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COMMENTARY

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Disruption of the biological activity of protease-activated receptors2/4 in adults rather than children in SARS CoV-2 virus-mediated mortality in COVID-19 infection

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Abstract

One of the most remarkable results in 2019 is the reduced prevalence and death of children from coronavirus infection (COVID-19). In 2019, a worldwide pandemic impacted around 0.1 billion individuals, with over 3.5 million mortality reported in the literature. There is minimal knowledge on SARS-CoV-2 infection immunological responses in kids. Studies have been focused mostly on adults and children since the course of pediatric sickness is often short. In adults, severe COVID-19 is related to an excessive inflammatory reaction. Macrophages and monocytes are well known to contribute to this systemic response, although numerous lines are indicative of the importance of neutrophils. An increased number of neutrophils and neutrophil to lymphocyte ratios are early signs of SARS-CoV-2 and a worse prognosis. In this study that it is crucial to monitor PAR2 and PAR4 expression and function (since nursing children have elevated levels) and the inhibiting the normal physiology through the use of anticoagulants may exacerbate the problem in adults. Thus, in COVID-19 infection, we propose the use of antiplatelet (thromboxane A2 inhibitors), if required rather than anticoagulants (FXa and thrombin Inhibitors).

KEYWORDS
SARS CoV-2, COVID-19, antiplatelet

One of the most remarkable outcomes of 2019 is the decline in the frequency and mortality of coronavirus infection (COVID-19) in children. In 2019, a worldwide pandemic impacted around 0.1 billion individuals, with over 3.5 million mortality reported in the literature. SARS-CoV 2 is an RNA-positive sensing virus with a genome size of approximately 30,000 nucleotides and a large unilateral RNA genome (Siddell et al., 1983). There are three protein classes: two big polypeptides, pp1a, and pp2ab, all clustered into 16 NSP necessary for the production of viral RNA (or presumably other activities), four structural proteins essential for entrance and assembly in virus (S, E, M, and N Proteins) to fight host immunities (Singh, Gupta, Kazmi, et al., 2020; Fehr & Perlman, 2015). The first stage of infection is viral entrance and a crucial stage in the viral life cycle, making it a primary target for vaccinations and therapies. The spike (S) protein is utilized on the SARS-CoV-2 envelope to connect with the host cell's receptor and promotes the subsequent membrane fusion required for viral material release into the cytoplasm (Singh, Gupta, Mishra, et al., 2020). The cell proteases split SARS-CoV-2S proteins into subunits of the S1 and S2, both remaining linked and ultimately forming trimmers of the S1/S2 heterodimer, during the cell invasion phase. The S1 subunit has two domains: the NTD and the CTD, later critical for interaction with the ACE2 host receptor, so referred to as the

RBD (Sriram & Insel, 2020). However, numerous studies also demonstrate that proteins such as tyrosine-protein kinase receptor UFO (AXL), kringle Containing Transmembrane Protein 1 (KREMEN-1), and asialoglycoprotein receptor 1 (ASGR-1) may function as receptors for SARS-CoV-2 entrance and contribute to widespread organ invasion in COVID-19 patients. In the absence of ACE2, each of the three molecules may be capable of mediating SARS-CoV-2 entry, therefore giving alternate paths for SARS-CoV-2 infection in various tissues (Peng et al., 2021).

Proteolysis at the S2 point of cleavage to remove the UH domain is crucial to activating the S protein fusogenic activity which leads to irreversible alterations in S2 fusion machines which start membrane fusion (Singh, Gupta, Mishra, et al., 2020). COVID-19 symptoms are highly varied following virus entry into cells, with a common stimulation of immune responses referred to as a "cytokine storm." Excessive cytokine release by hypersensitive persons includes interleukin (IL) 6 and IL-10, which are the strongest predictors of illness outcome. Additional consequences related to patients' atypical response to viral infection include increased thrombosis linked with micro coagulation and dysbiosis of the gut microflora.

The first SARS-CoV-2 infection in children was detected in a group of six persons who had a long history of travel to Wuhan, China, in January 2020. The study showed that children <18 years of age (the median age was 11 years), hardly form 1.7% of US cases (Team, 2020) and a 2% large UK observational cohort (Jiang et al., 2020). Almost one-third of the 2572 recorded pediatric cases occurred in children between 15 and 17 years of age (813; 32%), followed by youngsters between 10 and 14 years of age (682; 27%). Among younger children, 398 (15%) occurred in infants under the age of 1 year (Team, 2020) and 291 (11%) among children between the ages of 1 and 4 years. The primary trait revealed in recent nature literature, COVID 19 children with gastrointestinal symptoms. Followed by myocarditis and acute cardiac insufficiency developed. Other indicators such as irregularities in the coronary artery and pericardial disease (pericarditis and pericardial effusion) and neurological symptoms (meningeal signs, headache, confusion, irritability, etc.), last, not the least acute kidney damage, all of which have been described in childhood research (Dhar et al., 2021). According to data from China, pediatric COVID-19 infections may be less severe than adult infections, and children may exhibit symptoms diversely than adults (Figure 1).

There is minimal knowledge on SARS-CoV-2 infection immunological responses in kids. Studies have been focused mostly on adults and children since the course of pediatric sickness is often short. In adults, severe COVID-19 is related to an excessive inflammatory reaction. Macrophages and monocytes are well known to contribute to this systemic response, although numerous lines are indicative of the importance of neutrophils. An increased number of neutrophils and neutrophil to lymphocyte ratios are early signs of SARS-CoV-2 and a

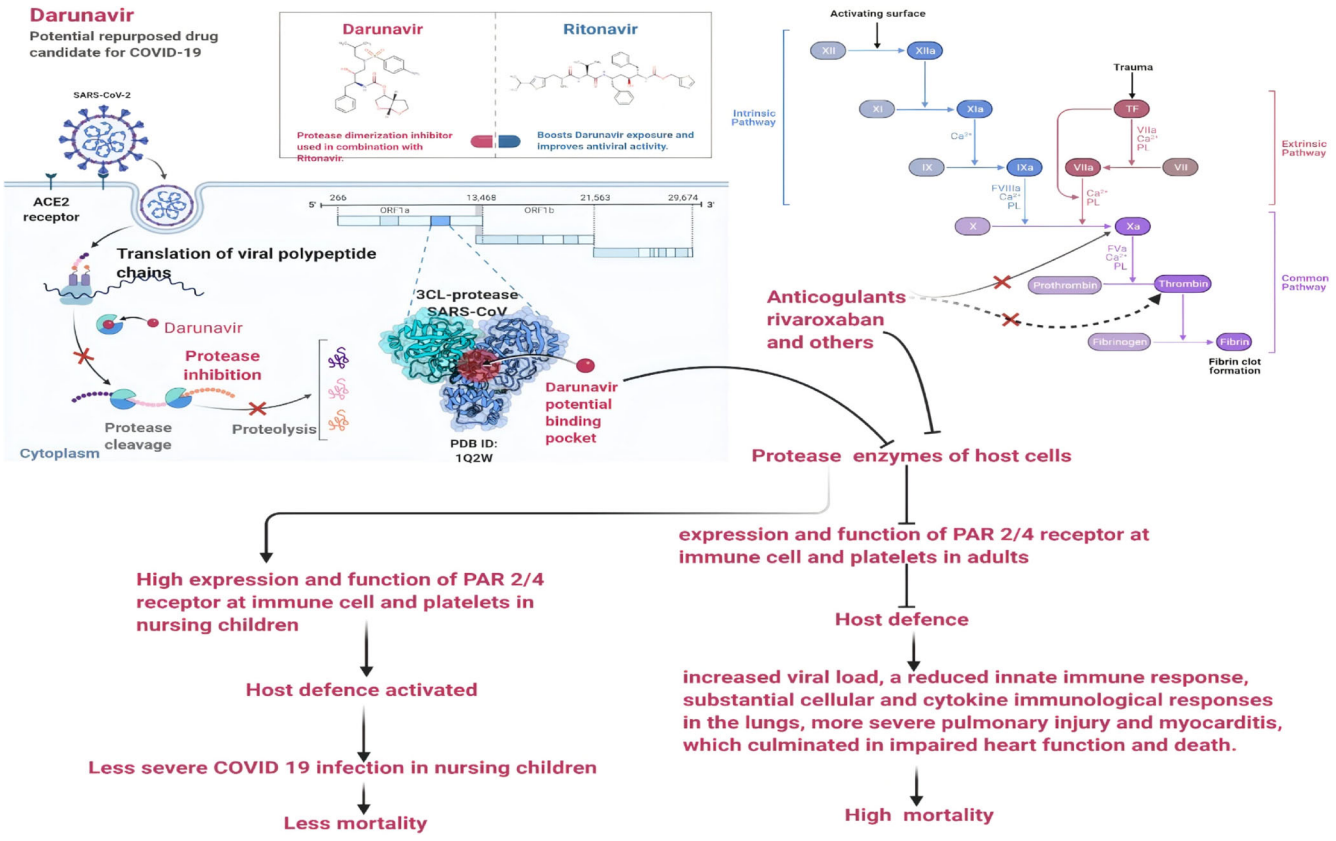

FIGURE 1 Explores disruption of the biological activity of protease-activated receptors2/4 in adults rather than children in SARS CoV-2 virus-mediated mortality in COVID-19 infection

worse prognosis. A high proportion of neutrophils was found in severe COVID-19 patients, while lung autopsy showed varying levels of neutrophil infiltration (Kumar Gothwal et al., 2021). Furthermore, the incidence and degree of thrombotic consequences of SARS CoV-2 infected adults have been increased about other breathing illnesses and thrombosis in these individuals has been proven to cause high mortality rates. Additionally, it is thought that increased oxidative stress with aging causes damage to DNA and mitochondrial dysfunction. The development of cardiovascular mortality generally involves oxidative stress. More investigations are necessary to clarify the mechanism by which thrombosis during COVID 19 infection might work to regulate precisely protease-activated receptors (PARs).

In particular, the cross-section of the coagulation case and the inflammatory reaction partially through PARs. In hemostasis and thrombosis, platelets play a crucial role. Aberrant activation of platelets can generate unanticipated thrombosis under many clinical situations, which might lead to cardiovascular illnesses including myocardial infarction and ischemic stroke. Human platelets exhibit the G-protein coupled receptors PAR1 and PAR4, but mouse platelets exhibit the functional thrombin receptor PAR4 in the absence of PAR1. Serine proteases and MMPs, particularly immune-cell and coagulation proteases, can either activate or inactivate PARs depending on the cell type and post-translational modification of the PAR. Numerous studies have shown that PARs affect antiviral responses to infections with the RNA viruses Coxsackievirus B3 and H1N1 influenza A virus. PAR2 expression is elevated in vivo during influenza infection, and its activation regulates cytokine release and suppresses viral replication through a mechanism dependent on IFN-γ release (Khoufache et al., 2009). However, its expression decreases as age progress but in breastfeeding children it is abundantly available in the GIT and respiratory cells and activated during infection and produce host defense mechanism.

PAR4 defective animals were thrombin- and platelet-PAR4-independent, which previously demonstrated that thrombin inhibition has little effect on disease development in mice infected with H1N1 IAV, whereas platelet inhibition is protective. According to a recent randomized clinical trial published in the Lancet, initial in-hospital anticoagulation with rivaroxaban has not been improved clinical outcome and increased bleeding in stable patients or enoxaparin for older participants followed by rivaroxaban for 30 days, in hospitalized COVID-19 patients within raised levels of D-dimer. In patients who are admitted to the hospital and have no evidence of oral anticoagulation, the therapeutic dose of rivaroxaban and another oral direct anticoagulant should be avoided (Lopes et al., 2021). Additionally, PAR4 deficiency in mice prompted an increased viral load, a reduced innate immune response, substantial cellular, and cytokine immunological responses in the lungs, more severe pulmonary injury, and myocarditis, which culminated in impaired heart function and death. (Tatsumi et al., 2019).

In this investigation, we found that monitoring PAR2 and PAR4 expression and function is critical (since nursing children have higher levels), and that suppressing normal physiology with anticoagulants may aggravate the problem in adults. Thus, in COVID-19 infection, we propose the use of antiplatelet (thromboxane A2 inhibitors), if required rather than anticoagulants (FXa and thrombin Inhibitors).

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Yogendar Singh, Neeraj Kumar Fuloria, and Shivkanya Fuloria gave the initial idea and contributed in drafted manuscript. Vetriselvan Subramaniyan Dhanalekshmi and Waleed Hassan almalki participated in all the sections of the manuscript development. Fahad A. Al-Abbasi participated in all the sections of the manuscript development and technical comments. Imran Kazmi finalized the manuscript for publication. All authors read and approved the final version of manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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