Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

individuals have life-threatening COVID-19 disease whereas others have no or mild symptoms.

Because this is not the conclusive report and we appreciate the attempt to explain the peculiar reactions of some patients with COVID-19, we would like to suggest some specific ideas with a view to more targeted therapeutic interventions.

First, it is not easy to determine the relation between risk factors predisposing people to a more severe reaction to COVID-19 infection with regard to vitamin D deficiency and genetic risk factors. On the other hand, genetic alterations suggest interesting ideas with regard to multigene expression, especially on large specific chromosomes for epithelial membrane proteins in the lungs, according to recent papers on this topic.[2]

Second, apparent contradictions in COVID-19 mortality and morbidity in patients with common variable immune deficiency allow the authors to produce a scholarly examination of the immune imbalance and dysregulation of innate and adaptive immune responses in patients with severe COVID-19. The factors analyzed, sometimes in a correlated manner, are (1) the importance of the type I interferon pathway; (2) immune-senescence; (3) age-independent comorbidities such as hypertension, diabetes, and obesity; (4) the uncontrollable proinflammatory response in the lungs driven by macrophage-activation syndrome; (5) the T cell and subtype response; and (6) the antibody response against the viral envelope S (spike) and N (nucleocapsid) proteins.

However, before concluding that "a combination of multiple genetic and non-genetic factors contribute to an individual's unique immune response and susceptibility to SARS-CoV-2 infection," in our opinion, it is of paramount importance to introduce the vascular endothelium into the discussion.[3] Endothelial damage to various organs was also highlighted by autopsy outcomes.[4]

With regard to the subject of the vascular endothelium, information reported on the AB0 blood group loci that were associated with severe SARS-CoV-2 infection may find a more complete and significant interpretation in this direction, as also may be the case regarding the integrity of endothelial glycoproteins.[5,6]

Thus, we encourage an examination of these points, not to negate any of the points made but to augment and improve this thought-provoking original article, which sheds further light on why some people develop serious COVID-19 disease after infection whereas others exhibit only mild symptoms.

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Reply to "Patient variability in severity of COVID-19 disease. Main suspect: vascular endothelium"

To the Editor:

We thank Drs Tricarico and Travagli[1] for their comments on our recent Rostrum publication.[2] Over the past year, we have learned much about the pathobiology and immunology of the disease caused by the SARS-CoV-2 virus. Vascular dysfunction, serum cytokines, and chemokines have important roles in the pathophysiology of COVID-19 disease, especially in severe cases. They raise an interesting comment regarding how severe COVID-19 can result from damage to the vascular endothelium and how this damage may induce thrombotic events that may correlate with ABO blood groups.

Although there is little question as to whether damage to the vascular endothelium has a role in COVID-19 progression and severity, there are questions regarding how this damage arises in SARS-CoV-2 infection. Certainly, studies have shown that patients with the non-O blood type have an elevated risk for thrombocytopathy and endotheliopathy. Cardiovascular risk factors such as diabetes,[3] hypertensive disorders,[4] and obesity[5] have also been shown to increase susceptibility to endotheliopathy and thrombosis; they correlate with increased morbidity and mortality in COVID-19 patients presenting with these comorbidities. Aging also decreases endothelial cell function through increased oxidative and nitrative stress responses.[6]

However, thrombosis and endothelial dysfunction may result from the response to the virus itself, outside preexisting genetic and health factors. For instance, Wu et al[7] recently showed that the receptor binding domain of the SARS-CoV-2 spike protein preferentially binds to cells expressing blood type A, potentially boosting the viral load. Thrombotic and endothelial dysfunction may result from an increased viral burden, because endothelial cells have also been shown to express the angiotensin-converting enzyme 2 receptor.[8] As we discussed in our article,[2] hyperinflammatory responses precipitated by inflammatory cytokines to SARS-CoV-2 infection may themselves elicit endothelial cell damage. In addition, thrombocytopathy and endotheliopathy may result from an errant humoral response that leads to the development of antiphospholipid antibodies. The production of these autoantibodies may cause symptoms of antiphospholipid syndrome,[9] of which vascular endothelial cell dysfunction is a key pathological hallmark.[10]

Nitric oxide (NO) has recently been addressed as an important component of vascular dysfunction in patients with COVID-19

(reviewed by Fang et al[11]). It has been reported to have an antiviral effect against SARS CoV-2.[12] Several reports have shown beneficial responses using inhaled NO therapy in COVID-19 patients.[13,14] Atopic asthmatic patients have higher inducible NO synthase and exhaled NO, which correlate with sputum eosinophil levels.[15] Kimura et al[16] reported reduction of angiotensin-converting enzyme 2 gene expression in asthmatic patients with the Th2 phenotype. Thus, could the connection between the T_H2 phenotype and exhaled NO contribute to less severe COVID-19 in asthmatic patients?[17]

Contributions to endotheliopathy of factors antecedent to infection versus the infection itself remain inconclusive. Certainly, risk and genetic factors can increase susceptibility to endothelial damage upon infection. However, hyperinflammatory and a disordered humoral response to SARS-CoV-2 infection itself significantly contribute to severe COVID-19.

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Proposal for a new classification of vibratory urticaria/angioedema

To the Editor:

We have read with interest the article published by Kulthanan et al[1] regarding the results of the systematic literature review on vibratory angioedema. The article shows a complete analysis of the published literature and proposes a classification of vibratory angioedema in 2 variants, namely hereditary and acquired. According to the authors, the hereditary forms significantly show wheals compared with the acquired forms.

Hereditary vibratory angioedema was originally described in 1972 by Patterson et al[2] in a family whose members were diagnosed with angioedema on vibratory stimuli shortly after they were born. Boyden et al[3] described several members of 3 Lebanese families carrying the *ADGRE2* (adhesion G protein-coupled receptor E2) mutation in whom hives on vibratory stimuli predominated in the clinical picture and referred to the condition as vibratory urticaria. These authors intended to study the *ADGRE2* mutation in Patterson's family members but were unable to contact them. In their opinion, based on the clinical manifestations, Patterson's patients and their own likely suffered from different conditions.[4,5] Both being hereditary, in Patterson's cases, lesions consisted of cutaneous/subcutaneous angioedematous lesions lasting hours to days,[2] and in Boyden's cases, lesions consisted of evanescent hives lasting less than 1 hour.[3-5] Thus, we propose to subclassify the hereditary variants into 2 subtypes: the hereditary vibratory angioedema (Patterson type) and the hereditary *ADGRE2*-related vibratory urticaria (Boyden type).

Regarding the acquired cases, they could be subclassified into 2 subtypes: the more frequent acquired vibratory angioedema, characterized by a sustained history of angioedema on vibratory stimuli without hives that may last months or years, and the rare secondary acquired vibratory urticaria,[6,7] described only twice in relation to *Candida glabrata* infection[6] and *Hymenoptera* sting.[7] In the latter, lesions consist of hives; a primary condition is necessary for it to develop and evolution is transient (symptoms triggered by the vibratory stimulus last until the primary condition is resolved).

On the basis of these observations, we believe that vibration can induce a heterogeneous set of diseases defined as vibratory urticaria or angioedema and propose a modification on the Kulthanan classification to incorporate some data included in the clinical descriptions of the cases (Table I).

In addition, Kulthanan et al[1] included the 12 volunteers working in 2 dermatology departments in Spain that we reported[8] as well as the population of 7 Chinese and 18 German medical students studied by Zhao et al.[9] These individuals had a previous history of symptoms on vibratory stimuli according to questionnaires and usually different degrees of alteration of the vortex provocation test. To the best of our knowledge, none suffered