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HEART FAILURE IN COVID-19 PATIENTS: PREVALENCE, INCIDENCE AND PROGNOSTIC IMPLICATIONS

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ABSTRACT

Aims: Data regarding impact of COVID-19 in chronic heart failure (CHF) patients and its potential to trigger acute heart failure (AHF) is lacking. The aim of this work was to study characteristics, cardiovascular outcomes and mortality in patients with confirmed COVID-19 infection and prior diagnosis of HF. Also, to identify predictors and prognostic implications for AHF decompensations during hospital admission and to determine whether there was a correlation between withdrawal of HF guideline-directed medical therapy (GDMT) and worse outcomes during hospitalization.

Methods and results: A total of 3080 consecutive patients with confirmed COVID-19 infection and at least 30-day follow-up were analyzed. Patients with previous history of CHF (152, 4.9%), were more prone to develop AHF (11.2% vs 2.1%; p<0.001) and had higher levels of NT-proBNP. Also, previous CHF group had higher mortality rates (48.7% vs 19.0%; p<0.001). In contrast, 77 patients (2.5%) were diagnosed of AHF and the vast majority (77.9%) developed in patients without history of HF. Arrhythmias during hospital admission and CHF were main predictors of AHF. Patients developing AHF had significantly higher mortality (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.

Conclusions: Patients with COVID-19 have a significant incidence of AHF, entity that carries within a very high mortality. Moreover, patients with history of CHF are prone to develop acute decompensation after COVID-19 diagnosis. Withdrawal of GDMT was associated with higher mortality.

KEY WORDS: COVID-19, heart failure, NT-proBNP, drugs withdrawal, mortality, morbidity.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the ongoing pandemic responsible for substantial morbidity and mortality all around the globe, has proven to be a multisystemic condition with frequent cardiac manifestations. Cardiovascular (CV) disease and classic CV risk factors are common comorbidities in COVID-19 patients and have been associated with poor outcomes[1].

Besides, heart failure (HF) is one of the leading causes of morbidity and mortality worldwide and should not be left unattended. Previous knowledge from other respiratory tract infections, such as influenza, has proven virus potential to trigger decompensation of HF patients[2]. Recent research has focused on the impact of the COVID-19 pandemic in the hospitalization rates, incidence and characteristics of patients attended in specialized HF units[3], but data regarding prevalence, incidence and prognostic implications of HF in patients with a confirmed diagnosis of SARS-CoV-2 infection is still lacking.

The aim of this work was to study characteristics, cardiovascular outcomes and mortality in patients with confirmed COVID-19 infection and prior diagnosis of HF. We also focused on identifying predictors and prognostic implications of HF decompensation during hospital admission and exploring whether there is an association between withdrawal of guideline-directed medical therapy (GDMT) and worse outcomes during hospitalization.

METHODS

Study design and participants

We screened all consecutive patients with clinical suspicion of COVID-19 disease attending to the Emergency Department of a tertiary hospital in Madrid, the most affected region in Spain, from March 1st to April 20th, 2020. Patients were only included in the study if they had confirmed COVID-19 infection by RNA reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay from nasopharyngeal swab specimens. We specifically aimed to include patients who have completed a follow-up of at least 30 days since microbiological diagnosis. Therefore, patients who were alive but diagnosed with less than 30 days from the lock of the database were excluded from the present analysis. This study was approved by the

Institutional Review Board at our center. Individual written informed consent was waived based on legal standards for national healthcare alarm situations.

Data collection:

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records from the index and subsequent hospital admissions using a standardized electronic data collection form. In addition, the central regional healthcare record system, which collects information and medical reports from all public hospitals and primary healthcare centers from Madrid, was reviewed for additional information and follow-up. All data were thoroughly reviewed by a team of 13 cardiologists. Any disagreements regarding data classification were reviewed by the whole team, and a decision was finally made by consensus. Special care was given to the identification of baseline CV profiles, clinical outcomes and specifically acute heart failure diagnosis.

Study definitions:

Chronic heart failure (CHF) was defined as history of previous congestive decompensation or diagnosis of left ventricular systolic dysfunction (LVEF<40%). Acute heart failure (AHF) refers to rapid onset or worsening of symptoms and/or signs of HF during the study period. Acknowledging the difficulty to distinguish between respiratory and cardiac causes of dyspnea in COVID-19, acute heart failure events were adjudicated on a case-by-case basis by consensus of all investigators. We based our decisions on all clinical information available for each patient: codified HF diagnosis, description of serial physical examinations in the electronic medical records, radiological tests (chest radiography and CT), echocardiographic studies. and NT-proBNP levels according to the recommended cut-off values of the Heart Failure Association of the European Society of Cardiology (ESC) for the diagnosis of AHF: >450 pg/ml in patients below 50 years, >900 pg/ml in patients between 50-75 years and >1800 pg/ml in patients over 75 years[4].

Categorization of echocardiographic measurements of left ventricular systolic function were based on published recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography[5]. Bleeding events were defined as specified in the Thrombolysis in Myocardial Infarction (TIMI) bleeding classification[6].

In order to minimize the risk of selection bias due to severe illness (i.e. hypotension due to septic shock), patients who had medication withdrawn were defined as those who had chronic treatment with angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blocker (ARB), beta-blockers (BB) or mineralocorticoid receptor antagonist (MRA) before hospital admission and did not receive any dose after hospital admission, as confirmed by the central pharmacy computerized information system, and irrespective of their clinical status.

Statistical analysis

Categorical variables are shown as rates and percentages, and continuous variables as mean ± SD or median (IQR) as appropriate. Means for continuous variables were compared using independent group t tests when data were normally distributed, otherwise, Mann-Whitney test was performed. Normality of distributions was assessed using Shapiro-Wilk test. Proportions for categorical variables were compared using the $\chi 2$ test or the Fisher exact test, as appropriate. Survival during follow-up was assessed using Kaplan Meier analysis and, when appropriate, the log-rank test. The association of CHF and AHF with mortality during follow-up was studied using a Cox-proportional hazard model accounting for relevant covariates (age, sex, CV risk factors, coronary heart disease, chronic kidney disease and cerebrovascular disease). Stepwise logistic regression was used to develop a predictive model for AHF during admission, using as candidate variables those which were statistically significant in the univariate analysis. All data were analyzed using the Stata v14.2 statistics package, (StataCorp, College Station, TX, USA). A two-sided p value <0.05 was considered statistically significant for every analysis.

RESULTS

During the study period, 3080 patients with confirmed COVID-19 infection fulfilled our selection criteria and were ultimately included in the present analysis (Figure 1, Graphical abstract). Mean age was 62.3±20.3 years and 1689 (54.8%) were male. Six hundred twenty-six patients (20.5%) died during a median follow-up of 59 (50-66) days, the time of death since SARS-CoV-2 diagnosis being 6 (3-12) days (range 0-53).

COVID-19 patients with CHF vs non-CHF

A total of 152 patients with CHF (4.9% of those with positive RT-PCR) were studied. Of those, 98 (64.5%) had some degree of left ventricular systolic dysfunction prior to COVID-19

diagnosis. The remaining 54 had normalized LVEF after the initiation of guideline-directed medical therapy or had HFpEF with other significant echocardiographic abnormalities such as LV hypertrophy or moderate to severe valvular disease. Baseline characteristics are shown in Table 1. Patients with history of CHF were older (81.9±11.9 vs 61.2±20.1; p<0.001) and had a higher cardiovascular risk profile, as well as different forms of atherosclerotic disease (coronary, cerebrovascular and peripheral). As expected, they were more frequently on treatment with cardiovascular medications. Regarding prescription of dedicated COVID-19 drugs, patients in the CHF group received more hydroxychloroquine (85.5% vs 77.0%; p=0.014) but less tocilizumab and azithromycin.

CHF group had significantly lower glomerular filtration rate (47.9±23.2 ml/min vs 76.6±19.7 ml/min; p<0.001) and hemoglobin (12.7±2.2 g/dl vs 13.6±1.7 g/dl; p<0.001). No differences were found in proinflammatory makers (ferritin, fibrinogen, C-reactive protein, IL-6) or in D-dimer. However, peak NT-proBNP (16802±30726 pg/ml vs 4726±13530 pg/ml; p<0.001) and hs-Troponin I (4331±23952 vs 306±2646, p<0.001) were significantly higher during hospital admission.

Patients with CHF were more prone to develop clinical findings suggestive of AHF as well as elevation of NT-proBNP above the AHF cut-off. The CHF group developed numerically more thrombotic events than the non-CHF group, but the numbers were small and without significant differences (2.0% vs 3.9%, p=0.234). However, CHF patients received significantly more chronic therapeutic anticoagulant therapy [86 (57.7%) vs 223 (7.7%), p<0.001].

CHF group was less frequently admitted to the intensive care unit (ICU) (1.4% vs 6.4%; p= 0.013) and had a higher mortality during follow-up (48.7% vs 19.0%; p<0.001; Figure 2 left panel). Nevertheless, after adjusting to other relevant covariates, CHF did not reach statistical significance to be identified as an independent predictor of mortality (Supplementary Table 1).

COVID-19 patients developing AHF

During the study period, 77 patients (2.5%) received a diagnosis of AHF (Table 2). Of these, 47 had documented abnormal NT-proBNP levels according to recommended cut-off for

diagnosis of AHF, while the remaining 30 did not undergo any NT-proBNP determination during hospital admission (Supplementary table 2). Thirty-one AHF patients had available qualitative information regarding point-of-care echocardiographic examinations: 12 with some degree of left ventricular systolic dysfunction, 17 with other pathological findings (such as significant valvular heart disease, pericardial effusion or right ventricular dysfunction) and 2 studies were reported as without significant abnormalities.

Mean age (78.6±12.6 vs 61.8±20.3, p<0.001) and cardiovascular risk profile (exception made for the proportion of smokers) were higher in the AHF group. Other associated comorbidities and cardiovascular medications were also more prevalent in this group, although numerically lower than those seen in the CHF group (Table 1). Interestingly, the vast majority of patients who developed AHF did not have a history of CHF (60, 77.9%). They had more severe presentations of COVID-19, as they had lower levels of oxygen saturation at admission (89.3±7.6 vs 92.3±6.2; p<0.001), higher need for supplementary oxygen (20.8% vs 8.9%; p=0.001) and showed a trend towards more frequent bilateral pneumonia.

As expected, peak NT-proBNP (10508±20374pg/ml vs 5469±16118; p<0.001) was higher in AHF patients. Regarding other laboratory findings, significant differences were observed in C-reactive protein and D-dimer. Even though high sensitivity TnI was mildly elevated in both groups, it did not differ significantly (417±1683ng/L vs 458±5403ng/L; p=0.963).

Patients with AHF received more hydroxychloroquine, systemic corticosteroids and underwent more frequent hospital admission (98.7% vs 70.4%; p<0.001), atrial arrhythmias (14.3 vs 2.5, p<0.001) and bleeding events. Indeed, their mortality was significantly higher (46.8% vs 19.7%; p<0.001 for the log-rank test; Figure 2 right panel). However, no differences regarding mechanical ventilation or ICU admission were noted. After adjusting for relevant covariates, development of AHF did not reach the threshold to be considered an independent predictor of mortality during follow-up [HR 1.40 (0.98-1.98), p=0.062, Supplementary Table 3].

We used stepwise logistic regression techniques for the development of a predictive model of AHF during hospital admission (Table 3). Such model illustrated that advanced age [OR 1.28 (95%CI 1.16-1.41) per 5-year increase)], atrial arrhythmias during admission [OR 4.64

(95%CI 2.19-9.83)], chronic heart failure [OR 2.51 (95%CI 1.33-4.76)], bleeding events [OR 1.60 (95%CI 0.98-2.62)] and chronic obstructive pulmonary disease [OR 2.51 (95%CI 1.40-4.49)] were independently associated with AHF after COVID-19 diagnosis.

Guideline-directed medical therapy and mortality

Among the 152 patients with CHF, 90 (59.2%), 94 (61.8%) and 47 (30.9%) received guideline-directed medical treatment with angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, beta-blockers or mineralocorticoid receptor antagonists respectively for HFrEF or HF with recovered left ventricular ejection fraction. These chronic prescriptions were not associated with worse outcomes after adjusting for relevant covariates (Supplementary Table 4).

Regarding the impact of withdrawing guideline-directed medical therapy (GDMT), 32 (35.6%), 15 (16.0%) and 22 (46.8%) patients discontinued ACEi, beta-blockers and MRA respectively during hospital stay. Differences between patients who discontinued HF drugs at admission and those who did not are presented in Table 4. We only identified statistically significant differences regarding the prevalence of baseline hypertension, treatment with MRA, systolic blood pressure at admission and use of lopinavir/ritonavir. Survival analysis using the log-rank test showed that discontinuation of GDMT was associated with a higher risk of in-hospital death (Figure 3).

These findings were subsequently assessed among the corresponding subgroup of patients receiving each type of GDMT using multivariable Cox regression adjusting for relevant covariates (Supplementary tables 5-7). This analysis confirmed that the withdrawal of ACEi/ARB [HR 4.50 (2.14-9.48)], BB [4.15 (1.61-10.71)] and MRA [3.36 (1.15-9.89)] were independent predictors of mortality. Indeed, the number of HF drugs discontinued during hospital admission was significantly associated with an increasing risk of in-hospital death (Supplementary Figure 1, Supplementary table 8). However, in this clinical context, we were unable to identify a higher incidence of AHF in patients withdrawing GDMT [odds ratios 1.10 (0.24-4.92), 0.48 (0.13-1.85) and 0.48 (0.14-1.63) for ACEi/ARB, BB and MRA discontinuation respectively].

DISCUSSION

The present work studied the prevalence and prognostic implications of HF in a large cohort of 3080 consecutive COVID-19 patients. The first key finding was that patients with CHF were at significant risk for acute decompensation after COVID-19 diagnosis. Furthermore, the development of clinical HF in our series was noteworthy and associated with poor outcomes.

CHF and COVID-19

SARS-CoV-2 potential to produce myocardial injury, along with impaired cardiopulmonary reserve and poorer baseline characteristics of patients with CHF may result in higher mortality and more frequent acute decompensation. Indeed, data from smaller cohorts had shown poor outcomes in patients with previous cardiac disease, even though details regarding baseline CV conditions were not reported[7,8].

In our series, CHF patients showed a significantly worse clinical picture at first medical contact, with subsequently higher all-cause mortality. In addition, CHF patients were less frequently admitted to the ICU (2.1% vs 8.0%; p=0.037) and received less mechanical ventilation (2.1% vs 7.6%; p=0.046). This apparent paradox illustrates the difficulties in allocating medical resources during the pandemic. The need for maximizing clinical benefit led physicians to give priority to those patients with higher chances of surviving with a reasonable life expectancy[9]. Therefore, a significant number of CHF patients with advanced age and comorbidities may have had limited access to critical care units and this may be one of the contributing causes of higher mortality in this population.

Regarding other in-hospital complications and given the significant concerns of a higher likelihood of thromboembolic disease in HF patients with COVID-19, it is remarkable that none but three of our CHF patients had a thrombotic event during admission. Indeed, we did not observe differences in thrombotic or inflammatory biomarkers between groups, but these findings may also be related with a higher prevalence of chronic therapeutic anticoagulation among the CHF patients.

COVID-19 patients developing AHF

A total of 77 patients (2.5%) developed clinical features of AHF during the study period. Heart failure has been described after respiratory infections and pneumonia[10] and, in this sense, a metanalysis of 25 studies regarding non-COVID-19 pneumonia reported major cardiac complications in one-quarter of the included patients, being AHF the most prevalent (14%)[11]. However, the incidence of AHF in patients with diseases caused by coronaviruses such as severe acute respiratory syndrome (caused by SARS-CoV-1) and Middle East respiratory syndrome (caused by MERS-CoV) has not been addressed in the medical literature prior to 2020 and remains still unknown.

In this large cohort of 3080 consecutive patients with a high prevalence of pneumonia at admission, the incidence of major cardiovascular complications is significant. Yet, extraordinary measures focused on reducing exposure of healthcare workers to the virus (i.e. simplified physical examinations or restrictive criteria for the indication of non-invasive imaging tests as recommended by international scientific societies[4,8,12,13]), may have limited our ability to detect incident cardiovascular disease. Besides, the overlapping clinical and radiological presentation of both COVID-19 and HF create an undeniable barrier for the proper diagnosis of this condition[8,12,13]. A low threshold for suspicion of COVID-19 have been advocated in chronic HF patients[8], but we are concerned that the same recommendation should be made the other way around.

Besides, information regarding the diagnostic and prognostic role of biomarkers such as NT-proBNP in this clinical context is lacking. Historically, studies like TOPCAT[14] have supported its value and over the past years NT-proBNP has had a growing role in the standardization of both the definition of HF and the inclusion criteria for major clinical trials[15]. This cardiac biomarker has proven useful for the diagnosis of AHF in patients presenting with dyspnea and no previous history of HF, especially if other imaging techniques such as transthoracic echocardiogram are not readily available[4]. The above scenario certainly resembles that of COVID-19 pandemic.

The proportion of patients developing AHF was higher in the CHF group (11.2% vs 1.8%, $p<0.001$), yet the vast majority of AHF cases (77.9%) developed in patients without history of HF. This supports the potential of SARS-CoV-2 to induce myocardial damage[16]. Indeed, we identified mildly elevated high-sensitivity troponin I both in patients with and without AHF. This is coherent with recent research showing raised myocardial native T1, T2 and

late-gadolinium enhancement in a large proportion of unselected patients recovered from COVID-19[17]. Pathophysiological mechanisms of these observations are not yet fully understood, but authors have raised concerns towards an intense proinflammatory cytokine-modulated reaction[16], pro-thrombotic state[18], endothelial dysfunction[19] as well as plaque rupture. Interestingly, a recent pathological investigation showed particles consistent with SARS-CoV-2 in the myocardial endothelial compartment, but not in the myocytes, and there was no evidence of lymphocytic myocarditis[20].

Mortality rates per year in patients admitted for AHF approaches 17%[21]. Although non-COVID-19 pneumonia presenting with a concomitant major cardiac complication has a non-negligible rise of 5-times the mortality[11], observed mortality rates of patients who develop AHF during the course of COVID-19 infection are dramatic (46.8% vs 19.7%, $p<0.001$).

Even though the main cause of death of our population was respiratory failure in direct relationship with viral pneumonia[1], it is undeniable that other cardiovascular comorbidities may coexist and not only under the shape of left-sided HF. Right ventricular dysfunction either due to so-called lung-restricted vascular immunopathology associated with COVID-19[22] or to thromboembolic disease[23], may also be behind abnormally high levels of NT-proBNP, proinflammatory markers and of course D-dimer.

In the frontline of the COVID-19 pandemic, whether a more liberal determination of cardiac biomarkers may improve early diagnosis and management of AHF, and other cardiovascular complications should be prospectively investigated.

Multivariable analysis confirmed that history of CHF, chronic obstructive pulmonary disease and older age, all three variables associated with a poorer baseline clinical profile, were independent predictors of AHF during hospital admission for COVID-19. Bleeding, a marker of patient vulnerability that usually requires volume resuscitation and administration of blood products, was also independently associated with this complication. However, the strongest predictor of AHF in these patients was the development of atrial arrhythmias during hospital admission. Atrial fibrillation was by far the most common arrhythmia in our series. Its effects may be mediated by multiple and well-known mechanisms, such as loss of atrial mechanical contraction, poor rate control, impaired diastolic filling, irregular R-R intervals and neurohormonal activation[24]. A better knowledge of the conditions related with the

development of AHF may promote early identification of high-risk patients who may benefit from more dedicated cardiac monitoring and early referral to a multidisciplinary HF management team.

Withdrawal of chronic HF therapies

Despite published recommendations from several scientific societies, many patients and physicians chose to stop chronic GDMT. Results of in vitro and animal SARS-Cov-2 models showing a greater potential of infection due to an over expression of the ACE2 enzyme could not be reproduced in real-life Chinese cohorts[25] or other larger recently publishes series[26,27]. Moreover, recent research including a meta-analysis[25,28] showed that chronic use of renin-angiotensin-aldosterone system inhibitors are actually associated with a reduction of in-hospital mortality, though none of these studies were originally designed to answer this specific question. Ongoing randomized clinical trials[29] are expected to address the specific hypothesis that withdrawal of RAAS inhibitors in the general population of COVID-19 patients may significantly impact survival.

In the context of chronic heart failure, withdrawal of GDMT in patients with dilated cardiomyopathy who have recovered normal left ventricular ejection fraction (LVEF) was specifically explored in TRED-HF[30]. In this study, up to 40% of the patients had a relapse in the form of either clinical HF or worsened LVEF.

In order to avoid selection bias (i.e. patients discontinuing GDMT due to COVID-19-related progressive clinical deterioration), we defined GDMT withdrawal as the absence of any received dose during hospital admission of HF medication in patients with chronic HF treatment. Our findings should be interpreted cautiously due to the observational nature of the study but strongly suggest that withdrawal of ACE/ARB inhibitors, BB and MRA is associated with higher mortality and argue in favor of the maintenance of these treatments as long as individual benefit is expected. Thus, even if severe presentations of COVID-19 may require temporary reduction or withdrawal of ACE/ARB inhibitors due to hemodynamic or renal deterioration[8], all efforts should be made at discharge to restore GDMT that have proven to favorably impact the clinical course of HF.

LIMITATIONS

This is an observational, retrospective and single-center study with the inherent limitations of this type of design. Data reflect the scenario at the beginning of the pandemic in Spain, a time when data were even more scarce than in the present situation. This may result in diagnostic and therapeutic differences with current international recommendations. We should acknowledge that NT-proBNP was not routinely performed in every COVID-19 patient, and that institutional policies focused on avoiding SARS-CoV-2 transmission may have limited our capacity to detect AHF and other cardiovascular complications.

CONCLUSION

COVID-19 patients have a significant incidence of AHF, which is associated with poor outcomes. Patients with CHF are also at high risk and are vulnerable to acute decompensation after COVID-19 diagnosis. Withdrawal of ACE/ARB inhibitors, BB and MRA in patients with CHF was associated with higher mortality during follow-up.

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DATA AVAILABILITY: The data underlying this article will be shared on reasonable request to the corresponding author.

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FIGURE LEGENDS

Figure 1. Study flow.

Figure 2. Left panel: Survival analysis showed significant differences ($p<0.001$) between patients with and without CHF. **Right panel:** Kaplan-Meier survival curves stratified by clinical diagnosis of AHF showing significant differences ($p<0.001$) in mortality.

Figure 3: Kaplan-Meier survival analysis in patients receiving chronic treatment with ACEi/ARB (**upper panel**), BB (**middle panel**) and MRA (**lower panel**) showed that patients discontinuing these drugs at the time of admission had worse survival during follow-up.

Table 1. "Baseline characteristics, drug therapy, vital signs, laboratory data and clinical outcomes according to a previous history of CHF or not".

Variable	All patients (N=3080)	Non-CHF (n=2928)	CHF (n=152)	p value
Baseline characteristics and coexisting disorder				
Age (years)	62.3±20.3	61.2±20.1	81.9±11.9	<0.001
Male sex	1689 (54.8%)	1595 (54.5%)	94 (61.8%)	0.075
Hypertension	1322 (43.1%)	1193 (40.9%)	129 (86.0%)	<0.001
Diabetes	559 (18.3%)	501 (17.2%)	58 (39.5%)	<0.001
Dyslipidemia	1103 (37.1%)	995 (35.2%)	108 (75.0%)	<0.001
Smoking habit	304 (9.9%)	273 (9.3%)	31 (20.3%)	<0.001
Obesity	430 (14.0%)	397 (13.6%)	33 (21.7%)	0.005
Peripheral artery disease	199 (6.5%)	157 (5.4%)	42 (28.6%)	<0.001
Ischemic stroke	187 (6.1%)	155 (5.3%)	32 (21.8%)	<0.001
Coronary artery disease	199 (6.5%)	155 (5.3%)	44 (29.7%)	<0.001
Atrial fibrillation / flutter	269 (8.7%)	190 (6.5%)	79 (52.0%)	<0.001
PM / ICD	53 (1.7%)	37 (1.3%)	16 (10.5%)	<0.001
COPD	236 (7.7%)	191 (6.5%)	45 (29.6%)	<0.001
Chronic kidney disease	180 (5.8%)	141 (4.8%)	39 (25.7%)	<0.001
Cancer	301 (9.8%)	273 (9.3%)	28 (18.4%)	<0.001
Baseline cardiovascular drug therapy				
Therapeutic anticoagulation	309 (10.1%)	223 (7.7%)	86 (57.7%)	<0.001
Antiplatelet	440 (14.3%)	390 (13.3%)	50 (32.9%)	<0.001
ACE inhibitor or ARB	1005 (32.6%)	915 (31.3%)	90 (59.2%)	<0.001
MRA	93 (3.0%)	46 (1.6%)	47 (30.9%)	<0.001
Sacubitril / valsartan	13 (0.4%)	2 (0.1%)	11 (7.2%)	<0.001
Beta-blocker	407 (13.2%)	313 (10.7%)	94 (61.8%)	<0.001
Diuretics	628 (20.4%)	521 (17.8%)	107 (70.4%)	<0.001
SGLT2 inhibitors	43 (1.4%)	37 (1.3%)	6 (4.0%)	<0.001
Digoxin	22 (0.7%)	12 (0.4%)	10 (6.6%)	<0.001
Statin	878 (28.5%)	782 (26.7%)	96 (63.2%)	<0.001
Antiarrhythmic	22 (0.7%)	19 (0.7%)	3 (2.0%)	0.059
Vital signs at hospital presentation				
Systolic blood pressure	129.0±21.4	129.0±21.3	129.4±23.9	0.804
Heart rate	93.6±19.7	94.3±19.5	82.7±20.3	<0.001
First oxygen saturation	92.2±6.3	92.3±6.2	90.4±7.4	<0.001
First oxygen saturation receiving oxygen	284 (10.4%)	248 (9.6%)	36 (25.2%)	<0.001
First chest radiography				
Without infiltrates Unilateral infiltrates Bilateral infiltrates	821 (27.8%) 592 (20.1%) 1537 (52.1%)	776 (27.7%) 572 (20.4%) 1455 (51.9%)	45 (30.6%) 20 (13.6%) 82 (55.8%)	0.132
Laboratory data				
Median GFR (ml/min/1.73m^2)	75.0±21.0	76.6±19.7	47.9±23.2	<0.001
Median hemoglobin (g/dl)	13.5±1.8	13.6±1.7	12.7±2.2	<0.001
Highest Ferritin (ng/dl)	1481±6298	1494±6445	1226±2220	0.730
Highest D-dimer (ng/ml)	9351±32509	9475±33038	7040±20125	0.468
Highest Troponina	456±5301	306±2646	4331±23952	<0.001
Highest NT-proBNP	6067±16730	4726±13530	16802±30726	<0.001
Highest fibrinogen (mg/dl)	820±282	820±282	825±274	0.854
Highest C reactive protein (mg/l)	131.5±109.3	131.1±110.2	138.0±92.1	0.464
Highest IL-6 (pg/ml)	311.4±591.8	310.6±590.6	339.1±650.6	0.840
Antimicrobial and inmunomodulatory agents against the COVID-19				
Hydroxychloroquine	2383 (77.4%)	2253 (77.0%)	130 (85.5%)	0.014

Lopinavir / ritonavir	319 (10.4%)	303 (10.4%)	16 (10.5%)	0.944
Azithromycin	1404 (45.6%)	1347 (46.0%)	57 (37.5%)	0.040
Tocilizumab	227 (7.4%)	223 (7.6%)	4 (2.6%)	0.022
Systemic glucocorticoid	444 (14.4%)	419 (14.3%)	25 (16.5%)	0.465
Clinical outcomes				
Hospital admission	2191 (72.1%)	2054 (71.1%)	137 (92.0%)	<0.001
Clinical diagnosis of AHF	77 (2.5%)	60 (2.1%)	17 (11.2%)	<0.001
Pulmonary embolism	76 (2.5%)	75 (2.6%)	1 (0.7%)	0.140
Thrombotic event	116 (3.8%)	113 (3.9%)	3 (2.0%)	0.234
Mayor bleeding No mayor bleeding	22 (0.8%) 66 (2.5%)	21 (0.8%) 61 (2.5%)	1 (0.7%) 5 (3.8%)	0.642
Atrial fibrillation / flutter during admission	87 (2.8%)	81 (2.8%)	6 (4.0%)	0.392
Ventricular arrhythmias during admission	11 (0.4%)	10 (0.3%)	1 (0.7%)	0.524
Critical care admission	182 (6.1%)	180 (6.4%)	2 (1.4%)	0.013
Mechanical ventilation	173(5.8%)	171 (6.1%)	2 (1.4%)	0.017
Death	626 (20.5%)	552 (19.0%)	74 (48.7%)	<0.001

Abbreviatures: PM pacemaker, ICD implantable cardioverter defibrillator, COPD chronic obstructive pulmonary disease, ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA mineralocorticoid receptor antagonist, SGLT2 sodium-glucose cotransporter 2, GFR glomerular filtration rate, AHF acute heart failure.

Data are expressed as no. (%) for categorical data or mean ± standard deviation for continuous data.

Table 2. "Baseline characteristics, drug therapy, vital signs, laboratory data and clinical outcomes according to the development or not of acute AHF during admission".

Variable	All patients (N=3080)	Non-AHF (n=3003)	AHF (n=77)	p value
Baseline characteristics and coexisting disorder				
Age (years)	62.3±20.3	61.8±20.3	78.6±12.6	<0.001
Male sex	1689 (54.8%)	1647 (54.9%)	42 (54.6%)	0.958
Hypertension	1322 (42.9%)	1260 (42.0%)	62 (80.5%)	<0.001
Diabetes	559 (18.2%)	532 (17.7%)	27 (35.1%)	<0.001
Dyslipidemia	1103 (35.8%)	1056 (35.2%)	47 (61.0%)	<0.001
Smoking habit	304 (9.9%)	296 (9.9%)	8 (10.4%)	0.877
Obesity	430 (14.0%)	413 (13.8%)	17 (22.1%)	0.037
Peripheral artery disease	199 (6.5%)	187 (6.2%)	12 (15.6%)	0.001
Ischemic stroke	187 (6.1%)	170 (5.7%)	17 (22.1%)	<0.001
Coronary artery disease	199 (6.5%)	190 (6.3%)	9 (11.7%)	0.051
Atrial fibrillation / flutter	269 (8.7%)	246 (8.2%)	23 (29.9%)	<0.001
Chronic heart failure	152 (4.9%)	135 (4.50)	17 (22.1)	<0.001
PM / ICD	53 (1.7%)	49 (1.6%)	4 (5.2%)	0.042
COPD	236 (7.7%)	217 (7.2%)	19 (24.7%)	<0.001
Chronic kidney disease	180 (5.8%)	165 (5.5%)	15 (19.5%)	<0.001
Cancer	301 (9.8%)	289 (9.6%)	12 (15.6%)	0.115
Baseline cardiovascular drug therapy				
Therapeutic anticoagulation	309 (10.0%)	284 (9.5%)	25 (32.5%)	<0.001
Antiplatelet	440 (14.3%)	420 (14.0%)	20 (26.0%)	0.003
ACE inhibitor or ARB	1005 (32.6%)	963 (32.1%)	42 (54.6%)	<0.001
MRA	93 (3.0%)	83 (2.8%)	10 (13.0%)	<0.001
Sacubitril / valsartan	13 (0.4%)	11 (0.4%)	2 (2.6%)	0.040
Beta-blocker	407 (13.2%)	376 (12.5%)	31 (40.3%)	<0.001
Diuretics	628 (20.4%)	588 (19.6%)	40 (52.0%)	<0.001
SGLT2 inhibitors	43 (1.4%)	41 (1.4%)	2 (2.6%)	0.292
Digoxin	22 (0.7%)	21 (0.7%)	1 (1.3%)	0.428
Statin	878 (28.5%)	837 (27.9%)	41 (53.3%)	<0.001
Antiarrhythmic	22 (0.7%)	19 (0.6%)	3 (3.9%)	0.016
Vital signs at hospital presentation				
Systolic blood pressure	129.0±21.4	128.9±21.2	132.0±27.4	0.229
Heart rate	93.6±19.7	93.8±19.6	86.7±22.1	0.002
First oxygen saturation	92.2±6.3	92.3±6.2	89.3±7.6	<0.001
First oxygen saturation receiving oxygen	284 (9.2%)	268 (8.9%)	16 (20.8%)	0.001
First chest radiography				
Without infiltrates Unilateral infiltrates Bilateral infiltrates	821 (26.7%) 592 (19.2%) 1537 (49.9%)	809 (26.9%) 576 (19.2%) 1489 (49.6%)	12 (15.6%) 16 (20.8%) 48 (62.3%)	0.052
Laboratory data				
Median GFR (ml/min/1.73m^2)	75.4±21.3	75.8±21.1	60.4±24.9	<0.001
Median hemoglobin (g/dl)	13.5±1.8	13.5±1.8	12.7±2.1	<0.001
Highest Ferritin (ng/dl)	1481±6298	1481±6400	1481±1744	1.000
Highest D-dimer (ng/ml)	9351±32508	9281±32674	11580±26887	0.001
Highest Troponin	456±5300	458±5403	417±1683	0.963
Highest NT-proBNP	6067±16730	5469±16118	10508±20374	<0.001
Highest fibrinogen (mg/dl)	820±281	818±282	878±273	0.267
Highest C reactive protein (mg/l)	131.5±109.3	130.4±108.9	167.9±115.6	0.004
Highest IL-6 (pg/ml)	311.4±591.8	310.3±598.3	339.1±400.0	0.125
Antimicrobial and inmunomodulatory agents against the COVID-19				
Hydroxychloroquine	2383 (77.4%)	2313 (77.0%)	70 (90.9%)	0.004

Lopinavir / ritonavir	319 (10.4%)	314 (10.5%)	5 (6.5%)	0.343
Azithromycin	1404 (45.6%)	1362 (45.4%)	42 (54.6%)	0.132
Tocilizumab	227 (7.4%)	220 (7.3%)	7 (9.1%)	0.558
Systemic glucocorticoid	444 (14.4%)	421 (14.0%)	23 (29.9%)	<0.001
Clinical outcomes				
Hospital admission	2191 (71.1%)	2115 (70.4%)	76 (98.7%)	<0.001
Pulmonary embolism	76 (2.5%)	72 (2.4%)	4 (5.2%)	0.120
Thrombotic event	116 (3.8%)	111 (3.7%)	5 (6.5%)	0.212
Mayor bleeding Non-mayor bleeding	22 (0.7%) 66 (2.1%)	21 (0.7%) 61 (2.0%)	1 (1.3%) 5 (6.5%)	0.045
Atrial fibrillation / flutter during admission	87 (2.8%)	76 (2.5%)	11 (14.3%)	<0.001
Ventricular arrhythmias during admission	11 (0.4%)	10 (0.3%)	1 (1.3%)	0.243
Critical care admission	182 (5.9%)	176 (5.9%)	6 (7.8%)	0.497
Mechanical ventilation	173 (5.6%)	168 (5.6%)	5 (6.5%)	0.623
Death	626 (20.3%)	590 (19.7%)	36 (46.8%)	<0.001

Abbreviations as in table 1.

Table 3. "Univariate and multivariate logistic regression model for the prediction of AHF during follow-up".

	Non-adjusted			Adjusted		
Variable	**OR (95% CI)**	**Standard error**	**P value**	**OR (95% CI)**	**Standard error**	**P value**
Age (per 5-year increase)	1.33 (1.23-1.45)	0.06	<0.001	1.28 (1.16-1.41)	0.06	<0.001
Atrial arrhythmias during admission	6.42 (3.26-12.64)	2.22	<0.001	4.64 (2.19-9.83)	1.78	<0.001
Chronic heart failure	6.02 (3.42-10.60)	1.74	<0.001	2.51 (1.33-4.76)	0.82	0.005
Bleeding during admission	1.77 (1.11-2.80)	0.42	0.016	1.60 (0.98-2.62)	0.40	0.061
COPD	4.21 (2.46-7.19)	1.15	<0.001	2.51 (1.40-4.49)	0.75	0.002