Letter to Editor

Role of ST2 as a biomarker of respiratory dysfunction after interstitial pneumonia

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Dear Editors,

Through stern social restraint measures, Italy has recently overcome the epidemic peak of COVID-19 (Coronavirus Disease-19) respiratory syndrome induced by SARS-CoV-2 and the attention is progressively moving toward its sequelae, especially on pulmonary fibrosis and the associated pulmonary functional decline [1-3].

To date, these events remain speculative, although, in the recent past, syndromes similar to COVID-19 with long term sequelae, have been sustained by other members of Coronaviridae Family, such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Coronavirus (MERS-CoV).

As SARS-CoV-2, SARS pneumonia too, on chest CT images shows ground glass lesions and consolidations, still persistent after four weeks in about half of the patients [4]. A fifteen year follow-up of SARS patients has shown that the interstitial involvement and functional decline revert almost completely in two years after rehab [5].

MERS pneumonia as well, has a typical CT presentation with bilateral basal and peripheral pulmonary ground-glass opacities. In a follow-up study, a third of the patients who underwent chest X-ray on a median of 43 days (32-320 days) had anomalies described as fibrosis [6].

To foretell and quantify the amount of fibrosis after COVID-19 pneumonia, could have an important role in diagnostic and therapeutic management of patients infected with SARS-CoV-2.

With this perspective, the marker sST2 could be an interesting prognostic index in the association of its serum level with the degree lung fibrosis.

The marker ST2 (Suppression of Tumorigenicity 2) is a member of IL-1 receptors family.

ST2 is encoded by the *IL1RL1* gene and consists of at least two isoforms, ST2L and sST2, which are produced via alternative splicing. ST2L is a transmembrane form and is expressed in a variety of cell types, including Th2 lymphocytes, macrophages and NK cells, whereas sST2 is a soluble form that is predominantly expressed in fibroblasts, epithelial cells and cancer cells [7,8].

The transmembrane isoform ST2L binds IL-33, activating immunomodulatory and anti-inflammatory biochemical pathways. The soluble form (sST2, serum dosable) inhibits the binding of the transmembrane receptor with IL-33, working as a decoy receptor, and it can be used as a marker to evaluate the fibrotic development of acute and chronic inflammatory pathologies [9,10].

In the cardiovascular field, sST2 has been studied for prognostic risk stratification in patients with heart failure [11,12] and as a marker of fibrosis in patients with atrial fibrillation [13,14]. In these pathologies, ischemic episodes and mechanical burden induced stress determines an increase of the soluble form expression, amplifying heart cellular apoptosis, fibrosis and hypertrophy.

In the pulmonary field, IL-33/ST2 axis is involved in the genesis and development of numerous illnesses: higher sST2 serum and broncho-alveolar lavage concentrations have been noted in patients with acute eosinophilic pneumonia [15], in allergic diseases as asthma [16], chronic obstructive pulmonary...
disease [17], allergic rhinitis [18], and non-allergic pulmonary diseases [19], chest trauma injuries [20], ARDS [21,22]. Moreover, a recent study on pediatric population has shown as a exacerbated IL-33/sST2 axis activity and persistently high concentration of sST2 can be correlated with acute viral low respiratory infections [23].

The relationship between asthma and COVID-19 is still unclear. Recent contributions raised the question if the allergic disease represents a possible risk factor for severe outcomes in COVID-19 patients. Recent studies [24,25] seem to refute this hypothesis, but the reasons are not clear. In particular, on the basis of the available results a negligible number of asthmatic patients were admitted for COVID-19 hospitalization. One possible explanation could be related to the T2 immunomediated response, peculiar of asthmatic patients, which could down regulate the strong inflammatory phase of the disease, typical of a severe outcome for the viral pathology.

Concluding, the promising role of sST2 is strongly supported by the recent researches on pulmonary diseases (asthma, ARDS, fibrosis) [26] and post COVID-19 heart failure [27].

With these premises, we hope to unearth a useful prognostic tool and to define its role in challenging days to come in the work of the scientific community against SARS-CoV-2.

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