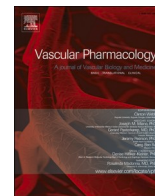




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## Review

## A possible role for ST2 as prognostic biomarker for COVID-19

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## ABSTRACT

COVID-19 is a pandemic illness caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). It has been estimated that 80% of subject infected are asymptomatic or have mild to moderate symptoms. Differently, in severe cases of COVID-19, cytokine storm, acute respiratory distress syndrome (ARDS), severe systemic inflammatory response and cardiovascular diseases were observed. Even if all molecular mechanisms leading to cardiovascular dysfunction in COVID-19 patients remain to be clarified, the evaluation of biomarkers of cardiac injury, stress and inflammation proved to be an excellent tool to identify the COVID-19 patients with worse outcome. However, the number of biomarkers used to manage COVID-19 patients is expected to increase with the increasing knowledge of the pathophysiology of the disease. It is our view that soluble suppressor of tumorigenicity 2 (sST2) can be used as biomarker in COVID-19. sST2 is routinely used as prognostic biomarker in patients with HF. Moreover, high circulating levels of sST2 have also been found in subjects with ARDS, pulmonary fibrosis and sepsis. Keeping in mind these considerations, in this review the possible mechanisms through which the SARS-CoV2 infection could damage the cardiovascular system were summarized and the possible role of sST2 in COVID-19 patients with CVD was discussed.

## 1. Introduction

Coronavirus disease-2019 (COVID-19) is a pandemic illness caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), a member of coronavirus family [1]. SARS-CoV2 showed high infectivity resulting in rapid global transmission of disease with 53,164,830 confirmed cases and 1,300,576 deaths in the world as of 13 November 2020 [2].

A rapid diagnosis of COVID-19 is essential for lower virus spread among subjects. The laboratory methods that are routinely employed for the COVID-19 diagnosis are Real-Time PCR and deep sequencing test that allow virus genome detection [3]. These tests use the RNA extracted from nose and throat swabs [3]. Generally, the E gene, that encode for envelope protein, is used for the first-line screening, followed by RNA-dependent RNA polymerase (RdRp) gene detection and nucleocapsid (N) gene determination, as additionally confirmatory tests [4]. However, false negative results can be obtained as a consequence of poor quality of specimen or of sample collection in the early stage of the disease [3]. For this reason, serological tests, such as IgM/IgG ELISA assay, should be used for the diagnosis of COVID-19 in combination with

Real-Time PCR method [3].

The median SARS-CoV2 incubation period before symptoms manifestation is 4 days [interquartile range (IQR) 2–7 days] [5]. It has been estimated that 80% of subject infected are asymptomatic or have mild to moderate symptoms, such as fever, cough, fatigue, sputum production and shortness of breath [5]. Generally, patients with mild symptoms recover at home with supportive cure and isolation [6]. Differently, the more severe cases of COVID-19 manifest “cytokine storm” followed to acute respiratory distress syndrome (ARDS), severe systemic inflammatory response and consequently multi-organ failure with poorer outcome and even death [1,6,7]. Clinical data suggest that cardiovascular diseases (CVD) are the most common adverse events in COVID-19 progression and that older age, pre-existing hypertension, diabetes, and pre-existing coronary heart disease or heart failure (HF) could be considered important risk factors for a worse prognosis in these patients [1,8,9].

Considering the role of inflammation in the severity of disease, the evaluation of cytokines profile in these patients could be useful for a quick recognition of a worsening in the prognosis and progression of multi-organ failure. Indeed, several studies found increased levels of

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cytokines [interleukin 6 (IL-6), tumor necrosis factor alpha (TNF $\alpha$ ), IL-2] and chemokines [monocyte chemoattractant protein-1 (MCP-1)] in the blood of patients with a fatal outcome of COVID-19 [6,8,10]. Moreover, changes in other markers as leucocytosis, lymphocytopenia and neutrophilia are described as important indicators of severe illness [6,10]. In addition to inflammatory markers, other bio-humoral elements such as lactic dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, bilirubin, procalcitonin, D-dimer have been identified for their ability to discriminate COVID-19 patients with poor prognosis [6,10]. Finally, considering that SARS-CoV2 infection combined with systemic inflammatory response could have deleterious effects on cardiovascular system, biomarkers of cardiac stress and injury as B-type natriuretic peptide B (BNP) and cardiac troponin (cTn) T and I were quickly included in the panel of COVID-19 prognostic biomarkers [11,12].

The advantage to use more biomarker for the diagnosis and prognosis of a disease is to ensure a better management of the patients. For this reason, we think that the panel of biomarkers employed in COVID-19 patients should be improved through the addition of soluble suppressor of tumorigenicity 2 (sST2). sST2 is one of more complex known biomarkers with different role in several diseases. sST2 is routinely used as prognostic biomarker in patients with HF [13]. However, high circulating levels of sST2 have also been found in subjects with ARDS, asthma and sepsis. [14]. With these considerations in mind, it was supposed that sST2 could be taken as common ground among SARS-CoV2 infection and cardiovascular disease (CVD).

In this review, the possible mechanisms through which the SARS-CoV2 infection could damage the cardiovascular system will be summarized. Moreover, the possible role of ST2 in COVID-19 patients with CVD will be discussed.

## 2. Cardiovascular disease is a common complication in COVID-19 patients

### 2.1. The phases of COVID-19 progression

The molecular and cellular mechanisms related to SARS-CoV2 infection have not been well clarified. However, it has been proposed to divide the COVID-19 disease progression in three phases [1].

During the first phase, SARS-CoV2 infects the alveolar epithelial cells and begins to proliferate [9]. Data suggested that SARS-CoV2 is able to contact the cell of host by the binding of its spike protein (S) to Angiotensin-Converting Enzyme 2 (ACE2), a membrane-bound glycoprotein [7]. Once internalized into the cell, via endocytosis, SARS-CoV2 released its genome, a positive-sense single-strand RNA, in the cytoplasm of host through a mechanism of membrane fusion mediated by transmembrane serine protease 2 (TMPRSS2) [1,7]. In the cytoplasm, the viral genome is massively replicated and translated in structural and non-structural virus proteins [1,7]. Upon completing the replication phase, the new copies of virus leave the host cell through exocytosis [1,7].

In the second phase of COVID-19 progression the devastating effect of virus on the pulmonary parenchyma can be observed. The replication of virus in the lungs can: reduce the physiological function of ACE2 with dysfunction of renin-angiotensin system (RAS) and pulmonary vasoconstriction; induce extreme epithelial and endothelial apoptosis followed to vascular injury; lead to a massive release of pro-inflammatory cytokines [type I interferon (type1 INF), TNF $\alpha$ , IL-1 $\beta$  and IL-6] and chemokines [chemokine (C-C motif) ligand 3 (CCL3), CCL5, CCL2, and chemokine (C-X-C motif) ligand 10 (CXCL10)] (cytokine storm) and inflammatory cellular infiltration in pulmonary parenchyma [15]. Even if the inflammatory response is a defence mechanism against the virus, a dysregulation of this system was observed in COVID-19 patients [15]. In this subjects the immune composition of lung is altered, with high presence of monocytes/macrophages and aberrant activation of T helper (Th) cell, type 1, 2 and 17 [15]. All these elements contributed to ARDS,

pulmonary fibrosis and systemic inflammatory response activation [15].

The third stage of COVID-19 progression is characterized by systemic hyper-inflammatory responses associated with multi-organ failure, in particular to cardiovascular diseases, and worse prognosis of patients [1].

#### 2.1.1. Severe COVID-19 without pulmonary complications

In a recent retrospective study, Dreher et al. showed that severe COVID-19 patients (>60 years, age) do not necessarily develop ARDS even if circulating cytokine levels were high and patients require oxygen therapy for a week [16]. Data suggest that patients that developed ARDS had a pre-existing respiratory disease, were frequently obese and were characterized to persistent elevated levels of IL-6, CRP, D-dimer and LDH compared to patients without ARDS [16].

#### 2.1.2. Severe COVID-19 with extra-pulmonary manifestation

COVID-19 is a syndrome characterized not only by respiratory complication, with varying degrees of severity, but other adverse events may be observed in these patients [17]. SARS-CoV2 principally by indirect ways such as systemic inflammatory response, endothelial dysfunction, coagulopathy and complement activation can induce neurological complication (cerebral hemorrhage and ischemia are found in 36% of old patients), acute kidney injury (AKI) and cardiovascular disease in some cases of severe COVID-19 patients [17–19].

### 2.2. Cardiovascular disease: Risk factor or result of COVID-19?

It has been estimated that around 40% of deaths in a Wuhan cohort of COVID-19 patients are related to myocardial injury or HF [1,8,9]. At the moment it has not been clarified whether the virus, by direct or indirect effects, can be considered the trigger of onset of complications to the cardiovascular system or if the COVID-19 progression worsening a pre-existing CVD [1,8,9].

#### 2.2.1. Pathophysiological mechanisms of myocardial injury in COVID-19 patients

As previously described ACE2 is the access point of SARS-CoV2 in the host cells. The presence of ACE2 in all cardiac cell types including cardiomyocytes, coronary endothelial cells and cardiac fibroblast gives a plausible theory for a direct viral infection in the heart resulting in cardiac injury [20–25]. Even if only few studies detected SARS-CoV2 genome in cardiac biopsies collected from COVID-19 patients [26], data obtained from patients infected with SARS-CoV1, a virus of the same family of SARS-CoV2, can be used to explain the possible direct actions of SARS-CoV2 in the heart [9,27]. Similar to SARS-CoV2, SARS-CoV1 used ACE2 as access point in cardiac cells. After infection SARS-CoV1 patients showed lower levels of ACE2 in the heart cells with a consequently increased of cardiac injury [9,27]. ACE2 is a mono-carboxypeptidase that can cleave both Ang I to Ang (1–9), limiting the substrate for ACE, and Ang II to Ang (1–7), reducing the RAS signal, and increasing the vasodilator, natriuretic/diuretic, and antifibrotic effects by Ang (1–7)/Mas receptor (MasR) pathway [20]. Moreover, an anti-inflammatory role for ACE2/Ang (1–7)/MasR axis was abundantly described in the last years. In a rat model of myocarditis, the use of angiotensin receptor blockers (ARBs) increased ACE2/Ang-(1–7)/MasR resulting in a reduction of leukocyte migration, release of pro-inflammatory cytokines as TNF $\alpha$ , IL-1 $\beta$ , IL-6, IFN $\gamma$ , and cardiac remodeling [28,29]. Possibly, intracellular translocation of SARS-CoV2 coupled with ACE2 leads to its depletion in cell membranes and the consequent loss of his cardioprotective function [20].

In addition to this direct effect of virus on the heart, there are other reports that describe the indirect effect of SARS-CoV2, such as cardiomyocyte necrosis or left ventricular dysfunction mediated by systemic inflammatory response and, consequently, macrophages and CD4<sup>+</sup> T cell infiltrate and release other pro-inflammatory cytokines in the heart [30–32]. The role of inflammation in the heart dysfunction has

been well documented. Indeed, on isolated myocytes, TNF $\alpha$  stimulation provokes changes in cells that are relevant to process of left ventricular dysfunction such as myocytes hypertrophy, contractile defects with fetal genes re-expression and apoptosis [33–35]. In particular, stimulation of cardiomyocytes with TNF $\alpha$  resulted in a negative inotropic action by alteration of calcium homeostasis or in an activation of apoptotic response by binding of TNF $\alpha$  to TNF receptor I (TNFRI) [33–35]. Moreover, the chronic stimulation of cardiac fibroblast with TNF $\alpha$  can destroy the balance among the synthesis and the release of matrix metalloproteinase and their inhibitors carried out to extracellular matrix (ECM) degradation and cardiac remodeling [33–36]. Moreover, the pro-inflammatory cytokine IL-1 $\beta$  demonstrated a negative inotropic effect much stronger than TNF $\alpha$  alteration of calcium homeostasis and destruction of the  $\beta$ -adrenergic receptor [36]. This cytokine can contribute also to apoptosis activation in cardiomyocytes and collagen synthesis in fibroblasts resulting in cardiac fibrosis [36]. Similarly, the exposition of cardiomyocytes to high levels of IL-6 depresses the basal contractility of the myocytes as well as the beta-adrenergic responsiveness of the cells leading to decreased heart function [37].

### 2.2.2. Acute coronary syndrome and acute myocardial infarction

In COVID-19 patients with pre-existing atherosclerotic plaque, high circulating levels of pro-inflammatory mediators such as IL-6, could stimulate endothelial cell to over express adhesion molecule and tissue factor, favouring the recruitment of more leukocytes in atheroma and making the lesion more thrombogenic [18:38]. Moreover, the same inflammatory mediators could stimulate the macrophages within atherosclerotic plaque to release more cytokines and so to promote the progression of disease up to the rupture of fibrous cap inducing acute coronary syndrome (ACS) [38].

The systemic hyper-inflammatory condition typical of SARS-CoV2 infection could contribute to coronary vessels dysfunction also in COVID-19 patients without pre-existing atherosclerotic plaque. Indeed, in these subjects the high circulating levels of IL-6, IL-1 $\beta$  and TNF $\alpha$  could promote endothelial dysfunction and subsequently myocardial ischemia by increased monocytes adhesion to vessel wall and activation of both the extrinsic and intrinsic coagulation pathway in a process defined immune-thrombosis [1,39].

Finally, among the effects of SARS-CoV2 infection, hypoxemia and hypotension, dependent to alveolar dysfunction and systemic inflammation, were described. These conditions reduced the blood flow in the coronary artery and increased the request of myocardial oxygen preparing the heart of COVID-19 patient to ischemia without atherothrombotic plaque disruption (type 2 of myocardial infarction) [1,9,38].

### 2.3. HF in post-COVID-19 patients

The association between COVID-19 infection and HF has been increasingly demonstrated in the last few months, [40]. It is currently known that myocarditis, endothelial damage, coagulopathies and respiratory failure can be considered as possible risk factors for the onset of HF in severe COVID-19 patients [40–42].

Recently, the researchers are beginning to wonder what will be the long-term consequences of COVID-19 in patients discharged after SARS-CoV2 infection. At the present, no studies have been conducted on post-COVID-19 subjects and many of the hypotheses made on the follow-up of these patients are only suggestions dependent on the data obtained from SARS and MERS survival [43–45]. It has been estimated that around 30% of survivors to SARS and MERS diseases developed pulmonary complications such as fibrosis and hypertension [43,44]. In a recent study, Yu M et al. observed in a cohort of 32 post-COVID-19 patients that 14 subject developed an irreversible pulmonary fibrosis [45]. These patients were older and had higher pulmonary hypertension than non-fibrotic patients [45].

In recovered COVID-19 patients as in post-SARS subjects, irreversible pulmonary fibrosis could develop as a consequence of ARDS and

cytokine storm activation after lung virus infection and progress even after eradicating the SARS-CoV2. The exacerbated release of IL-4, IL-8, IL-13, IL-33, IL-6, IL-1 $\beta$  and TNF $\alpha$  by Th2 and macrophages promotes the inflammatory response in the lungs but also the fibroblasts activation and collagen release [46]. The chronic increased of pulmonary resistance could contribute to cardiopulmonary diseases, in particular right ventricle hypertrophy and then HF. At present these are only suggestion and long-term studies in large cohorts are necessary to defined the quality of life and possible complications in post-COVID-19 patients.

### 3. Biomarkers of cardiac dysfunction in COVID-19 patients

Keeping in mind the relationship among COVID-19 and CVD, the evaluation of biomarkers of cardiac injury, stress and inflammation results essential for risk stratification purposes and for leading to beneficial interventions in patients.

#### 3.1. Cardiac troponins

Circulating cardiac troponins (cTn) T and I are usually used as biomarkers of myocardial injury [acute myocardial infarction (AMI), ACS and myocarditis] but also of HF. From early studies, it became clear that biomarkers of cardiac stress and damage could be used to monitor the outcome of COVID-19 patients. Indeed, the levels of cTnT and cTnI remain in normal range in the majority of COVID-19 survival patients, differently the concentration in the blood of cTns increases together with the severity of disease in the non-survival patients [12,47,48]. In these patients the growth of cTnT and cTnI in the blood were related to myocardial injury, tachycardia, systemic hypoxemia and respiratory failure [12,47]. Retrospective studies confirmed these data and a strong association between elevated high sensitive (hs)-cTnI levels, myocardial injury and increased mortality in patients with severe COVID-19 was validated [49,50]. It was therefore recommended to measure hs-cTnI levels immediately after admission in patients with SARS-CoV2 and to follow any changes of this biomarker over time. In this way it will be possible to promptly intercept the onset of damage to the myocardium in order to be able to intervene accordingly [49,50]. Moreover, in SARS-CoV2 infected patients, increasing levels of cTnI can be correlated with inflammatory biomarkers as IL-6, D-dimer, ferritin and LDH confirming the critical role of inflammatory response on cardiovascular system in COVID-19 patients [12].

#### 3.2. Natriuretic peptide

It is assumed that during SARS-CoV2 infection the reduction of ACE2 function and consequently the hyperstimulation of cardiovascular system by RAS and inflammatory mediators could contribute to increase the release of natriuretic peptides (NPs) [47,51]. Generally, these hormones help to regulate blood volume and arterial blood pressure by promoting vasodilation, diuresis, and natriuresis.

Among the NPs, B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP) are known as gold standard biomarkers for myocardial stress and HF. At this moment only few studies investigated the role of these biomarkers as risk factors for in-hospital death in patients with severe COVID-19 [47,51]. In these works, circulating levels of NT-proBNP showed a dynamic escalation in conjunction with markers of cardiac injury (cTns) and inflammation (IL-1 $\beta$ , CRP, and cardiotrophin I) in older patients with a worse prognosis [47,50,51].

However, these are only pilot studies with few patients and with NT-proBNP was measured only at hospitalization. In the *ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic*, it was suggested a continuous monitoring of BNP/NT-proBNP in all patients in order to be able to confirm the prognostic value of NPs in severe COVID-19 patients for appropriate therapeutic strategies [52].

### 3.3. Pro-inflammatory cytokines and chemokines

The systemic inflammatory response dependent on SARS-CoV2 infection can contribute with greater force to the damage in the cardiovascular system, both inducing a new damage or promoting the progression of pre-existing illness.

Several studies confirmed the key role of C reactive protein (CRP), IL-6, IL-10, IL-1 $\beta$  as excellent biomarkers of severity and mortality in COVID-19 disease [53–56]. Circulating levels of CRP are immediately higher in COVID-19 patient who will have a worse outcome [57]. Moreover, in severe COVID-19 patients, increased levels of IL-6, IL-1 $\beta$  and CRP can be related to activation of maladaptive remodeling pathways in different organs (including the heart), atrial fibrillation, in addition to endothelial activation, increased of adhesion molecules production and altered coagulation [58–60].

## 4. Suppressor of Tumorigenicity 2

In the attempt to improve the management of COVID-19 patients another biomarker could be added to the molecules described above, the Suppressor of Tumorigenicity 2 (ST2).

ST2, a member of IL-1 receptor family, was first described in a murine fibroblast cells line (BALB/c-3 T3) as a factor implicated in cell proliferation and so as element involved in cancer development [61]. Subsequently, the expression of ST2 was found also in other cell types such as macrophages, neutrophils, lymphocytes, endothelial cells, cardiomyocytes, osteoclasts, osteoblasts and adipocytes [62,63].

The ST2 gene is placed on human chromosome 2q12 and gives rise to four transcriptional products. However, only two isoforms, the transmembrane form (ST2L) and the soluble secreted form (sST2), are biologically relevant [62,63]. The ST2L containing 3 extracellular Ig domains, a trans membrane domain, and an intracellular SIR domain homologous of Toll/interleukin-1 receptor (TIR) cytoplasmic domain [64]. Differently, the circulating isoform, sST2, lacks the transmembrane and cytoplasmic domains observed in ST2L and includes only a unique nine amino acid C-terminal sequence [65].

The important roles of ST2 were achieved only after the discovery of its ligand, IL-33 [66]. IL-33 is an alarmin, member of IL-1 cytokine family that can be secreted by most cells type after damage [66]. Once release from damages tissue, IL-33 can bind its receptor ST2L and promote inflammatory responses by the activation of macrophages, mast cells, Th2 and cytokines and chemokines expression [67–69]. The IL-33/ST2L pathway can be locked in the presence of decoy receptor sST2. The soluble receptor binding avidly IL-33 prevents the interaction with ST2L and so the intracellular pathway activation [64].

In the last years, the role of sST2 as diagnostic and prognostic biomarker was discussed for several diseases. In particular, high circulating levels of sST2 were found closely involved to acute and chronic HF, AMI, pulmonary disease as asthma or ARDS, sepsis, fibrosis and gastro-intestinal disease [13,14].

### 4.1. ST2 in heart disease

As previously described, the ST2 gene can be expressed in several cell types and can be associated at different roles according to the tissue. In the heart, fibroblast and cardiomyocytes are involved in the expression of ST2 gene. Data suggested that the gene expression of IL-33 and ST2 increased in presence of cardiac stress or injury [70,71]. Consequently, IL-33/ST2L system plays a protective role in the heart [70,71]. Indeed, Sanada et al. demonstrated that IL-33/ST2L system abrogates Ang II and phenylephrine- hypertrophy on cardiomyocytes, whereas in mice subjected to overt pressure overload of ventricle, treatment with IL-33 reduced cardiac hypertrophy, fibrosis and premature mortality compared to ST2 knockdown mice [70]. In 2009, Seki et al. using an animal model of ischemia/reperfusion observed that IL-33 treatment reduced apoptosis, improved contractile function and survival in treated

group compared to control group [71]. Moreover, it was found that sST2 is able to abrogate these protective pathways seizing IL-33. Indeed, sST2 reversed the anti-hypertrophic effect of IL-33 in cardiomyocytes stimulates with Ang II or phenylephrine [70]. Moreover, the pre-incubation of IL-33 with sST2 reduces the beneficial effects of IL-33/ST2L signalling in cardiomyocytes exposed for 72 h' to a hypoxia state [71].

Several studies showed that circulating levels of sST2, but not circulating levels of IL-33, were higher in patient with AMI but also in patient with acute and chronic HF and these levels correlated with cardiac remodeling, reduction of ejection fraction and neurohormonal derangement [72–75]. The guidelines ACCF/AHA classified sST2 as a new prognostic biomarker for risk assessment of myocardial fibrosis and for predicting heart disease and life-threatening events [13]. The cut-off proposed for this new prognostic biomarker is 35 ng/mL (the measures are performed by Presage ST2 assay) [13]. It was found that increased levels of sST2 (>35 ng/mL) were always closely related with elevated mortality in patients with chronic HF, and that sST2 was a better predictor of long-term cardiovascular death than NPs for HF patients [76,77].

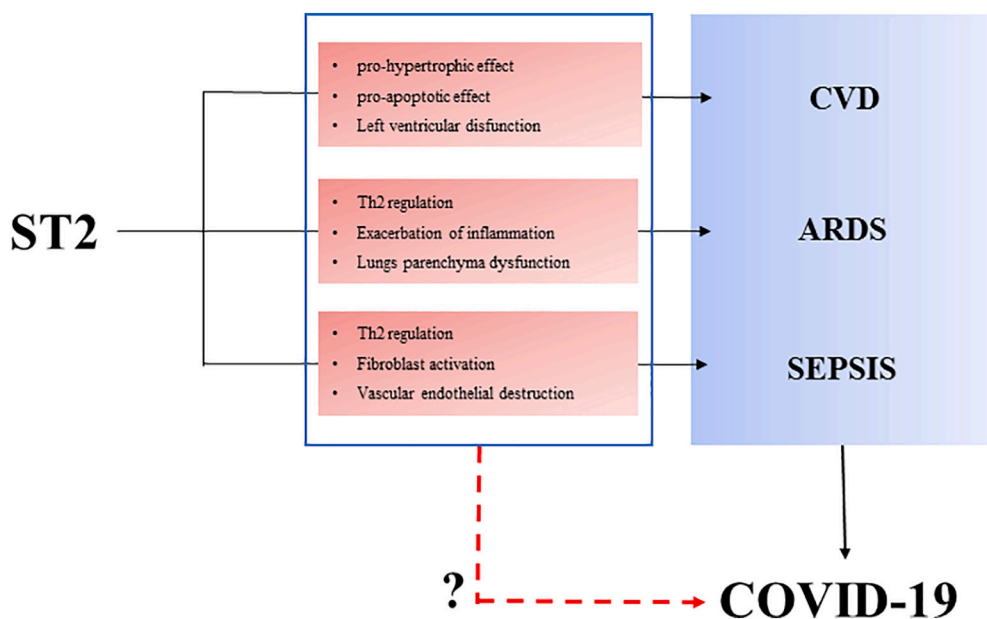
### 4.2. ST2 and pulmonary disease

Differently from the cardioprotective effect described for IL-33/ST2 system in the heart, data suggested a crucial role for this pathway in the pathogenesis and progression of lung disease [14].

As well-known IL-33 is an alarmin-cytokine that can be quickly released from endothelial alveolar cell after infection, stress or necrotic events. In the pathogenesis of pulmonary diseases such as asthma, growing levels of IL-33 promote the activation of inflammatory response by the interaction with ST2L [78]. In particular, IL-33/ST2L system induced the activation of mast cells, the differentiation of Th0 cell in Th2 and, consequently, the expression and release of pro-inflammatory cytokines, such as IL-6, IL-1 $\beta$ , TNF $\alpha$  and chemokines such as IL-8, IL-4, IL-5 and IL-13 [78]. The chemokines promote the recruitment of other inflammatory cells in the damaged tissue and the progression of inflammatory responses [78]. In murine model of asthma, Löhning et al. showed that the use of antibody against ST2L was able to reduce the activation of Th2 cell and so could reduce the severity of an inflammatory response in the lungs [79]. Similar results were obtained when the animal model was pre-treated with sST2 [80].

Overexpression of sST2 was found in asthmatic population compared to healthy subjects [81]. High levels of decoy receptor could suggest a natural mechanism to regulate the inflammation in the lungs, turning off IL-33/ST2L signalling. It was supposed that, in the severe cases of asthma, the IL-33 removal by sST2 binding promotes the differentiation of Th0 in Th1 and consequently exacerbates the pro-inflammatory process [14]. However, dedicated studies will be needed to confirm these assumptions. To date, it was found that when the circulating levels of sST2 were combined with neutrophilia provided a worse outcome for asthma patients [81].

In addition to allergic pulmonary disease, the pro-inflammatory effect of IL-33/ST2L axis was observed in ARDS patients [14]. ARDS can be the result of a direct insult, as pneumonia, or an indirect insult, as sepsis. Anyway, ARDS is characterized by a great release of pro-inflammatory cytokines (cytokines storm), neutrophils recruitment in the lungs, and alveolar endothelial barrier disruption [14,82]. In 2011, Le Goffic et al. observed the expression levels of IL-33 and other cytokines in mice treated with the influenza virus A/WSN/1933 (H1N1) [78]. The data showed that, until three days after infection, mRNA and protein levels of IL-33 increased both in pulmonary tissue and bronchoalveolar lavage in correlation with IL-6, TNF $\alpha$  and INF $\gamma$ , suggesting that IL-33/ST2L system could play a role in the exacerbation of ARDS by cytokines storm induction, as described for asthmatic population [78]. These results are confirmed in an in vitro study, where the authors observed that the concentration of IL-33 in the media of epithelial cell infected with H1N1 virus increased with the necrotic event [78].



**Fig. 1.** Possible role of ST2 in COVID-19 disease. Cardiovascular disease (CVD), acute respiratory distress syndrome (ARDS) and sepsis are described among the main complications of SARS-CoV2 infection. ST2 is involved in all these diseases. In cardiovascular system, high circulating levels of soluble ST2 (sST2) are associated with pro-hypertrophic and pro-apoptotic pathway activation and consequently with a reduction of left ventricular physiological function. In the lungs, ST2 is involved in alveolar parenchyma disruption by activation of inflammatory processes (Th2 differentiation and cytokines production). Similarly, during sepsis, ST2 can contribute to exacerbation of inflammatory response, activation of fibroblast, and endothelial disruption. The questions are: due to the pro-inflammatory, profibrotic, pro-hypertrophic and pro-apoptotic role described for ST2, could ST2 be involved in the effects of SARS-CoV2 in the lung and in the cardiovascular system? Moreover, will it be possible to use ST2 as a prognostic biomarker in COVID-19 patients?

However, in patients with ARDS circulating levels of IL-33 were lower. Differently, high circulating levels of sST2 (approximately ten times above those expected in HF) were found in ARDS patients and their relationship with worse severity disease and higher mortality rate have been verified [83,84].

Finally, the IL-33/ST2 system is involved in the pulmonary fibrosis. In vivo studies found that after the treatment of mice with pro-fibrotic drugs such as bleomycin, the expression levels of IL-33 increased simultaneously to pulmonary fibrosis [85–87]. In particular, the data suggest that the IL-33/ST2L pathway induces the polarization and activation of Th2 with a consequent release of IL-4, IL-5 and IL-13 [85–87]. These cytokines promote the differentiation of macrophages in type 2 macrophages (M2) and the activation of fibroblasts with consequently pulmonary extracellular matrix remodeling [85;87]. Li et al. showed that the pro-fibrotic effects of bleomycin decreased in mice after the use of ST2 antibody or silencing the ST2 gene [87]. In a retrospective study, Tajima et al. found that the circulating levels of sST2 were significantly higher in a group of 49 patients with idiopathic pulmonary fibrosis compared to control [88]. These data suggested the possibility to use sST2 as biomarker of pulmonary fibrosis [88].

#### 4.3. ST2 and sepsis

Sepsis is defined as dysregulated inflammatory response of host to infection that can lead to multiple organ dysfunction [89]. Generally, many inflammatory cells such as macrophages, mast cells, neutrophils and Th2 are activated during sepsis and a large amount of cytokines (IL-2, IL-4, IL-6 and IL-10) and chemokines (IL-8) are released [89]. Immuno-paralysis, vasodilation, hypoxia, endothelial dysfunction and immune-thrombosis are some of the effects related to high production of pro-inflammatory and anti-inflammatory cytokines within sepsis [89].

During the last years it has become clear that sepsis is able to cause elevation in circulating levels of sST2 that is independent from the source of infection [90,91]. Serum levels of sST2 were found higher in non-survival sepsis patients compared to survival and healthy subjects [21;90–91]. Moreover, the circulating levels of sST2 were related to IL-6, IL-8 and IL-10 levels in the blood of sepsis patients [14;90–91]. However, the levels of IL-6, IL-8 and IL-10 tended to decrease within 5 days from the beginning of the sepsis [14;90]. Differently, the circulating levels of sST2 remain elevated in non-survivor patients even after 14 days from the onset of the disease [14;90–91]. The data collected

suggest the use of sST2 as prognostic biomarker in subject with sepsis [14;89].

Unfortunately, the molecular mechanisms regulated by IL-33/ST2 system in the sepsis patients remain to be clarified. Hoogerwerf JJ et al. suggested that IL-33/ST2 system was involved in the differentiation of Th cells from Th0 to Th2 during sepsis and that the circulating levels of sST2 were directly correlated with the number of Th2 activated in these patients [90]. Other studies suggested that circulating levels of sST2 were related to degree of endothelial dysfunction [14]. Considering that the vessel wall is subjected to several insults in sepsis patients, it has been speculated that the fibroblast underneath the vascular endothelium produce sST2 and that the decoy receptor for IL-33 can be released in the blood only after endothelial disruption [14].

#### 5. COVID-19 and sST2

Cytokines storm, ARDS, fibrosis, systemic inflammatory state and cardiovascular diseases are the most common severe complications observed in COVID-19 patients. Based on what has just been described in relation to the levels of sST2 in ARDS patients, it seems theoretically correct to assume that after infection of lungs by SARS-CoV2 and cytokines storm activation, the circulating levels of decoy receptor for IL-33 could increase dramatically in the blood in the same manner observed for the other inflammatory mediators [47,53–56]. High sST2 concentration in the blood could affect the anti-hypertrophic and anti-apoptotic role of IL-33/ST2L system in the heart, contributing as IL-6 and TNF $\alpha$  to myocardial remodeling and worse outcome of COVID-19 patients.

Analysis of the circulating levels of sST2 in the blood and of cardiac expression on IL-33 and ST2 genes in the heart of COVID-19 patients will be needed to provide information about the involvement of these elements in the pathogenesis of disease and, eventually, to take into account a role for sST2 as prognostic biomarker in SARS-CoV2 infected patients (Fig. 1).

Finally, keeping in mind that pulmonary fibrosis could be the secondary complication in the post-COVID-19 patients and that IL-33/ST2 system is involved in fibroblast activation and extracellular matrix remodeling, the evaluation of circulating levels of sST2 could be used as prognostic biomarker in discharge COVID-19 patients. Obviously these are only hypotheses. Appropriate studies will clarify the long-term complications and the possible role of sST2 in post-COVID patients.

Very recently, Zeng Z et al. studied the role of sST2 in COVID-19 and

its relationship with inflammatory status and disease severity, suggesting that monitoring of serum sST2 could be helpful in the early screening of inflammatory status and critical illness of COVID-19 [92,93].

## 6. Conclusion

Although the molecular and cellular mechanisms leading to cardiovascular dysfunction in COVID-19 patients remain to be clarified, the excessive release of pro-inflammatory mediators in the blood from infected lungs would appear the main tool of SARS-CoV2 to damage the cardiovascular system and so to worsen the prognosis of patients.

In this review, it has been speculated the possible employment of sST2, the decoy receptor of IL-33, in the management of COVID-19 patients. It is known that high circulating levels of sST2 are involved in the aberrant inflammatory process of ARDS patients, whereas they are engaged in hypertrophy and apoptosis processes of HF subjects.

At the moment, the use of sST2 as marker of prognosis for COVID-19 remains merely a hypothesis. For this reason, new rigorous investigation will be necessary before to clarify its role in SARS-CoV2 infection. Increasing the number of information on COVID-19 patients by expanding the number of biomarkers used to date represents an opportunity to learn more about the pathophysiology of disease and to start thinking about adequate pharmacological treatments in order to improve patient outcome.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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