COVID-19 in patients with heart failure: the new and the old epidemic

Nicolò Sisti,1 Serafina Valente,1 Giulia Elena Mandoli,1 Ciro Santoro,2 Carlotta Sciacca,1 Federico Franchi,3 Paolo Cameli,4 Sergio Mondillo,1 Matteo Cameli1

1Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy
2Department of Advanced Biomedical Sciences, Federico II University Hospital, Napoli, Italy
3Department of Medicine, Surgery and Neuroscience, Respiratory Diseases and Lung Transplantation, University Hospital, Napoli, Italy
4Department of Medicine, Surgery and Neurosciences, Cardiology, University of Siena, Siena, Italy

Correspondence to
Nicolò Sisti, Department of Medical Biotechnologies, Division of Cardiology, Siena University Hospital, Siena, Italy; nic.sisti@gmail.com

ABSTRACT
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread in nearly 200 countries in less than 4 months since its first identification; accordingly, the coronavirus disease 2019 (COVID 2019) has affirmed itself as a clinical challenge. The prevalence of pre-existing cardiovascular diseases in patients with COVID19 is high and this dreadful combination dictates poor prognosis along with the higher risk of intensive care mortality. In the setting of chronic heart failure, SARS-CoV-2 can be responsible for myocardial injury and acute decompensation through various mechanisms. Given the clinical and epidemiological complexity of COVID-19, patients with heart failure may require particular care since the viral infection has been identified, considering an adequate re-evaluation of medical therapy and a careful monitoring during ventilation.

BACKGROUND
Since the beginning of December 2019, when first cases of pneumonia sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were detected, the infection has reached the levels of a pandemic within 4 months, attesting 465.915 confirmed cases in the world and 21.031 deaths in 199 countries (WHO, 27 March 2020). The clinical features related to this ‘new’ coronavirus are similar to the ones caused by other coronaviruses known for past epidemics, such as SARS-CoV and Middle East respiratory syndrome (MERS)-CoV although epidemiological data point at a lower mortality. The clinical characteristics of coronavirus disease 2019 (COVID-19) have rapidly increased interest and concerns. As described by the first analyses on the Chinese population, a severe clinical evolution of pneumonia, with a sustained risk of intensive care admission, intubation and death represents a recurrent in patients of advanced age or affected by chronic diseases.1 Chronic heart failure (CHF) involves more than 10% of population over 70 years in the developed countries, making it a known epidemic that is inevitably shattering with the one currently caused by SARS-CoV-2.2 The purpose of this review is to describe the actual evidences on COVID-19 in the population affected by CHF. Epidemiological characteristics, prognostic aspects and therapeutic implications are discussed according to the limited existing evidence from the first case reports in COVID-19 populations.

HEART FAILURE IN THE REPORTED POPULATIONS
Shi et al reported that 4.1% (seventeen patients) of the COVID-19 population included presented CHF as pre-existing condition.3 In a different Chinese cohort, the occurrence of heart failure (HF) affected the 23% of the patients with COVID-19, but no information was provided about the pre-existing condition, chamber involved or type of dysfunction.4 To obtain deeper insight about the connection between CHF and COVID-19, the prevalence of two of the main determinants of HF, such as arterial hypertension (AH) and coronary artery disease (CAD), need to be explored in the infected population. In the study by Guan et al, among 1099 patients, nearly 18% had one or both conditions,1 while this percentage rises to 30–38% in the reports by Huang et al and Zhou et al, even though smaller cohorts were included in these studies.5,6 In an additional metanalysis based on eight studies with a total of 46 248 patients,6 the combined prevalence of AH and CAD was about 20% (17±7%, 95% CI 14% to 22% and 5±4%, 95% CI 4% to 7% for AH and CAD, respectively). The main registries focused on the Chinese population with CHF indicate a prevalence of AH ranging from 50% to 70% and of CAD from 50% to 60%,7 allowing us to have an estimation of the burden of the disease. If diabetes is also included, such results could be even underestimated. All the featured studies agree that chronic heart diseases, including CHF, are among the variables that might promote a severe phenotype of COVID-19 characterised by worse prognosis and increased mortality.

INFECTION BY SARS-COV-2 AND THE FAILING HEART
HF is a recognised vulnerability during respiratory viral infections, due to physiopathological mechanisms which are also involved in SARS-CoV-2 infection. Such mechanisms predispose to a decomposition of HF and to increasing arrhythmic and ischaemic risk.8 The inflammatory status and the production of cytokines secondary to the infection increase blood viscosity and coagulability, cause endothelial dysfunction, and promote electrolyte and haemodynamic imbalance.9 The advanced phases of the infection seem to be characterised by a cytokine storm whose profile seems to be similar to the...
one encountered in haemophagocytic lymphohistiocytosis secondary to viral infections, with a typical increase of interleukin (IL) 3, IL-6, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α (TNF-α) and ferritin. As demonstrated for other viruses, this feature of SARS-CoV-2 could predispose to stress cardiomyopathy and cytokine-related myocardial dysfunction with consequent acute decompensation of CHF deteriorating subclinical pre-existing damage in well-compensated patients. Together with the inflammatory status, the respiratory failure caused by the viral infection can further aggravate the imbalance between the scarce supply of oxygen and the higher energy demand of the myocardium eliciting myocardial dysfunction. An additional aspect to be considered consisted in the myocardial damage induced by pulmonary hypertension, particularly involving the right chambers. Moreover, the use of elevated positive end-expiratory pressure during mechanical ventilation induces an increase in right ventricular afterload and wall stress, leading to a higher risk of further reducing cardiac output in the presence of a failing heart. Consistently with previous SARS- and MERS-epidemics, in patients with COVID-19, hypotension, tachycardia, bradycardia, cardiomegaly and arrhythmia are recurrent conditions recognized as predisposing to acute HF. Patients requiring intensive care show higher values of blood pressure than patients requiring standard care (145 mmHg vs 122 mmHg; p<0.001); on the other hand, an hypertensive profile seems to be reassuring regarding a minor risk of requiring inotropic support and developing cardiogenic shock. During the past coronavirus epidemics, some authors underlined a subclinical diastolic dysfunction of the left ventricle that seemed to be reversible on clinical recovery, while systolic dysfunction was associated with a higher need for mechanical ventilation. Mehra et al suggest that, in patients with pre-existing subclinical heart damage, during the early phases, when pulmonary complication and haemodynamic instability prevails, COVID-19 is associated with diastolic dysfunction, while systolic dysfunction subsequently upraises as a consequence of cytokine effect.

MARKERS OF MYOCARDIAL INJURY IN COVID-19

The myocardial injury, as expressed by the reported rise in troponin (Tn) during COVID-19, can be elicited by several mechanisms, besides the ones previously described (eg, systemic inflammation and hypoxia), that particularly concern patients with pre-existing cardiovascular disease. Among the most discussed features of SARS-CoV-2, its functional receptor, the aminopeptidase ACE2 (human ACE2), plays a central role, being overly expressed in patients with cardiovascular disease. Indeed, the viral infection of the cells, through the binding of ACE2, may set off direct myocardial damage, as it was demonstrated during the SARS outbreak. ACE2 expression in the heart is an essential regulator of function, and ACE2 knockout models are inclined to develop severe left ventricular dysfunction. SARS-CoV infection appears to downregulate ACE2, being a trigger to myocardial dysfunction. Even if a precise mechanism of cardiac injury is not identified, a direct role of the virus is suggested by autopsies in patients with myocarditis, which found viral genome by PCR in 35% of cases together with hypertrophy and low levels of ACE2 expression. Moreover, downregulation of ACE2 in cardiac muscle enhances TNF-α production and transforming growth factor-β signalling increasing local inflammatory response and fibrosis, respectively. The anti-inflammatory and antioxidant effects of ACE2 seem to oppose the deleterious effect of angiotensin II, especially when the renin-angiotensin–aldosterone system (RAAS) is upregulated, as it happens in AH, atherosclerosis and HF. As a consequence, alteration of ACE2 signalling pathways, determined by SARS-CoV-2 binding, may contribute to the poorer outcome of patients suffering from cardiovascular disease associated with the higher risk of developing severe conditions. In patients affected by both systolic and diastolic CHF, as well as acute decompensation, the increase in high-sensitivity Tn (hs-Tn) has a confirmed negative prognostic value. As confirmed in the report by Zhou et al, nearly 50% of ‘non-survivor’ patients present levels of hs-Tn >28 ng/mL with a maximal increase after 16 days from the onset of symptoms. Data regarding CHF emerged in a study on 416 patients with COVID-19 from the Renmin Hospital of Wuhan and divided at admission according to the presence of myocardial injury, indicated by hs-Tn blood levels above 99th percentile. In patients with myocardial injury, higher prevalence of CHF (15% vs 1.5%, p<0.01) and higher levels of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) (median 1689 (698–3327) pg/mL vs 139 (51–335) pg/mL, p<0.001) were reported compared with those without myocardial injury. The levels of NT-proBNP >900 pg/mL on admission were associated with an increased, although not significant, mortality (HR 1.52; 95% CI 0.74 to 3.10; p=0.25). Myocardial injury showed to be a significant predictor of mortality in patients with COVID-19 on admission. Among the first challenges following the spread of SARS-CoV-2 in patients with CHF, there was the need to distinguish the viral lung damage from acute pulmonary oedema during instrumental examination, enabling better prognostic stratification and therapeutic framing. Since chest X-ray is affected by low sensitivity in this context, integrated evaluation of both CT findings and lung ultrasound appear to be crucial. Zhu et al highlighted that both clinical conditions can present ground glass area and thickened interlobular septa. In case of pulmonary oedema, these alterations are less numerous and more represented near the hila and dorsally, and are frequently associated with pleural effusion, cardiomegaly, pulmonary vein enlargement and rapid resolution after diuretic therapy. The lung ultrasound in patients with cardiogenic pulmonary oedema frequently shows a well-defined B-line pattern with a ‘white lung’ evolution in severe forms. The typical lung ultrasound findings in COVID-19 highlight in early phases irregular pleural lines, B-lines with an irregular distribution associated with limited areas of ‘white lung’. Such a pattern is
TABLE 1 Summary of the main evidences on clinical variables in patients with HF who were affected by COVID-19

<table>
<thead>
<tr>
<th>Variable</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left diastolic dysfunction</td>
<td>Often subclinical and reversible in early phases(^a)(^b)(^c)(^d)</td>
</tr>
<tr>
<td>Left systolic dysfunction</td>
<td>Typical of forms with important cytokines release(^e)</td>
</tr>
<tr>
<td>Right heart dysfunction</td>
<td>Associated with secondary pulmonary hypertension(^f)</td>
</tr>
<tr>
<td>Troponin</td>
<td>Abnormal levels associated with pre-existing chronic heart failure(^g) Levels &gt;28 ng/mL associated with “nonsurvivor” phenotypes(^h)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Levels &gt;900 pg/mL associated with increased mortality(^i) Increased in presence of myocardial injury(^j)</td>
</tr>
<tr>
<td>ACEIs/ARBs</td>
<td>Associated with lower levels of troponin and NT-proBNP(^k) No difference in clinical course from patients not treated(^l) Associated with less severe disease, lower cytokines release, lower viral load(^m)</td>
</tr>
</tbody>
</table>

\(^b\) Review
\(^c\) Review
\(^d\) Downloaded from http://pmj.bmj.com/ Postgrad Med J: first published as 10.1136/postgradmedj-2020-138080 on 30 July 2020.
CONCLUSIONS
The prevalence of CHF in the population susceptible to COVID-19 is significant and so is the prevalence of predisposing conditions which put infected patients at risk of developing HF. For this reason, promoting a thorough knowledge of the clinical implications and the prognostic impact of COVID-19 in this vulnerable category is a priority. In particular, the management of these patients needs to be set on the early detection of peculiar clinical presentations and the prognostic impact of COVID-19 in this vulnerable group of patients. CHF prevalence in the population susceptible to COVID-19 is significant and so is the prevalence of predisposing conditions.

Multiple-choice questions
1. The advanced phases of the infection by SARS-CoV-2
   A. seem to be characterised by a cytokine storm
   B. is similar to haemophaegocytic lymphoidcytosis
   C. is characterised by the increase of interleukin-6
2. In patients with myocardial injury,
   A. higher prevalence of CHF is reported
   B. NT-proBNP is reduced
   C. levels of NT-proBNP >200 pg/mL on admission were associated with a poor prognosis
3. dose adjustment or drug discontinuation should be performed for
   A. baseline Qtc >500 ms
   B. Qtc increase >60 ms
   C. baseline Qtc <300 ms
4. Chronic heart failure (CHF) involves
   A. more than 10% of population aged over 30 years
   B. more than 10% of population aged over 70 years
   C. more than 50% of population aged over 40 years
5. In patients with pre-existing subclinical heart damage,
   A. COVID-19 is associated with diastolic dysfunction
   B. systolic dysfunction upraises as a consequence of cytokine effect
   C. diastolic function is usually preserved

Main messages
- COVID-19 represents a clinical challenge in patients with heart failure.
- Heart damage is an important prognostic predictor of poor outcome.
- Therapeutic management of patients with heart failure must be carefully re-evaluated accordingly to the clinical condition due to the infection.

Current research questions
1. Does SARS-CoV-2 exerts a direct or indirect action on myocardial tissue?
2. Are there better and worse choices for heart failure drugs among patients with COVID-19?
3. Are there long-term implications of SARS-CoV-2 infection for patients with heart failure?

Key references

Acknowledgements
We thank Luca Regnini for contributing to the improvement of this article.

Contributors
NS gathered all the articles about the topic and wrote the main draft. CSantoro gave useful suggestions according to latest evidences of literature. CSciaccaluga contributed to the final revision of the paper. SV read the final work and gave hints to update all the paragraphs. FF gave interesting advices about the management of COVID-19 in the ICU. PC gave useful information about the respiratory implications of COVID-19. SM suggested the paragraphs of the first version of the manuscript. MC had the idea of writing this manuscript and gave the final opinion before submitting it.

Funding
The authors received no funding for this article.

Competing interests
None declared.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the COVID-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD
Nicolò Sisti http://orcid.org/0000-0003-1795-855X

REFERENCES


https://doi.org/10.1136/postgradmedj-2020-138080 on 30 July 2020. Downloaded from http://pmj.bmj.com/ on October 11, 2022 by guest. Protected by copyright.


