Heart &Covid 19 In Children

Covid 19
7 OCT 2021

- Cases: 237,222,557
- Deaths:4,843,473
- Recovered:214,364,990

Based on previous studies, coronaviruses induce respiratory and interstitial infections in animals, as well as humans. Two highly pathogenic viruses; namely, severe acute respiratory syndrome related coronavirus SARS and MERS-Covid, result in ARDS and multi-organ failure(MOF), as well as mortality ARDS is the most common complication in COVID-19.

In this population, predominantly identified by the presence of symptoms (99%), <2% of cases occurred in children <19 years of age, suggesting that children either are either resistant to infection or rarely symptomatic. Of confirmed cases, most(87%) were mild, defined by no or mild pneumonia,14% were severe with significant infiltrates or signs of respiratory compromise, and 5% were critical, with respiratory failure (e.g., mechanical ventilation),shock, or multiorgan system failure.

CLINICAL PRESENTATION

the most common symptoms were fever in up to 90%, followed by cough, fatigue, sputum production, and shortness of breath and Less common symptoms included headache, myalgias, sore throat ,nausea, vomiting, and diarrhea. Also anosmia and dysgeusia as Median incubation period 4,(2 to 7) days and Another report detailed that 99% of infected patients develop symptoms within 14 days

Common laboratory tests:

Lymphopenia, elevations in C-reactive protein , lactate dehydrogenase, liver transaminases (ALT,AST), and D-dimer. Notably, procalcitonin was rarely elevated .Elevations in other inflammatory markers, such as interleukin6, ferritin, and erythrocyte sedimentation rate ,Chest computed tomography at the time of admission was abnormal in 87% of patients, with ground-glass opacities or local or patchy “shadowing .

DISEASE PROGRESSION.

Many of the more severe manifestations, such as ARDS, acute kidney injury (AKI), and myocardial injury, tend to occur as many as 8 to 14 days after the onset of symptoms and portend worse outcomes .

Hospitalized, rates of ICU admission range between 26% and 32%.

Several studies ;older age and baseline burden of comorbidity, such as diabetes,hypertension, prior coronary disease, and prior lung disease, as predictors of more significant disease progression, with higher rates of ARDS, AKI, cardiac injury, ICU admission, and death.

Increases in markers of inflammation, coagulation, and cardiac injury also correlate with disease severity and rise throughout the course of the disease.

In hospitalized patients, the timing of death at a median of 16 to 19 days after illness onset.

The median time to discharge in survivors was around 3 weeks .

Respiratory failure:

The most prominent complication of COVID-19 is respiratory failure. In hospitalized patients, respiratory symptoms are common and range in severity from cough (60% to 80%) or dyspnea (19%to 40%) to ARDS (17% to 42%) but this may be an underestimate due to a short average follow-up time of 12 days, with the vast majority of patients remaining hospitalized at the end of study

ARDS tends to occur 1 to2 weeks into illness and is often precipitous and protracted .For these reasons, and to avoid risk of provider infection with emergent intubation, professional societies recommend early intubation in the event of respiratory decline .Intubation was required in 10% to 33% in the various; however, rates of high-flow nasal cannula and noninvasive mechanical ventilation also were high .These therapies are believed to result in aerosolization and are generally not recommended—consequently, more patients will be intubated when unable to be supported by nasal cannula or a nonrebreather mask.

Older age, baseline hypertension, diabetes, high fever, lymphopenia, injury to other organs (e.g., AKI, acute liver injury [ALI]), and elevated D-dimer and inflammatory markers were predictors of ARDS ; advanced age, neutropenia, elevated D-dimer, and inflammation are associated with higher mortality in those with ARDS.

Development of ARDS, along with acute cardiac injury, was an independent predictor of death .Importantly, hypoxemic respiratory failure is the leading cause of death in COVID-19, contributing to 60% of deaths

Renal injury.

Estimates vary as to the incidence of AKI in COVID-19, ranging between 0.5% and 15% .Among hospitalized patients, the rates of proteinuria (43.9%) and hematuria (26.7%) appear to be even higher .AKI occurs in the first few days after admission in patients with baseline chronic kidney disease, and after 7 to 10 days in patients with normal baseline renal function . Mechanisms of renal injury have been hypothesized to include both acute tubular necrosis, direct cytotoxic effects of the virus itself, and immune-mediated damage

Liver injury.

Transaminitis is common, with an incidence of 21% to 37%, and as high as 48% to 62% of patients who are critically ill or who do not survive.

Acute Liver injury, defined as either alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, reported to occur in 19.1% of patients who were admitted to an ICU in Washington State .

Cardiovascular Manifestations and Mechanisms in Patients with COVID-19

Coronavirus disease 2019 (COVID-19) patients with pre-existing cardiovascular disease (CVD) or with cardiovascular complications have a higher risk of mortality.

Main cardiovascular complications of COVID-19 include: acute cardiac injury, acute myocardial infarction ,myocarditis, arrhythmia, heart failure, shock, and venous thromboembolism (VTE)/pulmonary embolism (PE).

COVID-19 can cause cardiovascular complications or deterioration of coexisting CVD.

through direct or indirect mechanisms, including viral toxicity, dysregulation of the renin–angiotensin–aldosterone system (RAAS), endothelial cell damage and thrombo-inflammation, cytokine storm, and oxygen supply–demand mismatch.

Acute Cardiac Injury

Acute cardiac injury is defined as a rise of cardiac troponin values, with or without ejection fraction decline or electrocardiographic abnormalities. The prevalence of acute cardiac injury among COVID-19 patients was 10–23%, with a higher frequency in intensive care unit (ICU) patients (and non-survivors .

Patients with acute cardiac injury were associated with more severe illness, including higher CRP, NT-proBNP, and creatinine levels, as well as more multiple mottling and ground-glass opacity, and were more likely to receive noninvasive or invasive ventilation.

Acute cardiac injury was also associated with cardiac dysfunction and malignant arrhythmias .Patients with acute cardiac injury exhibited a significant higher risk of mortality both during the time from symptom onset .

Greater magnitude and frequency of cardiac troponin elevation was also associated with higher mortality . COVID-19 patients with previous CVD were more prone to suffer acute cardiac injury; Compared with patients without cardiac injury, there was a higher prevalence of CVD and hypertension in those with cardiac injury . Moreover, once infected by SARS-CoV-2, patients with CVD comorbidities usually had a worse cardiac reserve and poorer tolerance to hypoxia, and were more likely to develop cardiac insufficiency (e.g., heart failure, malignant arrhythmia, or shock).

Acute MI

Respiratory viruses, such as SARS and influenza, are associated with AMI by increasing the risk of coronary plaque rupture .

AMI can occur in COVID-19 patients, but the incidence of such events is unknown. Newly diagnosed AMI was reported in 5.3% of cases in an electrocardiographic study of COVID-19 ,and in 2.9 % in another echocardiography study .

STEMI can present as the initial clinical manifestation of COVID-19 ,and 33.3–39.3% of patients with COVID-19 who had STEMI were diagnosed with non-obstructive coronary artery disease .This phenomenon indicated that COVID-19 itself may be connected to endothelial dysfunction as well as to the hypercoagulable state.

Many patients with AMI, perhaps owing to fear of contracting SARS-CoV-2, avoided hospitalization at the time of the COVID-19 pandemic, leading to delay and aggravation of AMI.

Myocarditis:

is defined as myocardial damages caused by direct viral attack on the heart. In the early period of COVID-19,and a patient who presented with third degree atrioventricular block was reported as myocarditis .

A few COVID-19-related myocarditis cases have been confirmed by cardiac magnetic resonance imaging. However, there is only limited evidence for viral entry into cardiomyocytes. Although endomyocardial biopsy found evidence of lymphocytic inflammatory infiltrates in the myocardium, SARS-CoV-2 particles were found only in interstitial cells of the myocardium .AnotherCOVID-19 case demonstrated lymphocytic myocarditis without SARS-CoV-2 in the myocardium.

Thus, immune-mediated hyperinflammation may play a more significant role than viral replication or toxicity in the pathophysiology of acute myocarditis associated with COVID-19. Pericardial involvement with cardiac tamponade has also been reported .

Arrhythmia

Arrhythmias were reported in 16.7% COVID-19 patients, with a greater proportion in ICU patients than in non-ICU patients . COVID-19 presenting with various arrhythmias has a strong association with the severity of the disease. electroencephalography (ECG) traces from the patients in the ICU group was significantly elevated.Ventricular arrhythmias are higher among patients with acute cardiac injury than in patients without acute cardiac injury . Atrial arrhythmias were more common among patients who required mechanical ventilation than among those who did not .Prolonged corrected QT(>500 ms) was found in 6% patients with COVID-19 in a New York cohort .

patients who experienced in-hospital cardiac arrest in covid19,asystole was the most common initial rhythm in 89.7% of cases, whereas shockable rhythms were found in only 5.9% of patients.

Sudden cardiac death has been reported in COVID-19 patients who initially had only mild symptoms but who were later discovered dead at home.

In contrast to the decline of patients with AMI in the early COVID-19 pandemic, out-of hospital cardiac arrest reported an increase of 58% during the first 40 days of the COVID-19 outbreak compared with the same period in 2019.

COVID-19 or other untreated diseases such as Acute MI combined with patient unwillingness to attend for treatment may have contributed to the phenomenon.

Arrhythmias in the population with COVID-19 developed secondary to hypoxemia, metabolic dysregulation, electrolyte disorder, systemic inflammation, electrical instability with adrenergic stress, AMI or myocarditis, and treatment with QT prolonging drugs.

Heart Failure

Heart failure was observed in 23% of patients with COVID-19.
Heart failure was higher in non-survivors than in survivors .
Cardiac markers such as troponin, and rise of BNP/NT-pro BNP are associated with poor prognosis in covid19 and in seriously ill patients,7–33% had biventricular failure and some patients RV failure .
Incidence of stress cardiomyopathy 7.8% increased significantly during the COVID-19 outbreak compared with pre -pandemic periods (1.5–1.8%).Microvascular disorder, cytokine storm, and sympathetic stress may participate in the pathophysiology of stress cardiomyopathy.
End-stage manifestation of CVD, heart failure may be the long-term consequence of cardiac infection COVID19.

Shock Cardiogenic, septic, or mixed shock is one of the criteria of critical illness in COVID-19.

Shock developed in 8.7% ,and was more frequent in ICU patients compared with non-ICU counterparts .

It is crucial to diagnose whether there is a concomitant cardiogenic factor to assist clinical decision-making, particularly when mechanical respiratory and circulatory assistance with ECMO are required because this may influence device selection .

In the later phase of the COVID-19 pandemic, healthy children displaying atypical Kawasaki disease (KD) in the USA and Europe ;and named pediatric inflammatory multisystem syndrome temporally associated (PIMS-TS) in covid.

with manifested as consistent fever, evidence of inflammation (neutrophilia, raised CRP, and lymphopenia), and single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) in conjunction with existing or previous infection with covid.

Comparison of PIMS-TS with KD or KD shock syndrome showed older age and greater elevation of inflammatory markers such as CRP .

Untreated KD can lead to coronary aneurysms in 25% of patients. SARS-CoV-2-induced immune dysregulation may lead to PIMS-TS onset because the majority of children with PIMS-TS were positive for antibodies against SARS-CoV-2 .

Venous ThromboEmboli and Pumonary Emboli

COVID-19 has been associated with proinflammatory and prothrombotic conditions that can result in thromboembolic events .

In fact, higher markers of thrombosis have been associated with worse clinical outcomes. In a multicenter study, elevated D-dimer levels (>1g/l) were independent predictors of in-hospital death ;Also, 71.4% of patients who died were diagnosed with disseminated intravascular coagulation .

A study reported a high incidence of VTE (69%) in ICU patients .However, other centers have reported lower VTE rates (22.2%) .Despite prophylactic anticoagulation, 31% of patients with COVID-19 still developed VTE , and 16.7% of patients were diagnosed with PE .

PE was more likely to occur in acute respiratory distress syndrome (ARDS) patients with COVID-19 compared with non-ARDS individuals. Another study reported a cumulative incidence of PE of 20.4% in critical COVID-19 patients, markedly higher than for patients in the same ICU during the same period .

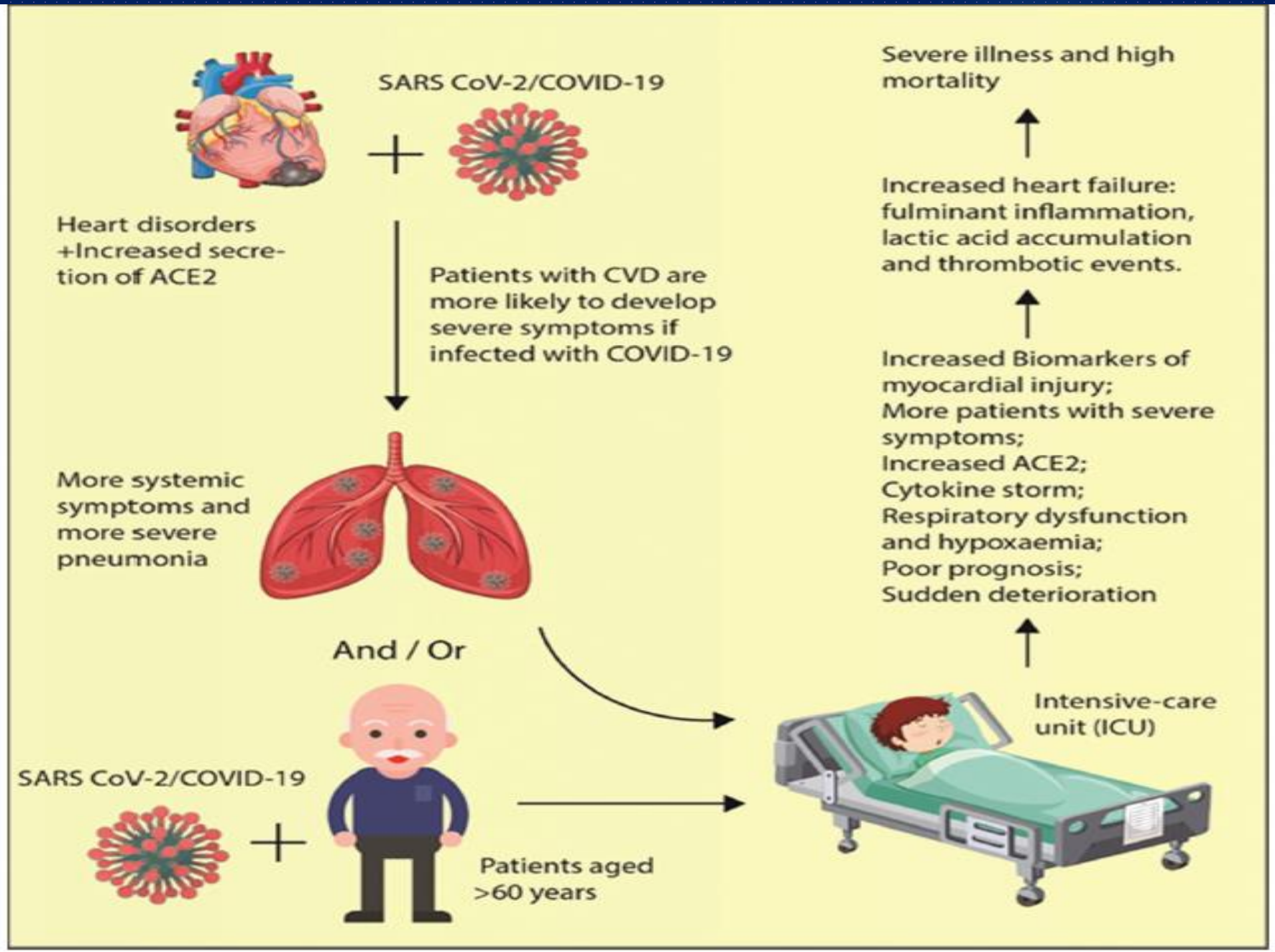

Figure 1. COVID-19 progression (severity of the disease) and prognosis. Patients with heart disorders can lead to an elevated risk of death. **CVD**: cardiovascular disease; **ACE2**: Angiotensin-converting enzyme2; **SARS-COV-2**: severe acute respiratory syndrome-associated coronavirus 2.

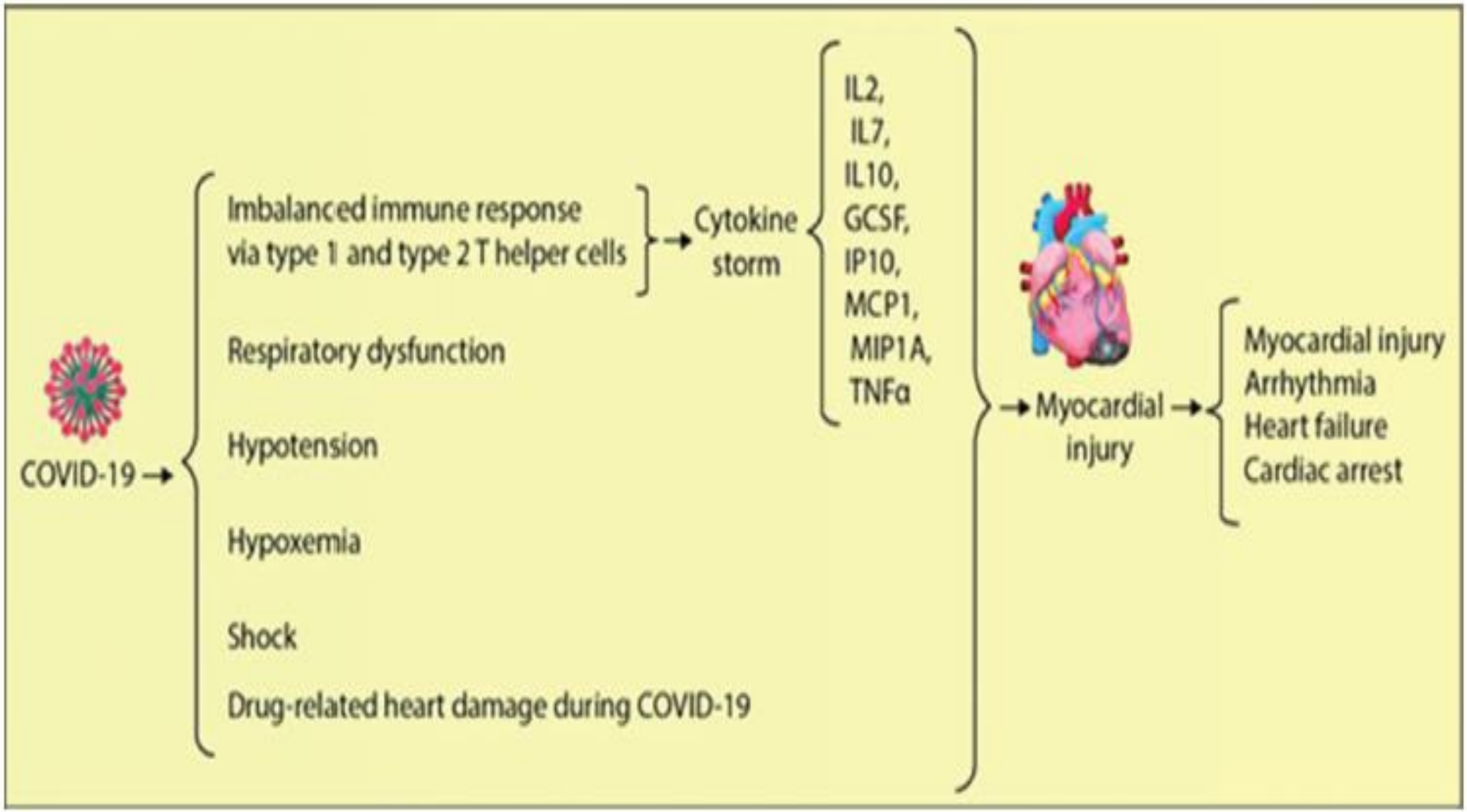

Figure 2. Causes and symptoms of cardiovascular disorders problems in patients with COVID-19.

IL: Interleukin; **GCSF**: Granulocyte-colony stimulating factor; **IP10**: Interferon γ-induced protein 10 kDa; **MCP1**: Monocyte chemoattractant protein-1; **MIP1a**: macrophage inflammatory protein 1a: **TNFα**: Tumor necrosis factor alpha.

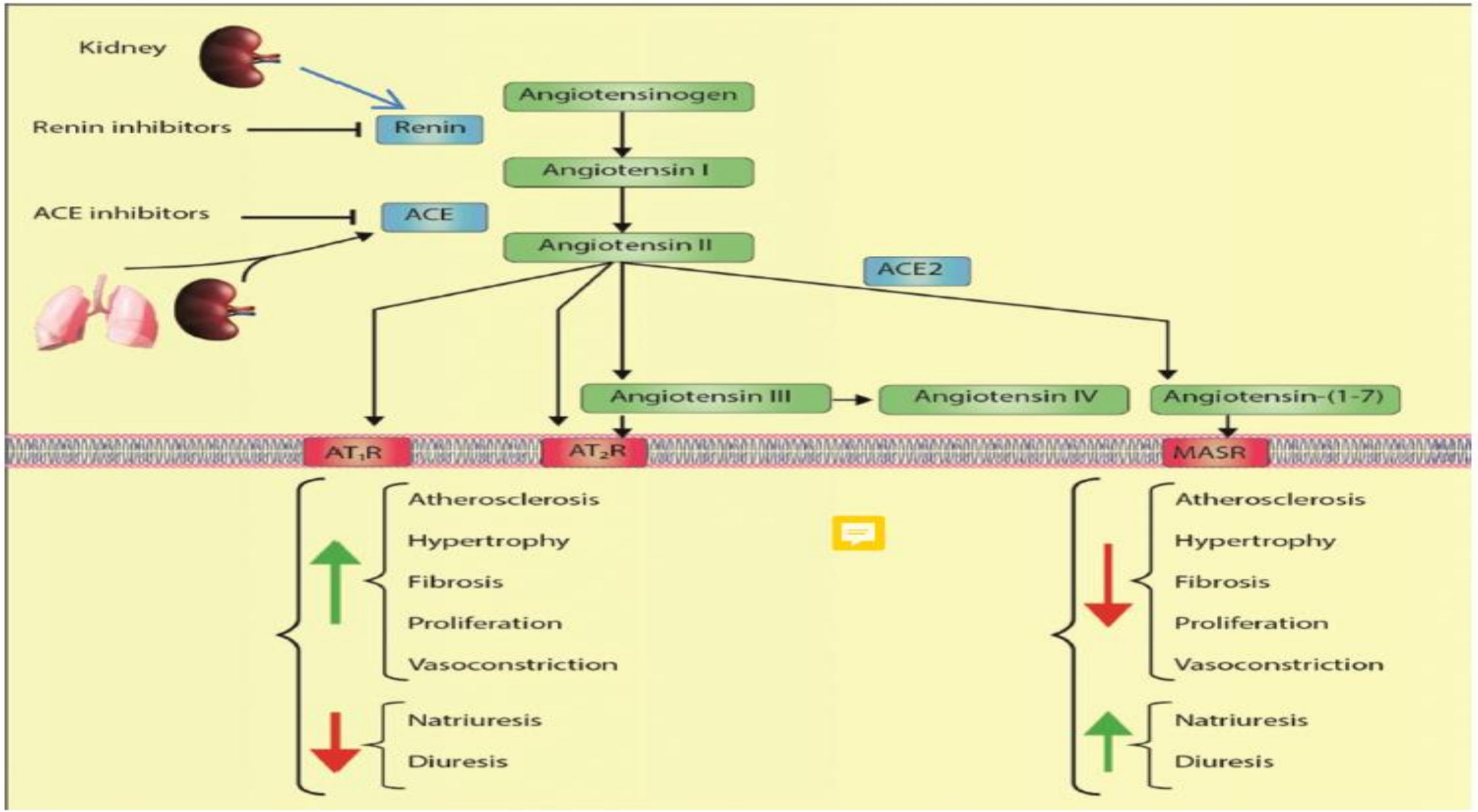

Figure 3. Renin-angiotensin system cascade and its cardiovascular effects.

AT_1R: Ang II type 1 receptor; **AT_2R**; Ang II type 1 receptor; **ACE**: Angiotensin-converting enzyme; **ACE2: MASR**: ACE2/Ang (1–7) receptor;

Mechanisms of Cardiac Manifestations in COVID-19

The pathology of COVID-19 results from both direct and indirect injuries:

Direct injuries are caused by infection of target cells by the virus.

Indirect injuries mainly result from immune response, inflammation reaction, circulatory dysfunction, and hypoxia.

ACE2-Mediated Viral Toxicity:Angiotensin-converting enzyme 2 (ACE2) is expressed in the vascular system (endothelial cells, vascular smooth muscle cells, and migratory angiogenic cells) and the heart (cardiofibroblasts , cardiomyocytes, endothelial cells, pericytes, and epicardial adipose cells) .

ACE2 functions as a virus entry receptor by binding to the spike (S) protein of SARS-CoV and SARS-CoV-2. In addition, completion of cell entry requires priming of the S subunit by the cellular serine protease TMPRSS2 (transmembrane protease serine 2) or other proteases (cathepsin L, cathepsin B, factor X, trypsin,elastase, and furin) .

The increased transmissibility of SARS-CoV-2 could be interpreted by the greater binding affinity of SARS-CoV-2 for ACE2 than of SARS-CoV .Furthermore, patients with previous CVD were associated with more severe COVID-19 disease, possibly because they had higher plasma levels of ACE2 . Nevertheless, compared with the lung, the human heart has higher expression of ACE2 and with much lower content of TMPRSS2.

The susceptibility of the heart in SARS-CoV-2 infection was diminished to some extent by a lower proportion of ACE2+/ TMPRSS2+ cells. Other S protein priming proteases that are prominently expressed in the human

heart, cathepsin L and furin, may increase heart vulnerability to SARS-CoV-2 .

Dysregulation of RAAS

ACE2 converts angiotensin II (Ang II) to Ang-(1–7), and the ACE2/Ang-(1–7)/Mas axis combats the adverse impacts of RAAS, which is essential for preserving the physiological and pathophysiological equilibrium of the body.

Entry of SARS-CoV-2 into cells is assisted by the interaction between S protein and ACE2 extracellular domains, leading to downregulation of surface ACE2 expression.

Ang-II/angiotensin 1 receptor (AT1R) activity is then increased at the expense of the ACE2/Ang 1–7/Mas axis, leading to comprehensive negative consequences, including aldosterone secretin, fibrosis ,proinflammation, hypertrophy, vasoconstriction, enhanced reactive oxygen species and vascular permeability ,cardiac remolding, gut dysbiosis, and multiple organ dysfunction syndrome (MODS) in COVID-19 .

ACE2 exerts multiple protective effects in numerous organs and various diseases,and genetic ACE2 deficiency is associated with adverse results. Ace2 knockout mice display myocardial hypertrophy and interstitial fibrosis, and aggravated heart dysfunction . ACE2 deficiency substantially worsened the pathogenesis in influenza virus H5N1-infected mice, and AT1R suppression relieved the severity of lung damage .

ACE2 can also stimulate insulin secretion and lower insulin resistance . Downregulation of ACE2 expression was seen in myocardial cells in both SARSCoV-infected mice and humans .

There is also a positive correlation between elevated circulating Ang II levels in COVID-19 patients and lung injury and/or viral load. In short, a direct link between tissue ACE2 downregulation and upregulation of Ang II is partially responsible for the development of cardiovascular complications or multiorgan failure following SARS-CoV-2 infection .

Endothelial Cell Damage and Thromboinflammation

Direct invasion of endothelial cells by SARS-CoV-2 infection and indirect generation of inflammation and prothrombotic conditions in vasculopathy both contribute to the pathophysiological mechanisms of COVID-19 .

Both venous and arterial endothelia are reported to express ACE2 . Furthermore, histopathological studies have provided microscopic evidence of SARSCoV-2 viral particles in endothelial cells of the kidney, as well as obvious endotheliitis characterized by activated neutrophils and macrophages in numerous organs including the lung, intestine,and heart .

Von Willebrand factor (VWF), a circulating blood coagulation glycoprotein associated with endothelial dysfunction, is significantly elevated in COVID-19 patients compared with normal individuals . VWF, a carrier of coagulation factor VIII, can trigger platelet aggregation and blood coagulation . Subsequent platelet–neutrophil interaction and macrophage activation can further promote proinflammatory responses including cytokine storm and the formation
of neutrophil extracellular traps (NETs) .

NETs damage the endothelium and stimulate both extrinsic and intrinsic coagulation pathways, resulting in microthrombus formation and microvascular dysfunction. High levels of NETs were reported in hospitalized patients with COVID-19, and these correlated positively with disease severity .

Inhibiting NETs may be a therapeutic Inhibiting NETs may be a therapeutic target to reduce NET-mediated thrombotic tissue damage associated with COVID-19.

Immune Dysregulation-Induced Cytokine Storm

Dysregulated immune response and subsequent cytokine storm characterize the presentation of severe COVID-19.

Previous studies with human coronaviruses have reported that rapid viral replication, interference with interferon signaling, and recruitment of inflammatory cells (neutrophils and monocyte/macrophages) are mediators of hyperinflammation .

Immunity measurements such as white blood cells, neutrophils, lymphocyte subtypes, and inflammation parameters (CRP and procalcitonin) were independently related to acute cardiac injury in patients with COVID-19 .

Subsequent cytokine storm, characterized by a sharp rise in the level of multiple proinflammatory cytokines triggered by infection, has been observed following infection with H1N1 , SARS, or MERS and is an important cause of death .

A comprehensive evaluation of the transcriptional response to SARS-CoV-2 uncovered an atypical inflammatory reaction characterized by decreased levels of type I and III interferons, increased chemokines, and high levels of interleukin (IL)-6.

Reduced innate antiviral defenses and raised proinflammatory responses contribute to COVID-19 pathology .

Higher levels of IL-6 in the serum have also been linked to worse prognosis and were found to correlate with fibrinogen levels in patients with COVID-19 .

.IL-6 can activate coagulation, induce thrombosis , inhibit heart function and cause endothelial dysfunction, leading to vascular leakage, tissue ischemia and hypoxia, and thus to a drop in blood pressure, disseminated intravascular coagulation (DIC).

Mismatch between Oxygen Supply and Demand

Hypoxemia is the main manifestation of COVID-19, and results in an insufficiency of oxygen supply to organs with a high demand for oxygen and energy, particularly the heart.

The imbalance of oxygen supply and demand caused by cytokine storm as well as by endothelial dysfunction, without acute atherothrombotic plaque disruption, similar to the pathophysiology of type 2 myocardial infarction, is thought to lead to cardiac injury in COVID-19 patients.

Type 2 MI is a potential cause of cardiac damage in acute infection and also, cytokine storm causes the release of IL-6 and catecholamines that increase core body temperature, heart rate, and cardiac oxygen consumption.

On the other hand, endothelial dysfunction and cytokine storm affect the cardiac microenvironment, causing pathological changes such as coronary artery spasm and thrombosis, all of which lead to decreased blood supply via the coronary artery.

The reflex elevation in heart rate will further decrease myocardial perfusion owing to decreased filling time. Severe hypoxemia, hypotension, and anemia in critically ill patients with COVID-19 further aggravate insufficient oxygen supply. The combination of these factors causes mismatch between oxygen supply and demand, leading to acute cardiac damage.

Indeed, compared with type 1 MI caused by plaque rupture and thrombus formation, patients with type 2 MI have higher mortality rates, and this may in part reflect a higher burden of acute and chronic multimorbidity conditions in the population with type 2 MI .

Given the age and comorbidity of hospitalized patients with severe COVID-19, it is reasonable to speculate that type 2 MI in these patients is likely to be an indicator of more severe COVID-19 disease and worse prognosis.

Myocarditis and peri-carditis during of covid 19 and after vaccination for COVID-19 reported with hypereosinphilia.

Polymerase chain reaction (PCR) was planned with thorax imaging and nasopharyngeal swab, considering COVID-19 in the foreground. In thorax computed tomography, patched ground glass consolidation areas were observed at the level of the middle and lower lobe segments of the lung In his examinations, hemoglobin was 12.3 g/dL, white blood cell count 56,410/mm^3, neutrophil was 31,720/mm^3, eosinophil was 20,000/mm^3, platelet was 402,000/mm^3, urea was 34 mg/dL, and creatinine 0.66 mg/dL. Lactate dehydrogenase (LDH) was 312 mg/dL and C-reactive protein (CRP) was 35 mg/dL. Retrospective examinations showed that he have had eosinophilia for more than 1 year

Eosinophils;has been identified as a factor that may facilitate disease diagnosis and determine prognosis, this finding is neither definitive nor pathognomonic for COVID-19.

While recent case reports document misdiagnosis and eosinophil-associated complications of COVID-19, current evidence suggests that patients with longstanding eosinophil-associated disorders are at no increased
risk for severe disease at this time.

Finally, although vaccine-associated aberrant inflammatory responses were observed in animal model studies of vaccines under development to combat SARS-CoV and MERS-CoV, no similar complications have been reported to date in response to the now widespread distribution of the two FDA-approved mRNA based COVID-19 vaccines.