Elevated circulating endothelin-1 as a potential biomarker for high-risk COVID-19 severity

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Graphical Abstract

Abstract

There is a disproportionately higher rate of adverse outcomes in coronavirus disease 2019 (COVID-19) patients of the male sex, select ethnicities, and individuals with obesity and those that tend to have endothelial dysfunction (e.g., hypertensives, diabetics and individuals with coronary heart disease and respiratory system diseases). Endothelitis across vascular beds of multiple organs, thrombosis and ischaemia, are among common pathological features of severe COVID-19 cases. Endothelin-1 (ET-1) is the most potent vasoconstrictor of the human cardiovascular system and a culprit of endothelial dysfunction. Elevated circulating ET-1 levels are a predictor of cardiovascular disease status and have been correlated with racial/ethnic differences in microvascular and macrovascular disease severity and prognosis as well as with older age-associated endothelial dysfunction. Here, we propose elevated circulating ET-1 levels as a plausible biomarker and prognostic tool in predicting individuals at high risk of developing severe COVID-19. In addition to this, we also propose ET-1 gene variants and expression patterns might also cause a predisposition for an increased risk of severe acute respiratory syndrome coronavirus-2 infection severity in some individuals and/or populations.

Keywords:

Biomarkers; COVID-19; Endothelin-1; Endothelin-1 gene; NF-κB; SARS-CoV-2

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**Purpose and Rationale**

Precision medicine is an emerging approach to disease management, which utilises data from genomics, environment and lifestyle to predict more accurate prevention and treatment strategies for a particular disease in different populations. The emergence of precision medicine is, therefore, helping with the discovery of novel drug targets, drug repurposing/repositioning, nanomedicine engineering, development of nanotechnology-based companion diagnostics, and improving clinical trial outcomes. The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has created a pandemic across the world with a disproportionately higher risk of adverse outcomes in some patients and populations. Precision medicine offers an opportunity to identify robust biomarkers that could predict individuals at higher risk of severe COVID-19 and to combat the pandemic. Such progress could trigger the potential development of robust and precise multifunctional nanotechnology-based diagnostics such as multiplex plasmonic platforms for simultaneous detection of the virus and risk biomarkers. Here, based on the available evidence of SARS-CoV-2 interaction with endothelium, the renin-angiotensin-aldosterone system (RAAS) and endothelin system, and the resultant disease manifestations [1–3], we propose endothelin-1 (ET-1) as a plausible robust biomarker and prognostic tool in predicting individuals at high risk of developing severe COVID-19.

**Introduction and Discussion**

**Endothelial dysfunction**

The vascular endothelium plays an essential role in the regulation of vascular tone and the maintenance of vascular homeostasis through secretions of potent vasorelaxant (e.g., nitric oxide) and vasoconstricting (e.g., ET-1) substances [1]. Endothelial dysfunction is a hallmark of various human disease states and is characterised by diminished production/bioavailability of nitric oxide presumably as a result of suppressed endothelial nitric oxide synthase, and/or an increase in endothelium-derived contracting factors (notably ET-1), which shifts the vascular equilibrium towards more vasoconstriction [1]. ET-1 is not only the most potent vasoconstrictor in the human cardiovascular system but also its complex and multifaceted interactions with the RAAS are well documented [2,3]. ET-1 plays multiple roles in cardiovascular, pulmonary, in renal and neural physiology, and as such, differential and tissue-specific production of ET-1 is tightly regulated. Biological factors and mediators such as angiotensin II, cytokines and free radicals promote ET-1 secretion, whereas nitric oxide, prostacyclin and cyclic GMP reduce ET-1 release [2,3]. The critical role of ET-1 in pathophysiological changes associated with both microvascular and macrovascular diseases are well known and include proinflammatory, proliferative and procoagulatory states [2].

Increased circulating ET-1 levels have been found in smokers and those with conditions such as hypertension, atherosclerosis, coronary heart disease, cerebrovascular diseases, diabetes and sepsis [2]. Elevated circulating ET-1 levels have further been correlated with population differences in disease severity and prognosis as well as older age [2,4–11]. For instance, there are higher rates of hypertension among African American and Hispanic persons than in non-Hispanic white persons [4]. As such, ET-1 has been implicated as a key mediator in the pathogenesis of hypertension and vascular disease among African Americans, as African Americans with systemic hypertension have higher circulating levels of both ET-1 and ET-1 precursors than white people with hypertension [5,6]. The aetiology of racial differences in the prevalence and severity of hypertension has further been noted in other parts of the world. For example, plasma concentrations of ET-1 were shown to be significantly higher in hypertensive Gulf Arab patients compared with white hypertensives [7]. Furthermore, the higher levels of ET-1 have predicted disease severity and mortality in many forms of pulmonary arterial hypertension, including in HIV infection [8]. Alterations in the ET-1 gene (edn1) expression patterns have also been documented in the pathogenesis and progression of various human diseases [12]. For instance, genetic polymorphisms such as a common adenine insertion in the 5’-untranslated region of edn1 results in elevated mRNA levels, and this has been associated with
essential hypertension [13]. Also, *edn1* variants leading to high circulating ET-1 levels have been identified as a risk factor for coronary artery disease and intracerebral haemorrhage in certain populations including a Chinese Han population [9,10]. Endothelial function also deteriorates with aging and plasma ET-1 concentration significantly increases with ageing, but exercise reduces plasma ET-1 level in older individuals [11].

**Can circulating ET-1 levels serve as a predictive biomarker for COVID-19 severity?**

Since the COVID-19 outbreak, we have witnessed a disproportionately higher rate of adverse outcomes in patients with pre-existing endothelial dysfunction, notably in those with hypertension, coronary heart disease, respiratory system diseases, diabetes, obesity and of the male sex [14,15]. Vascular and thrombotic complications, including symptomatic acute pulmonary embolism, deep-vein thrombosis, ischaemic stroke, myocardial infarction and systemic arterial embolism have been reported in severe COVID-19 cases [15,16]. These complications are presumably related to endothelial cell infection with SARS-CoV-2 through its cognate host angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed by arterial and venous endothelial cells [17], resulting in endotheliitis, thromboembolism and ischaemia. The overall COVID-19 severity in infants and children is significantly milder than in adults [18,19], but in rare cases, some children have developed an inflammatory, multisystem syndrome similar to Kawasaki disease [20,21]. Older age and race/ethnicity have further been identified as risk factors in severe COVID-19 cases and deaths [22]. For instance, the Centers for Disease Control and Prevention report a disproportionate burden of illness and death rates among Black/African Americans and Hispanic/Latino persons than white or Asian persons [23]. Some reports have attributed these differences to socioeconomic status levels and living conditions, combined with restricted access to healthcare services [24,25]. However, by considering the existing correlations between ET-1 and endothelial dysfunction, including in Kawasaki disease [26], we propose that elevated circulating ET-1 levels might also serve as a prominent biomarker and prognostic tool to identify individuals with the greatest risks of severe COVID-19. This suggestion might, therefore, explain the disparities seen in COVID-19 severity and patients with cardiometabolic comorbidities. For instance, nitric oxide deficiency in endothelial dysfunction may contribute to viral cellular entry and subsequent proinflammatory reactions, since nitric oxide apparently interferes with the interaction between coronavirus S-protein and ACE2 [27]. Furthermore, genetic differences such as ET-1 gene variants leading to high levels of circulating ET-1 and/or ET-1 receptor A and B type gene variants might also cause a predisposition for an increased risk of SARS-CoV-2 infection severity and endotheliitis in some individuals and/or populations.

The rate of transcription from *edn1* primarily controls ET-1 bioavailability [12], and alterations in cellular redox states are known to modify DNA binding and transactivation activities of many transcriptional activators [28]. The *edn1* promoter contains both common cis-acting elements and cell-type-specific and inducible elements. Many hormones (e.g., steroid hormones such as aldosterone), stimuli (e.g., hypoxia) and cell signals (e.g., the redox-sensitive transcriptional factor NF-κB) regulate *edn1* gene transcription through cis-acting elements in the *edn1* promoter [12]. The role of NF-κB is of particular interest due to the observed cytokine storm and hyper inflammation in severe COVID-19 cases [29]. Recently, dexamethasone, which reduces NF-κB-mediated transcriptional activity without altering IκB protein levels or the nuclear translocation of NF-κB, has shown efficacy in treating critically ill COVID-19 patients. The *edn1* promoter contains three functional NF-κB binding sites and many cytokines such as tumour necrosis factor-α, interferon-γ and interleukin-1β are capable of activating NF-κB-dependent *edn1* expression [12]. Glucose has also been shown to stimulate the recruitment of NF-κB as well as histone acetyltransferase p300 to the *edn1* promoter, leading to an increase in histone H3 acetylation [30]. Moreover, the *edn1* promoter also contains a consensus-binding motif for the vascular endothelial zinc factor 1 (Vezf1), which is
exclusively expressed in vascular endothelial and haematopoietic cells [31]. Rac1-specific GTPase p68RacGAP has been identified as a regulatory cell signal for Vezf1 and co-expression of Vezf1 and p68RacGAP in endothelial cells inhibits Vezf1 transcriptional activation of the edn1 gene in a dose-dependent manner [32]. It also appears that a Vezf1 binding site in the edn1 promoter is involved in both basal and insulin-stimulated increases in edn1 expression in endothelial cells [33]. The proposed mechanism involves phosphatidylinositol-3 kinase-dependent inhibition of the glycoprotein synthases kinase 3β leading to depression of Vezf1 [33]. Intriguingly, a recent study has suggested that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism, leading to new-onset diabetes in COVID-19 patients who seemingly were healthy before the infection [34]. Again, these observations may partly be related to glucose and insulin-mediated increase in edn1 expression, which in turn may be dependent on corresponding edn1 promoter polymorphisms. In line with this hypothesis, another important response element in the edn1 promoter is the transcriptional factor activator protein-1 (AP-1) binding site [12]. AP-1 is also known to mediate genomic responses to many proinflammatory and proliferative signals. For instance, protein kinase C-dependent activation of AP-1 is an important mechanism for edn1 stimuli such as thrombin and angiotensin II [35,36]. Since angiotensin II is hydrolysed to angiotensin-1–7 by ACE2 [1,3], dysregulation of ACE2 in SARS-CoV-2 may facilitate lung injury [37]. Thus, angiotensin II-mediated AP-1 activation and recruitment to the edn1 promoter resulting in ET-1 overproduction may be a plausible mechanism contributing to the lung injury. This suggestion is consistent with the observation from a small study showing elevated levels of plasma angiotensin II in COVID-19 patients, which further correlated with both total viral load and the extent of lung injury [38]. We further emphasise that in response to hypoxia, the edn1 promoter recruits AP-1 as well as other factors such as p300, hypoxia-inducible factor 1, and the transcriptional factor GATA-2 [39].

Finally, many other emerging regulatory mechanisms that can alter edn1 transcription in a tissue-specific manner and include intracellular calcium and calmodulin levels, mechanotransduction signals and extracellular hypertonicity [12], but their roles within the context of COVID-19 severity need detailed assessment. Epigenetic factors must further be considered since tissue-specific edn1 expression is also modulated by DNA methylation [12].

**Conclusions**

Here, we present a hypothesis suggesting that elevated circulating ET-1 levels might serve as a plausible biomarker for identifying individuals with the greatest risks of severe COVID-19. Immunoreactive ET-1 is routinely measured by both radioimmunoassay and enzyme immunometric assay [40]. However, plasma concentrations of ET-1 are in the low picomolar range making direct measurements in the plasma difficult [40]. Accordingly, endothelin is extracted from plasma and concentrated before measurement, but extraction procedures and recovery conditions can dramatically affect intra- and inter-assay variability [40]. However, recent developments in plasmonic gold chips with enhanced near-infrared fluorescence [41] could be adopted for ET-1 detection in plasma without prior extraction, since plasmonic platforms offer detection with up to several orders of magnitude higher sensitivity than with methods such as the conventional enzyme-linked immunosorbent assay. Finally, while the validity of ET-1 hypothesis is to be confirmed, concerted genetic testing of SARS-CoV-2 infected individuals is expected to reveal population genetic heterogeneity and related polymorphisms leading to the identification of broader biomarkers providing a greater understanding of the differences and disparities in COVID-19 outcomes and severity. These may include genes encoding the NF-κB DNA binding subunit (NFKB1) [42] and STING (stimulator of interferon genes, encoded by TMEM173) [43]. Collectively, these efforts could select and prioritise individuals for vaccination as well as improve clinical outcomes through patient stratification with appropriate drug combinations.
Conflict of interest
The authors declare no competing interests.

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