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ORIGINAL ARTICLE

Clinical characteristics and risk factors for mortality upon admission in patients with heart failure hospitalized due to COVID-19 in Spain☆

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KEYWORDS
Heart failure;
Coronavirus disease-2019;
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Risk factor;
Mortality

Abstract
Background: There are few studies on patients with heart failure (HF) hospitalized for COVID-19. Our aim is to describe the clinical characteristics of patients with HF hospitalized for COVID-19 and identify risk factors for in-hospital mortality upon admission.
Methods: We conducted a retrospective, multicenter study in patients with HF hospitalized for COVID-19 in 150 Spanish hospitals (SEMI-COVID-19 Registry). A multivariate logistic regression analysis was performed to identify admission factors associated with in-hospital mortality.
Results: A total of 1718 patients were analyzed (56.5% men; median age 81.4 years). The overall case fatality rate was 47.6% (n = 819). The independent risk factors at admission for in-hospital mortality were: age (adjusted odds ratio [AOR]: 1.03; 95% confidence interval [95%CI]: 1.02–1.05; $p < 0.001$); severe dependence (AOR: 1.62; 95%CI: 1.19–2.20; $p = 0.002$); tachycardia (AOR: 1.01; 95%CI: 1.00–1.01; $p = 0.004$); and high C-reactive protein (AOR: 1.004; 95%CI:1.002—1.004; $p < 0.001$), LDH (AOR: 1.001; 95%CI: 1.001—1.002; $p < 0.001$), and serum creatinine levels (AOR: 1.35; 95%CI: 1.18—1.54; $p < 0.001$).

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[2] The complete list of members of the SEMI-COVID-19 group is listed in the Appendix A.

Conclusions: Patients with HF hospitalized for COVID-19 have a high in-hospital mortality rate. Some simple clinical and laboratory tests can help to identify patients with a worse prognosis.

PALABRAS CLAVE
Insuficiencia cardíaca;
Enfermedad por coronavirus-2019;
Hospitalización;
Factor de riesgo;
Mortalidad

Características clínicas y factores de riesgo de mortalidad al ingreso en pacientes con insuficiencia cardíaca hospitalizados por COVID-19 en España

Resumen
Introducción: Existen pocos estudios sobre pacientes con insuficiencia cardíaca (IC) ingresados por COVID-19. Nuestro objetivo es describir las características clínicas de los pacientes con IC ingresados por COVID-19 e identificar los factores de riesgo al ingreso de mortalidad intrahospitalaria.
Material y métodos: Estudio retrospectivo y multicéntrico de pacientes con IC ingresados por COVID-19 en 150 hospitales españoles (Registro SEMI-COVID-19). Se realizó un análisis de regresión logística para identificar los factores de riesgo al ingreso asociados a la mortalidad.
Resultados: Se analizaron 1.718 pacientes (56,5% varones; edad mediana 81,4 años). La tasa de mortalidad global fue del 47,6% (n = 819). Los factores de riesgo independientes al ingreso para mortalidad fueron: la edad (odds ratio ajustado [ORA]: 1,03; intervalo de confianza 95% [IC95%]: 1,02−1,05; p < 0,001), la dependencia severa (ORA: 1,62; IC95%: 1,19−2,20; p = 0,002), la taquicardia (ORA: 1,01; IC95%: 1,00−1,01; p = 0,004), la proteína C reactiva (ORA: 1,004; IC95%:1,002−1,004; p < 0,001), la LDH (ORA: 1,001; IC95%: 1,001−1,002; p < 0,001) y la creatinina sérica (ORA: 1,35; IC95%: 1,18−1,54; p < 0,001).
Conclusiones: Los pacientes con IC hospitalizados por COVID-19 tienen una alta mortalidad intrahospitalaria. Existen factores clínico-analíticos simples que pueden ayudar a identificar a los pacientes con peor pronóstico.

Introduction

The coronavirus-2019 disease (COVID-19), caused by SARS-CoV-2, is associated with elevated morbidity and mortality[1,2]. Since the onset of the pandemic, cardiovascular disease has been identified as a risk factor for COVID-19, with cardiovascular complications being common over the course of the disease[3]. Spain is one of the countries with the highest number of patients with SARS-CoV-2 in the world. The first case of COVID-19 infection was confirmed on 31 January 2020, with 2,670,102 confirmed cases as of 27 January 2021[4].

Heart failure (HF) in Spain represents 3% of hospital admissions and is the number one cause of hospitalisation in patients over the age of 65[5]. The aging population and healthcare advancements are the main factors associated with this growing increase in admissions due to HF[5,6].

To date, few studies have been published regarding mortality in patients with HF and COVID-19 infection. Álvarez-García et al. found that patients with a history of HF show a significant increase in mortality and need for invasive mechanical ventilation associated with COVID-19 infection, regardless of their ventricular ejection fraction[7]. Rey et al. concluded that patients infected with COVID-19 are at higher risk of developing HF during hospital admission, with high mortality rates[8].

Given the significant impact of both diseases independent of one another and their potential feedback when combined, the main aim of this study is to describe the clinical characteristics of patients with a history of HF and/or new-onset HF who are admitted for COVID-19, and to identify risk factors at admission for in-hospital mortality.

Material and methods

Study design

An observational, retrospective, multicentre national study was conducted with patients hospitalised due to COVID-19 from 01 March to 01 October 2020. The data was obtained from the SEMI-COVID-19 Registry from the Spanish Society for Internal Medicine (SEMI). A total of 150 Spanish hospitals participated in the registry[9]. The SEMI-COVID-19 Registry includes consecutive patients over the age of 18 with COVID-19 disease microbiologically confirmed via reverse transcription polymerase chain reaction testing (RT-PCR) obtained via nasal swab, saliva sample, or bronchoalveolar lavage[9].

For this study, we selected those patients with a history of HF and/or that had suffered from HF as a complication during hospital admission due to COVID-19.

Variables

Clinical, epidemiological, radiological, and therapeutic variables were analysed as well as mortality during admission or early readmission, defined as a new episode of hospital admission within 30 days post-discharge.

The researchers collected the data from the SEMI-COVID-19 Registry database[9].

Diagnosis of HF was determined according to the clinical congestion criteria (dyspnoea, oedema, and increased jugular venous pressure) in the medical history. The comorbidity burden of patients was established with the Age-Adjusted Charlson Comorbidity Index[10].

The Barthel Index was used to establish functional condition prior to hospital admission[11] (independent or slight dependency: 100-91; moderate dependency: 90-61; severe dependency: ≤60). Patients were considered to have arterial hypertension, diabetes mellitus, or dyslipidaemia if they had a prior diagnosis in their medical history or were receiving medical treatment for these diseases.

Diabetes mellitus was classified according to 2 subgroups: with target organ damage (brain, heart, kidney, or retinal involvement) or without target organ damage. Chronic lung disease was defined as a prior diagnosis of chronic obstructive pulmonary disease and/or asthma. Arteriosclerotic cardiovascular disease was defined as a prior history of ischaemic heart disease (acute myocardial infarction, acute coronary syndrome, angina, or coronary revascularization). Neoplastic disease included all non-metastatic solid tumours (excluding non-melanoma skin tumours). Moderate-severe kidney disease was defined as glomerular filtration < 45 mL/min/1.73 m^2 according to the CKD-EPI equation[12]. Moderate-severe liver disease was defined as class B or C according to the Child-Pugh score[13]. Obesity was considered a body mass index ≥ 30 kg/m^2. Comorbidities were recorded from the medical histories from each hospital.

The laboratory data (hemogram, biochemical profile, blood gas, coagulation tests) and imaging tests were collected at admission. Treatments used were classified as: (1) antimicrobial therapy (hydroxychloroquine, lopinavir/ritonavir or remdesivir); (2) immunomodulatory therapy (systemic glucocorticoids, immunoglobulins, baricitinib or tocilizumab); (3) anticoagulant therapy (low molecular weight heparin); (4) ventilator support (high flow nasal cannula, invasive and non-invasive mechanical ventilation), and (5) pronation therapy.

In-hospital complications included: admission to the intensive care unit (ICU) and presence of acute respiratory distress syndrome (ARDS), acute coronary syndrome, acute HF, arrhythmia, shock, sepsis, acute kidney failure, venous thromboembolism, or acute arterial ischaemia.

Statistical analysis

Patients were classified according to the categorical variable of mortality as deceased or not deceased. The categorical and continuous variables were expressed as absolute values and percentages and as medians (ranges), respectively. The differences between groups were analysed using Student's *t*-test or the Mann–Whitney *U* test for continuous variables or Pearson's chi-squared test for categorical variables. A *p*-value <.05 was considered statistically significant; subsequently, a multivariate analysis was performed expressed as an adjusted odds ratio (AOR), with a 95% confidence interval (95% CI).

A logistic regression analysis was used to identify independent factors at admission for in-hospital mortality, including variables with statistical significance in the bivariate analysis and with a percentage of missing data of less than 20%. The statistical analysis was conducted with SPSS software version 26.0 (IBM SPSS Statistics©).

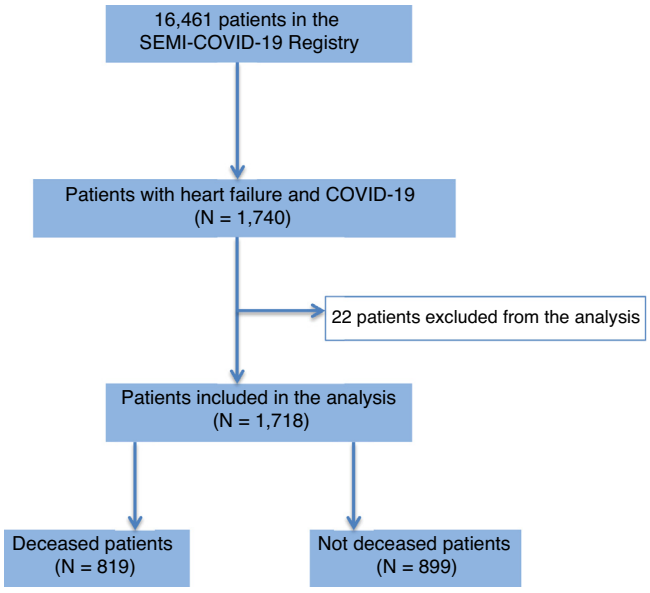

Figure 1 Flow diagram of the study.

Ethical aspects

All the patients gave their informed consent. This study was conducted according to the Declaration of Helsinki and was approved by the Málaga Ethics Committee (Code: SEMI-COVID-19 27-03-20). The STROBE initiative for the publication of observational studies was followed (available at www.strobe-statement.org).

Results

Of the 16,461 patients included in the SEMI-COVID-19 Registry, 1740 had documented history of HF and/or had suffered from HF as a complication during hospital admission due to COVID-19[9]. A total of 22 patients were excluded due to a lack of basic data for correct demographics, meaning the final analysis was conducted with 1718 patients (10.4%). Of these, 819 (47.6%) died during admission (Fig. 1).

The clinical characteristics and laboratory data for the patients classified as deceased and not deceased are included in Table 1. The patients who died were significantly older, were male, and had higher comorbidity and

Table 1 Clinical characteristics, presentation, and laboratory and radiology data for patients with heart failure hospitalised for COVID-19.

	Total (n = 1,718)	Deceased (n = 819)	Not deceased (n = 899)	*p*-value
Age (years)	81.4 (22–102.1)	83.6 (26–102.1)	79.4 (26.5–101.5)	<0.001
Male sex	971 (56.5%)	489 (59.7%)	482 (53.6%)	0.011
Comorbidities				
Charlson Index > 4	155 (9%)	93 (11.3%)	62 (6.8%)	0.002
Barthel Index $\leq$ 60	648 (37.7%)	380 (46.3%)	268 (29.8%)	<0.001
Tobacco	93 (5.4%)	36 (4.3%)	57 (6.3%)	0.049
DM without organ damage	313 (18.2%)	147 (17.9%)	166 (18.4%)	0.758
DM with organ damage	261 (15.1%)	149 (18.2%)	112 (12.5%)	0.001
Arterial hypertension	1350 (78.5%)	670 (81.9%)	680 (75.7%)	0.002
Dyslipidaemia	929 (54%)	453 (55.4%)	476 (53%)	0.311
COPD	269 (15.6%)	142 (17.3%)	127 (14.2%)	0.072
Coronary artery disease	312 (18.1%)	157 (19.2%)	155 (17.3%)	0.311
Atrial fibrillation	709 (41.2%)	357 (43.6%)	352 (39.2%)	0.065
Chronic HF	1167 (67.9%)	526 (64.2%)	641 (71.3%)	<0.001
Solid neoplasm	158 (9.1%)	83 (10.1%)	75 (8.4%)	0.205
Moderate-severe chronic kidney disease	296 (17.2%)	169 (20.7%)	127 (14.1%)	<0.001
Liver disease	43 (2.5%)	22 (2.7%)	21 (2.3%)	0.648
Obesity	435 (25.3%)	190 (23.1%)	245 (27.2%)	0.135
Physical examination				
HR (bpm)	84 (34–180)	85 (34–180)	83 (34–170)	0.004
Tachypnoea (> 20 RR)	785 (45.6%)	459 (51.1%)	326 (36.2%)	<0.001
$SatO_2$ (%)	93 (53–100)	92 (53–100)	94 (54–100)	<0.001
SBP (mmHg)	129 (50–225)	128 (50–225)	130 (69–225)	0.124
Radiology				
Bilateral pulmonary consolidation	515 (29.9%)	297 (36.2%)	218 (24.2%)	<0.001
Laboratory				
CRP (mg/ L)	69.5 (0–950)	90 (0.4–950)	55.1 (0–597)	<0.001
D-dimer (ng/mL)	946 (21–489,000)	1205 (21–489,000)	801 (1618–90,000)	<0.001
LDH (U/L)	342 (18–5209)	390 (92–5209)	316 (18–1735)	<0.001
Leukocytes ($x10^6$/L)	6860 (324–90,000)	7500 (1618–90,000)	6400 (324–90,000)	<0.001
Lymphocytes ($x10^6$/L)	850 (0–75,500)	768 (0–57,830)	910 (49–75,500)	<0.001
Urea (mg/dL)	58 (10–369)	69.5 (10–369)	50 (10–364)	<0.001
Creatinine (mg/dL)	1.18 (0.2–14.3)	1.35 (0.33–14)	1.02 (0.27–10)	<0.001
Lactate (mmol/L)	1.8 (0–100)	1.9 (0.1–100)	1.7 (0.1–100)	<0.001

The categorical and continuous variables were expressed as absolute values and percentages and as medians (ranges), respectively. BPM: beats per minute; COPD: chronic obstructive pulmonary disease; COVID-19: disease caused by coronavirus-2019; CRP: C-reactive protein; DM: diabetes mellitus; HF: heart failure; HR: heart rate; LDH: lactate dehydrogenase; RR: respiratory rate (breaths per minute); $SatO_2$: baseline oxygen saturation; SBP: systolic blood pressure.

dependency. In addition, there was a higher proportion of diabetics with target organ damage, arterial hypertension, and moderate-severe kidney failure among the deceased. Other conditions that were also more frequent in the deceased patients were high heart rate, presence of tachypnoea, low oxygen saturation, and the present of bilateral pulmonary consolidation at admission. Likewise, high mortality was associated with higher blood levels of c-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), urea, creatinine and lactate, and a lower number of lymphocytes at admission.

A total of 1167 patients (67.9%) had a history of chronic HF prior to admission, and 526 of those died (45%). Mortality was higher for patients who experienced acute HF complications during admission than for those with a history of chronic HF prior to admission (53% vs. 45%, $p < 0.05$). The data for treatment and in-hospital complications can be seen in Table 2.

Following the logistic regression analysis, the risk factors at admission associated with higher in-hospital mortality were: age (>80 years), severe dependency class, tachycardia (>100 beats per minute), and elevated levels of CRP, LDH, and serum creatinine (Table 3).

Discussion

Heart failure represents one of the main reasons for hospitalisation in our environment[14,15]. In recent years, the mortality rate for HF in Spain has been trending downwards thanks to the incorporation of different treatments that have shown significant benefits[5], the high level of adher-

Table 2 Treatments and in-hospital complications of patients with heart failure hospitalised for COVID-19.

	Total (n = 1718)	Deceased (n = 819)	Not deceased (n = 899)	*p*-value
Antimicrobial treatment				
Lopinavir-ritonavir	776 (45.1%)	348 (42.4%)	428 (47.6%)	0.039
Remdesivir	18 (1.0%)	4 (0.4%)	14 (1.5%)	0.030
Hydroxychloroquine	1327 (77.2%)	577 (70.4%)	750 (83.4%)	<0.001
Immunomodulators				
Tocilizumab	132 (7.6%)	66 (8.0%)	66 (7.3%)	0.575
Immunoglobulins	6 (0.3%)	2 (0.2%)	4 (0.4%)	0.689
Baricitinib	8 (0.4%)	1 (0.1%)	7 (0.7%)	0.072
Glucocorticoids	764 (44.4%)	389 (47.4%)	375 (41.7%)	0.015
Anticoagulant therapy				
LMWH	1358 (79.8%)	627 (46.2%)	731(53.8%)	0.013
Ventilation support				
High-flow nasal cannula	185 (10.7%)	117 (14.2%)	68 (7.5%)	<0.001
NIMV	139 (8.0%)	92 (11.2%)	47 (5.2%)	<0.001
IMV	141 (8.2%)	86 (10.5%)	55 (6.1%)	0.001
Pronation therapy	219 (12.7%)	130 (15.8%)	89 (9.8%)	<0.001
Complications				
Admission to ICU	177 (10.3%)	100 (12.2%)	77 (8.5%)	0.013
PAD	20 (1.1%)	14 (1.7%)	6 (0.6%)	0.044
VTE	47 (2.7%)	18 (2.1%)	29 (3.2%)	0.238
Sepsis	239 (13.9%)	183 (22.3%)	56 (6.2%)	<0.001
Acute kidney failure	602 (35.0%)	389 (47.4%)	213 (23.6%)	<0.001
Shock	174 (10.1%)	140 (17.0%)	34 (3.7%)	<0.001
Acute coronary syndrome	55 (3.2%)	39 (4.7%)	16 (1.7%)	<0.001
Acute HF	551 (32%)	293 (35.7%)	258 (28.6%)	<0.001
Arrhythmia	231 (13.4%)	117 (14.2%)	114 (12.6%)	0.019
ARDS	889 (51.7%)	629 (76.8%)	260 (28.9%)	<0.001

The categorical variables are expressed in absolute values and percentages.
ARDS: acute respiratory distress syndrome; COVID-19: disease caused by coronavirus-2019; HF: heart failure; IMV: invasive mechanical ventilation; LMWH: low molecular weight heparin; NIMV: non-invasive mechanical ventilation; PAD: peripheral arterial disease; VTE: venous thromboembolism.

ence to guidelines by health professionals[15], and the change of components of disease decompensation such as ischaemic heart disease, which has also been decreasing in recent years[16].

In a recent study, Bromage et al. showed a clear increase in the mortality of patients admitted for HF and COVID-19, though it is unknown whether this is due to true mortality or due to a selection of critical patients who were admitted during the pandemic[17].

Our study has shown that the presence of HF, both in patients with a prior history and those who developed it as a complication during admission, is associated with high hospital mortality rates close to 50%. In addition, it makes clear that patients who experienced decompensation due to acute HF while admitted died at a higher rate than patients with a history of HF prior to admission, with the former affecting mortality more than the latter. This reflects the impact of COVID-19 on developing acute HF. These percentages represent a significant increase compared to the mortality described in previous studies of patients hospitalised with HF, which range from 9.5% to 11%[18,19].

The most frequent causes of death in patients with a history of HF have been described as decompensated HF, sudden death, and non-cardiovascular causes[20,21]. At the present moment, as our study suggests, SARS-CoV-2 is the primary cause of death in hospitalised HF patients.

Older age, elevated comorbidity burden, and degree of dependency are characteristic elements of patients with HF hospitalised due to COVID-19 in our country. This clinical profile, with figures close to 80% for arterial hypertension, 40% for atrial fibrillation, 20% for diabetes mellitus, 17% for moderate-severe chronic kidney disease, 25% for obesity, and 38% for severe functional dependency, represents a continuation of previous studies performed in our setting which have reported similar figures for these HF-related pathologies[22,23].

The patients with HF hospitalised due to COVID-19 from our study presented a large number of complications. The most frequent complication was ARDS, which exposes the inflammatory process that occurs in this patient profile induced by SARS-CoV-2. The severe inflammatory response triggered in COVID-19 has been described in previous studies.

Old age and chronic conditions are just some of the various clinical conditioning factors that could favour its development and predispose patients to the onset of

Table 3 Risk factors at admission associated with in-hospital mortality of patients with heart failure hospitalised due to COVID-19. Multiple regression analysis.

	AOR (95% CI)	*p*-value
Age > 80 years	1.035 (1.021−1.050)	<0.001
Male sex	1.33 (0.998−1.771)	0.051
Severe dependency	1.625 (1.195−2.209)	0.002
Arterial hypertension	1.23 (0.865−1.756)	0.248
$SatO_2$ > 90%	0.956 (0.934−0.979)	<0.001
HR > 100 bpm	1.011 (1.003−1.018)	0.004
CRP > 3 mg/L	1.004 (1.002−1.004)	<0.001
Creatinine > 1.17 mg/dL	1.354 (1.185−1.548)	<0.001
Lymphocytes < 1500×10^6/L	1.000 (1.000−1.001)	0.927
LDH > 480 U/L	1.001 (1.001−1.002)	<0.001
D-dimer > 1000 ng/mL	1.000 (1.000−1.000)	0.474

95% CI: 95% confidence interval; AOR: adjusted odds ratio; BPM: beats per minute; CRP: C-reactive protein; HR: heart rate; LDH: lactate dehydrogenase; $SatO_2$: baseline oxygen saturation.

complications and adverse events[24,25]. In this sense, in our study we identified factors at admission that have been associated as risk factors for mortality in patients with HF hospitalised due to COVID-19. Old age has been determined to be one of the main factors associated with higher mortality due to COVID-19[25], and we confirmed this in our population with HF.

On the other hand, the importance of assessing clinical condition at the time of admission is worth mentioning. Patients who present in critical condition will have a significantly worse prognosis than those presenting with these characteristics, with the former requiring stricter monitoring and follow-up. Other studies have also stressed this issue and its severity in COVID-19 illness[26,27].

In addition, the presence of certain altered biological markers in patients with HF can be aggravated by COVID-19 infection. In this way, kidney failure and high CRP and LDH levels were significantly associated with an increase in mortality. However, other markers of poor prognosis in COVID-19, such as lymphopenia or elevated D-dimer levels[28], were not related to higher mortality in our population of patients with HF.

In any case, though the variables of heart rate and elevated LDH and CRP have been statistically associated with mortality, we must bear in mind that the association of these factors has been less important from the clinical perspective than other variables such as dependency or age. All of these factors, which are easily identifiable when patients are being admitted to hospital, define a patient profile that requires special care due to the high risk of complications and death that they entail.

This study presents important data regarding the clinical profile of a large number of patients with HF hospitalised due to COVID-19 and identifies at admission diverse clinical and analytical factors that are associated with mortality. Though it is the first study with these characteristics in our country and one of few around the world, it does have some limitations.

First, as an observational and retrospective study focusing on hospitalised patients, we analysed patients with more critical clinical situations, which could limit the results of the patient profile and not allow it to be extrapolated to the rest of the population of patients with HF. In addition, despite conducting a multivariate regression analysis, the possibility of unmeasured confounding variables cannot be ruled out.

On the other hand, the data were collected by a large number of researchers from hospitals with different levels of care, which entails a great degree of heterogeneity in its processing. It is also worth noting that, despite the large number of variables included in this registry, we are lacking important data about the characterisation of HF such as aetiology, the New York Heart Association functional class, the left ventricular ejection fraction, the level of natriuretic peptides, and the proportion of patients receiving other treatments such as beta blockers, neprilysin receptor antagonists, aldosterone antagonists, or diuretics. Lastly, nor does the provided information include data on the degree of compliance or the duration of the treatments prior to admission.

In terms of the strength of our study, the large number of patients with HF included in our series is worthy of mention, as it represented different centres from around the entire country, offering a wide-reaching vision of this patient group.

Conclusions

This study shows that patients with HF hospitalised due to COVID-19 in Spain have a high rate of mortality. Older age, severe dependency class, greater severity at initial presentation, kidney function decline, and elevated inflammatory blood parameters have been identified as predictors of mortality.

Given the impact of HF on COVID-19 and the involvement of various factors, it is necessary to develop prognostic scales that are easy to implement for these patients.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Appendix A. Members of the SEMI-COVID-19 Registry

Coordinator of the SEMI-COVID-19 Registry: José Manuel Casas Rojo.

Members of the SEMI-COVID-19 Registry Scientific Committee: José Manuel Casas Rojo, José Manuel Ramos Rincón, Carlos Lumbreras Bermejo, Jesús Millán Núñez-Cortés, Juan Miguel Antón Santos, Ricardo Gómez-Huelgas.

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