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Potential biomarkers for the early prediction of SARS-COV-2 disease outcome

Vignesh Mariappan [a], P.S. Manoharan [b], Pajanivel R [c], Lokesh Shanmugam [c], S.R. Rao [d], Agieshkumar Balakrishna Pillai [a,*]

[a] Central Inter-Disciplinary Research Facility (CIDRF), Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, 607 402, India
[b] Indira Gandhi Institute of Dental Science (IGIDS), Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, 607 402, India
[c] Mahatma Gandhi Medical College and Research Institute (MGMCRI), Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, 607 402, India
[d] Vice-President (Research, Innovation & Development), Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, 607 402, India

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ABSTRACT

The current pandemic due to the fast spreading of SARS-CoV-2 infection has caused severe impairment in health, social, economic, scientific, and medical sectors across the globe. Owing to the not so well understood mechanism of disease pathogenesis in terms of variations in immune responses, there remains obscure why some of the patients who are infected by the novel SARS-CoV-2 develop an unpredictable clinical course that rapidly causes severe and deadly complications/manifestations. Currently, several assays are available for the confirmation of SARS-CoV-2 infection at the point of care. However, none of these assays can predict the severity of the COVID-19 disease. Thus, the identification of a prognostic biomarker that forecasts the condition of SARS-CoV-2 patients to develop a severe form of the disease could enable the clinicians for more efficient patient triage and treatment. In this regard, the present review describes the role of selected biomolecules that are crucially involved in the immune-pathogenesis of SARS-CoV-2 infection such as hyper-immune responsiveness, bradykinin storm and vascular leakage assuming these may serve as an effective prognostic biomarker in COVID-19 to understand the outcome of the disease. Based on the review, we also propose the development of a cost-effective SERS-based prognostic biosensor for the detection and quantification of biomolecules for use as a point-of-care system during a disease outbreak.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by a highly transmittable novel virus known as Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2) designated by the International Committee on Taxonomy of Virus (ICTV) based on its homology with SARS and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

The mode of disease transmission and associated symptoms of this pandemic are well documented. However, the disease pathogenesis mechanism is not properly understood. For instance, the virus affects humans irrespective of age groups and race. The severity of the disease outcomes is highly susceptible to the adults and elderly (≥60 years) individuals connected with comorbidities like hypertension, diabetes, and pulmonary disease [1]. Most of the patients infected with COVID-19 have a flu-like illness or may be asymptomatic, but few cases develop severe pneumonia, acute respiratory distress syndrome (ARDS), a multi-organ failure that may lead to death [2]. While drugs or vaccines are being developed or deployed on a limited scale to treat the virus, no accurate means exist to monitor the disease progression and outcome. Thus, indiscriminate hospitalizations of COVID-19 patients have led to further stress in hospital beds, particularly as hospital resources are already burdened by the aging population. To minimize hospitalization, hospitals had to implement new admission criteria which included clinical, laboratory, and COVID-19 severity predictive parameters. Thus identification of new potential biomarkers would allow hospitals to intelligently triage COVID-19 patients rapidly during epidemics, improve the overall clinical outcome and, most importantly, save lives. It will also save patients, insurance companies, and government programs from unwarranted hospitalization costs, thus improving the

* Corresponding author.
E-mail addresses: vigneshvickey585@rocketmail.com (V. Mariappan), manoharanps@igids.ac.in (P.S. Manoharan), pajanivelr@mgmcri.ac.in (P. R), lokeshs@mgmcri.ac.in (L. Shanmugam), vp@sbvu.ac.in (S.R. Rao), agiesh.b@gmail.com, agiesh.b@gmail.com (A.B. Pillai).

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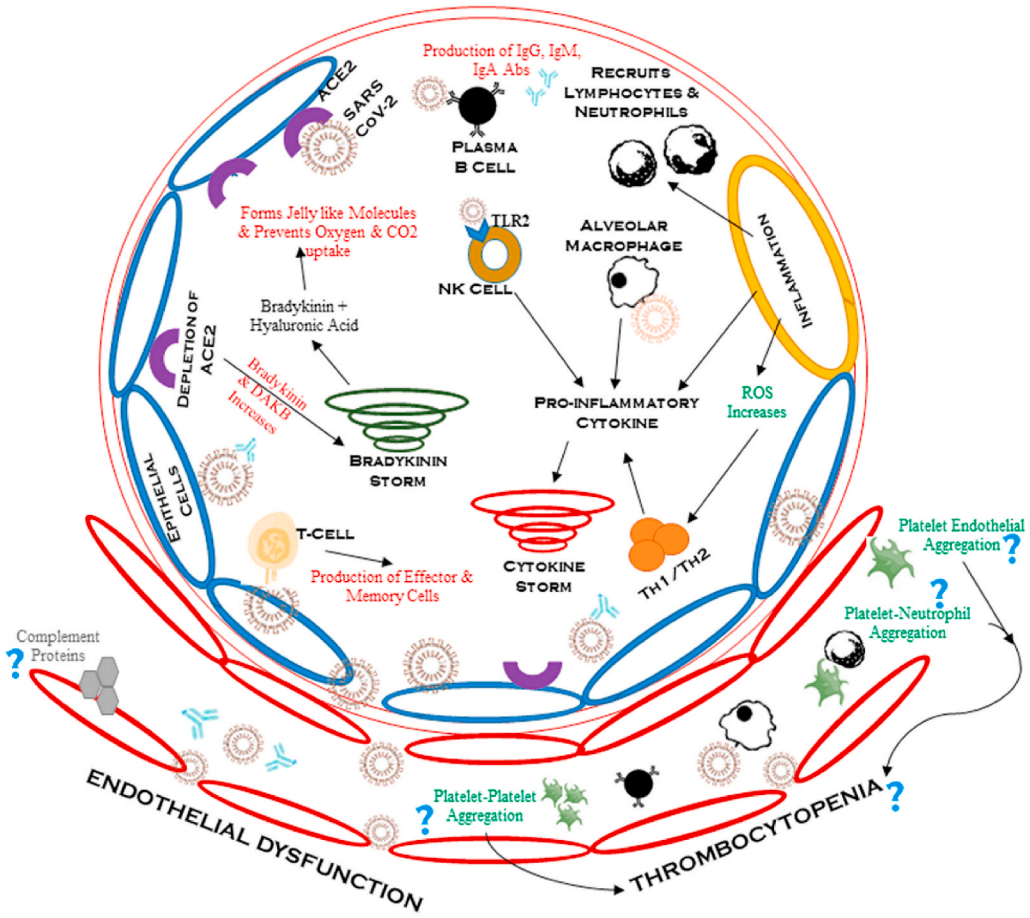

Fig. 1. Current Understanding of COVID-19 Molecular Immunopathogenesis.

control and management of this communicable disease. Thus, in the present review, we have summarized the various biomarker that is involved in the disease progression which may serve as an effective prognostic marker for severity prediction.

2. Pathogenesis of SARS-CoV-2 – known to hypothetical

SARS CoV-2 finds its access into the host cell using the well-defined ACE-2 receptor [3]. Other than ACE2, the virus uses CD147 and glucose-regulated protein 78 (Grp-78) [4,5] receptors, and the entry is assisted by a cellular serine protease namely transmembrane serine protease 2 (TMPRSS2) that helps in Spike (S) protein priming [3]. Interestingly, a single mutation in N501 of the spike protein of SARS-CoV-2 was reported to exhibit increased binding capacity with angiotensin-converting enzyme – 2 (ACE2) by the virus [6]. Upon entering the target cell, the viral RNA gets encapsulated, poly-adenylated, and translates several of its structural and non-structural (NS) genes. These polyproteins are cleaved by a protease that has chymotrypsin-like activity [7] such as TMPRSS2, cathepsin B, and L [8]. The distribution of ACE2 receptors could allow the virus to exhibit broad tissue tropism. For example, higher expression in enterocytes as recently reported [9] may be a possible reason for the fecal-oral transmission of the virus and gastrointestinal abnormalities in some of the COVID-19 positive cases [10]. Understanding this could provide insights into the mechanism of disease pathogenesis and drawing therapeutic strategies.

Once the virus propagates and emigrates towards the conducting cells of the lower respiratory tract, the SARS-CoV-2 suppresses/depletes the ACE2 expression (Fig. 1) which in turn decreases the angiotensin 2 metabolism thereby contributing towards the accumulation of angiotensin 2 [11]. This may be involved in pulmonary manifestation and inflammation which could be a possible reason for severe lung injury or ARDS [12]. The innate immune candidate molecules like TLR's are overproduced to counter the replicating SARS-CoV-2 RNA genome [13,14]. This is evidenced by studies that have documented the expression of both TLR and RIG/MDA (Retinoid-inducible gene/melanoma differentiation-associated gene 5) on bronchial epithelial cells and alveolar macrophages [15–17]. This recognition activates signalling pathways like nuclear factor Kappa B (NF-ĸB), activator protein 1 (AP-1), interferon response factor 3 (IRF3), and IRF7, leading to the expression of pro-inflammatory cytokines like IL6, IL1B, and CCL genes [18]. Another side, the activated IRF3, and IRF7 trigger the type I interferon (IFNα and IFNβ) expression. The exact immune-modulatory status of IFN production post-SARS-CoV-2 infections is not known though an animal study has mentioned a moderate increase in IFN α and IFN β production in the lungs following day 3 viral infection, whereas an increase in IFN γ on day 7. All these IFN's activates the IFN-stimulated genes (ISGs) that are responsible for the suppression of viral replication and spreading of the virus at the early phase [19,20]. Also, respiratory viral infections have been documented to induce influxes of lymphocytes, neutrophils, and macrophages into the alveolar space [21,22], which is essential for an effective antiviral response, but it may induce hyper-inflammatory reactions to regulate the disease severity which is currently not known.

Though several mechanisms are put forth for the antiviral immune response against SARS-CoV-2 infection, how the virus evades/hijacks the immune system remains to be elusive. Whether the virus follows the same pattern of SARS-CoV and MERS-CoV in inhibiting the early type 1 interferon response remains to be ascertained [23]. At the onset of SARS-CoV-2 infection, B cells evoke an early antibody response against N protein, while antibody against S protein occurs after 4–8 days from

the appearance of initial symptoms. Specific antibody IgA, IgM, and IgG against SARS-CoV can be detected in the infected patient at different time intervals [24]. In this regard, a study reported that SARS-specific IgG antibody can be detected for a long time than SARS-specific IgM antibody that declines after 3 months [25]. In SARS-CoV-2, the IgA and IgM declines in the third week after the onset of illness whereas IgG declines in the sixth week after illness onset. However, the proportion of detecting IgG is 84% and 53% for IgA and IgM after the seventh week after illness onset [26].

3. Diagnostic & prognostic tools at clinical practice

Virus isolation and culture are the primary and traditional methods that can be employed for the detection of COVID-19 causing virus [27]. But it is not recommended for the routine purpose because it requires skilled and trained personnel as well as Bio-Safety Level-3 (BSL-3) facilities which is applicable for working with indigenous or exotic agent that can cause serious disease because of exposure by inhalation route.

The reference technique for the detection of SARS-CoV-2 infection is based on the amplification of unique viral sequences via nucleic acid amplification tests (NAATs) using Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-qPCR) [28]. The assay should target the viral genome of SARS-CoV-2 such as E, RdRP, N, and S gene. Since SARS-CoV-2 can rapidly mutate, the mismatch between the primers and/or probes can reduce the accuracy and sensitivity of detection. Thus, it is recommended to use two different sets of primers/probes for a target region thereby reducing the false-negative results [29].

Antigen detection is a unique method in which the presence of SARS-CoV-2 proteins (antigens) is detected in biological fluids. The majority of them take <15 min [30]. On the other hand, ELISA and microarray are also used as diagnostic tools for SARS-CoV-2 detection. This method uses a solid matrix coated with a specific gene (oligonucleotides) or antigen derived from COVID-19 causing a virus. It is also used for the detection of SARS-CoV-2 induced specific antibodies such as IgM, IgG, and/or IgA in the suspected patients [31]. However, a false-positive result may occur if the antibody recognizes the antigen of other human coronaviruses due to cross-reactivity [32].

Loop-Mediated Isothermal Amplification (LAMP) is a field diagnostic assay with the capacity to detect various viral infections including the SARS-CoV-2 virus [33].

Currently, Mass spectrometry-based methods such as MALDI – MS, MassTag PCR are available to identify and characterize these glycoproteins in suspected biological samples with high sensitivity, specificity, and resolution. Recently, a study has reported the identification of SARS-CoV-2 in nasal swabs using MALDI-MS [34].

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is an instrumental component of the prokaryotic immune system that enables the prokaryotes to detect foreign DNA particles and destroy them. A recent study has reported the development of a CRISPR-Cas12-based assay for the detection of SARS-CoV-2 from the patient's RNA sample known as SARS-CoV-2 DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR). In addition, the positive predictive agreement and negative predictive agreement of SARS-CoV-2 DETECTR was 95% and 100% respectively [35].

4. Regular clinical biomolecules

4.1. D-dimer

D-dimer is an important indicator of coagulation and fibrinolysis which originates from the lysis of cross-linked fibrin. A significant ($p < 0.001$) increase in D-dimer levels in non-survivor (2.12 μg/ml) than the survivor (0.61 μg/ml) was reported [36]. A retrospective study reported that patient with D-Dimer level >2.0 μg/ml was strongly correlated with increased mortality among COVID-19 patients [37]. The study suggested a level of 2.0 μg/ml or more during the time of admission is an optimum cut-off to predict in-hospital mortality for COVID-19. In addition to this, about 90% of patient with pneumonia has increased coagulation activity with a rise in D-dimer levels [38]. Further, Huang et al. reported D-dimer level on admission can be used to triage patients into critical care. The study reported a significant increase in the median level of D-dimer ($p \leq 0.0042$) in ICU patients than non-ICU patients (2.4 mg/L vs 0.5 mg/L) [39]. Thus, a meta-analysis study is needed to determine the cut-off point which may be used for the early prediction of disease outcomes in COVID-19.

4.2. C - reactive protein

C-reactive protein (CRP) is produced by the liver which is elevated during inflammation [40]. Previous reports mentioned that CRP levels were much higher in bacterial infection than viral infection [41,42]. Studies have suggested that CRP levels can be used for the early prognosis of pneumonia as well as an important index for the diagnosis and treatment of severe pulmonary infectious diseases [43,44]. Interestingly, a meta-analysis report has shown a significant ($P = 0.000$) elevation of CRP levels in non-survivor than survivor among COVID-19 patients [45]. Besides, it was reported a positive correlation between CRP levels and lung lesions at the early stages of COVID-19 cases [46]. The levels of CRP were reported to be very high in critically ill cases than in non-severe COVID-19 cases with an optimal threshold of 26.9 mg/ml serum CRP could be a potential predictor of disease progression in non-severe COVID 19 patients [47].

4.3. Macrophage activation marker

4.3.1. Ferritin, a strong clinical biomarker that predicts the COVID-19 severity

Macrophage activation syndrome (MAS) is a clinical state of hyper inflammation observed in patients with infection, malignancy, and certain rheumatological conditions like systemic juvenile idiopathic arthritis [48]. MAS is typically characterized by the severe upregulation of several pro-inflammatory cytokines leads to a process called a cytokine storm. COVID-19 shares its clinical features with MAS and thus COVID-19 may be defined as MAS-like syndrome [49] with elevated levels of pro-inflammatory and chemokine molecules such as IL-2, IL-7, TNF-α, G-CSF, CXCL10, CCL3, and MCP1 in ICU admitted COVID-19 cases than those in non-ICU [39]. Besides hypercytokinemia, upregulation of ferritin, D-Dimer, C-reactive protein correlates with MAS-like severe inflammation and fibrinolysis in COVID-19 patients [50]. Although several cell types such as hepatocytes, Kupffer cells, proximal tubular renal cell, and macrophage have been reported to secret ferritin both in vivo and in vitro condition, characterizing macrophage released ferritin might lead to a better disease prognosis and most the viral diseases targets macrophages.

In this regard, several studies reported the elevation of ferritin in COVID-19 patients. A study suggested that the median level of ferritin was significantly ($p < 0.01$) higher in the non-survivor group than in the control (233.3 ng/ml vs 451.25 ng/ml) with a ROC cut-off value of 304.30 [51]. Similarly, a meta-analysis study reported that the pooled mean ferritin level was 673 ng/ml ($p < 0.001$) [52]. Furthermore, a cross-sectional study in Israel with 39 COVID19 confirmed patients showed that severe patients have significantly ($p < 0.02$) higher ferritin levels (2817.6 ng/ml) than non-severe patients (708.6 ng/ml) [53]. A similar result was obtained in another study, where the mean ferritin level of survivor and non-survivor was 1463.36 ng/ml and 2757.42 ng/ml (at the time of admission with the p-value 0.066) and 1130.40 ng/ml and 3462.06 ng/ml (at the time of discharge with the p-value 0.001) [54].

A retrospective study reported that the median ferritin level was 4.7 fold higher ($p < 0.049$) in severe cases of COVID-19 compared to healthy control [55]. In reference to this, the level of ferritin was significantly ($p < 0.0001$) higher in non-survivor (1435.5 μg/L) than survivors (503.2

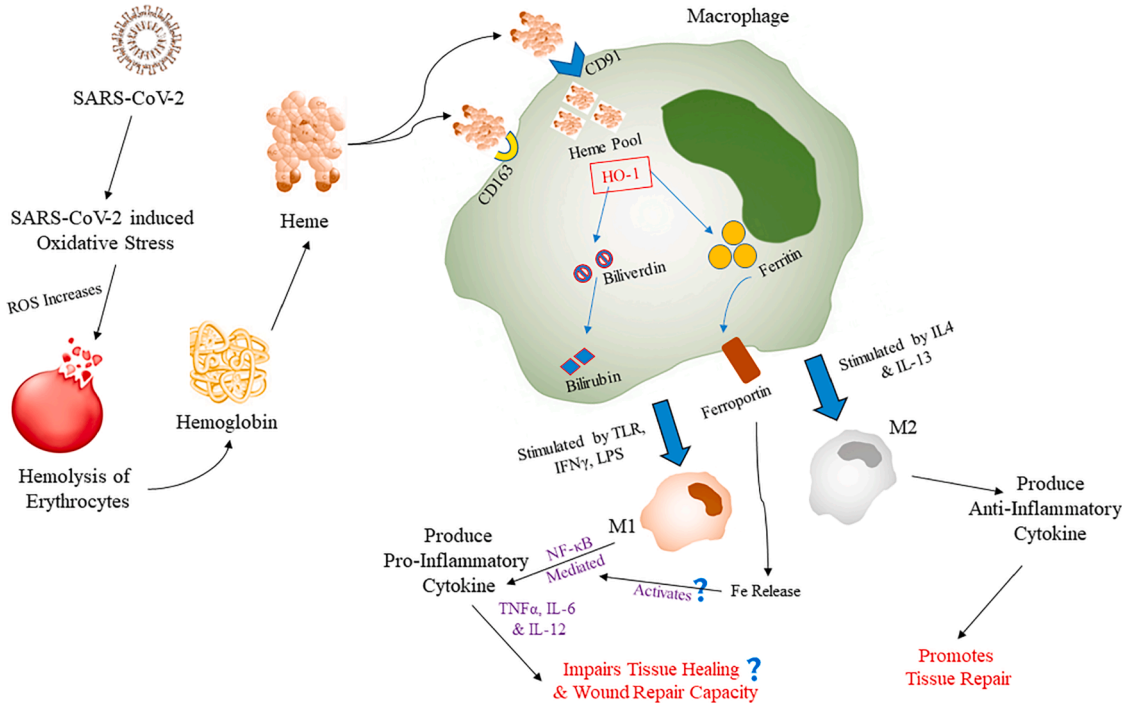

Fig. 2. Macrophage Released Markers in Severe COVID-19.

μg/L) throughout the clinical course of infection [56]. Based on the recently published data, ferritin levels above 500 ng/ml may be considered as a cut-off point for severe cases, however meta-analysis studies are needed for further conclusion.

Intriguingly the superoxide radicals released due to reduced oxygen supply in COVID could convert the iron (III) into iron (II) that triggers apoptosis/necrosis and induces coagulation in affected individuals [57,58]. All this above evidence shows that ferritin plays a crucial role in the disease pathogenesis of SARS-CoV-2 infection and maybe serve as a valuable prognostic marker for the early prediction of disease outcomes. Fig. 2 describes the role of ferritin during the SARS-CoV-2 infection.

4.3.2. CD14 and CD163

CD14 and CD163 are myeloid differentiation markers predominantly produced by monocytes and macrophages. A soluble form of these molecules serves as a good biomarker for monocyte-macrophage activation [59,60]. For instance, elevated levels of sCD14 in plasma are strongly associated with morbidity and mortality in HIV-infected patients [61]. While sCD163 plasma levels indicated the monocytes' expansion and disease progression [62]. An elevated level of sCD14 and sCD163 was reported to be strongly associated with clinical laboratory parameters like ferritin, CRP, and procalcitonin and IL-6 in SARS-CoV-2 patients [63]. In this line of research, a study reported that plasmatic sCD163 level >2032 ng/ml during the time of admission can be used to predict COVID-19 disease severity ($p = 0.0022$) [64]. We have earlier reported the correlation of sCD163 & ferritin in dengue disease progression [65,66]. All these studies indicate a close relationship between monocyte-macrophage activation and immunopathogenesis of SARS-CoV-2 infection (Fig. 2). Thus, the assessment of CD markers associated with macrophage activation in PBMC's by flow cytometry may shed some light on the predicting disease in COVID-19 patients.

4.4. Cellular ACE2 and soluble ACE2 levels

Detectable quantities of ACE2 protein have been found across the human tissue. Many studies reported the expression of ACE2 in coronary vessels, capillaries, lung microvascular endothelial cells, kidney interlobular arteries, endothelial cells, and smooth muscle of the brain [67–70]. Indeed, ACE2 expression has been reported in blood cells like platelet and macrophage but not in the B and T lymphocytes [71]. In the human heart, it has been found in the stromal region in spongiosa layer in aortic valves [72],. Similarly, the higher expression of ACE2 protein was observed in the human kidney, particularly in the proximal tubular cells, and lesser extent in the glomeruli, Henle's loop, and collecting ducts [71,73]. In the case of the human respiratory tract, ACE2 expression levels have been observed in the epithelial lining, lamina propia, and in the salivary gland duct epithelium of the upper respiratory tract [74]. ACE2 expression was observed in the small vessel endothelium and bile duct epithelial cells and insignificant expression in hepatocytes [75]. Notably, abundant expression of ACE2 was reported in enterocytes of the small intestine including duodenum, jejunum, and ileum but not in the enterocytes of the colon [71]. Moreover, the ACE2 expression was observed in the inner layer of the retina but the photoreceptors [76]. Furthermore, the basal cell layer of the epidermis of human skin was also positive for ACE2 expression [71]. During SARS-CoV2 infection, ACE2 is cleaved by ADAM metallopeptidase domain 17 (ADAM17) and other proteases from the epithelial surface in which turn releases a soluble form of ACE2 (sACE2) in the circulation [77]. ACE2 is reported to be involved in multi-organ failure in critically ill patients in SARS-CoV-2 infected patients [78,79] Further characterizing the circulating levels of ACE2 in COVID-19 patients would throw light in understanding the role of ACE2 in disease pathogenesis.

5. Cytokine storm & inflammatory markers

Like many other viral hemorrhagic diseases, the abrupt release of cytokines called cytokine storm is reported to be responsible for disease severity in the case of COVID-19. Virus-mediated host immune response leads to the IL6 dependent activation of the transcription factor STAT3 (Single Transducer and Activator of transcription 3) in various IL-6Ra negative cells (airway epithelial cells) and nuclear factor Kappa B (NF-KB) pathway thereby contributing to the cytokine storm [80]. On one hand, IL-6 is a functional marker for cellular senescence, the age-depended enhancement of IL-6 may be directly associated with an

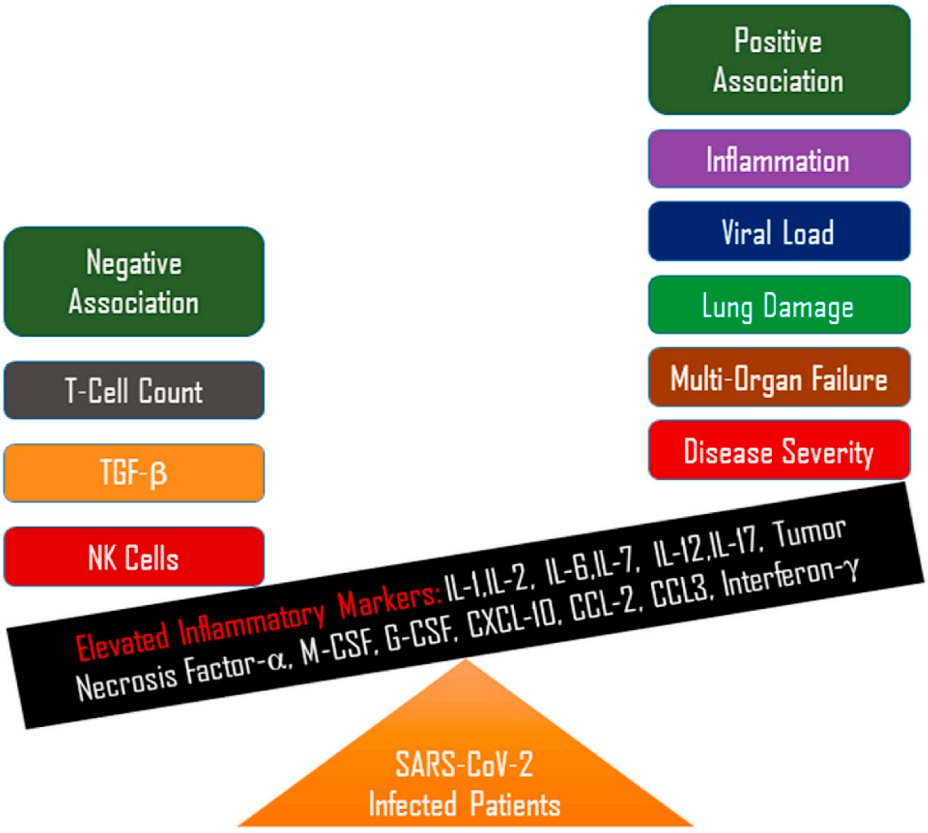

Fig. 3. Status of Pro-inflammatory Marker and its Association in SARS-CoV-2 Infection.

age-dependent increase in COVID-19 mortality [80].

On the other hand, elevated levels of IL-6 as observed in COVID-19 patients can inhibit cytotoxicity activity of natural killer (NK) cells and decreases the expression of perforin and granzyme B thereby failure in killing the targeted cell by perforin/granzyme induced apoptosis [81]. This leads to prolonged survival of targeted cells and magnifies antigen stimulation, with frequent overproduction of pro-inflammatory cytokines [81,82]. Thus extensive studies on the dynamic expression of IL6 and factors influencing the differential expression of IL6 in various cohorts could further ascertain the role of IL6 as a strong marker for clinical prognosis. The process of cytokine storm involves several molecules and cell signalling pathways. For instance, the active replication and release of viruses from the infected cell induce pyroptosis which triggers damage-associated molecular patterns (DAMPs) [83] and

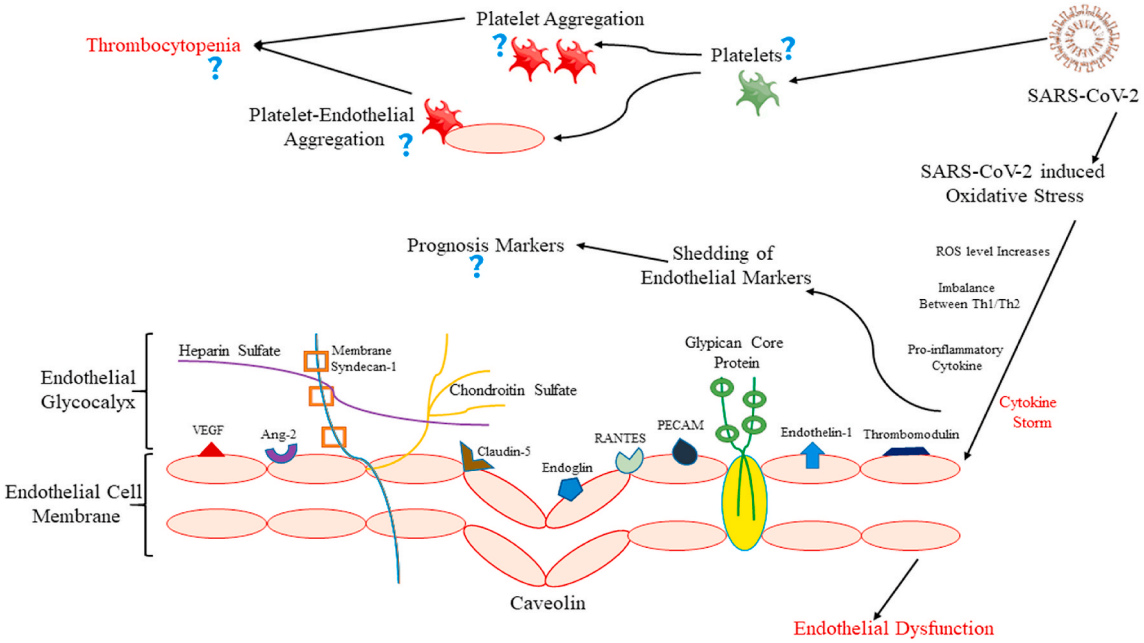

Fig. 4. Endothelium Dysfunction: A Major Cornerstone of COVID-19 Pathogenesis.

cellular autophagy [84], RIG-I and mitochondrial antiviral signalling (RIG-I-MAVS) [85], nod-like receptors (NLR) family pyrin domain-containing protein 3 (NLRP3)/inflammasomes. All these lead to the activation of NF-ΚB and IRF3 and results in the continuous production of pro-inflammatory cytokines [86].

In addition to the above, a single-cell analysis reported increased production of IL-1β and IL-17 inflammatory cytokines in COVID-19 infected patients by monocytes and Th17 cells [87,88]. Moreover, eosinophils are known to play a crucial role against RNA viruses and can release a large amount of cytokine [89]. Cytokine storm is a pathological event of COVID-19 where an aggressive release of proinflammatory cytokine is induced by the virus which results in inflammation, acute lung injury, and ARDS. In line with this, multiplex analysis of pro-inflammatory markers in moderate and severe COVID-19 patients may shed some light on understanding disease pathogenesis and outcome. The consolidated effect of increased expression of selected cytokines and chemokines during SARS CoV2 infection is shown in Fig. 3.

6. Endothelial markers

Vascular Endothelium is a continuous monolayer of endothelial cells that maintain vascular integrity and inhibition of excessive coagulation, and clot formation. Endothelium damage may occur either directly or indirectly through an elevated level of pro-inflammatory along with dysfunction of the coagulation pathway has reported in the various viral infections [90,91]. Recently, our group has reviewed the role of oxidative stress and vascular damage in viral infections such as dengue, HBV, HCV, and HIV [92]. The presence of viral inclusion structures within the endothelial cells of glomerular capillary loops and signs of endotheliitis in the lungs, heart, kidney, liver, and gastrointestinal tract of severe COVID-19 patients was reported [93]. A study with 22 SARS patients reported the development of autoantibodies against human umbilical venous and pulmonary endothelial cells suggests the role of pathogenesis [94]. Further, inflammation of endothelial cells and vasculitis have been observed in the post-mortem analysis of SARS patients [95]. Based on the available reports pathophysiology of endothelial damage during the SARS-CoV-2 infection has been depicted in Fig. 4.

Upregulation of endothelial proteins and platelet activation molecules observed in severe COVID-19 patients could serve as biomarkers for understanding disease pathogenesis [96]. For example, endothelin 1 (ET-1) is a potent vasoconstrictor of the cardiovascular system and a culprit of endothelial dysfunction. Biological factors such as angiotensin II, cytokine, and free radical promotes ET-1 secretion whereas nitric oxide, prostacyclin, and cyclic GMP inhibit ET-1 release [97,98]. With the above piece of evidence between ET-1 and endothelial dysfunction, assessing the levels of ET-1 in moderate to severe COVID-19 cases could relate its significance in terms of biomarkers for the detection of COVID-19 disease outcome.

Endothelial dysfunction or injury may be the result of direct infection of SARS-CoV-2, thereby inducing intracellular oxidative stress [99]. Under such conditions, several endothelial cells are activated via matrix metalloproteinase (MMP) which results in the formation of soluble endothelial mediators and increases the vascular permeability in severe cases [100]. To support this, elevated levels of ICAM-1 were observed in COVID-19 patients than H1N1 and control groups showing the involvement of endothelial cells in disease virulence. In this context, assessing the role of various endothelial markers during SARS-CoV-2 infection could pave a way to identify novel and potential prognostics biomarkers for the prediction of disease severity. For example, endoglin is an endothelial marker that is highly expressed during the inflammation process. The soluble form of endoglin (sEng) is released into circulation by activated cells and is reported to be potential markers for vascular leakage in dengue disease severity [101,102]. Similar to Eng, another important marker of vascular endothelial activations called SDC-1 is reported to induce neutrophil chemotaxis, inhibit alveolar epithelial wound healing, and promote pulmonary fibrosis [103]. A study has reported the significant ($p < 0.0001$) elevation of SDC-1 in severe COVID-19 (336.5 ng/ml) compared to healthy control (41.5 ng/ml) [104]. Thus, exploring the in vitro/in vivo role of Eng and SDC-1 in COVID-19 might provide an important conclusion in the disease pathogenesis of COVID-19 and may serve as a prognostic marker for the prediction of severe cases.

7. Bradykinin

Bradykinin (BK) is a small peptide and a potent regulator of blood pressure as similar to the renin-angiotensin system (RAS). It is believed that manifestations like ARDS, inflammation, and edema in the COVID-19 are due to cytokine storms triggered by the host immune system as observed in dengue infection (antibody-dependent enhancement). Recent studies reported that these manifestations may also occur due to bradykinin storm along with pro-inflammatory cytokines, clotting factor, and kinin molecules [105–107]. An increase in ACE2 levels in the lungs during SARS-CoV-2 infection increases the levels of BK referred to as bradykinin storm. This BK is produced through two distinct mechanisms via activation of serine protease kallikrein (i) the plasma kallikrein/high molecular weight kallikrein pathways (activated by clotting factor known as Hageman factor) and (ii) the tissue kallikrein/low molecular weight kallikrein pathway (activated by tissue enzymes and plasmin). Finally, the BK is converted into des-Arg9-bradykinin (DAKB) and binds with its corresponding receptors B1R and B2R, respectively [106]. Early studies have reported that BK induces pain and blood vessel expansion [108,109], thereby contributing towards leakage, swelling, and inflammation of surrounding tissues. This causes depletion of ACE2 and accumulation of BK and DAKB leads to endothelial dysfunction. Thus, bradykinin storm-induced leakage of fluid combines with the excess of hyaluronic acid leads to the formation of jelly-like molecules that prevents the uptake of oxygen and release of carbon dioxide in the lungs of COVID-19 patients [106]. This finding suggested that bradykinin storm may a possible explanation for the severe complication of SARS-CoV-2 infection. This observation suggests that BK, DAKB, and BK receptors maybe serve as effective prognostic markers for the prediction of severe SARS-CoV-2 infections.

8. Neprilysin or neutral endopeptidase (NEP)

NEP is a member of zinc-metalloendopeptidase which is highly expressed in the lungs and kidney [110,111]. NEP can hydrolyze a wide variety of substance-related to physiological processes. For instance, NEP was reported to hydrolyze 7 peptides in “in vivo” including natriuretic peptides (NPs) (Atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and B-type natriuretic peptide (BNP), BKs, neuropeptides (substance P, enkephalins) [112–114].

Studies demonstrated that decreased enzymatic activity of NEP in the lung of mice with acute lung injury (ALI) is strongly correlated with the inactivation of tachykinins degradation mechanism, thereby resulting in a reduction of uncontrolled inflammation in ALI/ARDS [115,116]. Notably, NEP can play a vital role during lung inflammation by activating neutrophils and induce further tissue damage [117]. Studies have reported that NEP is involved in reducing the pro-inflammatory, oxidative, and pro-fibrotic effect and inhibition of bradykinin-induced inflammatory cell influx [118,119]. This indicates that the NEP could play a protective role during pathological conditions. Further studies are required to explore its therapeutic properties for treating COVID-19 diseases.

9. MicroRNAs (miRNAs)

MicroRNAs are the smallest endogenous regulatory non-coding RNAs known to regulate post-transcriptional expression affecting various biological processes such as cell proliferation, apoptosis, and

differentiation. MiRNAs binding to the viral genome increases the viral replication and/or alters the level of free miRNAs in the cell [120–122]. For instance, binding of miRNA-122 to the 5′UTR region of hepatitis C virus (HCV) RNA can protect it from host exonuclease activity and can enhance the viral RNA stability and replication [120]. Another piece of evidence shows that the viral protein of avian influenza (H5N1) upregulates the expression of miRNA-200c-3p in the lungs. Interestingly the miRNA could alter the expression of ACE2 which may play a crucial role in inducing ARDS pathogenesis [123]. *Nersisyan* et al. suggested that various host miRNAs could potentially regulate ACE2 and TMPRSS2 during SARS-CoV-2 infection thereby regulates the disease mechanism [124].

A recent study reported cellular miRNAs (miR-21-3p, miR-16-5p, miR-195-5p, miR-424-5p, miR-3065-5p, and miR-421) that are upregulated after SARS-CoV infection and suggested that these miRNAs are potentially involved in regulating all human coronaviruses via binding directly to the viral RNAs [125]. Similarly, an *in silico* study reported 28 host miRNAs that could potentially interact with SARS-CoV-2 [126]. A few of the miRNAs (miR-376a-3p, miR-99b-5p, miR-10a-5p, miR-376a-3p, miR-548av-5p, and miR-99b-5p) are involved in the immune modulation of disease [126]. On the other hand, the study had identified another set of 10 host miRNA which has higher miRNA targeting sites (MTSs) in pathogenic (SARS-CoV-2, SARS-CoV, and MERS-CoV) compared to non-pathogenic (HCoV-OC43, HCoV-229E, HCoV-HKU1, and HCoV-NL63) coronavirus strains. Of these 10 miRNAs, few of them are involved in UPR regulator (miR-34c-5p and miR-34a-5) or modulator of the immune system (miR-149-3p). Hence, the study concluded that human coronavirus can act as specific miRNA sponges to alter the host's gene expression that downregulates immune response or to prevent the activation of unfolded protein response (UPR) – related apoptosis, thereby promotes cell survival [126].

A study reported a panel of host miRNAs (hsa-miR-654-5p, hsa-miR-198, hsamiR- 622, and hsa-miR-323a-5p) and three (hsa-miR-17-5p, hsa-miR-20b-5p, and hsa-miR-323a-5p) against SARS-CoV and SARS-CoV-2, respectively. Among these miRNA, hsa-miR-654-5p and hsa-miR-323a-5p are found to downregulate H1N1 viral replication [127] whereas hsa-miR-17-5p and hsa-miR-20b-5p are shown to upregulate H7N9 influenza infection [128]. Thus, miRNAs can be assessed during the various phases of the infection on critically ill patients. Differentially expressed miRNA during the early and late phase of the infection could be effectively used to aid anticipate prognosis. Thus, these small endogenous miRNA may serve as a favorable clinical prognostic marker to distinguish different phases of COVID-19 disease and could pave a way for potential therapeutic approaches.

10. Saliva – a reliable diagnostic fluid

Saliva is considered to be one of the diagnostic indicators to diagnose various diseases or conditions such as autoimmune diseases, hereditary diseases, cardiovascular diseases, malignancies, viral infections (HIV and Zika), dental caries, and periodontal disease [129]. Salivary diagnostic approaches may serve as a strategy a convenient method of screening in infants, children, elders, other uncooperative patients for rapid diagnosis of many diseases including COVID-19 [130]. In this regard, viral load ranging from 9.9×10^2 to 1.2×10^8 copies/ml was reported in the saliva of the COVID-19 patients [131]. which makes saliva a reliable diagnostic tool [132]. Also, a study has reported that glandular and ductal epithelial cells of the salivary gland are the initial target of SARS CoV-2 [74]. Thus, salivary diagnostic approaches may be a cost-effective and point-of-care platform for faster and early diagnosis of this disease. However scanty evidence is available for the role of salivary molecules as markers for disease prognostics. Interestingly, salivary IgA levels were estimated in other viral diseases, optimizing this in the case of COVID-19 could lead to a better way of assessing disease prevalence [133].

Table 1
List of potential biomarkers.

S. No.	Role	Potential Biomarkers
1	Cytokine Strom Markers	IL-1, IL-2, IL-6, IL-7, IL-12, IL-17, IL-18 TNF-α, M-CSF, G-CSF, CXCL-10/IP-10, CCL-3, CCL-5, IFN-γ, MCP-1
2	Macrophage Marker	CD14, CD163, TLR2, TLR4, CD86, CD80, CD68, SOCS3, CD200R, CD206, Ferritin
3	Endothelial Markers	Endoglin, Syndecan-1, Endothelin-1, Cluadin-5, Angiopoietin −1 (Ang-1), Ang-2, PECAM, S1P, VCAM, vWF, Tie2
4	Bradykinin Strom Markers	Bradykinin (BK), des-Arg9-bradykinin (DAKB), Bradykinin-1 Receptor (B1R), B2R, Neprilysin (NEP), Kallikrein, Kininogen (LW & HW)
5	Clinical Biochemical Biomarker	D-mer, C-Reactive Protein (CRP), Ferritin

11. Proteomic and genomic profiling

The Severe COVID-19 Genome wide Association Study (GWAS) group identified the 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure [134]. Similarly, a team identified six novel biomarkers (CLM-1, IL12RB1, CD83, FAM3B, IGFR1R, and OPTC) that are elevated in severe COVID-19 patients admitted in ICU. They also found that when these molecules are measured at the time of ICU admission, the molecules can predict which patient will survive standard ICU treatment [135].

Based on the available literature, we have compiled a list of potential biomarkers for the prediction of COVID disease outcome (Table 1) However, to the best of our knowledge no strong biomarkers are clinically validated to date. Thus studies on the validation of biomolecules for their efficacy in predicting disease severity due to SARS-CoV2 infection on various cohorts should be undertaken. Identification of a panel of strong markers may further be used in developing prognostic kits for understanding the disease outcome.

12. Future perspective & conclusion

A compact and cheap device that could accurately detect the virus and predict the disease outcome is the need of the hour. Though there are several diagnostics methods (Chest CT Scan, RT-PCR, Lateral Flow Immunoassay, and ELISA) available for the detection of SARS-CoV-2 infection, these methods still suffer from certain practical limitations or drawbacks. For example, conducting of CT scan is limited to a central hospital; small hospitals, clinics, and test laboratories may not have access to CT scans. Optimization of Chest CT scan protocol and a strong reporting system based on clinical findings may enhance the use of CT as a diagnostic aid. Also, a CT scan is not a confirmatory tool for the identification of the virus.

On the other hand, RT-PCR results may take 1–2 days to report, and sometimes results may be false-negative. Thus, the individual who tests has false-negative can contribute to the spread of the virus. As the antibody response is produced after 4–6 days after the onset of infection, early screening of antibodies may not a suitable diagnostic method and could increase the false-positive rate. The potential markers reported in this review deserve further investigations in terms of their efficacy in predicting the disease severity. A portable nano-device or a biosensor incorporating one or a cocktail of serum proteins would be ideal in screening a large population during disease outbreaks. A biosensor is an analytical bio-sensing tool composed of a bio-receptor, a transducer portion, and a digit output detector that aims to detect the biochemical and biological agent either by undergoing chemical reaction (enzyme-based bio-sensor) or binding to the target molecule (analyte-based biosensor) in a highly specific manner. Such binding can be converted into a measurable signal via a transducer which can be detected either directly (surface plasma resonance or through impedance measurement)

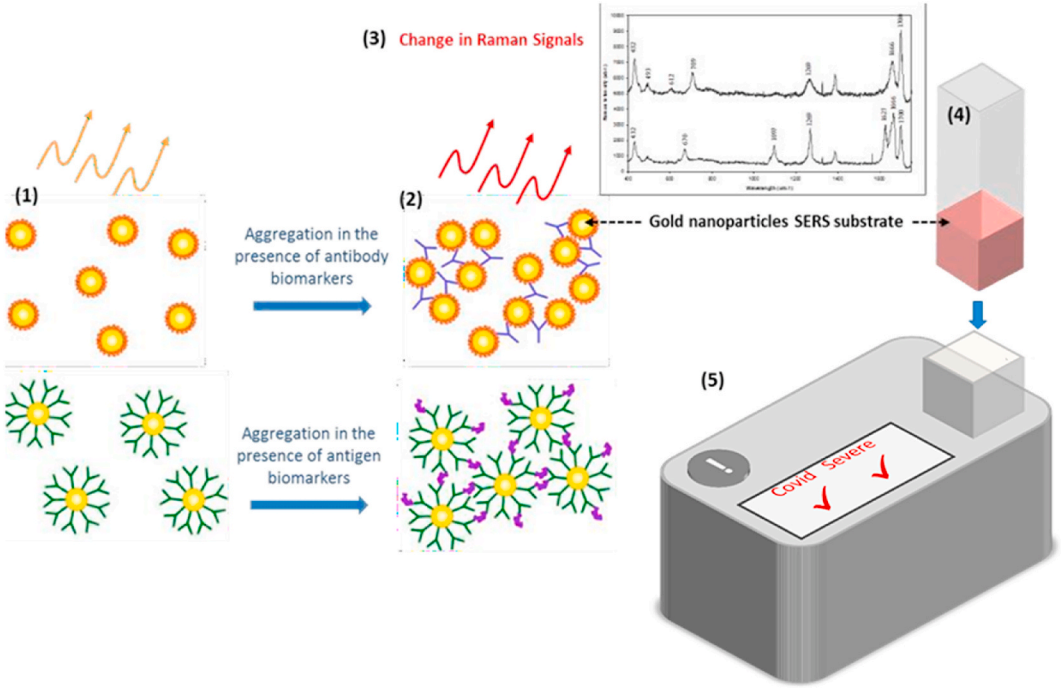

Fig. 5. Surface-Enhanced Raman Scattering (SERS) Biosensor Model for the Prediction of COVID-19 Severity.

or employing signalling molecules (fluorophores, enzymes, electrochemically active molecules) [136]. Therefore, biosensors like electrochemical biosensor (EC biosensor) [137], lab-on-chip biosensors [138], field-effect transistors (FET) biosensor [139], colorimetric based biosensor [140], quartz crystal microbalance (QCM) [141], piezoelectric microcantilever sensor (PEMS) [142], localized surface plasmon resonance (LSPR) [143], and surface-enhanced Raman scattering (SERS) [144] may be developed for the prediction of disease severity. In this, label-free electrical/EC biosensor and SERS are most popular because they have advantages like simplicity, small, low cost, and amenability for mass fabrication. Thus, the biosensor incorporating a panel of vascular endothelial or bradykinin markers would be ideal for the detection of SARS-CoV-2 biomarkers and serve as a point-of-care device (Fig. 5).

Author's contribution

Conceptualization of the Work: Agieshkumar Balakrishna Pillai.
Writing of the Manuscript and Literature Review: Vignesh Mariappan, P.S. Manoharan, Lokesh Shanmugam.
Reviewing and editing of the Manuscript: Agieshkumar Balakrishna Pillai, Pajanivel R & S.R. Rao.
Designing and editing of the Figures – Vignesh Mariappan. All authors read and approved the final manuscript.

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