release of procoagulant factors in the blood all leading to ischemic or thrombotic risks to patients [6].

Case Series

The question of ischemic stroke risk in COVID-19 was elevated by a case series from providers in New York City, describing 5 patients under 50 years of age who presented with large vessel occlusion and SARS-CoV-2 infection in just two weeks [10]. The mean NIH Stroke Scale (NIHSS) score was 17, indicating that these were clinically severe stroke symptoms and these large cerebrovascular accidents were often the presenting symptom, followed by a diagnosis of COVID-19 [10]. A second case series in NY described 3 cases that presented with large vessel thrombosis, later found to test positive for SARS-CoV-2 infection with only mild respiratory symptoms [11]. This series distinguished the presentation of large vessel ischemic stroke from the venous thrombosis, pulmonary microemboli and angiopathy most associated with severe COVID-19 illness, proposing a mechanism of viral involvement in arterial endothelium distinct from systematic inflammation pathways [11].

This was quickly followed by series published from investigators in Paris, northern Italy, and Los Angeles among others. The study from Paris described 10 consecutive patients (median age of 59.5 years) with large vessel ischemic strokes treated with thrombectomy (50% also received alteplase), resulting in a 90% recanalization rate but followed by a 60% mortality rate [12]. All this in spite of the fact that 7 of the 10 cases presented with mild or no symptoms of COVID-19 at onset of their stroke [12].

The Italian series reported on 6 cases (4 ischemic, 2 hemorrhagic strokes; median age of 69 years) with severe respiratory infections prior to their stroke [13]. The cases

were notable for liver enzyme and lactate dehydrogenase elevation in all cases, and abnormal coagulation tests in four cases. Ischemic cases often first showed evidence of bilateral "ground-glass opacities" on lung CT imaging, and coagulation testing included evidence of elevated D Dimer, but also International Normalized Ratio (INR) values. The course of illness was fatal in 5 of these cases with severe neurological disability persisting in the remaining case (modified Rankin Score =4) [13]. The Los Angeles case report actually preceded the NYC series, but focused on the careful treatment of an in-hospital stroke code in order to avoid nosocomial infection. However, the report also noted some important clinical features of the stroke including renal failure, lack of thrombocytopenia (i.e. normal platelets), but an elevated activated partial thromboplastic time (aPTT > 85.5) on heparin treatment [14].

Cohort studies

A small sample of hospitalized, ischemic stroke patients across New York City showed that just 32 (0.9%) of hospitalizations with COVID-19 (n=3,556) had an imaging-confirmed ischemic stroke [7]. Looking at consecutive ischemic stroke presentations over a 5 week period of the outbreak (n=46; i.e. 14 SARS-CoV-2 negative cases), strokes with a COVID-19 diagnosis demonstrated increased determination of a cryptogenic etiology (65.6% vs 30.4%), higher NIHSS scores and D Dimer laboratory values than strokes without infection [7]. A second cohort from New York University Langone Health (n=3,218) showed that the acute ischemic stroke rate was approximately 0.8% of all hospitalized COVID-19 patients in just over a month.[8] Unsurprisingly, COVID-19-associated ischemic or hemorrhagic stroke resulted in substantially higher mortality rates as well [7,8].

A third cohort study from two NYC hospitals showed a higher rate of stroke incidence, with 31 (1.5%) acute ischemic stroke diagnoses out of 2,132 COVID-19 positive hospital and Emergency Department cases.[9] These cases were compared to a historical sample of influenza A and B patients seen in the same setting (n=1,516), which showed an incidence rate of just 0.2% for acute ischemic stroke [9]. Multivariate adjustment for demographic differences between the two groups confirmed a 7.5-fold increase in odds of stroke (95% CI: 2.3-24.9) for COVID-19 compared to influenza [9].

Thrombosis in Severe COVID-19 Illness

Progression to severe illness with COVID-19 is associated with much higher thrombotic risk. A Dutch study of 184 ICU patients showed a 31% composite thrombotic event rate, even though all subjects received thromboprophylaxis and only 25% of the sample had been followed to discharge when reported in early April [15]. While an Italian cohort showed a combined thrombotic event rate of 27.6% in the ICU and just 6.6% in the general ward [16]. However, the Dutch study estimated a cumulative stroke incidence of just 3.7%, while a large majority of events (27% incidence rate) were pulmonary emboli [15]. A similar disparity was found in the Italian study which showed an ischemic stroke rate of just 2.5% overall, with 6.3% in the ICU and 1.9% in all lower levels of care [16]. This may indicate that anticoagulation treatment addresses the mechanisms for formation of arterial thrombosis in cases of severe illness, but is still insufficient to prevent emboli from the venous return depositing in the lungs. On the other hand, a study of heparin prophylaxis with severe COVID-19 illness showed that mortality was only reduced in those cases with the highest levels of inflammation, indicated by sepsis-induced coagulopathy scores and D Dimer values [17].

A scoping review of multiple studies of thrombosis and coagulopathy in COVID-19 found the rate of ischemic stroke to be slightly lower at 3% and the rate of venous thromboembolism to be approximately 20% [18] Reflecting what was found across international cohort studies, thrombotic risk increased with severity of illness, with the highest rates of either outcome being recorded in samples taken from the ICU [18].

ACE2 and Furin

Unique features of the interaction between SARS-CoV-2 and its cellular receptor protein Angiotensin-Converting Enzyme 2 may illustrate why COVID-19 patients with mild symptoms experience large vessel occlusions. SARS-CoV-2 binds to ACE2-r protein as its host cellular receptor, the same host cellular receptor as SARS-CoV [3]. The protein structure of SARS-CoV-2 was used to demonstrate that the ACE2 receptor has a 10- to 20-fold greater attraction to fusion with the SARS-COV-2 virus compared to the earlier SARS-CoV virus [19]. The ACE2 receptor is also expressed widely in the epithelia of the body, particularly the pulmonary, cardiovascular, and renal systems [3].

Preliminary studies conducted in New York have suggested an increased risk of thrombus formation even in patients without severe COVID-19 [7,10-12]. While previously described inflammatory mechanisms of ARDS may be responsible for the pulmonary microangiopathies, pulmonary and other thrombosis seen in patients with severe COVID-19-associated pneumonia and sepsis [20-22], the presence of large vessel occlusions in asymptomatic COVID-19 patients suggests the existence of a possible procoagulopathic mechanism of COVID. The search for possible procoagulopathic mechanisms has led some of the research community to look for novel features of SARS-Cov2 to understand how its unique pathology and interaction

with its cellular receptor protein, ACE2, may contribute to a coagulopathic state.

Corona-viruses typically have four structural elements: a glycoprotein spike (or S protein), a nucleocapsid phosphoprotein, an envelope glycoprotein, and a membrane glycoprotein. Two key findings on the S protein of SARS-CoV-2 show the novel coronavirus may have greater access to the endothelial tissues throughout the body than SARS-CoV. First, a study published by Shang et al. in *Nature* demonstrated that unique features of the SARS-CoV-2 spike protein's receptor binding domain allow SARS-CoV-2 to bind ACE2 at an affinity much higher than the original SARS-CoV [23]. In addition, the study found that SARS-CoV-2 keeps its RBD in an inactive conformation more often than SARS-CoV, possibly allowing it to evade host immune cell recognition when not in use [23]. Lastly, the findings suggest SARS-CoV-2 relies on a strategy of increased host cell protease use that may account for its higher pathogenicity despite having a less accessible RBD [23].

In particular, the gain-of-function mutation of a Furin Cleavage Complex between the S1 and S2 subunits in SARS-CoV-2 suggests the SARS-CoV-2's ability to egress from the respiratory tract may be enhanced via Furin protease activity [24,25]. For coronaviruses to fuse to the cell membrane, host cell proteases must cleave the viruses' spike proteins to reveal membrane fusion sequences. The spike protein of SARS-CoV-2 has two polybasic sites acted upon by proteases between its S1 and S2 spike protein subunits with a particularly unique difference to the original SARS-CoV at a boundary site called the Furin Cleavage Complex [26]. Hoffman et al. demonstrated that cleavage at the site by Furin with the presence of TMPRSS, and cathepsin must occur for SARS-CoV-2 to fuse with the cellular membrane [27]. This novel Furin Cleavage Complex is not present in SARS-CoV or other phylogenetically related coronaviruses [4,25]. Shang et al. suggested that a preactivation mechanism may occur whereby the abundant Furin proteases in the epithelial cells of the respiratory tract cleave SARS-CoV-2's spike protein, thereby "preactivating" SARS-CoV-2 to spread throughout the body and better bind to its target cells [23].

Additional studies have confirmed the ability of SARS-Cov-2 to infect and damage various organ systems. Puelles et al. found the presence of SARS-CoV-2 in kidneys, brain, lung, and liver tissue through autopsy measurements of viral load [28]. The same study demonstrated through RNA-sequencing that cathepsin, TMPRSS2, and ACE2 are all highly expressed in a vast array of normal kidney cell types, making these easy targets for SARS-CoV-2 [28]. Lastly, the autopsies found preferential targeting of the glomerular cells via single-strand RNA sequencing [28]. Another series of autopsies demonstrated through electron microscopy the presence of virions in the proximal tubular cells of nephrons (which express ACE2) and bone-marrow megakaryocytes [29]. In all cases, even ones with full anticoagulation, the autopsies revealed an abundance of megakaryocytes with platelet-rich thrombi found throughout cardiac, pulmonary, and renal microvasculature, in addition to macrovascular thrombosis. The authors suggested that a massive multiorgan platelet response due to viral infection may account for a possible coagulopathy mechanism [29]. Combined with the evidence of severe pulmonary vascular endothelial damage reported in the series of autopsy reports from Ackermann, et al. [20], a case can be made for further investigation of procoagulopathic mechanisms.

Thrombosis formation in COVID-19

A study of blood samples at Wuhan University showed decreased antithrombin levels and prothrombin time, and substantially elevated levels of D Dimer, fibrin/fibrinogen degradation products, and fibrinogen in COVID-19 cases compared to controls. D dimer and fibrin degradation markers were correlated with severity of illness [30]. Thrombin time was also shortened in cases with severe infection compared to controls [30]. These findings stand in contrast to the thrombocytopenia (platelet loss) recognized in many cases of COVID-19, which is likely tied to the ability of SARS-CoV-2 to over-stimulate the immune system, clearing platelets [31].

The role of the ACE2 receptor in the renin-angiotensin system is fundamental to understanding the coagulopathic function. ACE2 acts contrary to the ACE1 and angiotensin II proteins, which are proinflammatory, vasoconstrictive, and quickly lead to organ damage when left unchecked [32]. If SARS-CoV-2 fusion and destruction of the ACE2 supply in the lungs and/or throughout the body shifts the balance of this system, then angiotensin II surplus may promote tissue injury, inflame and damage the smooth vascular endothelium, and increase the risk of clot formation [32].

The SARS-CoV-2 virus can also infect the endothelial cells themselves, which line the inside of the vascular network, through the widely expressed ACE2 receptors [33]. These cells normally serve to provide a smooth surface on the walls of blood vessels and release proteins that regulate everything from coagulation to immune system responses when attacked [33].

Conclusion

In lieu of a debate, there is a possible middle path that ties these mechanisms all together. Coagulation and inflammation reactions of the immune system are complementary and interrelated, but may also operate independently. The distinction between the two is difficult to parse because many

markers of coagulopathy such as the D dimer, which has a well-documented association with COVID-19 severity [7,17] are really markers for inflammation and tissue damage. Many inflammation markers are also commonly overlapping with biomarkers for cardiovascular damage.

The inflammation response to infection in the lungs and elsewhere in the body and the endothelialitis-driven coagulopathy are likely to occur in parallel in some circumstances. It has been demonstrated that acute respiratory distress syndrome leads to systemic inflammatory pathways which can predispose clotting in vivo, particularly reflected in pulmonary emboli and microemboli at other sites of infection-associated tissue damage [20-22].

Hypothetically, these two systems (inflammatory and coagulopathic) are not just overlapping, but synergistic in their biochemical pathways and therefore in their influence on clinical outcomes of patients infected with SARS-CoV-2. There is undoubtedly still a need for more research needed to draw the connections between these suspected biochemical pathways and the unique clinical manifestations being examined by epidemiologists and clinical researchers.

Conflicts of Interest

The authors have no relationships to disclose.

References

1. Akhmerov A, Marbán E (2020) COVID-19 and the Heart. Circ Res 126(10): 1443-1455.

2. Follis KE, York J, Nunberg JH (2006) Furin Cleavage of the SARS Coronavirus Spike Glycoprotein Enhances Cell-Cell Fusion but Does Not Affect Virion Entry. Virology 350(2): 358-369.

3. Gheblawi M, Wang K, Viveiros A, Quynh N, Jiu-Chang Z, et al. (2020) Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res 126(10): 1456-1474.

4. Hasan A, Paray BA, Hussain A, Fikry Ali Qadir, Farnoosh Attar, et al. (2020) A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin. J Biomol Struct Dyn 2020: 1-9.

5. Mao L, Jin H, Wang M, Yu H, Shengcai Chen, et al. (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 77(6): 683-690.

6. Zhou F, Yu T, Du R, Guohui F, Ying L, 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.

7. Yaghi S, Ishida K, Jose Torres, Brian Mac Grory, Eytan Raz, et al. (2020) SARS-CoV-2 and stroke in a New York healthcare system. Stroke 51(7): 2002–2011.

8. Jain R, Young M, Dogra S, Helena K, Vinh Nguyen, et al. (2020) COVID-19 related neuroimaging findings: A signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. J Neurol Sci 414: 116923.

9. Merkler AE, Parikh NS, Saad Mir, Ajay Gupta, Hooman Kamel, et al. (2020) Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. JAMA Neurol.

10. Oxley TJ, Mocco J, Majidi S, Christopher P Kellner, Hazem Shoirah, et al. (2020) Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 382: e60.

11. Fara MG, Stein LK, Skliut M, Susan Morgello, Johanna T Fifi, et al. (2020) Macrothrombosis and stroke in patients with mild Covid-19 infection. J Thromb Haemost. EPub ahead of print.

12. Escalard S, Maier B, Redjem H, François Delvoye, Solène Hébert, et al. (2020) Treatment of Acute Ischemic Stroke due to Large Vessel Occlusion With COVID-19: Experience From Paris. Stroke 51: EPub ahead of print.

13. Morassi M, Bagatto D, Cobelli M, Serena D'Agostini, Gian Luigi Gigli, et al. (2020) Stroke in Patients With SARS-CoV-2 Infection: Case Series. J Neurol EPub ahead of print 267: 2185-2192

14. Moshayedi P, Ryan TE, Mejia LLP, May Nour, David S Liebeskind (2020) Triage of Acute Ischemic Stroke in Confirmed COVID-19: Large Vessel Occlusion Associated With Coronavirus Infection. Front Neurology 11: 353.

15. Klock FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, et al. (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 191: 145-147.

16. Lodigiani C, Iapichino G, Carenzo L, Maurizio Cecconi, Paola Ferrazzi, et al. (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 191: 9-14.

17. Tang N, Bai H, Chen X, Jiale Gong, Dengju Li, et al. (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18(5): 1094-

1099.

18. Al-Ani F, Chehade S, Lazo-Langner A (2020) Thrombosis risk associated with COVID-19 infection. A scoping review Thromb Res 192: 152-160.

19. Wrapp D, Wang N, Corbett KS, Jory A Goldsmith, Ching-Lin Hsieh, et al. (2020) Cryo-EM structure of the 2019-nCOV spike in the perfusion conformation. Science 367(6483): 1260-1263.

20. Ackermann M, Verleden SE, Mark Kuehnel, Axel Haverich, Tobias Welte, et al. (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. Epub ahead of print.

21. Connors JM, Levy JH (2020) COVID-19 and its implications for thrombosis and anticoagulation. Blood. 135(23): 2033-2040.

22. Frohman EM, Villemarette-Pittman NR, Melamed E, Roberto Alejandro Cruz, Reid Longmuir, et al. (2020) Part I. SARS-CoV-2 triggered 'PANIC' attack in severe COVID-19. J Neurol Sci 415: 116936.

23. Shang J, Wan Y, Luo C, Gang Ye, Qibin Geng, et al. (2020) Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci USA. 117(21): 11727-11734.

24. Andersen KG, Rambaut A, Lipkin WI, Edward C Holmes, Robert F Garry (2020) The proximal origin of SARS-CoV-2. Nat Med 26: 450-452.

25. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, et al. (2020) The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res 176: 104742.

26. Hoffmann M, Kleine-Weber H, Pöhlmann SA (2020) Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell 78(4): 779-784.e5.

27. Hoffmann M, Kleine-Weber H, Schroeder S, Nadine Krüger, Tanja Herrler, et al. (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 181(2): 271-280.e8.

28. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Jan P Sperhake, Milagros N Wong, et al. (2020) Multiorgan and Renal Tropism of SARS-CoV-2. N Engl J Med.

29. Rapkiewicz, A, Mai X, Steven E Carsons, Stefania Pittaluga, David E Kleiner, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. EClinical Medicine, Article ID: 100434.

30. Han H, Yang L, Liu R, Fang Liu, Kai-Lang Wu, et al. (2020) Prominent Changes in Blood Coagulation of Patients With SARS-CoV-2 Infection. Clin Chem Lab Med 58(7): 1116-1120.

31. Xu P, Zhou Q, Xu J (2020) Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 99(6): 1205-1208.

32. Hess DC, Eldashan W, Rutkowski E (2020) COVID-19-Related Stroke. Transl Stroke Res 11(3): 322-325.

33. Varga Z, Flammer AJ, Steiger P (2020) Endothelial cell infection and endothelialitis in COVID-19. Lancet 395(10234): 1417-1418.