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Comment on an article: "Coagulopathy in COVID-19"

Dear Editors-in-Chief Lillicrap and Morrissey,

We have read with great attention the article "Coagulopathy in COVID-19" written by Toshiaki Iba et al, published in the September issue of the journal.[1] The authors performed an effective and informative review. Nevertheless, we welcome the opportunity to make a short comment as well.

This very interesting article evaluates current literature regarding the harmful hypercoagulable milieu of COVID-19. Surprisingly, we cannot see that the authors recommended other diagnostic considerations such as checking for hyperhomocysteinemia in patients with COVID-19. Undoubtedly, hyperhomocysteinemia has neurotoxic, neuroinflammatory, neurodegenerative, prooxidative, as well as proatherogenic/prothrombotic effects.[2] Also, recent evidence introduces the role of hyperhomocysteinemia as a strong risk factor for thromboembolism, given its influence in platelet reactivity.[3,4] In our opinion, it is very important to have this finding, because the simultaneous occurrence of hyperhomocysteinemia and pulmonary embolism in patients with COVID-19.

Herein, as a consequence of SARS-CoV-2 infection, a high number of pulmonary embolism has been noted in COVID-19 pneumonia patients (20.6%--28%), despite the fact that 90% of them were receiving prophylactic antithrombotic treatment according to the current guidelines.[5,6] Interestingly, according to studies of Yang et al[7] as well as Ponti et al[8] on 273 and 40 COVID-19 patients, respectively, levels of homocysteine were significantly higher and showed predictive value for computed tomography imaging progressions in pulmonary embolism. In this setting, hyperhomocysteinemia may be also a predisposing but not well-recognized risk factor for vascular accidents in the coagulopathic state of COVID-19.

Hopefully, values of folic acid (B9 vitamin) and B12 vitamin are in negative correlation with levels of homocysteine.[9] Furthermore, B vitamins are enhancers of the immune system.[10] Our studies from Bosnia and Herzegovina showed that the intake of folic acid, sometimes with B12 vitamin as well, was efficient in creating normalized homocysteine levels in older patients with ischemic stroke and Parkinson's disease.[11,12]

Despite knowledge gaps and lack of randomized controlled trials, there is an urgent need for different opinions and recommendations, when proper data are absent due to the speed of the COVID-19 disaster. Perhaps, it is necessary to add-on other medications in an attempt to minimize evident cardiovascular risk and improve health condition of COVID-19 patients with the possibility of pulmonary embolism. So, intake of B vitamins as a co-prophylaxis and proper diet control should be established as early as possible, not only in the COVID-19 population but also in other healthy individuals in the age of SARS-CoV-2, on the basis of Latin phrase *primum non nocere*.

Taken together—inadequate evidence, expert opinions, and previous experiences—we hypothesize about a potential connection between pulmonary embolism and hidden hyperhomocysteinemia in patients with COVID-19. In light of this, we suggest that levels of homocysteine, folic acid, and B12 vitamin should be measured at clinical follow-up in all patients with COVID-19, immediately after hospitalization. If persistant, hyperhomocysteinemic hypercoagulability should be promptly decreased in the acute phase of COVID-19 with folic acid, and in some cases with the addition of B12 vitamin. All in all, B vitamins can, ad hoc, become the medication of second echelon in the treatment of unhidden COVID-19 hyperhomocysteinemia. In conclusion, we emphasize that further studies will show harmful potential of hyperhomocysteinemia on pulmonary embolism in COVID-19 patients as well as beneficial therapeutic add-on effects of various B vitamins.

KEYWORDS

COVID-19, coagulopathy, folic acid, homocysteine, vitamin B12

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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Letter in response to: Coagulation markers are independent predictors of increased oxygen requirements and thrombosis in COVID-19

We read with interest the recent publication by Rauche et al and congratulate them on highlighting the potentially significant role von Willebrand factor (VWF) may play in the progression and prognosis of COVID-19.[1] Since SARS-Cov2 first presented there has been an increasing recognition that the disease may trigger a widespread endotheliopathy. This fact could help to explain the highly varied presentation of patients with COVID-19 from bowel ischemia to large vessel occlusion causing strokes in addition to the more common presentation of respiratory symptoms. At the same time there has been an increased understanding that the infection may result in microthrombosis as well as macrothrombosis both on the arterial and venous side of the circulation. Contrast enhanced ultrasound was recently used to identify microthrombi and wedge-shaped perfusion defects in vivo in the pulmonary, renal, and gastrointestinal beds.[2,3] Routine imaging methods, such as computed tomography (CT) and CT angiography, do not have the spatial or contrast resolution to detect microvascular thrombosis and therefore, the demonstration of perfusion defects in vivo has been delayed. Post mortem studies have also shown microthrombosis within the lungs confirming the in vivo imaging findings. In the study of Carsana et al, microthrombi, in vessels < 1mm in diameter, were seen in 87% of cases.[4] A further case series of COVID-19 pulmonary autopsies revealed that, alongside diffuse alveolar damage, numerous localized platelet-rich microthrombi, and foci of hemorrhage were present in the lungs.[5] The authors posited a pulmonary-localised thrombotic microangiopathy as key to the pathogenesis of COVID-19 with others also suggesting the micro-thrombosis is a critical driver in the disease process.[6]

Von Willebrand factor is synthesized only in megakaryocytes and endothelial cells (ECs). The vast majority of VWF found in the plasma is derived from the VWF synthesized within the ECs, where it is stored within the Weibel-Palade bodies (WPB). Although restricted to ECs there are differences in the synthesis of VWF within the different vascular beds of the body with the small vessels of the lung and brain expressing higher levels of VWF than similar sized vessels of the liver or kidney and higher levels in venous rather than arterial ECs.[7] A major portion of the VWF stored in the WPBs of endothelial cells is made up of ultra-large VWF (ULVWF). These larger multimers are more adhesive than the smaller multimers in the circulation and upon secretion ULVWF can spontaneously bind

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