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## Heart failure outcomes and Covid-19



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### ABSTRACT

Pre-existing heart failure (HF) in diagnosed patients with coronavirus disease 2019 (COVID-19) is associated with a close to two-fold increased mortality rate compared to COVID-19 patients without prior HF history. Moreover, based both on biomarker as well as imaging findings, widespread endothelial and cardiac injury seems to be present in many patients presenting with COVID-19, associated with adverse outcomes including new onset HF. Systematic echocardiographic studies in patients with COVID-19 indicate that the most common cardiac pathology is right ventricular (RV) dilatation (39%) over and above both left ventricular (LV) diastolic dysfunction (16%) and LV systolic dysfunction (10%). In addition, myocardial injury, assessed by magnetic resonance imaging (MRI), is observed in some 55% to 70% of patients recently recovered from COVID-19 even in those who didn't get very sick during the acute illness. These observations seem to indicate a potentially rather high risk of clinical HF emerging in patients post-COVID-19, warranting close long-term monitoring of patients during recovery. On the other hand, given the established adverse prognostic role that pre-existing HF plays as a comorbidity in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, it not only seems important in the still ongoing COVID-19 pandemic that all patients with known HF should proactively be well controlled and treated according to current guidelines, but also additionally be considered for priority vaccination against the SARS-CoV-2 infection if not yet vaccinated.

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### 1. Introduction

The unprecedented worldwide spread of severe and potentially life-threatening infections caused by the newly arisen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still ongoing and has truly reached pandemic dimensions [1–8], posing new challenges to patients suffering from non-communicable diseases such as obesity, diabetes mellitus, hypertension, cardiovascular diseases and heart failure. In fact, these diseases, often associated with an unhealthy metabolism, when being present as pre-existing co-morbidities in people developing coronavirus disease

2019 (COVID-19) may largely determine an adverse outcome including a high mortality rate [2–11]. The loss of lives related to COVID-19 seems to be enormous and an excess death toll of about 20% over and above the normally observed mortality rates in populations has been shown, e.g. in the United States [12]. Indeed COVID-19 has emerged as a leading cause of death during the pandemic in this country [13]. People not only died from the primary affection of the lungs, an extensive interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS), but also due to acute cardiovascular events, ventricular fibrillation, heart failure, acute coagulopathies, thrombo-embolic disease, acute kidney and/or liver

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injury, and multi-organ failure [14–17]. Besides infecting multiple organs such as the lungs and the heart, SARS-CoV-2 was found causing widespread endotheliitis by entering and infecting endothelial cells inducing massive injury to the vasculature [18] and further augmenting pre-existing organ damage.

The present overview seeks to highlight the prognostic impact of concomitant heart failure (HF) on adverse COVID-19 outcomes as well as – *vice versa* – the potential for long-term cardiac damage and risk of developing HF in survivors of COVID-19.

## 2. Epidemiologic associations

A number of retrospective observational studies as well as a meta-analysis and systematic review including some 20,000 patients have looked into the prognostic impact of prior HF in patients hospitalized with COVID-19 [9,10,19]. At Mount Sinai Health System hospitals New York, a total of 6,439 patients were admitted for COVID-19 during the study period of whom 422 (6.6%) had a history of HF. Of those, 250 (59.3%) had HFpEF (heart failure with preserved ejection fraction), 128 (30.3%) HFrEF (HF with reduced EF), and 44 (10.4%) HFmrEF (HF with mid-range EF), respectively [9]. Mean age was 63.5 years, and 45% were women. Compared with patients without HF, those with a history of HF were older, had a higher prevalence of comorbidities, and were receiving a greater number of medications for cardiovascular disease. Patients with a history of HF presented with higher systolic blood pressure (126 mm Hg vs. 119 mm Hg;  $p < 0.001$ ) and lower oxygen saturation (91% vs. 94%;  $p < 0.001$ ) while the respiratory rate and body temperature were similar to those in patients without HF. Compared with patients without HF, those with previous HF experienced longer length of hospital stay (8 days vs. 6 days;  $p < 0.001$ ), increased risk of mechanical ventilation (22.8% vs. 11.9%; adjusted odds ratio: 3.64; 95% confidence interval CI: 2.56 to 5.16;  $p < 0.001$ ), and mortality (40.0% vs. 24.9%; adjusted odds ratio: 1.88; 95% CI: 1.27 to 2.78;  $p < 0.002$ ). Outcomes among patients with HF were similar, regardless of LVEF or renin-angiotensin-aldosterone (ACE or ARB) inhibitor use.

Another report from Spain analyzed 3,080 consecutive patients with confirmed COVID-19 infection and at least 30-day follow-up, of whom 152 (4.9%) had a previous HF history [10]. The latter developed acute HF during hospitalisation significantly more often (11.2% vs 2.1%;  $p < 0.001$ ), had higher levels of NT-proBNP and showed higher mortality rates (48.7% vs 19.0%;  $p < 0.001$ ). Remarkably, also 60 patients without previous history of HF experienced acute HF during hospitalization for COVID-19 with a high mortality risk compared with those without acute HF (46.8% vs 19.7%;  $p < 0.001$ ). Finally, withdrawal of beta-blockers, mineralocorticoid antagonists and ACE/ARB inhibitors was associated with a significant increase of in-hospital mortality.

These findings were largely consistent with results of a meta-analysis and systematic review based on 21,640 patients from 18 studies derived from a global literature search in PubMed, EuropePMC, SCOPUS, Cochrane Central Database, and medRxiv with the search terms, “Heart failure”

and “COVID-19” [19]. HF was found to be significantly associated with need of hospitalization for COVID-19 (Table 1). Moreover, HF was associated with adverse outcome of COVID-19 (defined by mortality or incidence of severe COVID-19 infection, admission to intensive care unit (ICU), and use of ventilator, Table 1). Finally, patients with pre-existing HF were associated with higher mortality. Particularly noteworthy was the highly increased incidence of new-onset HF in hospitalized patients with COVID-19 (see also Table 1).

## 3. Evidence for widespread endothelial and myocardial injury

Along with the first publications on patients suffering from COVID-19, it soon became apparent that a wide array of biomarkers not only was abnormally elevated but also that this increase was associated with a more adverse clinical outcome with requirement of intensive care and mechanical ventilation etc., often heralding a fatal course [2,6–11,20–23]. These biomarkers signalled inflammatory activation, cytokine storm and distress, endothelial damage, thrombosis and hypercoagulation, but also bleeding, and not the least, myocardial injury. Biomarkers involved encompassed CRP, interleukin 1 $\beta$ , interleukin 6, TNF-alpha, ferritin, procalcitonin, D-dimer, PAI-1, and prothrombin time, as well as troponin I, CK-MB, and natriuretic peptides [2,6–11,20–25].

Although biomarker abnormalities must not be confused with definitive diagnosis, they fit well with clinical observations made in patients with COVID-19. Those findings clearly indicated that patients developed signs and symptoms of myocardial infarction, myocarditis, stroke, deep venous thrombosis and subsequent pulmonary embolism, but also gastrointestinal or intracranial bleeding, all contributing to multi-organ disease and failure, and ultimately to fatal outcomes [14–17]. Single case reports described the occurrence of acute myopericarditis with systolic dysfunction in otherwise healthy middle-aged people on admission for COVID-19, based on an increase in levels of NT-proBNP and high-sensitivity troponin T and confirmed by echocardiography changes and diffuse biventricular myocardial oedema and late gadolinium enhancement on cardiac magnetic resonance imaging [26,27].

In a systematic echocardiographic study in patients with COVID-19 [28], the most common cardiac pathology was RV dilatation (39%) which was more common than both left ventricular (LV) diastolic dysfunction (16%) and LV systolic dysfunction (10%). In fact, it was concluded that LV systolic function may be preserved in these patients, although LV diastolic function and RV function are impaired [27–29].

Post mortem studies showed COVID-19 causing profound multisystem pathology [16,30–32]. Both pulmonary and cardiovascular involvement were predominant pathological features. In the lung, the major histological feature exhibited diffuse alveolar damage with extensive hyaline membrane formation and oedema, alongside microthrombi in small pulmonary vessels. In the heart, massive inflammatory infiltrates with myocarditis, pericarditis, vasculitis, focal necrosis, and vascular fibrosis were seen. In fact, direct viral

**Table 1 – Outcomes of patients diagnosed with COVID-19 and with pre-existing heart failure versus those without pre-existing heart failure (19, meta-analysis of available studies\*).**

- 1) Risk of hospitalization in patients with pre-existing heart failure (3 studies) HR 2.37 [1.48, 3.79;  $p < 0.001$ ], high heterogeneity [ $I^2 = 82\%$ ;  $p < 0.001$ ]
- 2) Heart failure and poor outcome (defined by mortality or incidence of severe COVID-19 infection, admission to ICU, and use of ventilator, 15 studies)OR 2.86 [2.07; 3.95;  $p < 0.001$ ] high heterogeneity [ $I^2 = 80\%$ ;  $p < 0.001$ ]
- 3) Pooled HR of mortality in patients with COVID-19 with pre-existing HF (7studies) Pooled HR 1.70 [1.44, 2.02;  $p < 0.001$ ] with moderate heterogeneity [ $I^2 = 59\%$ ;  $p = 0.02$ ]
- 4) Comparison of mortality in patients with COVID-19 accompanied with pre-existing heart failure and without heart failure (14 studies) OR 3.46 [2.52, 4.75;  $p < 0.001$ ] moderately high heterogeneity [ $I^2 = 77\%$ ;  $p < 0.001$ ]
- 5) Incidence of new-onset heart failure in patients with COVID-19 (3 studies)OR 11.67 [6.96, 19.56;  $p < 0.001$ ] with moderate heterogeneity [ $I^2 = 44\%$ ;  $p = 0.17$ ].

\*Footnote: HR = hazard ratio or OR = odds ratio with 95% confidence intervals.

infection of endothelial cells and diffuse endothelial inflammation has been demonstrated in the heart, the lungs, the small bowels, and the kidneys [18]. Moreover, patients with COVID-19 requiring admission to intensive care units (ICU) had significantly higher circulating numbers of endothelial cells, i.e. stressed cells detached from injured vessels, than non-ICU patients and the extent of endothelial injury was correlated with putative markers of disease severity and inflammatory cytokines [33]. Together, these data provide in vivo evidence that endothelial injury is a key feature of COVID-19.

This is also in line with impressive post mortem extra-cardio-pulmonary manifestations in deceased COVID-19 patients showing hepatic, kidney, splenic, and bone marrow involvement, as well as microvascular injury and thrombosis [16,30–32]. Notably, the findings appear to be similar in patients with or without pre-existing medical comorbidities. Hence, SARS-CoV-2 infection can cause multisystem disease and significant pathology in most organs, including in the heart, regardless of comorbidities. The underlying widespread endotheliitis and T-cell related inflammation of cardiac tissue seem to be particularly important pathogenetic mechanisms, probably shedding some light on the high risk of incident heart failure occurring in patients hospitalized for COVID-19 [9,26,27,29] and may allude to a potential long-term risk of developing heart failure in patients seemingly having recovered from a SARS-CoV-2 infection.

#### 4. Presence of myocardial injury post COVID-19 illness

Indeed, presence of myocardial injury assessed by MRI has been observed in a series of unselected patients recently recovered from COVID-19 illness [34]. Of the 100 study patients with recent recovery from COVID-19, 67 (67%) recovered at home, while 33 (33%) required hospitalization. At the time of cardiac MRI, high-sensitivity troponin T (hsTnT) was detectable (3 pg/mL or greater) in 71 patients and significantly elevated (13.9 pg/mL or greater) in 5 patients (5%). Compared with healthy controls and risk factor-matched controls, patients recently recovered from COVID-19 had lower left ventricular ejection fraction, higher left ventricle volumes, higher left ventricle mass, and raised native T1 and T2 on MRI. A total of 78 had abnormal cardiac MRI findings, including raised myocardial native T1 ( $n = 73$ ), raised myocardial native T2 ( $n = 60$ ), myocardial late gadolinium enhancement ( $n = 32$ ), and pericardial enhancement ( $n = 22$ ). High-sensitive TnT was significantly correlated with native T1 mapping ( $r = 0.35$ ;  $P < 0.001$ ) and native T2 mapping ( $r = 0.22$ ;  $P = 0.03$ ). Endomyocardial biopsy in patients with severe findings revealed active lymphocytic inflammation. These findings are consistent with a recent report on patterns of myocardial injury assessed by cardiovascular MRI after a median follow-up time of 68 days in 148 patients recovered from severe troponin-positive COVID-19 of whom 32% required ventilatory support [35]. Late gadolinium enhancement and/or ischaemia was present in 54% (80/148), with 26% (39/148) showing myocarditis-like scars, 22% (32/148) infarction and/or ischaemia, and 6% (9/148) dual pathology.

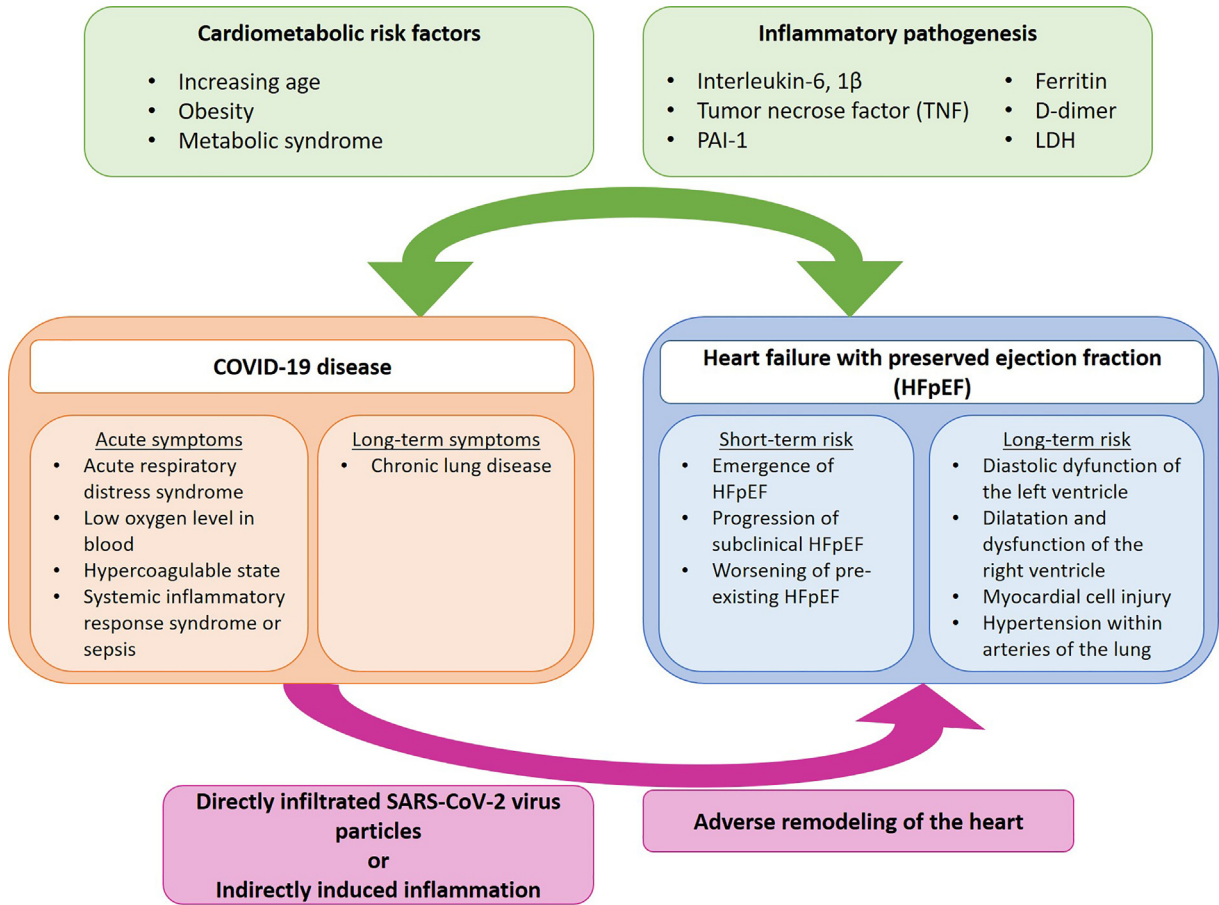


Fig. 1 – Conceptual interactions between acute and chronic phases of COVID-19 and risk of heart failure with preserved ejection fraction. (Modified from Freaney et al. JAMA 2020;324(15):1499–1500.)

### Hospitalized patients with Covid-19: algorithm based on CV risk factors (RF) and prior cardio-pulmonary & vascular disease predicting adverse outcomes and related cardio-metabolic assessment & care

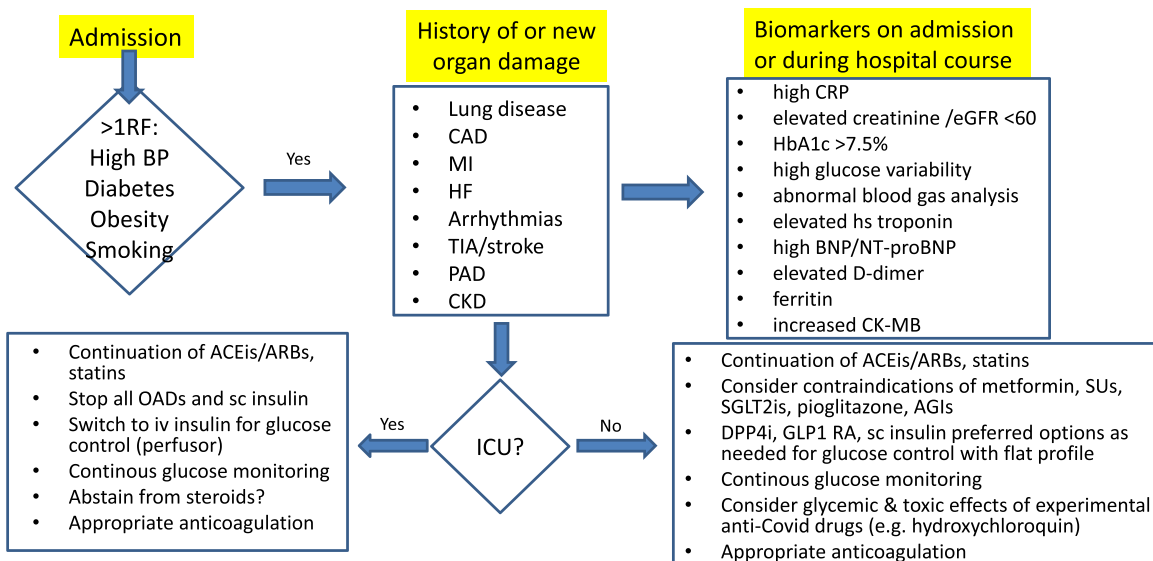


Fig. 2 – Modified from Ceriello et al., Diabetes Care 2020; 43:1427-1432.

Of patients with ischaemic injury pattern, 66% (27/41) had no past history of coronary disease. Whether these observed findings represent pre-existing clinically silent disease or de novo COVID-19-related changes remain undetermined, with follow-up evaluation of the further evolving course pending [36].

An instructive post-COVID single case study reported rapid worsening dyspnoea, yet without pulmonary lesions or pleural effusion on x-ray [37] in a previously healthy 59-year-old man with serologic evidence of a recent SARS-CoV-2 infection by a positive serum SARS-CoV-2 IgG test, but without acute COVID-19 based on negative naso-pharyngeal swab tests. Transthoracic echocardiography with strain analysis documented moderate left ventricle (LV) dilatation with mild hypertrophy at septal level, diffuse hypokinesia, more evident at septal and inferior walls, and mildly reduced LV ejection fraction (LVEF 42%). CV magnetic resonance (CMR) showed moderate LV dilatation and thickened mid inferior septum, with overall moderately reduced LVEF (37%). At tissue characterization, T2-weighted images showed increased signal intensity at basal and mid septum, late sequences demonstrated mid-wall enhancement at basal septal and inferolateral levels, with increased T1 and T2 values, and extracellular volume was shown to be diffusely increased, ranging between 35% and 50%. All CMR findings suggested an acute/subacute myocarditis. Histological analysis revealed mildly increased cardiomyocyte diameters with some perinuclear halos and dysmetric and dysmorphic nuclei; furthermore, interstitial oedema with lymphocytic aggregates, myocyte necrosis, and focal areas of fibrosis were apparent. Presence of SARS-CoV-2 was detected in myocardial specimens as well as in endothelial cells, with all findings adding up to a diagnosis of an acute/subacute myocarditis and myocardial injury mediated by endotheliitis due to infection with SARS-CoV-2.

In aggregate, the results suggest that otherwise healthy people, who recovered from COVID-19, even if it was not very serious, can have potentially harmful inflammation lingering in their hearts for a long time. These and other observations seem to be indicative for a potentially rather high risk of clinical HF emerging in patients post-COVID-19 [38], warranting close monitoring of those patients during recovery and longer term. Fig. 1 outlines the concept of the complex interactions between COVID-19 and HF.

## 5. Clinical implications

In view of the established adverse prognostic role that pre-existing HF plays as a comorbidity in the context of SARS-CoV-2 infection, it seems an important clinical guidance that HF should proactively be well controlled and managed according to best clinical guideline-based medicine in every diagnosed patient with this condition like all the other crucial comorbidities listed in Fig. 2. Moreover, priority vaccination against SARS-CoV-2 should be considered for patients with established HF [39], given the high risk for adverse outcomes in connection with COVID-19 infections including death.

Regarding HF therapy, this also involves the appropriate use of ACE inhibitors or angiotensin receptor blockers (ARBs)

[8]. Issues had been raised over the theoretical possibility that because SARS-CoV-2 utilizes ACE2 receptor to enter into host cells, particularly pneumocytes [40], and because both ACE inhibitors and ARBs can increase ACE2 expression [41], these drugs may potentially indirectly facilitate the penetration of the virus into the cells. These fears could convincingly be dismissed by a large number of studies showing not only the safety of both ACE inhibitor and ARB use in COVID-19 but also a potential benefit of these drugs [8–10,42]. Also, the prompt positioning of several scientific societies and of the European Medicines Agency very clearly pointed out that no evidence was available to justify the stop of using these drugs, which have been demonstrated to save millions of lives [43]. So, continuation of the guideline-based use of ACE inhibitors and ARBs in all HF patients along with meticulously striving for best treatment and control of HF is an important clinical recommendation.

A second clinical implication refers to the need of monitoring for emerging HF in all patients having recovered from COVID-19, even if the acute illness has not been severe. It should be acknowledged, however, that there might be some publication bias of more unusual single cases being reported, requiring further comprehensive and representative evaluation on what the true threat of developing HF is in mild cases, especially in young people suffering from the disease without almost any symptoms. Nevertheless, regular screening for signs and symptoms of HF seems advisable post COVID for the time being which should be provided by the responsible physician and diagnosis established in cooperation with the cardiologist, as also outlined in several manuscripts of this special issue on HF.

## 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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