

Heart in patients infected With 2019 Novel Coronavirus (Covid-19)

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging infectious disease with currently a pandemic state. Cardiac function can be involved, affecting prognosis, in addition with lung feature severity, particularly in patients with comorbidities. Since the renin angiotensin aldosterone (RAA) system may interact with SARS-Cov-2, researches are still ongoing to assess the prognostic value of RAA blockers in cardiology.

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Introduction

In December 2019, a subset of clusters of unknown pneumonia cases emerged in Wuhan, Hubei Province (China). This unknown pneumonia onset was found to be linked to a local seafood wholesale market (1). It was found to be due to a novel beta-coronavirus, namely the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2, 3). This novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) on 7 January 2020, named 2019-nCoV by the World Health Organization (WHO)(4) and thereafter COVID-19. This emerging disease, rapidly, spread out of China, reaching other Asian countries, the USA (5) and the Europe (6) through Italy, with currently a global pandemic state, declared on March 11, 2020 by the WHO (4). Confirmed COVID-19 cases reached the number 1,924,878 persons over the world the 14th of April 2020 (7). In many countries, governments decided plans to include quarantine measures in order to modify the epidemic curve and to slow the pandemic (8). Clinical presentation of infected patients ranges from asymptomatic status to severe pneumonia (2, 3). Currently, it appears that 81% of people with COVID-19 infection disclose a mild disease. Cardiac comorbidities are often present in patients with severe COVID-19 infection (9). Cardiac injury may occur in patients infected with COVID 19 (3) and affects the prognosis (10). Also, the renin angiotensin-aldosterone system seems to interact with the Covid-19 lung infection process, especially ACE2 receptors, which would allow the virus to particularly entry in the pulmonary level, arguing the discontinuation of angiotensin converting enzyme (ACE) inhibitors drugs or angiotensin receptors blockers (ARB) in patients with cardiovascular diseases.

We aimed to review the cardiac features among patients suffering from COVID-19 infection as well as its prognosis.

Clinical characteristics and biological features in patients with Covid-19

After an incubation period, in patients presenting with symptoms, the most common clinical manifestations are fever (83-98.6%), cough (59%-79%), dyspnea (31%-63.5%), asthenia (23%-69%), myalgia (11%-35%), gastro intestinal disorders (1%-10%), headache (6.5%-8%) (3, 11, 12, 13). Some patients may require hospitalization and a subset of patients (about one third) (2, 3) need admission in intensive care unit (ICU) because of a severe respiratory failure. In ICU wards, complications include acute respiratory failure, acute respiratory distress syndrome (ARDS) (14), cardiac injury and death (11). In the study by Chen *et al* (11), 75% and 17% of patients disclosed bilateral pneumonia and ARDS, respectively. The median time from first symptoms to hospital admission was globally reported to be around 7 days (3), whereas the median duration from onset of symptoms to ICU admission was reported to be at 9.5 days (15). Biological results are classically disturbed with reduced total lymphocytes, elevated lactate dehydrogenase and prolonged prothrombin time (3). The following blood abnormalities have been found in ICU patients (3): an increase of cardiac troponin I, creatinine, urea nitrogen, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatine kinase and a decrease of white blood cell counts. Lymphopenia is common in infected patients, from 40% to 83% (9, 12, and 13). Hepatitis is common with an increase of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and lactate dehydrogenase. D-dimers are classically increased with a coagulopathy state, reaching 34% (10).

Diagnosis of COVID-19 pneumonia relies on nasopharyngeal swab specimen or bronchial aspirates, using real time reverse –transcriptase-polymerase-chain –reaction assay (RT-PCR). Plasma can also be used to detect coronavirus (16). In addition, CT chest is commonly used to

precise extension and severity of the pneumonia and support the diagnosis in case of negative RT-PCR (17).

Thoracic Imaging findings

Thoracic imaging reveals usually COVID 19 features characteristics in pneumonia-infected patients. These impairments are due to lung damages, caused by the SARS-COV2. It has been reported with lung histological studies, diffuse alveolar damages, pulmonary edema, and interstitial mononuclear inflammatory infiltrates (15). Ground glass opacities, bilateral patchy shadow and areas of consolidation (*figure 1*) are classical findings in thoracic computed tomography (CT) scans (3). In the study by Yang et al (13), the median duration from onset of symptoms to radiological confirmation of pneumonia was 5 days. Ground glass opacities were found in 48%-56.4% of patients and 52%-75% of patients disclosed bilateral reticular nodular opacities on chest X ray (9, 11, 18). In ICU, 100% of patients presented with bilateral involvement on chest X ray (2). Lung ultrasound (*figure 2*) can also be used to assess lung involvement and severity, searching for diffuse B lines, particularly in patients with thoracic scan unavailability (19).

Cardiac features in COVID - 19 infected patients

Cardiovascular comorbidities are often present in patients infected with COVID 19. In the study by Zhou *et al* (13), comorbidities were present in 48% of patients, mainly arterial hypertension, diabetes and coronary artery disease. It should be noted that smoking is associated with an increase of ACE2 binding with Covid-19 and might explain why those comorbidities are usually encountered in severe clinical presentation of covid-19 in those patients (20). Also COVID19 classically affects more male rather than female, possibly because of a different background and susceptibility (11). In the study by Wang *et al* (3) that

included ICU patients, a history of hypertension was found in 58% of patients, 25% of patients had a history of cardiovascular diseases, and diabetes, history of cerebrovascular diseases and chronic kidney disease were present in 22%, 16.7% and 5.6% of patients, respectively. In two previous studies (2, 11), cardiovascular diseases were present in 15% and 40% of patients. In the study by Bhatraju *et al* (21), diabetes mellitus was present 58% of patients, obstructive sleep apnea in 21% of patients and chronic kidney disease in 21% of patients. In a large study including 1591 ICU patients (aged around 63 years) admitted in the Lombardy Region in Italy (22) arterial hypertension was present in 49% of patients, cardiovascular diseases in 21% of patients and 17% of patients have a history of diabetes.

In the meantime, cardiac injury has been found to be frequent in patients with COVID- 19 pulmonary infection and this feature affects prognosis. In general, in patients with pneumonia, the risk factors for cardiac events include preexisting cardiac diseases, older age and pneumonia severity (23). In the study by Chen *et al* (11), that included 99 patients (age 55.5 years) with COVID 19 pneumonia, 2% of patients disclosed chest pain. In the study by Zhou *et al* (13), non-survivor's patients had a history of arterial hypertension (48%), diabetes (31%) and coronary disease (24%). Heart failure is significantly present in non-survivor patients ($p<0.0001$) and acute cardiac injury, defined as an increase of cardiac biomarkers (high-sensitivity cardiac troponin I) or new electrocardiographic and echocardiographic abnormalities (13). Acute cardiac injury occurred in 22% of ICU patents *vs* 2% in non-ICU patients ($p<0.001$) (3). In 21 critically ill patients (aged around 70 years old) with COVID 19 (18), cardiomyopathy occurred in 33% of patients. Brain-type natriuretic peptide level was elevated, 4720 pg/ml, as well as troponin level (3ng/ml) (18). In the study by Guo *et al* (10), 27.8% disclosed cardiac injury and this feature is significantly associated with mortality. Cardiac injury is frequently found in patients hospitalized in ICU, from 19.7% to 31% (2,13,24). This feature was particularly present in older patients, patients with comorbidities

(hypertension 59.8%), higher levels of C-reactive protein, procalcitonin, creatine kinase – myocardial band, myohemoglobin, high-sensitivity troponin I, N-terminal pro-B-type natriuretic peptide, higher leukocytes counts, creatinine, aspartate aminotransferase, higher radiologic involvement (ground-glass opacity) (24). Ruan Q *et al* (25) reported also myocarditis among 68 deaths in a case series of 150 patients with COVID-19, where 7% were associated with myocarditis with circulatory failure. It has been found a relationship between the pulmonary severity and the cardiac injury (3). In ICU patients, admitted because of hypoxemic respiratory failure, Bhatraju *et al* (21), reported troponin increase in 15% of patients. Dyspnea is also a classical feature in patients, mainly in relation with lung injury. In the study by Huang *et al* (1), dyspnea was present in 55% of patients and time from illness onset to dyspnea was at 8 days. The median time from illness onset to dyspnea onset was 13 days, in the study by Zhou *et al* (12). Acute pulmonary embolism may be present in COVID 19 infected patients, without clear causal relationship (26). Finally, in ICU, hemodynamic features are frequent and vasoconstrictive agents were used in 35% of critically ill patients (13). In addition with cardiac injury, arrhythmia may occur in COVID 19 infected patients (3). Sudden cardiac arrests have also been reported (15). Arrhythmia occurred in 44% of ICU COVID -19 patients vs 6.9% in non-ICU COVID-19 patients ($p < 0.001$) (3). Ventricular fibrillation/ventricular tachycardia (VF/VT) occurred in 5.9% of patients and increased troponin was associated with onset of VF/VT (17.3%) (10).

In summary, risk factors for cardiac injury (2, 10, 13, 18, and 24) are as follows: older age, hypertension, cardiovascular diseases, cardiomyopathy, diabetes, chronic kidney diseases. The **table 1** summarizes principal studies in infected COVID 19 patients, associated with cardiac injury.

Renin angiotensin aldosterone system and Covid -19

Cardiac comorbidities are thus frequent in patients with Covid-19 (9, 27). Angiotensin converting enzyme (ACE) inhibitors and ARB are commonly prescribed in patients with hypertension, chronic heart failure and diabetes. The renin angiotensin system (RAA) may interact with the COVID 19 infection process (28, 29). Indeed, ACE 2 is an enzyme present in the lung epithelial cells and is functionally as a receptor for SARS Cov2 (30). Physiologically, the ACE 2 degrades angiotensin 2 to angiotensin (1-7), reducing, in the way, fibrosis and vasoconstriction (29). Since ACE 1 inhibitors and ARB increase ACE 2 activities, these drugs, in theory, may be harmful in patients infected with Covid 19 (31). Researches are needed to clarify mechanisms and outcomes in patients treated with RAA blockers. Currently, The European Society of Cardiology (ESC) as well as the American Heart Association recommends continuing these previous drugs, since there is no scientific evidence to discontinue ACE inhibitors or ARB in patients with Covid -19 infection (32, 33). However, the community is still investigating if there is a clear association between COVID-19 mortality and the renin-angiotensin system (34).

Cardiac features, ARDS, prognosis and mortality

The **table 2** summarizes risk factors associated with mortality in COVID-19 infected patients. In patients infected with COVID 19, the onset of cardiac injury and the association between cardiac injury and onset of ARDS affects prognosis (13, 24). Mortality rate dramatically increases in case of previous cardiovascular diseases, comorbidities and in ICU patients (13, 35). Older age is also a significant factor for ICU mortality, reaching up to 67% in patients older than 70 years (18).

In critically ill patients, mortality may reach 61% (13, 21). In the study by Arentz *et al* (18), that included ICU patients with a mean age of 70 years, in the Washington state,

cardiomyopathy occurred in 33% of patients and vasopressors were used in 67% of patients. In the study by Zhou *et al* (12), that included 191 patients (median age: 56 years), non-survivor patients disclosed high sensibility cardiac troponin I ($p < 0.00001$). Zhou *et al* (12), using multivariate regression, found that in-hospital mortality was associated with older age (OR 1.1), higher sequential organ failure assessment (SOFA) score (OR 5.6) and d-dimer $> 1 \mu\text{g/mL}$ (OR 18.4) at admission. Also, the mortality group disclosed sepsis ($p < 0.0001$), respiratory failure ($p < 0.0001$), ARDS ($p < 0.0001$), coagulopathy ($p < 0.0001$), acute kidney injury ($p < 0.0001$), acidosis ($p < 0.0001$) and ICU admission ($p < 0.0001$). In the study by Shio *et al* (24), patients with cardiac injury mostly require mechanical ventilation and have complications that include ARDS, acute kidney injury, hypoproteinemia, coagulation disorders and electrolytes disturbances. Using multivariate Cox regression, they found that cardiac injury (HR=3.4, $p = 0.001$) and ARDS (HR 7.11, $p < 0.001$) were associated with mortality (24). Increased troponin is a major marker of mortality (10): 59.6% versus 8.9% without elevated troponin ($p < 0.001$). Whatever the rate of mortality in studies, patients with previous cardiovascular disease have a worst prognosis. In the study by Wu *et al* (36), mortality was 10.5% in patients with cardiovascular disease versus 2.3% without cardiovascular disease. In the recent Italian study including 1591 ICU patients (mean age: 63 years old), ICU mortality was at 26% and affects mainly older man (age ≥ 64 years) (22) and prevalence of hypertension was higher in patients died in ICU ($p < 0.001$) (22).

Acute respiratory distress syndrome (ARDS) is present in 67% of patients in critically ill patients and is a major cause of mortality (2, 3, 13, 18, and 35). In the study by Wu *et al* (27), which included 201 patients (mean age: 51 years), ARDS occurred in 41.8% of patients. The following parameters were found to predict the onset of ARDS: older age, neutrophilia, organ and coagulation dysfunction.

Acute kidney failure is another complication in ICU patients: from 8 to 29% (2, 3, 13, 18) and renal replacement therapy may be used in 17% of patients (13). Thus, this is a frequent complication of Covid-19 that affects the prognosis of our patients.

Conclusion

COVID-19 spares no organ including heart, as other major virus. Better identify patients at risk of cardiovascular failure may help to reduce mortality induced by physiological stress and adjust cardiological drugs. Also, those patients might be subject to a subsequent episode of cardiac dysfunction after discharge and should be particularly followed-up.

Conflicts of interest: none

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Figures and tables

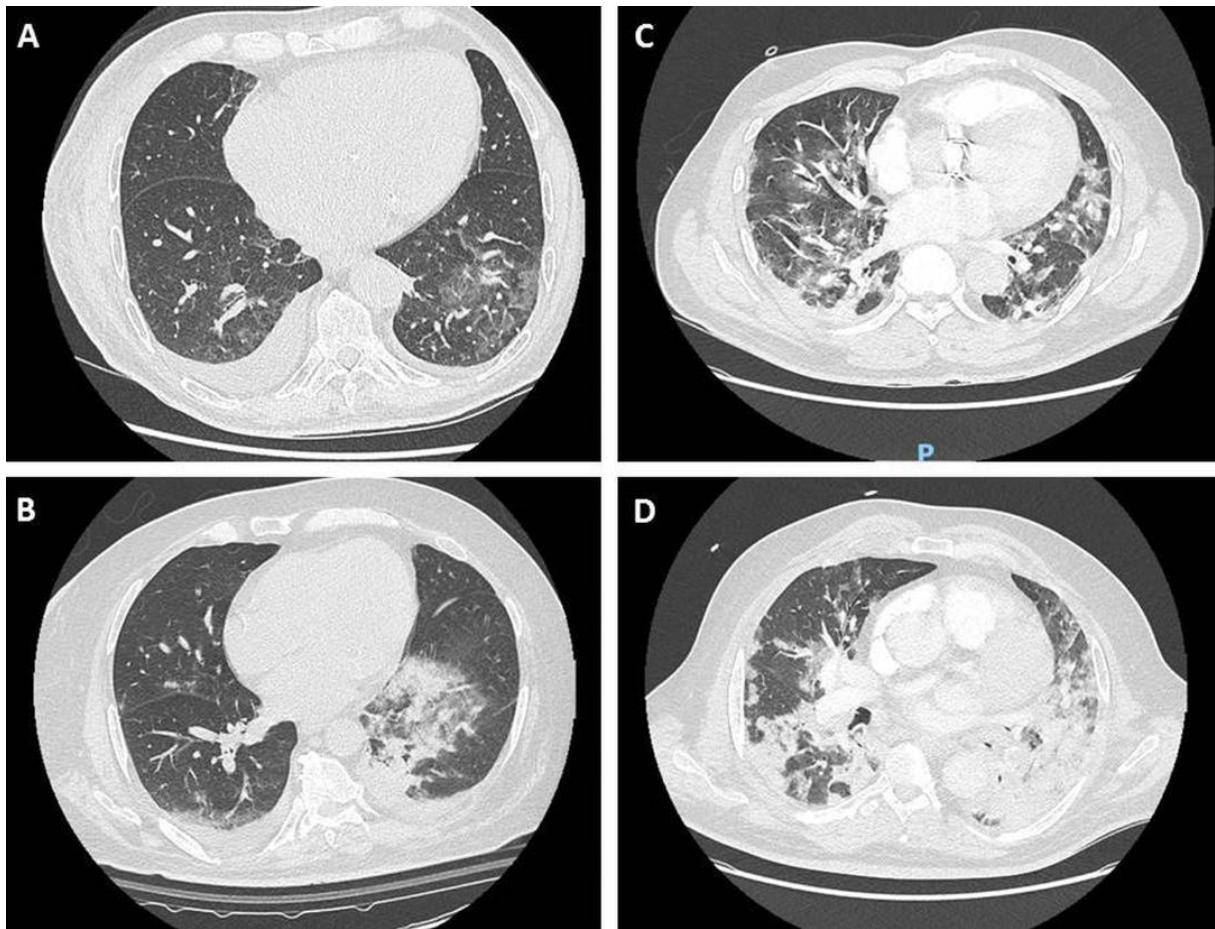


Figure 1: *thoracic computed tomography scans* (CT) in patients infected with COVID19, showing typical lung feature with ground glass opacities and bilateral patchy shadow, from minor (A) to severe pattern (D).



Figure 2: Lung ultrasound showing B line in a patient with COVID-19 infection

Table 1. Studies about heart, ARDS and mortality in patients with COVID19

N Patients	Critically ill patients /ICU admission	MV	Comorbidities or Chronic illness	ARDS	Cardiac Injury	Mortality in hospital	Mean age at inclusion	First author (ref)
191	26% (ICU)	17%	48%	31%	23% (HF)	28%	56 y	Zhou (12)
52	100% (ICU)	71%	40%	29%	29%	61% (at 28 days)	59.7 y	Yang (13)
138	26% (ICU)	23%	72%	19%	16.7% (arythmia) 7.2% (ACI)	4.3%	56 y	Wang (3)
99	23% (ICU)	17%	51%	17%	15% (myoglobin increase)	11%	55.5 y	Chen (11)
41	32% (ICU)	10%	32%	29%	12%	15%	49 y	Huang (2)
21 (ICU)	100% (ICU)	71%		100%	33%	67%	70 y	Arentz (18)
24	100%(ICU)	75%	58% (diabetes) 21% (CKD)		15%	50%	64+-18 y	Bhatraju (21)
1099	5% (ICU)	6.1 %	23.7%	3.4%	23.7% (increase CK)	1.4%	47 y	Guan (9)
416		20%	30.5% (HBP) 14.4% (diabetes) 10.6% (coronary disease)	23.3%	19.7%	55.7%	64 y	Shi (24)
187		24.1%	32.6%(HBP) 11.2%(CHD) 15% (diabetes)	24.6%	27.8%	23%	58.7 y	Guo (10)

ACI: acute cardiac injury; ARDS: acute respiratory disease syndrome; CK: creatine kinase; CKD: chronic kidney disease; CHD: coronary heart disease; HBP=high blood pressure; HF: heart failure; ICU: intensive care unit MV: mechanical ventilation; ref: number of reference; y: years

Table 2: Risk factors associated with mortality in patients with COVID-19 infection.

Factors associated with mortality	OR or HR	N (patients)	First author (ref)
Older age	1.1 (OR)	N= 191	<i>Zou (12)</i>
Higher SOFA	5.6 (OR)		
D-Dimers>1microg/ml	18.4 (OR)		
Cardiac injury	3.4 (HR)	N=416	<i>Shio (24)</i>
ARDS	7.11 (HR)		
Age ≥64 years		N=1591	<i>Grasselli (22)</i>
Age 70 years		N=21	<i>Arentz (18)</i>

HR: hazard ratio; N: number of patients; OR: odd ratio; SOFA: sequential organ failure assessment