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ORIGINAL ARTICLE

Association of chronic heart failure with mortality in old intensive care patients suffering from Covid-19

Raphael Romano Bruno[1‡], Bernhard Wernly[2‡], Georg Wolff[1], Jesper Fjølner[3], Antonio Artigas[4], Bernardo Bollen Pinto[5], Joerg C. Schefold[6], Detlef Kindgen-Milles[7], Philipp Heinrich Baldia[1], Malte Kelm[1,8], Michael Beil[9], Sigal Sviri[9], Peter Vernon van Heerden[10], Wojciech Szczeklik[11], Arzu Topeli[12], Muhammed Elhadi[13], Michael Joannidis[14], Sandra Oeyen[15], Eumorfia Kondili[16], Brian Marsh[17], Finn H. Andersen[18,19], Rui Moreno[20], Susannah Leaver[21], Ariane Boumendil[22,23], Dylan W. De Lange[24], Bertrand Guidet[22,23], Hans Flaatten[25,26], Christian Jung[1*] and COVIP study group[†]

[1]*Department of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany;* [2]*Center for Public Health and Healthcare Research, Paracelsus Medical University Salzburg, Salzburg, Austria;* [3]*Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark;* [4]*Department of Intensive Care Medicine, CIBER Enfermedades Respiratorias, Corporacion Sanitaria Universitaria Parc Tauli, Autonomous University of Barcelona, Sabadell, Spain;* [5]*Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland;* [6]*Department of Intensive Care Medicine, Inselspital, Universitätsspital Bern, University of Bern, Bern, Switzerland;* [7]*Department of Anesthesiology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany;* [8]*Cardiovascular Research Institute, Medical Faculty of the Heinrich-Heine University, Düsseldorf, Germany;* [9]*Department of Medical Intensive Care, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel;* [10]*General Intensive Care Unit, Department of Anaesthesiology, Critical Care and Pain Medicine, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel;* [11]*Center for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Kraków, Poland;* [12]*Division of Intensive Care, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey;* [13]*Faculty of Medicine, University of Tripoli, Tripoli, Libya;* [14]*Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria;* [15]*Department of Intensive Care 1K12IC, Ghent University Hospital, Ghent, Belgium;* [16]*Intensive Care Unit, Department of Intensive Care Medicine, University Hospital of Heraklion, Heraklion, Greece;* [17]*Mater Misericordiae University Hospital, Dublin, Ireland;* [18]*Department of Anaesthesia and Intensive Care, Ålesund Hospital, Ålesund, Norway;* [19]*Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway;* [20]*Unidade de Cuidados Intensivos Neurocríticos e Trauma, Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Faculdade de Ciências Médicas de Lisboa, Nova Medical School, Lisbon, Portugal;* [21]*General Intensive Care, St George's University Hospitals NHS Foundation Trust, London, UK;* [22]*Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe: épidémiologie hospitalière qualité et organisation des soins, Paris, France;* [23]*Assistance Publique—Hôpitaux de Paris, Hôpital Saint-Antoine, service de réanimation médicale, Paris, France;* [24]*Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands;* [25]*Department of Clinical Medicine, University of Bergen, Bergen, Norway; and* [26]*Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway*

Abstract

Aims Chronic heart failure (CHF) is a major risk factor for mortality in coronavirus disease 2019 (COVID-19). This prospective international multicentre study investigates the role of pre-existing CHF on clinical outcomes of critically ill old (≥70 years) intensive care patients with COVID-19.

Methods and results Patients with pre-existing CHF were subclassified as having ischaemic or non-ischaemic cardiac disease; patients with a documented ejection fraction (EF) were subclassified according to heart failure EF: reduced (HFrEF, n = 132), mild (HFmrEF, n = 91), or preserved (HFpEF, n = 103). Associations of heart failure characteristics with the 30 day mortality were analysed in univariate and multivariate logistic regression analyses. Pre-existing CHF was reported in 566 of 3917 patients (14%). Patients with CHF were older, frailer, and had significantly higher SOFA scores on admission. CHF patients showed significantly higher crude 30 day mortality [60% vs. 48%, $P < 0.001$; odds ratio 1.87, 95% confidence interval (CI) 1.5–2.3] and 3 month mortality (69% vs. 56%, $P < 0.001$). After multivariate adjustment for confounders (SOFA, age, sex, and frailty), no independent association of CHF with mortality remained [adjusted odds ratio (aOR) 1.2, 95% CI 0.5–1.5; P = 0.137]. More patients suffered from pre-existing ischaemic than from non-ischaemic disease [233 vs. 328 patients (n = 5 unknown aetiology)]. There were no differences in baseline characteristics between ischaemic and non-ischaemic disease or between HFrEF, HFmrEF, and HFpEF. Crude 30 day mortality was significantly higher in HFrEF compared with HFpEF (64% vs. 48%, P = 0.042). EF as a continuous variable was not independently associated with 30 day mortality (aOR 0.98, 95% CI 0.9–1.0; P = 0.128).

Conclusions In critically ill older COVID-19 patients, pre-existing CHF was not independently associated with 30 day mortality. Trial registration number: NCT04321265.

Keywords COVID-19; Heart failure; Elderly

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*Correspondence to: Christian Jung, Department of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich Heine University Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany. Email: christian.jung@med.uni-duesseldorf.de
‡See the Supporting Information.
†Both authors contributed equally to this study.

Introduction

Critically ill intensive care patients with severe coronavirus disease 2019 (COVID-19) suffer from mortality rates up to 50%.[1–3] Early in the pandemic, pre-existing chronic heart failure (CHF) was reported as a major risk factor for adverse outcomes in hospitalized patients.[4] COVID-19 itself is associated with both systolic and diastolic left ventricular dysfunction, pulmonary hypertension, and right ventricular dysfunction—even in patients without known pre-existing CHF[5] and in asymptomatic patients.[6] These disease effects may further contribute to a worse prognosis in patients with pre-existing CHF. It is not known how the aetiology of CHF or baseline ejection fraction (EF) is associated with outcome in patients with severe COVID-19 admitted to the intensive care unit (ICU).

Older patients, in whom there is a high prevalence of CHF,[3,7,8] are particularly vulnerable. They have been disproportionally affected by the pandemic with an increased need for intensive care and a high mortality.[3,9,10] Co-morbidities such as frailty and limitations in daily life activity[3,7] further contribute to a worse prognosis and may enhance the effect of CHF on prognosis. Older patients are thus important to study in this setting.

The main aim of this study was to investigate the potential association of pre-existing CHF with 30 day mortality among patients ≥70 years old admitted to the ICU with COVID-19.

Methods

Design and settings

This analysis is part of the multicentre international COVIP study [COVID-19 in very old intensive care patients (VIP)], which investigates outcome in critically ill COVID-19 patients ≥70 years of age. The COVIP study is a project of the VIP initiative, which has been endorsed by the European Society of Intensive Care Medicine (ESICM) (www.vipstudy.org). The study was registered at ClinicalTrials.gov (ID: NCT04321265). COVIP followed the European Union General Data Privacy Regulation directive. National coordinators recruited the ICUs, coordinated national and local ethical permission, and supervised patient recruitment at the national level. The study complied with the Declaration of Helsinki. This procedure was adopted from previous successful VIP studies.[3,11,12] Ethical approval was obtained in each country for study participation.

Study population

All patients with an acute ICU admission due to severe COVID-19 and ≥70 years of age were eligible for inclusion in COVIP. Patients were recruited consecutively. The present data set was extracted from the COVIP study database on 15 July 2021 and included patients from 19 March 2020 to 15 July 2021. Data collection commenced at ICU admission, which was defined as Day 1; all consecutive days were numbered sequentially from this date.

Data collection

All centres used a uniform online electronic case report form (eCRF). The first arterial blood gas analysis, including pO_2 (mmHg) and the F_iO_2 (%), was recorded to calculate the pO_2/FiO_2 ratio on admission. Data were entered for the Sequential Organ Failure Assessment (SOFA) score on admission, and the eCRF calculated the total score. Furthermore, we assessed the need for and duration of non-invasive or invasive ventilation, prone positioning, tracheostomy, vasopressor use, and renal replacement therapy. The eCRF also documented any limitation of life-sustaining therapy during the ICU stay. The frailty level prior to hospital admission was assessed using the Clinical Frailty Scale (CFS).[3,11,12] In addition, the eCRF included information about sex, age, length of ICU stay, symptom onset, and duration of symptoms before ICU and hospital admission. Pre-existing co-morbidities were recorded: diabetes, ischaemic heart disease, renal insufficiency, arterial hypertension, pulmonary co-morbidity, and CHF. The eCRF and database were hosted on a secure server in Aarhus University, Denmark.

Definition of chronic heart failure

Chronic heart failure was defined as 'any kind of chronic heart failure of any aetiology, medicated, clinical, echocardiographic or radiological signs of chronic heart failure, or as documented in patient records'.

Ischaemic CHF was assumed for CHF patients with a 'documented pathological coronary angiography, known coronary artery disease according to the patient's records, previous percutaneous coronary intervention (PCI) or coronary bypass surgery'; all others were assigned to the non-ischaemic CHF group. Classification of a patient as 'heart failure' was at the discretion of the treating physician based on these definitions.

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Left ventricular EF (LVEF; %) was recorded where available. All patients with documented LVEF were classified according to the latest European Society of Cardiology guidelines[13]:

i EF ≤ 40% = heart failure with reduced EF (HFrEF);
ii EF between 41% and 49% = heart failure with mildly reduced EF (HFmrEF); and
iii EF ≥ 50% = heart failure with preserved EF (HFpEF).

Statistical analysis

The primary outcome was 30 day mortality; secondary outcomes were ICU mortality and 3 month mortality. Continuous data points were expressed as median and inter-quartile ranges. Differences between independent groups were calculated using the Mann–Whitney *U* test. Categorical data were expressed as numbers (percentages). The χ^2 test was applied to calculate differences between groups. Univariate and multivariate logistic regression analyses were performed to assess associations between pre-existing CHF (binary variable, Step 1), ischaemic cardiac disease (binary variable, Step 2), LVEF (continuous variable, Step 3), and 30 day mortality (dependent variable). Baseline models with ICU as a random effect (Model 1) were fitted, and then patient characteristics (Model 2) were added to the models. Co-variables for multivariate models (age, SOFA score, CFS, and sex) were chosen based on clinical experience and previous literature.[14,15] Marginal predictive means with respective 95% confidence intervals were calculated. Kaplan–Meier differences were tested by log-rank test. All tests were two-sided, and a *P*-value of <0.05 was considered statistically significant. Because not all parameters were available for all categories, patients had to be excluded for the subgroup analyses (listwise). For this reason, not all patient numbers add up to 100% (*Tables 1–3*). Stata 16 was used for all statistical computations (StataCorp LLC, College Station, TX, USA). GraphPad Prism 9 for Windows 64-bit [Version 9.2.0 (322), GraphPad Software LLC, San Diego, CA, USA] was used to produce figures.

Results

Study population

A total of 3917 patients were analysed (Supporting Information, *Figure* S1, with consort diagram). In 1.5% of the patients, no information about pre-existing CHF was available. Most patients did not suffer from pre-existing CHF (84%). In 561 patients, the database contained data about pre-existing CHF and pre-existing coronary artery

Table 1 Baseline characteristics for patients with and without CHF

Variables	Patients with pre-existing CHF (*n* = 566)	Patients without pre-existing CHF (*n* = 3293)	*P*-value
Male sex	72% (407)	68% (2255)	0.14
Age	77 (5)	76 (5)	<0.001
SOFA	7 (3)	5 (3)	<0.001
CFS	4 (2)	3 (2)	<0.001
Co-morbidities			
Diabetes	282 (50%)	35% (1166)	<0.001
Ischaemic heart disease	328 (58%)	574 (17%)	<0.001
Chronic kidney disease	197 (35%)	432 (13%)	<0.001
Arterial hypertension	458 (81%)	2097 (64%)	<0.001
Pulmonary co-morbidity	175 (31%)	660 (20%)	<0.001

CFS, Clinical Frailty Scale; CHF, chronic heart failure; SOFA score, Sequential Organ Failure Assessment for the first 24 h.
Numbers do not add up to 100% because of missing values.

Table 2 Baseline characteristics of patients with and without ischaemic cardiac disease

Variables	Ischaemic cardiac disease (*n* = 328)	Non-ischaemic cardiac disease (*n* = 233)	*P*-value
Male sex	77% (251)	66% (154)	0.007
Age	77 (5)	77 (5)	0.73
SOFA	7 (3)	6 (3)	0.78
CFS	5 (2)	4 (2)	0.009
Co-morbidities			
Diabetes	168 (51%)	109 (47%)	0.055
Chronic kidney disease	120 (37%)	76 (33%)	0.35
Arterial hypertension	272 (83%)	182 (78%)	0.11
Pulmonary co-morbidity	111 (34%)	63 (27%)	0.019

CFS, Clinical Frailty Scale; SOFA score, Sequential Organ Failure Assessment for the first 24 h.
Numbers do not add up to 100% because of missing values.

Table 3 Baseline characteristics of different stages of chronic heart failure

Variables	HFrEF *n* = 132	HFmrEF *n* = 91	HFpEF *n* = 103	*P*-value
Male sex	73% (96)	70% (64)	64% (66)	0.35
Age	78 (5)	78 (5)	77 (5)	0.31
SOFA	7 (4)	7 (3)	6 (3)	0.035
CFS	5 (2)	4 (2)	4 (2)	0.23
Co-morbidities				
Diabetes	67 (51%)	48 (53%)	38 (37%)	0.18
Coronary artery disease	92 (70%)	57 (63%)	61 (59%)	0.23
Chronic kidney disease	63 (48%)	31 (34%)	37 (36%)	0.070
Arterial hypertension	108 (82%)	77 (85%)	93 (90%)	0.35
Pulmonary co-morbidity	40 (31%)	30 (33%)	38 (37%)	0.59

CFS, Clinical Frailty Scale; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SOFA score, Sequential Organ Failure Assessment for the first 24 h.
Numbers do not result in 100% because of missing values.

disease. Information on prior LVEF was available in 326 CHF patients.

Comparison of patients with and without pre-existing chronic heart failure

Table 1 shows baseline characteristics of patients with and without pre-existing CHF: there was no difference in sex, but CHF patients were older and had a higher degree of frailty at ICU admission. Patients with pre-existing CHF suffered more frequently from other chronic co-morbidities such as diabetes, chronic coronary artery disease, chronic kidney disease, arterial hypertension, and pulmonary co-morbidities. SOFA scores on admission were significantly higher in patients with pre-existing CHF. In addition, ICU-treatment strategies differed: CHF patients received renal replacement therapy significantly more often, but fewer required intubation and mechanical ventilation and tracheostomy insertion. There was no difference in the use of non-invasive ventilation or vasoactive drugs between groups. Patients with CHF received more treatment limitations a priori, although there was no difference in withdrawal of life-sustaining therapy.

Comparison of patients with ischaemic and non-ischaemic cardiac disease

Table 2 presents details regarding CHF aetiology: there were more patients with ischaemic than non-ischaemic cardiac disease, and they were significantly more often male and frailty was more common. There were no significant differences with regard to age, pre-existing chronic kidney disease, arterial hypertension, and diabetes. ICU treatment did not differ between the two aetiologies, except for tracheostomy, which was performed more frequently in patients with non-ischaemic CHF (*Table 2*).

Comparison of patients with different stages of chronic heart failure according to left ventricular ejection fraction

Table 3 reports details of subgroups stratified by EF: the subgroup of HFrEF patients was larger than the group with HFmrEF or HFpEF. There were no differences between patients with HFrEF, HFmrEF, and HFpEF with regard to age, patient sex, frailty, and intensive care treatment. Patients suffering from HFrEF received significantly more limitations of life-sustaining therapy.

Clinical outcomes of COVID-19

Mortality outcomes are depicted in *Figure 1*: patients with pre-existing CHF showed significantly higher 30 day mortality, ICU mortality, and 3 month mortality (*Figures 1A* and *2*). Length of ICU stay was shorter in patients with CHF compared with patients without. After multilevel analysis with adjustment for SOFA, age, sex, and frailty (CFS), no independent risk for 30 day mortality attributable to CHF remained.

Both primary and secondary outcomes did not differ between patients with ischaemic and non-ischaemic cardiac disease (*Figures 1B* and *3*): 30 day mortality, ICU mortality, and 3 month mortality were similar. Patients with ischaemic cardiac disease had a shorter ICU length of stay. Ischaemic cardiac disease was not an independent risk factor for 30 day mortality in multivariable regression analysis adjusted for SOFA, age, sex, and frailty.

When stratifying CHF according to LVEF (*Figure 1C*), there was a significantly higher 30 day mortality in HFrEF compared with HFpEF patients, but only trends towards a detrimental outcome in ICU mortality and 3 month mortality when comparing HFrEF with HFmrEF/HFpEF patients. ICU length of stay was shortest in HFrEF patients and longest in HFpEF patients. LVEF modelled as a continuous variable was not independently associated with 30 day mortality in the multivariable-adjusted analysis.

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Figure 1 Mortality (%) of very old intensive care patients suffering from COVID-19. (A) Comparison of patients with and without pre-existing chronic heart failure (CHF). (B) Comparison of patients with ischaemic and non-ischaemic cardiac disease. (C) Comparison of patients with heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. ICU, intensive care unit.

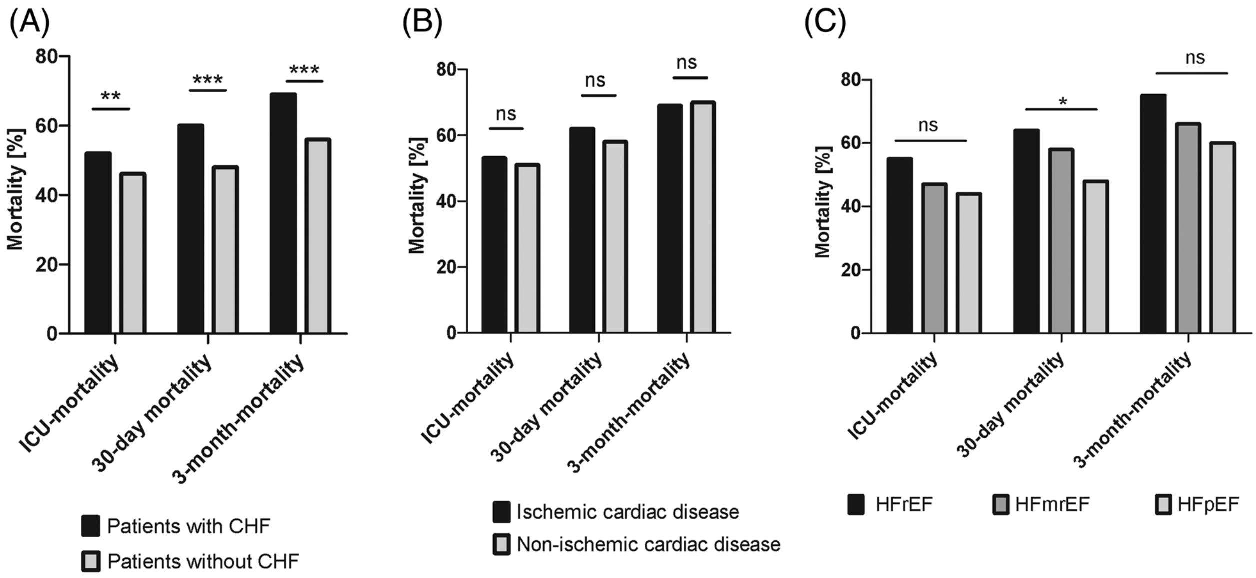
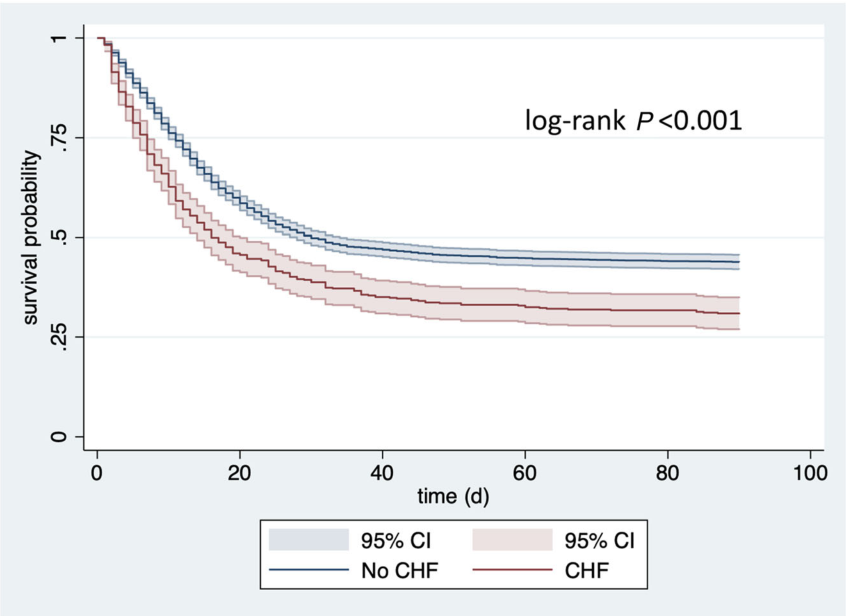


Figure 2 Kaplan–Meier for patients with chronic heart failure (CHF, red line) compared with patients without CHF (blue line) (3 month mortality, ±standard deviation). Log-rank test $P < 0.001$. CI, confidence interval.



Discussion

In this large international multicentre study of 3917 critically ill patients ≥70 years of age with COVID-19, pre-existing CHF was associated with worse outcomes; however, after multivariate adjustment, it appeared not to be an independent risk factor for 30 day mortality. To our knowledge, this is the first study investigating the role of CHF in elderly critically ill COVID-19 patients (summary of the findings in *Figure 4*).

Figure 3 Kaplan–Meier for patients with ischaemic heart failure (ICM, blue line) compared with patients with non-ischaemic heart failure (non-ICM, red line) (3 month mortality, ±standard deviation). Log-rank test P = 0.48. CI, confidence interval.

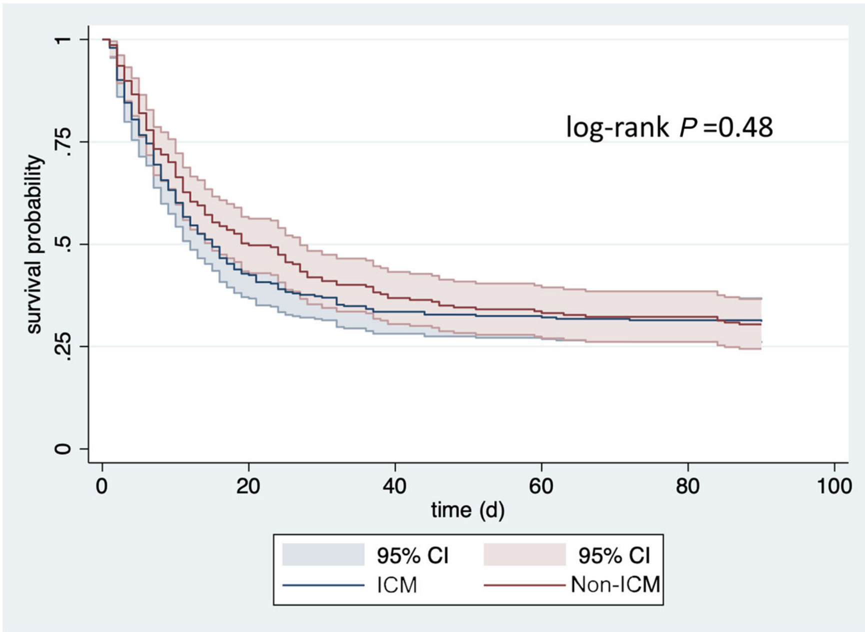
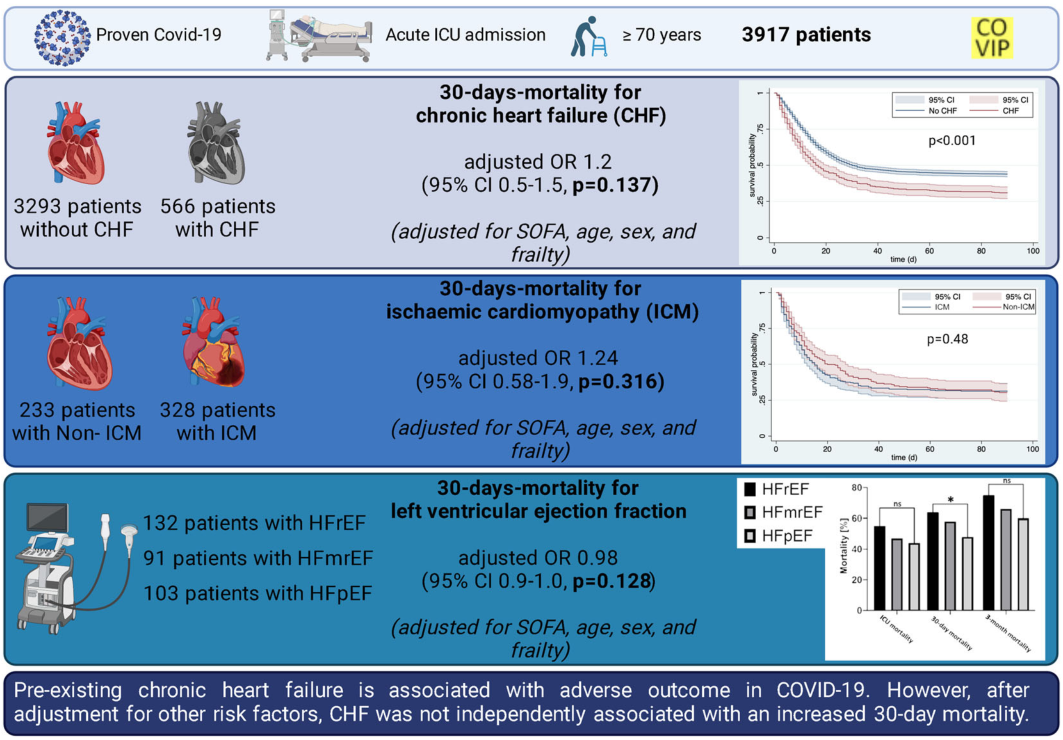


Figure 4 Graphical summary of the methods and results.



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Early in the pandemic, heart failure was found to be an important risk factor for an adverse outcome. Petrilli *et al*. examined a prospective cohort of 5279 patients suffering from COVID-19. In a multivariable logistic regression analysis, they found heart failure to be associated with a 4.4-fold risk for hospitalization and 1.9-fold risk for critical illness.[4] In COVIP, due to the inclusion criteria, all patients were critically ill from COVID-19. For this reason, we do not know to what extent CHF is a particular risk factor for severity of disease in this selected group of critically ill old patients.

Bhatt *et al*. used the Premier Healthcare Database to analyse patients with at least one heart failure hospitalization or two heart failure outpatient visits from January 2019. Out of 1 212 153 patients with known CHF, 132 312 patients were admitted from April to the end of September 2020 for various reasons. The subgroup of patients with heart failure hospitalized due to COVID-19 had the highest mortality: 24% compared with 2.6% of the patients admitted with acute heart failure without COVID-19.[16] Tomasoni *et al*. enrolled 692 patients with COVID-19.[17] In this study, patients with heart failure suffered a significantly higher risk of in-hospital complications such as acute decompensated heart failure, acute kidney injury, sepsis, and multi-organ failure even after adjustment for other important risk factors.[17] Recently, Sokolski *et al*. published their International retrospective Postgraduate Course in Heart Failure registry containing data from 1974 patients hospitalized with COVID-19 and cardiovascular disease and/or other risk factors (arterial hypertension, diabetes, or dyslipidaemia) in 28 centres from 15 different countries. In their analysis, pre-existing heart failure remained associated with in-hospital mortality even after adjustment for multiple confounders.[18] Chatrath *et al*. performed a retrospective analysis of 134 patients with CHF hospitalized from 1 March to 6 May 2020; one-third were admitted with COVID-19. These patients suffered from a significantly increased risk of in-hospital mortality (50% vs. 11%) and more complications such as acute kidney and myocardial injury.[19]

Vascular disease is a known risk factor for adverse outcome in COVID-19.[20] Mok *et al*. investigated the impact of having an additional vascular disease (venous thromboembolism or peripheral arterial disease) on the prognosis of 211 patients with CHF admitted with COVID-19. They found an increased length of stay and mortality in patients with an additional vascular disease.[20]By contrast, in the present *post hoc* analysis, we found no differences between CHF aetiologies. Ischaemic heart disease was not associated with a worse outcome compared with patients with non-ischaemic disease.

Focusing on LVEF, our study found no independent association with 30 day mortality. This finding is partly in line with a retrospective analysis of 6439 patients by Alvarez-Garcia *et al*., who found CHF to be an independent risk factor for adverse outcome in COVID-19 regardless of LVEF.[21] Overall, Alvarez-Garcia *et al*. demonstrated that pre-existing heart failure was associated with an increased length of stay and mortality. Further, renin–angiotensin–aldosterone system inhibition did not affect clinical outcome, which is in line with a recent subgroup analysis of the COVIP study by Jung *et al*.[22] By contrast, Rey *et al*. found an increased mortality in CHF patients who stopped their guideline-directed medical therapy because of COVID-19. In a cohort of 152 patients, pre-existing heart failure was associated with increased mortality.[23] Another important study was conducted by Matsushita *et al*., who found that patients with a chronically reduced LVEF had an increased risk of COVID-19-related hospitalization or death compared with patients with a mildly reduced or preserved LVEF.[24]

The pandemic has impacted CHF patients in different ways: it has been shown that usual heart failure hospitalizations occurred less frequently.[25] Patients hospitalized during the early pandemic had a shorter hospital stay and increased in-hospital mortality despite not being affected directly by COVID-19.[26] Interestingly, patients with CHF were also affected by national ‘lock-downs’. Recent studies found a significant reduction in daily physical activity among these patients.[27] This might be an additional significant risk factor for frail older patients. Furthermore, Chagué *et al*. observed a behavioural change towards an unhealthy lifestyle.[28]

Although many studies investigated the impact of COVID-19 on the heart,[29,30] there is growing evidence of there being no additional risk of myocardial/endothelial damage when compared with other severe viral pneumonia. Indeed, Jirak *et al*. reported a lower incidence of myocardial injury in a prospective multicentre study of 156 mechanically ventilated patients.[31]

Limitations

Our analysis lacks some data: we do not have detailed information about structural abnormalities, myocardial tissue (myocardial scars and storage diseases), or laboratory values such as N-terminal prohormone of brain natriuretic peptide. The study pragmatically defines ischaemic cardiac disease according to the reported co-morbidities: heart failure with coexisting relevant coronary artery disease was classified as ischaemic, whereas heart failure without coexisting relevant coronary artery disease was classified as non-ischaemic. This might misclassify some patients, which needs to be taken into account when interpreting the data. The CRF did not question coronary angiographic findings, image morphology, or histopathology. However, overall, the definitions are in line with the latest European Society of Cardiology guidelines[13]: the COVIP database does not contain information about the individual adherence to guidelines, medical treatment, or device therapy. However, focusing on a few central pieces of information avoids the risk of having an inhomogeneous and erroneous database with so many centres.

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Furthermore, pre-existing CHF might influence SOFA, and the correction for SOFA might 'overfit' the model. Another limitation is that this study focuses on left ventricular heart failure, not right heart function. Furthermore, dyspnoea is an important symptom in CHF and can be used for the New York Heart Association (NYHA) classification. The COVIP database did not include NYHA before admission because dyspnoea is one of the cardinal symptoms for COVID-19 disease as well. Thus, the differentiation, based on symptoms, was not methodically possible. With the last reported LVEF and classification into HFrEF, HFmrEF, and HFpEF, the study captures other prognostically important parameters in CHF. Our study shares methodological limitations with the other COVIP-studies[3,7,22,32–34]: our study lacks a control group of younger COVID-19 patients for comparison or a comparable age cohort of patients who were not or could not be admitted to the ICU. Furthermore, the COVIP database does not store information on pre-ICU care and triage. These treatment limitations may affect the care of older ICU patients.[35] Because COVIP recruited patients in 26 countries, the participating countries varied in their care structure resulting in considerable heterogeneity of treatment. However, this limitation is also a major strength of this database, as it does not show selective data from a particular level of care.

Conclusions

This large international multicentre study with 3917 critically ill patients ≥70 years of age with COVID-19 demonstrates that pre-existing CHF is on univariate analysis associated with adverse outcomes. However, in multivariable analysis, after adjustment for other risk factors, CHF was not independently associated with 30 day mortality.

Conflict of interest

The authors declare that they have no competing interests. J.C.S. reports grants (full departmental disclosure) from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestlé, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, PanGas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, GlaxoSmithKline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Astellas, AstraZeneca, CSL Behring, Novartis, Covidien, Philips Medical, Phagenesis Ltd, Prolong Pharmaceuticals, and Nycomed outside the submitted work. The money went into departmental funds. No personal financial gain applied.

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Author contributions

R.R.B., B.W., G.W., and C.J. analysed the data and wrote the first draft of the manuscript. H.F., B.G., D.L., and I.S. contributed to the statistical analysis and improved the paper. J.S., D. K.-M., M.B., S.S., P.V.v.H., A.T., M.E., M.J., E.K., S.L., S.B., P.H. B., J.M., M.K., A.B., A.M., F.A., A.A., B.G., M.C., S.C., L.F., J.F., M.L., B.M., R.M., S.O., C.Ö., B.P., W.S., A.V., C.W., T.Z., and J.C. S. contributed the data, gave guidance, and improved the paper. All authors read and approved the final manuscript.

Ethics statement

The primary competent ethics committee was the Ethics Committee of the Heinrich Heine University Düsseldorf, Germany. Institutional research ethics board approval was obtained from each study site. The manuscript does not contain any individual person's data in any form.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. COVIP - study group.
Figure S1. CONSORT diagram. HFrEF - Heart failure with reduced ejection fraction, HFmrEF - Heart failure with mildly reduced ejection fraction, HFpEF – Heart failure with preserved ejection fraction.

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