Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study

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Abstract (267 words)

Background: To assess the prognostic value of a history of heart failure (HF) in patients with coronavirus disease 2019 (COVID-19).

Methods and Results. We enrolled 692 consecutive patients admitted for COVID-19 in 13 Italian cardiology centres between 1st March and 9th April, 2020. Mean age was 67.4 ± 13.2 years, 69.5% patients were males, 90 (13.0%) had a history of HF, median hospitalization length was 14 days, interquartile range, 9-24. In-hospital death occurred in 37 of 90 patients (41.1%) with HF history versus 126 of those with no HF history (20.9%). The increased risk of death associated with HF history remained significant after adjustment for clinical variables related to COVID-19 and HF severity, including comorbidities, oxygen saturation, lymphocyte count and plasma troponin (adjusted hazard ratio (HR) for death, 2.25; 95% confidence intervals (CI), 1.26-4.02; p=0.006 at multivariable Cox regression model including 404 patients). Patients with a history of HF also had more in-hospital complications including acute HF (33.3% vs 5.1%, p<0.001), acute renal failure (28.1% vs 12.9%, p<0.001), multiorgan failure (15.9% vs 5.8%, p=0.004) and sepsis (18.4% vs 8.9%, p=0.006). Other independent predictors of outcome were age, sex, oxygen saturation and oxygen partial pressure at arterial gas analysis/fraction of inspired oxygen ratio (PaO2/FiO2). In hospital treatment with corticosteroids and heparin had beneficial effects (adjusted HR for death, 0.46; 95% CI, 0.29-0.74; p=0.001; N=404 for corticosteroids and adjusted HR, 0.41; 95%CI, 0.25-0.67; p< 0.001; N=364 for heparin).

Conclusions: Hospitalized patients with COVID-19 and a history of HF have an extremely poor outcome with higher mortality and in-hospital complications. HF history is an independent predictor of increased in-hospital mortality.

Introduction

Coronavirus disease 2019 (COVID-19) outbreak is a pandemic affecting more than 27 million people worldwide so far, a major cause of morbidity and mortality and a major challenge for healthcare systems. Earlier reports already showed the high prevalence and negative impact on prognosis of older age and cardiovascular comorbidities.[1] Heart failure (HF) is a major cause of mortality and morbidity. However, its prevalence has been reported in only relatively few studies.[2-9] Acute HF may also occur as a major complication during the in-hospital course of patients with COVID-19 although it was assessed in only a few studies.[4,10,11]

Italy has been one of the first countries involved in the COVID-19 outbreak and this had a major impact on its healthcare system with many cardiology clinics receiving almost exclusively COVID-19 patients.[12,13] Cardio-COVID-Italy is a multicentre retrospective, observational study based on data collection from consecutive patients hospitalized for COVID-19 in 13 Italian cardiology centres. This article reports the clinical impact of pre-existing HF on the clinical course of the patients hospitalized for COVID-19.

Methods

Study population

This is an analysis of consecutive patients with COVID-19 and available data regarding HF history admitted in 13 Italian cardiology units from 1st March to 9th April, 2020 (see Appendix S1 for the list of centres and investigators). Patients with a history of left ventricular assist device implantation or heart transplant were excluded because of distinct characteristics of such population (N=4). All patients had a laboratory-confirmed SARS-CoV-2 infection, diagnosed through real time reverse transcriptase–polymerase chain reaction (RT-PCR) assay

of rino-pharyngeal swabs or lower respiratory tract aspirates. Patients` follow-up was carried on until April 23rd, 2020. This study complied with the edicts of the Declaration of Helsinki and was approved by the ethical committee of Civil Hospitals of Brescia Italy (no. NP 4105) and of each recruiting centre.

Data collection

Patients' data including demographics, medical history, in-hospital clinical course, treatment and outcomes were extracted from the in-hospitals medical records. History of HF was assessed through the collection of anamnestic data. Patients were also stratified in HF with reduced or preserved left ventricular ejection fraction (LVEF) based on the values before hospitalization, <50%, and ≥50%, respectively. Patients with mid-range LVEF were included in the group of reduced LVEF given recent findings that suggest a similar response to treatment and a similar pathophysiological profile.[14] In-hospital acute HF was defined by the occurrence of dyspnoea and clinical signs of congestion requiring intravenous diuretic treatment. The presence of congestion was evaluated with physical examination, laboratory biomarkers (N-terminal-pro hormone Brain Natriuretic Peptide, NT-proBNP), chest X-ray or echocardiography. A similar definition was used in acute HF studies.[15] Laboratory exams were collected at the time of hospitalization and during the hospital stay upon clinical indications. Different hospitals used different troponin assays, including either troponin I or troponin T. Because of the different assays used, we did not report specific values but categorized patients as those with normal or elevated plasma troponin levels (i.e. above the 99% percentile of normal values as per manufacturer indications). Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate (eGFR). Chest-X ray and echocardiography were performed when clinically indicated. Right ventricular (RV) dysfunction was defined by the presence of tricuspid annular plane systolic

excursion (TAPSE) < 17 mm and fractional area change (FAC) < 35% at echocardiography and free lateral wall (S') <9.5 cm/sec at tissue Doppler imaging. Acute RV failure was defined by the development of peculiar clinical signs during the hospitalization.[16]

Statistical analyses

Patients were stratified based on their history of HF. Differences between patients with LVEF <50% and those with LVEF ≥ 50% are analysed in supplementary material. Normally distributed continuous variables were reported as means and standard deviations, skewed variables as medians and interquartile ranges, dichotomous variables as counts and percentages. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline checklist for data reporting. Accordingly, we showed the number of non-missing data for each variable in the tables. Comparisons between groups were made, respectively, using Student's t-test for means, Wilcoxon test for medians, and Chi-squared test for proportions. Survival curves were obtained using the Kaplan-Meier method and compared between patients with vs without history of HF using the log-rank test.

Cox regression analysis was performed to identify the variables which were independently associated with an increased risk of death. We used a complete case-approach so that participants with missing data were excluded. The number of variables entered into the Cox regression model was limited according to the number of events, based on the principle of not having more than one variable every 10 events. The variables selected had to be clinically significant and associated with an increased risk of death at univariate analysis with a p value ≤ 0.01 between survivors and non-survivors. The variables entered into the Cox regression model were demographic and clinical variables, including age, sex, HF, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, hypertension,

hyperdyslipidemia, chronic kidney disease and variables measured at the time of admission, including oxygen saturation, oxygen partial pressure at arterial gas analysis/fraction of inspired oxygen ratio (PaO2/FiO2), serum troponin, C-reactive protein, lymphocyte count, haemoglobin and eGFR. Additional exploratory analyses were performed for other variables potentially related with death and with >25% missing data. Each of these variables was entered into the previous model and the analysis repeated with all the patients with complete data. The variables tested in these exploratory analyses were treatment before hospitalization with angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilisin inhibitors (ARNI), mineralocorticoids, beta blockers, statins and anticoagulants, other laboratory findings, including red blood cell count, platelets count, D-dimer, aspartate transaminase, albumin and in-hospital treatment. The association with mortality of NT-proBNP and LVEF was also tested in those patients where these data were available. A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA statistical software version 9.4 (StataCorp LLC, TX, USA).

Results

Clinical characteristics

Demographic and clinical characteristics are shown in **Table 1**. We included 692 consecutive patients, mean age was 67.4 ± 13.2 years, 69.5% were males. Ninety patients (13%) had a history of HF. Compared with the others, patients with a history of HF were older, with a higher prevalence of cardiovascular risk factors (hypertension, hyperdyslipidemia, diabetes), coronary artery disease and atrial fibrillation. Also, other comorbidities, including chronic kidney disease and chronic obstructive pulmonary disease, were more frequent in those with

a history of HF. Patients with a history of HF were more likely to receive chronic treatment with ACEi/ARBs/ARNI, mineralocorticoids, beta-blockers, anticoagulants, and statins. At admission, vital parameters were similar between the patients with or without a HF history, except for the lower oxygen saturation and the higher heart rate in the subjects without HF.

Laboratory findings are summarized in **Table 1** (see **Supplementary Table 1** for reference ranges). HF patients had lower blood cell counts, lower haemoglobin levels and worse renal function. Serum troponin levels were elevated in 71.4% of HF patients versus 40.7% of controls ($p<0.001$). NT-proBNP plasma levels were higher in patients with HF (4088 [1344-11200] versus 212 [89-697] pg/mL in those without HF; $p<0.001$). In-hospital echocardiographic measurements were only available for 261 patients, of whom 63 in the HF group and 198 in non-HF group. HF patients had lower LVEF (42.1 ± 13.1 vs 55.3 ± 8.9%; $p<0.001$) and more frequently showed echocardiographic signs of RV dysfunction (28.6 vs 11.2%; $p<0.001$).

Further details of patients with HF history are reported in **Table 2**. Among the 90 patients with history of HF, 64 (71%) had a reduced LVEF and 26 (29%) had a preserved LVEF, based on the values before hospitalization. There were no differences between patients with reduced and preserved LVEF, except for a higher BMI and a higher proportion of patients with risk factors, smoking history and hyperlipidaemia, in the patients with preserved LVEF. Respiratory rate and PaO2/FiO2 were higher in the patients with reduced LVEF (**Supplementary Table 2**).

In-hospital management

Data about in-hospital management are shown in **Table 1**. Patients without a history of HF were more likely to be treated with hydroxychloroquine, anti-interleukin agent (tocilizumab) and corticosteroids. Oxygen requirements were similar but both non-invasive ventilation and

intubation were performed less in HF patients, compared with the non-HF ones (31.1% vs 45.6% and 5.6% vs 17.0%, p=0.010 and p=0.006, respectively). Patients "too sick" for invasive ventilatory support were more frequent in HF group (35.3% vs 20.5% p=0.003) (**Table 1**).

In-hospital mortality

Median hospitalization length of stay was of 14 days (interquartile range [IQR], 9-24). In-hospital death occurred in 163 patients (23.6%). Patients with a history of HF had higher mortality (41.1% versus 20.9% p<0.001) (**Table 1**). Kaplan-Meier survival curves are shown in **Figure 1**. History of HF was associated with an increased risk of death both at univariate analysis (hazard ratio [HR], 2,43; 95% confidence intervals [CI], 1.69-3.50; p<0.001) (**Table 3**) and at multivariable analysis including demographic and clinical variables (adjusted HR, 2.25; 95% CI, 1.26-4.02; p=0.006) (**Table 3**). At exploratory analyses including patients in whom these data were available, the association between a HF history and in-hospital mortality was not modified by the inclusion of either LVEF or NT-proBNP levels (p for interaction 0.51 and 0.96, respectively). Similarly, RV dysfunction was associated with an increased risk of death at univariate analysis (HR, 3.26; 95% CI, 1.88-3.63; p<0.001) but not at multivariable analysis.

Other variables independently associated with in-hospital mortality at multivariable analysis were age, sex, oxygen saturation and PaO2/FiO2 (**Table 3**). The role of in-hospital treatment was evaluated in exploratory analyses that included less patients than in the main model. Among in-hospital treatments, corticosteroids and heparin were associated with lower mortality at both univariate and multivariable analysis (HR, 0.60; 95% CI, 0.44-0.82; p=0.001; adjusted HR 0.46; 95% CI, 0.29-0.74; p=0.001; N=404 for corticosteroids and HR, 0.57; 95% CI, 0.41-0.81; p<0.001; adjusted HR, 0.41; 95% CI, 0.25–0.67; p<0.001; N=364 for heparin, **Table 4**). Patients with HF were less likely to be treated with corticosteroids (38.2% versus 51.5%;

p=0.019) and had a similar likelihood to receive heparin (**Table 1**). History of HF maintained its association with mortality also when corticosteroids or heparin were entered into the multivariable model (HR, 2.21; 95%CI 1.26-3.89; p=0.004; and HR, 1.95; 95%CI 1.05-3.62; p=0.034; **Supplementary Table 3**). Despite treatment with ACEi/ARBs/ARNI was more prevalent in the patients who died, it was not associated with death at multivariable analysis (HR, 1.40; 95% CI, 0.85-2.30; p=0.17). Similarly, within the population with a history of HF, treatment with ACEi/ARBs/ARNI did not modify outcome (HR, 0.58; 95% CI, 0.25-1.33; P=0.196; **Supplementary Table 4**).

In-hospital complications

Patients with a history of HF were also at higher risk of complications during hospitalization, namely acute HF (33.3% vs 5.1%, p<0.001), sepsis (18.4% vs 8.9%, p=0.006), acute renal failure (28.1% vs 12.9%, p<0.001) and multiorgan failure (15.9% vs 5.8%, p=0.004) (**Figure 2**) Acute HF occurred during hospitalization in 50 (9.1%) of the 550 patients in whom these data were available. Twenty-four (48%) of these events were new onset HF in patients with no HF history. Acute RV failure occurred more frequently in HF patients (10.0% vs 2.7%; p=0.016). On the other hand, pulmonary embolism was more common in patients without a history of HF (2.2% vs 8.5%; p=0.040). No significant difference was observed in acute respiratory distress syndrome (ARDS).

Clinical characteristics, laboratory findings, in-hospital management and outcome of patients who develop in-hospital acute HF are shown in **Supplementary Table 5 and Supplementary Figure 1**.

Discussion

In our study, 13% of the patients hospitalized for COVID-19 had a history of HF and this was associated with an increased risk of death, in-hospital worsening-HF, acute renal failure, sepsis and multiorgan failure. In-hospital death occurred in 41% of the patients with a HF history versus 21% of those without a HF history. The association between HF and mortality remained significant after adjustment for variables associated with COVID-19 and HF severity at multivariable analysis.

The proportion of patients hospitalized for COVID-19 with a history of HF ranged from 3% to 10% in previous reports.[2-8] The higher prevalence of HF in our study may be explained by the older age of our population and the selection of subjects who were admitted to cardiology units because of concomitant cardiac disease during the pandemic.

Our study confirms previous findings that history of HF is a powerful independent predictor of mortality and in-hospital complications.[4,6,8,9] A previous single-centre study showed a mortality of 57% in patients with a history of HF, compared with the others, who had a mortality rate of 18%.[9] In an analysis of the Danish nationwide administrative databases, 90 patients with HF who had COVID-19 had a 37% mortality in 15 days.[17] In an analysis of a large database from Spain, including 152 of 3080 consecutive COVID-19 patients with a history of HF (4.9%), mortality was of 48.7% in the patients with HF versus 19.0% in the others.[18] Similarly, in a study in the New York area, history of HF was associated with a 50% increase in the risk of in- hospital death.[6] Our data were collected in a large study group of consecutive patients from 13 Italian centres and confirm and extend the role of HF as a major risk factor in COVID-19 with an adjusted HR for mortality of 2,25; 95% confidence intervals: 1.26-4.02; p=0.006.

Our patients with HF history were also more likely to develop myocardial injury,

defined as increased troponin levels, as well as to have higher NT-proBNP serum levels. Elevated levels of troponins were found in 71.4% of our patients with a history of HF. Similar values were found in previous studies.[2,3,5,7] However, elevated troponin levels, but not HF, were independent predictors of increased mortality in these studies. In contrast, our results show that a HF history has an additive prognostic significance, regardless of troponin and NT-proBNP plasma levels, also when they are included in the multivariable models. This is likely caused by the higher prevalence of HF and cardiac comorbidities in our study group. On the other hand, troponin did not result as an independent marker of poor prognosis probably due to an insufficient statistical power of our study (adjusted HR, 1.57; 95% CI, 0.97-2.54; p=0.067). Other analyses, including one from a larger number of patients, though with less data about HF history, from the same database, showed the independent prognostic value of elevated serum troponin levels.[2,7,19]

The relationship between COVID-19 and HF seems to be bidirectional. HF may increase the incidence and severity of COVID-19 and COVID-19 may favour episodes of acute HF.[20-22] In our study, acute HF developed during hospitalization in 9.1% of the patients and this event was not preceded by a HF history in 48% of the cases. Acute HF was reported also in other series as a frequent complication of COVID-19 and a predictor of death, along with sepsis and ARDS, suggesting a relationship between these two conditions.[1,8,10,18] Acute respiratory infections may be precipitant factors of acute HF.[23] Influenza is associated with increased mortality and morbidity in patients with HF and influenza vaccination may have a protective role.[24]

Our study also showed that RV dysfunction, assessed by echocardiography, was associated with three-fold increased risk of death at univariate analysis. However, statistical significance was not reached at multivariable analysis, probably due to the limited number of

events and the relatively small number of patients undergoing a thorough echocardiographic assessment. Recent studies showed that RV dysfunction, namely RV longitudinal strain, and RV volume are powerful predictors of poorer outcomes in COVID-19.[25,26]

A somehow unexpected finding of our study is the lower rate of non-invasive ventilation and intubation in patients with a history of HF. Such results are consistent with the higher values of both oxygen saturation and PaO_2/FiO_2 ratio (an index of lung function) in these patients. These findings may be explained by the higher protection from capillary fluid leakage in the patients with HF and are consistent with a prominent role of the cardiac involvement as a cause of reduced survival and symptoms in these patients.[27] However, another possible explanation could be the severity of the disease in HF patients. Patients with HF were more likely to be judged as "too sick" for intubation, compared with the others. During the pandemics, due to the limited number of supports in Italy, only patients with a long-life expectancy were selected for such treatments. This is consistent with our different results, compared with those by Petrilli et al.[6]

As expected, patients suffering from HF were more likely to be treated with ACEi and ARBs. Consistent with recent studies, chronic treatment with these agents was not an independent predictor of an increased risk of death.[28] Randomized controlled trials are needed to show whether they may have protective effects for the lung and heart injury related to the COVID- 19 hyperinflammatory response.[29]

Patients with HF were more often treated with anticoagulants and this likely occurred because of their comorbidities, i.e. atrial fibrillation. Anticoagulant therapy could have had a protective role against pulmonary embolism which was more common in non HF patients. This may explain the low rate of pulmonary embolism in our patients with HF, compared with the others, although this may also be due to the competing risk between HF and pulmonary

embolism as major causes of complications and death. In our patients, heparin treatment was associated with a lower mortality both at univariate and at multivariable analysis. This finding supports recent studies showing the major role of thromboembolic events as determinants of the high mortality of COVID-19 with recent indication to thromboembolic prophylaxis in this disease.[30]

Corticosteroid treatment was also associated with better outcomes at multivariable analysis in our study. This result is consistent with recent preliminary results from the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial of dexamethasone in patients hospitalized with Covid-19. In this study dexamethasone administration was associated with a lower 28-day mortality in the patients receiving either invasive mechanical ventilation or oxygen alone at randomization whereas it had a neutral effect in those patients with no ventilatory support.[30] Our study group, including mainly patients with severe COVID-19 and, thus, with characteristics similar to those of the sicker ones in RECOVERY, confirms the beneficial effects of corticosteroids administration in COVID-19 severe presentations.

In our study, patients with HF were less likely to be treated with corticosteroids, 38.2% versus 51.5% in the other subjects. One explanation may be the competing risk of HF versus the other COVID-19 related complications. The clinical course was dominated by cardiac complications in the patients with HF and they less frequently receive other non-cardiac medications. Consistently, patients with HF were also less likely to receive antiviral therapy in our study. The difference in corticosteroid treatment was, on the other hand, relatively small, although statistically significant, and can be considered also as a chance finding favoured by the relatively small number of patients. Importantly, corticosteroid treatment does not modify the prognostic role of HF.

One main limitation of our analysis is the lack of post-discharge follow-up data. Furthermore, given the logistical limitations during this emerging outbreak, some cases had incomplete data. Consequently, our Cox model was limited to some variables selected according clinical and potential relevance. Particularly, plasma levels of NT-proBNP were not available in all patients, at baseline and over time. Nevertheless, among our patients with available data, no interaction was observed on clinical outcomes. Similarly, echocardiographic parameters were not routinely collected.

Conclusion

History of HF is a frequent comorbidity in patients hospitalized for COVID-19. It is associated with a higher mortality and more complications during the clinical course and this association is independent from other variables related with HF and COVID-19 severity. Corticosteroids and heparin were associated with lower mortality in our patients and these results require further investigations.

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Author Contributions: Marco Metra had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Daniela Tomasoni and Riccardo M. Inciardi contributed equally to this work and are co–first authors.

Conflict of interest

P.A. received speaker and advisor honoraria from Novartis, AstraZeneca, Vifor, Daiichi-Sankyo, Boehringer Ingelheim, Pfizer, GSK and MSD.

V.C. received consulting honoraria from CVie Therapeutics Limited, Servier, and Windtree Therapeutics.

A.M. reports personal consulting honoraria from Novartis, Servier, Astra Zeneca for participation to advisory board meetings and receives grants from Novartis and Niccomo for research trials.

M.P. received research grant and speaking fees from Novartis, Servier, Vifor.

M.M. reports personal consulting honoraria from Abbott, Actelion, Amgen, Bayer, Servier, Vifor Pharma and Windtree Therapeutics for participation to advisory board meetings and executive committees of clinical trials.

All other authors declare no conflict of interest.

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Figures legend

Figure 1. Kaplan-Meier survival curves stratified by history of heart failure .

HF, heart failure

Figure 2. In-hospital clinical outcome stratified by history of heart failure

HF, heart failure; MOF, multiorgan failure.

Supplementary figure 1. In-hospital clinical outcome stratified by acute heart failure event.

HF, heart failure; MOF, multiorgan failure.

Table 1. Clinical characteristics, laboratory and echocardiographic findings, in-hospital management and outcome of the study population stratified by history of heart failure

Variable	No. assessed	Total (N=692)	No History of Heart Failure (N=602)	History of Heart Failure (N= 90)	p value
Clinical characteristics					
Age (years)	692	67.4 ± 13.2	66.5 ± 13.3	73.0 ± 11.4	< 0.001
Sex (male)	692	481 (69.5)	415 (68.9)	66 (73.3)	0.40
Body mass index (Kg/m2)	533	27.3 ± 5.3	27.3 ± 5.2	27.1 ± 5.9	0.83
Smoker, n (%)	586	160 (27.3)	118 (23.1)	42 (55.3)	< 0.001
Hypertension, n (%)	692	396 (57.2)	328 (54.5)	68 (75.6)	< 0.001
Hyperdyslipidemia, n (%)	691	192 (27.8)	136 (22.6)	56 (62.2)	< 0.001
Diabetes, n (%)	692	162 (23.4)	125 (20.8)	37 (41.1)	< 0.001
Atrial fibrillation, n (%)	692	106 (15.3)	64 (10.6)	42 (46.7)	< 0.001
Coronary artery disease, n (%)	692	148 (21.4)	93 (15.4)	55 (61.1)	< 0.001
COPD, n (%)	692	67 (9.7)	45 (7.5)	22 (24.4)	< 0.001
CKD, n (%)	692	126 (18.2)	77 (12.8)	49 (54.4)	< 0.001
Treatment before hospitalization					
ACE-i/ARBs/ARNI, n (%)	651	247 (37.9)	205 (36.2)	42 (50.0)	0.015
Mineralocorticoids, n (%)	535	43 (8.0)	20 (4.3)	23 (34.8)	< 0.001
Beta-blockers, n (%)	652	248 (38.0)	179 (31.6)	69 (81.2)	< 0.001
Direct oral anticoagulants, n (%)	646	48 (7.4)	31 (5.5)	17 (20.5)	< 0.001
Warfarin, n (%)	647	48 (7.4)	30 (5.3)	18 (21.6)	< 0.001
Statins, n (%)	655	179 (27.3)	132 (23.1)	47 (56.0)	<

					0.001
Baseline findings					
Temperature (°C)	680	37.3 ± 1.0	37.3 ± 1.0	37.2 ± 1.0	0.62
Fever, n (%)	690	443 (64.2)	386 (64.3)	57 (63.3)	0.85
Systolic blood pressure (mmHg)	680	129.7 ± 21.6	130.3 ±21.6	126.0 ± 21.6	0.08
Heart rate (bpm)	679	86.8 ± 18.1	87.5 ± 18.5	81.6 ± 14.3	0.004
Respiratory rate ≥ 22, n (%)	535	278 (52.0)	245 (52.4)	33 (49.3)	0.64
Oxygen saturation (%)	681	90.4 ± 7.7	90.2 ± 8.0	91.9 ± 5.4	0.047
SOFA score ≥ 3, n (%)	453	196 (43.3)	156 (40.2)	40 (61.5)	< 0.001
Laboratory measurements					
PaO2/FiO2 (mmHg/%)	577	235.3 ± 131.6	232.5 ± 134.2	255.5 ± 110.0	0.17
Red blood cell count (x10^6/µL)	642	4.5 (4.0-4.9)	4.6 (4.1 - 4.9)	4.1 (3.5 - 4.6)	<0.001
Hemoglobin (g/dL)	638	13.4 (11.8-14.4)	13.5 (12.1-14.5)	11.8 (10.0-13.5)	< 0.001
Hematocrit (%)	637	39.1 (35.5-42.8)	39.5 (36.2-42.9)	35.8 (30.3-40.5)	< 0.001
White blood cell count (per µL)	642	6830 (5000-9350)	6945 (5100-9350)	6155 (4655-9145)	0.15
Lymphocytes count (per µL)	524	930 (625-1300)	970 (650-1300)	800 (550-1102)	0.008
Platelets count (x10^3/µL)	638	204 (156-270)	209 (158-275)	176 (141-241)	0.007
Creatinine (mg/dL)	631	1.0 (0.8 – 1.3)	1.0 (0.8 – 1.2)	1.4 (0.9 – 2.5)	<0.001
eGFR (CKD-EPI) (mL/min)	631	74 (50-90)	78 (57-92)	45 (25-73)	< 0.001
Sodium (mEq/L)	622	138 (135-140)	137 (135-140)	138 (136-141)	0.19
Potassium (mEq/L)	587	3.9 (3.6-4.3)	3.9 (3.6-4.3)	3.9 (3.6-4.2)	0.56
CRP on admission (mg/dL)	598	23.7 (11.0-36.0)	23.1 (10.6-35.9)	26.6 (15.2-36.9)	0.25
Peak CRP (mg/dL)	662	98.8 (29.9-179.0)	99.3 (29.3-182.5)	95.7 (41.0-151.4)	0.61
Procalcitonin (ng/mL)	243	0.2 (0.1 – 0.5)	0.1 (0.1 – 0.4)	0.3 (0.1 – 1.0)	0.03
Elevated troponin*, n (%)	605	272 (45.0)	212 (40.7)	60 (71.4)	< 0.001
NT-proBNP (pg/mL)	215	303 (96-1201)	212 (89-697)	4088 (1344-11200)	< 0.001
D-dimer (ng/mL)	460	870 (433 – 1807)	860 (427 – 1686)	1074 (556 – 2733)	0.19
Bilirubin (mg/dL)	542	0.6 (0.4 – 0.8)	0.6 (0.4 – 0.8)	0.6 (0.5 – 0.8)	0.27
Aspartate transaminase (u/L)	646	41 (26 – 64)	42 (27 – 67)	32 (21 – 51)	<0.001
Lactate dehydrogenase (u/L)	517	364 (253 – 520)	369 (256 – 542)	317 (243 – 480)	0.15
Creatinine phosphokinase (u/L)	357	113 (57 – 302)	110 (56 – 296)	152 (63 – 373)	0.41
Albumin (g/dL)	374	3.2 (2.8 – 3.6)	3.2 (2.7 – 3.5)	3.3 (3.0 – 3.6)	0.07
INR	599	1.1 (1.0 – 1.2)	1.1 (1.0 – 1.2)	1.2 (1.0 – 1.4)	0.007
Arterial Ph	592	7.5 (7.4 – 7.5)	7.5 (7.4 – 7.5)	7.5 (7.4 – 7.5)	0.29
In-hospital echocardiographic measurements					
Left Ventricular Ejection Fraction (%)	261	52.5 ± 11.3	55.3 ± 8.9	42.1 ± 13.1	< 0.001
RV dysfunction**, n (%)	253	38 (15.0)	22 (11.2)	16 (28.6)	< 0.001
In-hospital treatment					
Hydroxychloroquine, n(%)	687	578 (84.1)	520 (87.0)	58 (65.2)	< 0.001
Lopinavir/Ritonavir, n (%)	687	184 (26.8)	166 (27.8)	18 (20.2)	0.13
Darunavir/Ritonavir, n (%)	687	174 (25.3)	158 (26.4)	16 (18.0)	0.09

Tocilizumab, n (%)	687	80 (11.6)	76 (12.7)	4 (4.5)	0.024
Corticosteroids, n (%)	687	342 (49.8)	308 (51.5)	34 (38.2)	0.019
Antibiotics, n (%)	687	605 (88.1)	527 (88.1)	78 (87.6)	0.89
Heparin, n (%)	643	470 (73.1)	416 (74.2)	54 (65.9)	0.11
Ventilatory support***					
Oxygen support with FiO2 <50%	685	299 (43.6)	253 (42.4)	46 (51.7)	0.10
Oxygen support with FiO2 ≥50%	677	378 (55.8)	331 (56.1)	47 (54.0)	0.72
Non-invasive ventilation, n (%)	686	300 (43.7)	272 (45.6)	28 (31.1)	0.010
Intubation, n (%)	688	107 (15.6)	102 (17.0)	5 (5.6)	0.006
Too sick for intubation, n (%)	581	132 (22.7)	102 (20.5)	30 (35.3)	0.003
Outcomes					
Death, n (%)	692	163 (23.6)	126 (20.9)	37 (41.1)	< 0.001
Cause of death					
- Respiratory insufficiency	163	110 (67.5)	84 (66.6)	26 (70.2)	0.52
- Acute MI	163	4 (2.4)	4 (3.2)	0 (0)	0.24
- Pulmonary embolism	163	11 (6.7)	10 (7.9)	1 (2.7)	0.22
- Stroke	163	4 (2.4)	4 (3.2)	0 (0)	0.24
- Multiorgan failure	163	34 (20.9)	24 (19.0)	10 (27.0)	0.15
Acute Heart Failure, n (%)	550	50 (9.1)	24 (5.1)	26 (33.3)	< 0.001
Acute RV failure, n (%)	248	11 (4.4)	5 (2.7)	6 (10.0)	0.016
STEMI, n (%)	679	11 (1.6)	10 (1.7)	1 (1.1)	0.69
NSTEMI, n (%)	550	17 (3.1)	14 (3.0)	3 (3.8)	0.68
Ventricular Arrhythmia, n (%)	679	8 (1.2)	3 (0.5)	5 (5.6)	< 0.001
Pulmonary embolism, n (%)	680	52 (7.6)	50 (8.5)	2 (2.2)	0.040
Other Thromboembolic events, venous or arterial, n (%)	692	61 (8.8)	57 (9.5)	4 (4.4)	0.12
ARDS, n (%)	577	99 (17.2)	92 (18.2)	7 (9.9)	0.08
Sepsis, n (%)	671	68 (10.1)	52 (8.9)	16 (18.4)	0.006
Acute renal failure, n (%)	484	72 (14.9)	54 (12.9)	18 (28.1)	<0.001
Multiorgan Failure, n (%)	475	34 (7.2)	24 (5.8)	10 (15.9)	0.004

Values are reported as means ± standard deviations or medians (interquartile ranges)

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/m2); CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; fever, temperature > 37.5°C; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio; MI, myocardial infarction; No., number of patients; NSTEMI, non ST elevation myocardial infarction; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis; RV, right ventricular; SOFA, sequential organ failure assessment; STEMI, ST elevation myocardial infarction.

*Elevated troponin value was defined as above the 99% percentile of normal values.

** RV dysfunction was defined by echocardiography as tricuspid annular plane systolic excursion (TAPSE) < 17 mm, fractional area change (FAC) < 35% and tissue Doppler of the free lateral wall (S') <9.5 cm/sec.

***Patients could receive more than one ventilatory support during hospitalization.

Table 2. Clinical characteristics and echocardiographic findings of the patients with heart failure

	No. assessed	No. (%)
Clinical characteristics		
Primary aetiology, n (%)	90	
Ischaemic		46 (51.1)
Idiopathic		9 (10.0)
Valvular		8 (8.9)
Hypertensive		8 (8.9)
Arrhythmic		7 (7.8)
Genetic cardiomyopathies*		5 (5.5)
Other		7 (7.8)
LV ejection fraction before hospitalization	90	
Reduced LVEF, n (%)		64 (71)
Preserved LVEF, n (%)		26 (29)
Treatment before hospitalization		
Loop diuretics, n (%)	90	65 (72.2)
ACE-i/ARBs/ARNI, n (%)	84	42 (50.0)
Mineralocorticoids, n (%)	66	23 (34.8)
Beta-blockers, n (%)	85	69 (81.2)
Direct oral anticoagulants, n (%)	83	17 (20.5)
Warfarin, n (%)	83	18 (21.6)
Statins, n (%)	84	47 (56.0)
Device implantation, n (%)	90	
ICD		20 (22.2)
CRT		8 (8.9)
In-hospital echocardiographic measurements		
LVEF (%) mean±SD	63	42.1±13.1
RV dysfunction, n (%)	56	16 (28.6)
Left atrium enlargement, n (%)	62	30 (48.4)
Mitral regurgitation ≥ moderate, n (%)	63	13 (20.6)
Tricuspid regurgitation ≥ moderate, n (%)	63	7 (11.1)
Aortic stenosis ≥ moderate, n (%)	63	5 (7.9)
Other valve disease, n (%)	63	5 (7.9)
sPAP ≥ 35mmHg, n (%)	49	27 (55.1)

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; No., number of patients; preserved LVEF, LVEF ≥ 50%; reduced LVEF, LVEF<50%; RV, right ventricular; SD, standard deviation; sPAP, systolic pulmonary artery pressure.

*Genetic cardiomyopathies include hypertrophic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy; left ventricular non compaction; muscular dystrophies.

Table 3. Univariate and multivariable Cox regression model for in-hospital death (N = 404)

		Univariable		Multivariable*	
	Level/Units	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Clinical characteristics					
Age	+5 years	1.35 (1.26-1.45)	<0.001	1.28 (1.13-1.45)	<0.001
Sex	M vs F	1.33 (0.92 - 1.90)	0.125	2.14 (1.16-3.94)	0.015
Smoker	Yes vs No	1.44 (1.01-2.06)	0.046	-	-
Heart failure	Yes vs No	2.43 (1.69-3.50)	<0.001	2.25 (1.26-4.02)	0.006
Hypertension	Yes vs No	1.96 (1.40-2.74)	<0.001	1.21 (0.72-2.01)	0.47
Hyperdyslipidemia	Yes vs No	2.30 (1.69-3.14)	<0.001	0.82 (0.47-1.44)	0.49
Diabetes	Yes vs No	1.34 (0.95-1.89)	0.096	-	-
Atrial fibrillation	Yes vs No	2.48 (1.74-3.54)	<0.001	1.27 (0.73-2.23)	0.39
Coronary artery disease	Yes vs No	2.29 (1.65-3.17)	<0.001	1.20 (0.67-2.14)	0.55
COPD	Yes vs No	1.79 (1.16-2.76)	0.009	1.41 (0.72-2.75)	0.32
CKD	Yes vs No	2.78 (2.00-3.84)	<0.001	1.09 (0.56-2.10)	0.81
Treatment before hospitalization					
ACE-i/ARBs/ARNI	Yes vs No	1.33 (0.92–1.92)	0.125	-	-
Mineralcorticoids	Yes vs No	1.30 (0.73 – 2.30)	0.37	-	-
Beta-blockers	Yes vs No	1.97 (1.42 – 2.69)	< 0.001	-	-
Direct oral anticoagulants	Yes vs No	1.70 (1.01 – 2.85)	0.046	-	-
Warfarin	Yes vs No	1.24 (0.70-2.19)	0.456	-	-
Statins	Yes vs No	1.93 (1.39 – 2.67)	<0.001	-	-
Baseline findings					
Heart rate	+5 bpm	1.01 (0.99 – 1.02)	0.088	-	-
Oxygen saturation	+5%	0.84 (0.77 - 0.90)	<0.001	0.97 (0.94-0.99)	0.010
Laboratory measurements					
PaO_2/FiO_2	+5 mmHg/%	0.98 (0.97-0.99)	0.002	0.98 (0.97-0.99)	<0.001
Red blood cell count	+ 1 $x10^6$/µL	0.68 (0.55 – 0.86)	0.001	-	-
Hemoglobin	+ 1 g/l	0.91 (0.85 – 0.98)	0.015	0.94 (0.84-1.06)	0.33
Hematocrit	+ 1 %	0.97 (0.95 – 0.99)	0.038	-	-
Lymphocytes count	+1000 U/µL	0.92 (0.88–0.95)	<0.001	0.95 (0.90-1.00)	0.067
Platelets count	+ 1 $x10^3$/µL	0.99 (0.99 – 0.99)	0.016	-	-

Creatinine	+ 1 mg/dl	1.12 (1.05 – 1.20)	0.001	-	-
eGFR (CKD-EPI)	+10 ml/min	0.98 (0.98-0.99)	<0.001	0.99 (0.98-1.01)	0.60
CRP on admission	+ 1 mg/dl	1.01 (1.01-1.01)	<0.001	1.00 (0.99-1.00)	0.16
Procalcitonin	+1 ng/ml	1.00 (0.98 – 1.02)	0.77	-	-
Troponin	Elevated vs Normal	3.22 (2.26-4.58)	<0.001	1.57 (0.97-2.54)	0.067
NT-proBNP	1 log U increase	1.38 (1.19 – 1.56)	<0.001	-	-
D-dimer	1 log U increase	1.37 (1.18 - 1.58)	< 0.001	-	-
Aspartate transaminase	+1	1.00 (0.99 – 1.01)	0.93	-	-
Albumin	+1	0.92 (0.66 – 1.28)	0.64	-	-
INR	+1	1.23 (1.04 – 1.45)	0.018	-	-

*HR and 95% CIs are reported only for those variables entered into the main multivariable model.
Legend: ACE-i, angiotensin-converting enzyme -inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/m2); CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis.

Table 4. Univariate and multivariable Cox regression model for death adding in-hospital medications to the main model (N=404 for hydroxychloroquine and corticosteroids; N=364 for heparin)

	Univariate analysis		Multivariable analysis*	
Medication	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Hydroxychloroquine	0.45 (0.32-0.65)	<0.001	0.60 (0.33-1.11)	0.106
Lopinavir/Ritonavir	1.14 (0.81-1.60)	0.453	-	-
Darunavir/Ritonavir	0.76 (0.52-1.10)	0.149	-	-
Tocilizumab	0.76 (0.47-1.21)	0.244	-	-
Corticosteroids	0.60 (0.44-0.82)	0.001	0.46 (0.29-0.74)	0.001
Antibiotics	1.31 (0.73-2.36)	0.371	-	-
Heparin	0.57 (0.41-0.81)	<0.001	0.41 (0.25 – 0.67)	< 0.001

*The variables significant at univariate analysis were entered into the main model including age, sex, history of heart failure, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, hyperdyslipidaemia, chronic kidney disease, PaO2/FiO2, oxygen saturation, troponin, C-reactive protein, lymphocytes count, haemoglobin and eGFR.

Supplementary table 1. Reference ranges for laboratory variables

Variable	Reference range
PaO2/FiO2 (mmHg/%)	> 300
Red blood cell count (x10^6/µL)	4.0-5.2
Hemoglobin (g/dL)	12.0-16.0
Hematocrit (%)	37.0-47.0
White blood cell count (per µL)	4000-10800
Lymphocytes count (per µL)	900-4000
Platelets count (x10^3/µL)	130-400
Creatinine (mg/dL)	0.60 – 1.0
eGFR (CKD-EPI) (mL/min)	90 – 120
Sodium (mEq/L)	136-145
Potassium (mEq/L)	3.5 – 4.5
CRP on admission (mg/dL)	<5.0
Peak CRP (mg/dL)	<5.0
Procalcitonin (ng/mL)	<0.5
Elevated troponin*	
NT-proBNP (pg/mL)	<93
D-dimer (ng/mL)	<232
Bilirubin (mg/dL)	<1.2
Aspartate transaminase (u/L)	18 – 39
Lactate dehydrogenase (u/L)	135 – 225
Creatinine phosphokinase (u/L)	39 – 308
Albumin (g/dL)	4.5 – 5.2
INR	0.9 – 1.2
Arterial pH	7.37 – 7.45

Legend: CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis. *Elevated troponin value was defined as above the 99% percentile of normal values.

Supplementary table 2. Clinical characteristics, laboratory findings, in-hospital management and outcome of patients stratified on the basis of LVEF before hospitalization (LVEF <50% vs LVEF ≥50%)

Variable	No. assessed	Total (N=90)	LVEF<50% (N=64)	LVEF≥50% (N= 26)	p value
Clinical characteristics					
Age (years)	90	73.0 ± 11.4	73.3 ± 11.1	72.3 ± 12.3	0.72
Sex (male)	90	66 (73.3)	47 (73.4)	19 (73.1)	0.97
Body mass index (Kg/m2)	66	27.1 ± 5.9	26.3 ± 4.8	29.7 ± 8.1	0.047
Smoker, n (%)	76	42 (55.3)	26 (48.1)	16 (72.7)	0.05
Hypertension, n (%)	90	68 (75.6)	48 (75.0)	20 (76.9)	0.85
Hyperdyslipidemia, n (%)	90	56 (62.2)	36 (56.3)	20 (76.9)	0.07
Diabetes, n (%)	90	37 (41.1)	26 (40.6)	11 (42.3)	0.88
Atrial fibrillation, n (%)	90	42 (46.7)	32 (50.0)	10 (38.5)	0.32
Coronary artery disease, n (%)	90	55 (61.1)	39 (60.9)	16 (61.5)	0.96
COPD, n (%)	90	22 (24.4)	13 (20.3)	9 (34.6)	0.15
CKD, n (%)	90	49 (54.4)	33 (51.6)	16 (61.6)	0.39
Treatment before hospitalization					
ACE-i/ARBs/ARNI, n (%)	84	42 (50.0)	29 (48.3)	13 (54.2)	0.63
Mineralocorticoids, n (%)	66	23 (34.8)	16 (37.2)	7 (30.4)	0.58
Beta-blockers, n (%)	85	69 (81.2)	49 (81.7)	20 (80.0)	0.86
Direct oral anticoagulants, n (%)	83	17 (20.5)	14 (23.7)	3 (12.5)	0.25
Warfarin, n (%)	83	18 (21.6)	10 (17.2)	8 (32.0)	0.12
Statins, n (%)	84	47 (56.0)	34 (56.7)	13 (54.2)	0.83
Baseline findings					
Temperature (°C)	88	37.2 ± 1.0	37.2 ± 1.1	37.3 ± 0.8	0.74
Fever, n (%)	90	57 (63.3)	42 (65.6)	15 (57.7)	0.48
Systolic blood pressure (mmHg)	89	126.0 ± 21.6	126.4 ± 22.4	124.8 ± 20.2	0.74
Heart rate (bpm)	89	81.6 ± 14.3	81 ± 15	82 ± 11	0.74
Respiratory rate ≥ 22, n (%)	67	33 (49.3)	26 (60.5)	7 (29.2)	0.014
Oxygen saturation (%)	89	91.9 ± 5.4	92.1 ± 5.0	90.9 ± 6.2	0.34
SOFA score ≥ 3, n (%)	65	40 (61.5)	26 (59.1)	14 (66.7)	0.56
Laboratory measurements					
PaO2/FiO2 (mmHg/%)	71	255.5 ± 110.0	283.0 ± 102.7	189.6 ±100.1	<0.001
Red blood cell count (x10^6/µL)	84	4.1 (3.6 - 4.6)	4.1 (3.5-4.7)	4.3 (3.9-4.5)	0.41
Hemoglobin (g/dL)	83	11.8 (10.0-13.5)	11.3 (9.9-13.6)	12.4 (10.9-13.4)	0.36
Hematocrit (%)	82	35.8 (30.3-40.5)	35.2 (30.1-40.5)	37.1 (33.3-40.4)	0.37
White blood cell count (per µL)	84	6155 (4655-9145)	6055 (4570-7460)	7455 (5300-11000)	0.13
Lymphocytes count (per µL)	70	800 (500-1102)	790 (500-1000)	900 (600-1430)	0.10
Platelets count (x10^3/µL)	83	176 (141-241)	180 (153-229)	175 (110-271)	0.83
Creatinine (mg/dL)	83	1.4 (0.9 – 2.5)	1.3 (0.9-2.5)	1.6 (1.1-2.5)	0.30
eGFR (CKD-EPI) (mL/min)	83	45 (25-73)	48 (25-79)	37 (25-62)	0.37
Sodium (mEq/L)	80	138 (136-141)	138 (136-140)	139 (136-141)	0.50
Potassium (mEq/L)	77	3.9 (3.6-4.2)	3.9 (3.5-4.2)	4.0 (3.7-4.2)	0.25
CRP on admission (mg/dL)	82	26.6 (15.2-36.9)	26.7 (17.0-35.1)	25.1 (9.2-36.9)	0.80
Peak CRP (mg/dL)	84	95.7 (41.0-151.4)	87.7 (29.9-151.0)	122.6 (52.1-157.3)	0.45
Procalcitonin (ng/mL)	30	0.3 (0.1 – 1.0)	0.3 (0.2-4.1)	0.2 (0.1-0.4)	0.19
Elevated troponin*, n (%)	84	60 (71.4)	44 (73.3)	16 (66.7)	0.54

NT-proBNP (pg/mL)	22	4088 (1344-11200)	3630 (1201-8947)	10006 (2857-11200)	0.41
D-dimer (ng/mL)	40	1074 (556 – 2733)	1074 (581-3142)	1066 (216-2259)	0.60
Bilirubin (mg/dL)	68	0.6 (0.5 – 0.8)	0.7 (0.5-0.9)	0.5 (0.4-0.7)	0.18
Aspartate transaminase (u/L)	81	32 (21 – 52)	34 (22-51)	25 (19-53)	0.17
Lactate dehydrogenase (u/L)	58	317 (243 – 480)	299 (244-450)	413 (220-540)	0.37
Creatinine phosphokinase (u/L)	44	152 (63 – 373)	141 (66-346)	221 (61-441)	0.82
Albumin (g/dL)	48	3.3 (3.0 – 3.6)	3.3 (3.0-3.7)	3.0 (2.7-3.2)	0.12
INR	74	1.2 (1.0 – 1.4)	1.2 (1.1-1.4)	1.2 (1.0-1.3)	0.43
Arterial Ph	74	7.5 (7.4 – 7.5)	7.5 (7.4-7.5)	7.5 (7.4-7.5)	0.55
In-hospital echocardiographic measurements					
Left Ventricular Ejection Fraction (%)	63	42.1 ± 13.1	42.1 ± 13.1	54.1 ± 8.9	< 0.001
RV dysfunction**, n (%)	56	16 (28.6)	16 (29.1)	0 (0)	0.52
In-hospital treatment					
Hydroxychloroquine, n(%)	89	58 (65.2)	46 (73.0)	12 (46.1)	0.016
Lopinavir/Ritonavir, n (%)	89	18 (20.2)	15 (23.8)	3 (11.5)	0.19
Darunavir/Ritonavir, n (%)	89	16 (18.0)	10 (15.9)	6 (23.1)	0.42
Tocilizumab, n (%)	89	4 (4.5)	4 (6.3)	0 (0.0)	0.19
Corticosteroids, n (%)	89	34 (38.2)	27 (42.9)	7 (26.9)	0.16
Antibiotics, n (%)	89	78 (87.6)	54 (85.7)	24 (92.3)	0.39
Heparin, n (%)	82	54 (65.9)	37 (63.8)	17 (70.8)	0.54
Ventilatory support***					
Oxygen support with FiO2 <50%	89	46 (51.7)	33 (52.4)	13 (50.0)	0.84
Oxygen support with FiO2 ≥50%	87	47 (54.0)	33 (53.2)	14 (56.0)	0.81
Non-invasive ventilation, n (%)	90	28 (31.1)	18 (28.1)	10 (38.5)	0.34
Intubation, n (%)	90	5 (5.6)	3 (4.8)	2 (7.7)	0.59
Too sick for intubation, n (%)	85	30 (35.3)	21 (34.4)	9 (37.5)	0.79
Outcomes					
Death, n (%)	90	37 (41.1)	27 (42.2)	10 (38.5)	0.74
Cause of death					
- Respiratory insufficiency	37	26 (70.2)	19 (70.3)	7 (70.0)	0.97
- Acute MI	37	0 (0)	0 (0)	0 (0)	
- Pulmonary embolism	37	1 (2.7)	1 (3.7)	0 (0)	0.52
- Stroke	37	0 (0)	0 (0)	0 (0)	
- Multiorgan failure	37	10 (27.0)	7 (25.9)	3 (30.0)	0.87
Acute Heart Failure, n (%)	78	26 (33.3)	20 (35.7)	6 (27.3)	0.48
Acute RV failure, n (%)	60	6 (10.0)	6 (13.3)	0 (0)	0.14
STEMI, n (%)	89	1 (1.1)	1 (1.6)	0 (0)	0.52
NSTEMI, n (%)	78	3 (3.8)	2 (3.6)	1 (4.5)	0.84
Ventricular Arrhythmia, n (%)	89	5 (5.6)	3 (4.8)	2 (7.7)	0.59
Pulmonary embolism, n (%)	89	2 (2.2)	2 (3.2)	0 (0.0)	0.36
Other Thromboembolic event, venous or arterial, n (%)	90	4 (4.4)	4 (6.3)	0 (0)	0.19
ARDS, n (%)	71	7 (9.9)	3 (6.0)	4 (19.0)	0.09
Sepsis, n (%)	87	16 (18.4)	15 (24.6)	1 (3.8)	0.022
Acute renal failure, n (%)	64	18 (28.1)	14 (29.2)	4 (25.0)	0.75
Multiorgan Failure, n (%)	63	10 (15.9)	7 (14.9)	3 (18.8)	0.72

Values are reported as means ± standard deviations or medians (interquartile ranges)

Legend: ACE-i, angiotensin-converting enzyme -inhibitors; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/m2); CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; fever, temperature > 37.5°C; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio;

MI, myocardial infarction; No., number of patients; NSTEMI, non ST elevation myocardial infarction; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis; RV, right ventricular; SOFA, sequential organ failure assessment; STEMI, ST elevation myocardial infarction.
*Elevated troponin value was defined as above the 99% percentile of normal values.
** RV dysfunction was defined by echocardiography as tricuspid annular plane systolic excursion (TAPSE) < 17 mm, fractional area change (FAC) < 35% and tissue Doppler of the free lateral wall (S') <9.5 cm/sec.
***Patients could receive more than one ventilatory support during hospitalization.

Supplementary table 3. Hazard ratio of HF for in-hospital death with the inclusion of additional potentially relevant variables in multivariable Cox regression analysis

	No.	HR for HF (95%CI)	p-value
Main model*	404	2.25 (1.26-4.02)	0.006
+ Smoker	328	1.85 (0.97-3.55)	0.063
+ ACE-i/ARBs/ARNI	369	1.92 (1.05-3.52)	0.034
+ Mineralcorticoids	271	2.09 (0.95-4.60)	0.067
+ Beta-blockers	371	1.98 (1.08-3.63)	0.026
+ Direct oral anticoagulants	365	1.96 (1.08-3.65)	0.030
+ Statins	373	1.99 (1.10-3.61)	0.022
+ Red blood cell count	403	2.20 (1.27-3.94)	0.007
+ Platelets count	403	1.98 (1.11 -3.56)	0.020
+ D-dimer	264	2.69 (1.19-6.04)	0.016
+ Aspartate transaminase	390	2.24 (1.24-4.06)	0.007
+ Albumin	230	2.23 (0.98-5.05)	0.053
+ In hospital corticosteroids	404	2.21 (1.26-3.89)	0.004
+ in-hospital heparin	364	1.95 (1.05-3.62)	0.034

*Main model was developed with the inclusion of age, sex, history of heart failure, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, hyperdyslipidemia, chronic kidney disease, oxygen saturation, PaO2/FiO2, troponin, C-reactive protein, lymphocytes count, haemoglobin and eGFR.

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; No., number of patients

Supplementary table 4. Treatment before hospitalization, in-hospital medications and mortality in patients with a history of HF

Variables	No.	HR (95% CI)	p-value
Treatment before hospitalization			
ACE-i/ARBs/ARNI	84	0.58 (0.25-1.33)	0.196
Mineralcorticoids	66	0.89 (0.36-2.22)	0.810
Beta-blockers	85	0.84 (0.39-1.81)	0.658
In-hospital treatment			
Hydroxychloroquine	89	0.58 (0.30-1.12)	0.106
Lopinavir/Ritonavir	89	1.16 (0.54-2.45)	0.707
Darunavir/Ritonavir	89	1.12 (0.49-2.56)	0.782
Tocilizumab	89	1.21 (0.37-3.97)	0.754
Corticosteroids	89	0.62 (0.32-1.23)	0.175
Antibiotics	89	0.38 (0.15-0.95)	0.039
Heparin	82	0.45 (0.22-0.91)	0.026

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; No., number of patients

Supplementary table 5. Clinical characteristics, laboratory and echocardiographic findings, in-hospital management and outcome of the study population stratified by acute heart failure event

Variable	No. assessed	Total (N=550)	No Acute Heart Failure (N=500)	Acute Heart Failure (N= 50)	p value
Clinical characteristics					
Age (years)	550	68.2 ± 13.1	68.1 ± 13.1	69.8 ± 13.1	0.38
Sex (male)	550	372 (67.6)	334 (66.8)	38 (76.8)	0.18
Body mass index (Kg/m2)	410	26.7 ± 4.8	26.8 ± 4.9	25.7 ± 4.5	0.14
Smoker, n (%)	455	142 (31.2)	123 (29.9)	19 (44.2)	0.05
Hypertension, n (%)	550	323 (58.7)	286 (57.2)	37 (74.0)	0.021
Hyperdyslipidemia, n (%)	550	157 (28.5)	133 (26.6)	24 (48.0)	<0.001
Diabetes, n (%)	550	130 (23.6)	115 (23.0)	15 (30.0)	0.27
History of heart failure, n (%)	550	78 (14.2)	52 (10.4)	26 (52.0)	< 0.001
Atrial fibrillation, n (%)	550	91 (16.5)	68 (13.6)	23 (46.0)	< 0.001
Coronary artery disease, n (%)	550	119 (21.6)	100 (20.0)	19 (38.0)	0.003
COPD, n (%)	550	59 (10.7)	51 (10.2)	8 (16.0)	0.21
CKD, n (%)	550	118 (21.5)	97 (19.4)	21 (42.0)	< 0.001
Treatment before hospitalization					
ACE-i/ARBs/ARNI, n (%)	513	194 (37.8)	176 (37.4)	18 (41.9)	0.57
Mineralocorticoids, n (%)	406	32 (7.9)	26 (6.8)	6 (23.1)	0.003
Beta-blockers, n (%)	513	203 (39.5)	175 (37.1)	28 (68.3)	< 0.001
Direct oral anticoagulants, n (%)	504	36 (7.1)	26 (5.6)	10 (25.0)	< 0.001
Warfarin, n (%)	506	32 (6.3)	28 (6.0)	4 (10.0)	0.32
Statins, n (%)	516	141 (27.3)	120 (25.3)	21 (50.0)	< 0.001
Baseline findings					
Temperature (°C)	539	37.3 ± 1.0	37.3 ± 1.0	37.2 ± 0.9	0.42
Fever, n (%)	548	361 (65.9)	330 (66.3)	31 (62.0)	0.57
Systolic blood pressure (mmHg)	539	129.7 ± 22.1	130.4 ±21.5	121.2 ± 25.4	0.013
Heart rate (bpm)	538	87.1 ± 18.2	86.9 ± 17.5	88.9 ± 24.4	0.49
Respiratory rate $\geq$ 22, n (%)	403	173 (42.9)	163 (43.8)	10 (32.3)	0.21
Oxygen saturation (%)	540	91.5 ± 7.1	91.4 ± 7.0	91.7 ± 7.7	0.76
SOFA score $\geq$ 3, n (%)	443	193 (43.5)	171 (41.4)	22 (55.0)	0.13
Laboratory measurements					
PaO2/FiO2 (mmHg/%)	441	256.5 ± 132.9	255.5 ± 135.2	268.5 ± 108.0	0.56
Red blood cell count (x10^6/µL)	548	4.5 (4.0 – 4.9)	4.5 (4.0 - 4.9)	4.3 (3.7 – 5.0)	0.39
Hemoglobin (g/dL)	544	13.4 (11.8 – 14.4)	13.5 (11.9 - 14.4)	12.1 (10.5 - 14.1)	0.008
Hematocrit (%)	543	39.1 (35.4 – 42.8)	39.2 (35.6 - 42.8)	36.1 (30.9 - 42.7)	0.07
White blood cell count (per µL)	548	6615 (4895 – 9100)	6605 (4824 - 8990)	7475 (5200 - 11300)	0.044
Lymphocytes absolute (per µL)	463	930 (600 – 1300)	945 (615 - 1300)	900 (600 - 1200)	0.40
Platelets count (x10^3/µL)	545	201 (154 – 269)	201 (154 - 269)	197 (164 - 282)	0.68
Creatinine (mg/dL)	539	1.0 (0.8 - 1.3)	1.0 (0.8 – 1.3)	1.4 (0.9 – 2.2)	< 0.001
eGFR (CKD-EPI) (mL/min)	539	74 (49 – 89)	75 (52 – 89)	45 (28 – 84)	< 0.001
Sodium (mEq/L)	530	137 (135 – 140)	137 (135 - 140)	137 (133 - 140)	0.68
Potassium (mEq/L)	498	3.9 (3.6 – 4.3)	3.9 (3.6 - 4.3)	4.0 (3.6 - 4.6)	0.23
CRP on admission (mg/dL)	506	23.4 (10.4 - 35. 8)	23.9 (10.4 – 35.7)	19.8 (11.3 – 38.6)	0.68

Peak CRP (mg/dL)	524	93.5 (26.1 – 162.3)	94.2 (27.1- 161.2)	87.7 (17.7 - 165.8)	0.90
Procalcitonin (ng/mL)	223	0.1 (0.1 – 0.4)	0.1 (0.1 – 0.3)	0.3 (0.2 – 1.1)	0.011
Elevated troponin*, n (%)	463	223 (48.2)	181 (43.7)	42 (85.7)	< 0.001
NT-proBNP (pg/mL)	207	341 (94 – 1331)	253 (89 - 940)	8686 (3552 - 11200)	< 0.001
D-dimer (ng/mL)	355	829 (430 – 1473)	820 (423 – 1495)	834 (536 – 1110)	0.89
Bilirubin (mg/dL)	472	0.6 (0.4 – 0.8)	0.6 (0.4 – 0.7)	0.6 (0.4 – 0.9)	0.10
Aspartate transaminase (u/L)	516	38 (25 – 61)	38 (24 – 60)	42 (29 – 68)	0.11
Lactate dehydrogenase (u/L)	416	331 (243 – 486)	333 (244 – 487)	297 (243 – 465)	0.59
Creatinine phosphokinase (u/L)	349	113 (59 – 302)	110 (54 – 299)	167 (67 – 502)	0.07
Albumin (g/dL)	301	3.2 (2.7 – 3.5)	3.1 (2.7 – 3.5)	3.2 (2.8 – 3.5)	0.28
INR	474	1.1 (1.0 – 1.2)	1.1 (1.0 – 1.2)	1.2 (1.1 – 1.4)	< 0.001
Arterial Ph	454	7.5 (7.4 -7.5)	7.5 (7.4 – 7.5)	7.5 (7.4 – 7.5)	0.023
In-hospital echocardiographic measurements					
Left Ventricular Ejection Fraction (%)	209	52.0 ± 11.2	53.4 ± 10.1	42.0 ± 13.4	< 0.001
RV dysfunction**, n (%)	203	26 (12.8)	15 (8.9)	11 (31.4)	< 0.001
In-hospital treatment					
Hydroxychloroquine, n(%)	546	460 (84.2)	423 (85.1)	37 (75.5)	0.08
Lopinavir/Ritonavir, n (%)	546	149 (27.3)	132 (26.6)	17 (34.7)	0.22
Darunavir/Ritonavir, n (%)	546	115 (21.1)	108 (21.7)	7 (14.3)	0.22
Tocilizumab, n (%)	546	62 (11.4)	55 (11.1)	7 (14.3)	0.50
Corticosteroids, n (%)	546	270 (49.5)	251 (50.5)	19 (38.8)	0.12
Antibiotics, n (%)	546	486 (89.0)	444 (89.3)	42 (85.7)	0.44
Heparin, n (%)	501	355 (70.9)	331 (71.8)	24 (60.0)	0.12
Ventilatory support***					
Oxygen support with FiO2 <50%	544	250 (46.0)	227 (45.8)	23 (47.9)	0.78
Oxygen support with FiO2 ≥50%	537	283 (52.7)	256 (52.4)	27 (56.3)	0.61
Non-invasive ventilation, n (%)	545	206 (37.8)	187 (37.6)	19 (38.8)	0.88
Intubation, n (%)	547	49 (9.0)	46 (9.2)	3 (6.1)	0.47
Too sick for intubation, n (%)	499	111 (22.2)	99 (21.9)	12 (25.5)	0.57
Outcomes					
Death, n (%)	550	129 (23.5)	109 (21.8)	20 (40.0)	0.004
Cause of death					
- Respiratory insufficiency	129	83 (64.3)	77 (70.6)	6 (30.0)	0.041
- Acute MI	129	4 (3.1)	3 (2.8)	1 (5.0)	0.21
- Pulmonary embolism	129	7 (5.4)	7 (6.4)	0 (0)	0.15
- Stroke	129	1 (0.8)	1 (0.9)	0 (0)	0.66
- Multiorgan failure	129	34 (26.4)	21 (19.3)	13 (65.0)	< 0.001
NSTEMI, n (%)	550	17 (3.1)	15 (3.0)	2 (4.0)	0.70
Ventricular Arrhythmia, n (%)	550	7 (1.3)	4 (0.8)	3 (6.0)	0.002
Pulmonary embolism, n (%)	550	31 (5.6)	29 (5.8)	2 (4.0)	0.60
Other Thromboembolic even, venous or arterial, n (%)	550	38 (6.9)	35 (7.0)	3 (6.0)	0.79
ARDS, n (%)	441	49 (11.1)	46 (11.4)	3 (7.7)	0.48
Sepsis, n (%)	541	55 (10.1)	46 (9.4)	9 (18.0)	0.05
Acute renal failure, n (%)	474	70 (14.8)	52 (12.2)	18 (38.3)	< 0.001
Multiorgan Failure, n (%)	473	34 (7.1)	21 (4.9)	13 (27.7)	< 0.001

Values are reported as means ± standard deviations or medians (interquartile ranges)

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/m2); CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; fever, temperature > 37.5°C; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio; MI, myocardial infarction; No., number of patients; NSTEMI, non ST elevation myocardial infarction; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis; RV, right ventricular; SOFA, sequential organ failure assessment.
*Elevated troponin value was defined as above the 99% percentile of normal values.
** RV dysfunction was defined by echocardiography as tricuspid annular plane systolic excursion (TAPSE) < 17 mm, fractional area change (FAC) < 35% and tissue Doppler of the free lateral wall (S') <9.5 cm/sec.
***Patients could receive more than one ventilatory support during hospitalization.

Table 1. Clinical characteristics, laboratory and echocardiographic findings, in-hospital management and outcome of the study population stratified by history of heart failure

Variable	No. assessed	Total (N=692)	No History of Heart Failure (N=602)	History of Heart Failure (N= 90)	p value
Clinical characteristics					
Age (years)	692	67.4 ± 13.2	66.5 ± 13.3	73.0 ± 11.4	< 0.001
Sex (male)	692	481 (69.5)	415 (68.9)	66 (73.3)	0.40
Body mass index (Kg/m2)	533	27.3 ± 5.3	27.3 ± 5.2	27.1 ± 5.9	0.83
Smoker, n (%)	586	160 (27.3)	118 (23.1)	42 (55.3)	< 0.001
Hypertension, n (%)	692	396 (57.2)	328 (54.5)	68 (75.6)	< 0.001
Hyperdyslipidemia, n (%)	691	192 (27.8)	136 (22.6)	56 (62.2)	< 0.001
Diabetes, n (%)	692	162 (23.4)	125 (20.8)	37 (41.1)	< 0.001
Atrial fibrillation, n (%)	692	106 (15.3)	64 (10.6)	42 (46.7)	< 0.001
Coronary artery disease, n (%)	692	148 (21.4)	93 (15.4)	55 (61.1)	< 0.001
COPD, n (%)	692	67 (9.7)	45 (7.5)	22 (24.4)	< 0.001
CKD, n (%)	692	126 (18.2)	77 (12.8)	49 (54.4)	< 0.001
Treatment before hospitalization					
ACE-i/ARBs/ARNI, n (%)	651	247 (37.9)	205 (36.2)	42 (50.0)	0.015
Mineralocorticoids, n (%)	535	43 (8.0)	20 (4.3)	23 (34.8)	< 0.001
Beta-blockers, n (%)	652	248 (38.0)	179 (31.6)	69 (81.2)	< 0.001
Direct oral anticoagulants, n (%)	646	48 (7.4)	31 (5.5)	17 (20.5)	< 0.001
Warfarin, n (%)	647	48 (7.4)	30 (5.3)	18 (21.6)	< 0.001
Statins, n (%)	655	179 (27.3)	132 (23.1)	47 (56.0)	< 0.001
Baseline findings					
Temperature (°C)	680	37.3 ± 1.0	37.3 ± 1.0	37.2 ± 1.0	0.62
Fever, n (%)	690	443 (64.2)	386 (64.3)	57 (63.3)	0.85
Systolic blood pressure (mmHg)	680	129.7 ± 21.6	130.3 ±21.6	126.0 ± 21.6	0.08
Heart rate (bpm)	679	86.8 ± 18.1	87.5 ± 18.5	81.6 ± 14.3	0.004
Respiratory rate ≥ 22, n (%)	535	278 (52.0)	245 (52.4)	33 (49.3)	0.64
Oxygen saturation (%)	681	90.4 ± 7.7	90.2 ± 8.0	91.9 ± 5.4	0.047
SOFA score ≥ 3, n (%)	453	196 (43.3)	156 (40.2)	40 (61.5)	< 0.001
Laboratory measurements					
PaO2/FiO2 (mmHg/%)	577	235.3 ± 131.6	232.5 ± 134.2	255.5 ± 110.0	0.17
Red blood cell count (x10^6/µL)	642	4.5 (4.0-4.9)	4.6 (4.1 - 4.9)	4.1 (3.5 - 4.6)	<0.001
Hemoglobin (g/dL)	638	13.4 (11.8-14.4)	13.5 (12.1-14.5)	11.8 (10.0-13.5)	< 0.001
Hematocrit (%)	637	39.1 (35.5-42.8)	39.5 (36.2-42.9)	35.8 (30.3-40.5)	< 0.001
White blood cell count (per µL)	642	6830 (5000-9350)	6945 (5100-9350)	6155 (4655-9145)	0.15

Lymphocytes count (per µL)	524	930 (625-1300)	970 (650-1300)	800 (550-1102)	0.008
Platelets count (x10^3/µL)	638	204 (156-270)	209 (158-275)	176 (141-241)	0.007
Creatinine (mg/dL)	631	1.0 (0.8 – 1.3)	1.0 (0.8 – 1.2)	1.4 (0.9 – 2.5)	<0.001
eGFR (CKD-EPI) (mL/min)	631	74 (50-90)	78 (57-92)	45 (25-73)	< 0.001
Sodium (mEq/L)	622	138 (135-140)	137 (135-140)	138 (136-141)	0.19
Potassium (mEq/L)	587	3.9 (3.6-4.3)	3.9 (3.6-4.3)	3.9 (3.6-4.2)	0.56
CRP on admission (mg/dL)	598	23.7 (11.0-36.0)	23.1 (10.6-35.9)	26.6 (15.2-36.9)	0.25
Peak CRP (mg/dL)	662	98.8 (29.9-179.0)	99.3 (29.3-182.5)	95.7 (41.0-151.4)	0.61
Procalcitonin (ng/mL)	243	0.2 (0.1 – 0.5)	0.1 (0.1 – 0.4)	0.3 (0.1 – 1.0)	0.03
Elevated troponin*, n (%)	605	272 (45.0)	212 (40.7)	60 (71.4)	< 0.001
NT-proBNP (pg/mL)	215	303 (96-1201)	212 (89-697)	4088 (1344-11200)	< 0.001
D-dimer (ng/mL)	460	870 (433 – 1807)	860 (427 – 1686)	1074 (556 – 2733)	0.19
Bilirubin (mg/dL)	542	0.6 (0.4 – 0.8)	0.6 (0.4 – 0.8)	0.6 (0.5 – 0.8)	0.27
Aspartate transaminase (u/L)	646	41 (26 – 64)	42 (27 – 67)	32 (21 – 51)	<0.001
Lactate dehydrogenase (u/L)	517	364 (253 – 520)	369 (256 – 542)	317 (243 – 480)	0.15
Creatinine phosphokinase (u/L)	357	113 (57 – 302)	110 (56 – 296)	152 (63 – 373)	0.41
Albumin (g/dL)	374	3.2 (2.8 – 3.6)	3.2 (2.7 – 3.5)	3.3 (3.0 – 3.6)	0.07
INR	599	1.1 (1.0 – 1.2)	1.1 (1.0 – 1.2)	1.2 (1.0 – 1.4)	0.007
Arterial Ph	592	7.5 (7.4 – 7.5)	7.5 (7.4 – 7.5)	7.5 (7.4 – 7.5)	0.29
In-hospital echocardiographic measurements					
Left Ventricular Ejection Fraction (%)	261	52.5 ± 11.3	55.3 ± 8.9	42.1 ± 13.1	< 0.001
RV dysfunction**, n (%)	253	38 (15.0)	22 (11.2)	16 (28.6)	< 0.001
In-hospital treatment					
Hydroxychloroquine, n(%)	687	578 (84.1)	520 (87.0)	58 (65.2)	< 0.001
Lopinavir/Ritonavir, n (%)	687	184 (26.8)	166 (27.8)	18 (20.2)	0.13
Darunavir/Ritonavir, n (%)	687	174 (25.3)	158 (26.4)	16 (18.0)	0.09
Tocilizumab, n (%)	687	80 (11.6)	76 (12.7)	4 (4.5)	0.024
Corticosteroids, n (%)	687	342 (49.8)	308 (51.5)	34 (38.2)	0.019
Antibiotics, n (%)	687	605 (88.1)	527 (88.1)	78 (87.6)	0.89
Heparin, n (%)	643	470 (73.1)	416 (74.2)	54 (65.9)	0.11
Ventilatory support***					
Oxygen support with FiO2 <50%	685	299 (43.6)	253 (42.4)	46 (51.7)	0.10
Oxygen support with FiO2 ≥50%	677	378 (55.8)	331 (56.1)	47 (54.0)	0.72
Non-invasive ventilation, n (%)	686	300 (43.7)	272 (45.6)	28 (31.1)	0.010
Intubation, n (%)	688	107 (15.6)	102 (17.0)	5 (5.6)	0.006
Too sick for intubation, n (%)	581	132 (22.7)	102 (20.5)	30 (35.3)	0.003
Outcomes					
Death, n (%)	692	163 (23.6)	126 (20.9)	37 (41.1)	< 0.001
Cause of death					
- Respiratory insufficiency	163	110 (67.5)	84 (66.6)	26 (70.2)	0.52
- Acute MI	163	4 (2.4)	4 (3.2)	0 (0)	0.24
- Pulmonary embolism	163	11 (6.7)	10 (7.9)	1 (2.7)	0.22
- Stroke	163	4 (2.4)	4 (3.2)	0 (0)	0.24

- Multiorgan failure	163	34 (20.9)	24 (19.0)	10 (27.0)	0.15
Acute Heart Failure, n (%)	550	50 (9.1)	24 (5.1)	26 (33.3)	< 0.001
Acute RV failure, n (%)	248	11 (4.4)	5 (2.7)	6 (10.0)	0.016
STEMI, n (%)	679	11 (1.6)	10 (1.7)	1 (1.1)	0.69
NSTEMI, n (%)	550	17 (3.1)	14 (3.0)	3 (3.8)	0.68
Ventricular Arrhythmia, n (%)	679	8 (1.2)	3 (0.5)	5 (5.6)	< 0.001
Pulmonary embolism, n (%)	680	52 (7.6)	50 (8.5)	2 (2.2)	0.040
Other Thromboembolic events, venous or arterial, n (%)	692	61 (8.8)	57 (9.5)	4 (4.4)	0.12
ARDS, n (%)	577	99 (17.2)	92 (18.2)	7 (9.9)	0.08
Sepsis, n (%)	671	68 (10.1)	52 (8.9)	16 (18.4)	0.006
Acute renal failure, n (%)	484	72 (14.9)	54 (12.9)	18 (28.1)	<0.001
Multiorgan Failure, n (%)	475	34 (7.2)	24 (5.8)	10 (15.9)	0.004

Values are reported as means ± standard deviations or medians (interquartile ranges)

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/m2); CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; fever, temperature > 37.5°C; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio; MI, myocardial infarction; No., number of patients; NSTEMI, non ST elevation myocardial infarction; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis; RV, right ventricular; SOFA, sequential organ failure assessment; STEMI, ST elevation myocardial infarction.

*Elevated troponin value was defined as above the 99% percentile of normal values.

** RV dysfunction was defined by echocardiography as tricuspid annular plane systolic excursion (TAPSE) < 17 mm, fractional area change (FAC) < 35% and tissue Doppler of the free lateral wall (S') <9.5 cm/sec.

***Patients could receive more than one ventilatory support during hospitalization.

Table 2. Clinical characteristics and echocardiographic findings of the patients with heart failure

	No. assessed	No. (%)
Clinical characteristics		
Primary aetiology, n (%)	90	
Ischaemic		46 (51.1)
Idiopathic		9 (10.0)
Valvular		8 (8.9)
Hypertensive		8 (8.9)
Arrhythmic		7 (7.8)
Genetic cardiomyopathies*		5 (5.5)
Other		7 (7.8)
LV ejection fraction before hospitalization	90	
Reduced LVEF, n (%)		64 (71)
Preserved LVEF, n (%)		26 (29)
Treatment before hospitalization		
Loop diuretics, n (%)	90	65 (72.2)
ACE-i/ARBs/ARNI, n (%)	84	42 (50.0)
Mineralocorticoids, n (%)	66	23 (34.8)
Beta-blockers, n (%)	85	69 (81.2)
Direct oral anticoagulants, n (%)	83	17 (20.5)
Warfarin, n (%)	83	18 (21.6)
Statins, n (%)	84	47 (56.0)
Device implantation, n (%)	90	
ICD		20 (22.2)
CRT		8 (8.9)
In-hospital echocardiographic measurements		
LVEF (%) mean±SD	63	42.1±13.1
RV dysfunction, n (%)	56	16 (28.6)
Left atrium enlargement, n (%)	62	30 (48.4)
Mitral regurgitation ≥ moderate, n (%)	63	13 (20.6)
Tricuspid regurgitation ≥ moderate, n (%)	63	7 (11.1)
Aortic stenosis ≥ moderate, n (%)	63	5 (7.9)
Other valve disease, n (%)	63	5 (7.9)
sPAP ≥ 35mmHg, n (%)	49	27 (55.1)

Legend: ACE-i, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; No., number of patients; preserved LVEF, LVEF ≥ 50%; reduced LVEF, LVEF<50%; RV, right ventricular; SD, standard deviation; sPAP, systolic pulmonary artery pressure.

*Genetic cardiomyopathies include hypertrophic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy; left ventricular non compaction; muscular dystrophies.

Table 3. Univariate and multivariable Cox regression model for in-hospital death (N = 404)

		Univariable		Multivariable*	
	Level/Units	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Clinical characteristics					
Age	+5 years	1.35 (1.26-1.45)	<0.001	1.28 (1.13-1.45)	<0.001
Sex	M vs F	1.33 (0.92 - 1.90)	0.125	2.14 (1.16-3.94)	0.015
Smoker	Yes vs No	1.44 (1.01-2.06)	0.046	-	-
Heart failure	Yes vs No	2.43 (1.69-3.50)	<0.001	2.25 (1.26-4.02)	0.006
Hypertension	Yes vs No	1.96 (1.40-2.74)	<0.001	1.21 (0.72-2.01)	0.47
Hyperdyslipidemia	Yes vs No	2.30 (1.69-3.14)	<0.001	0.82 (0.47-1.44)	0.49
Diabetes	Yes vs No	1.34 (0.95-1.89)	0.096	-	-
Atrial fibrillation	Yes vs No	2.48 (1.74-3.54)	<0.001	1.27 (0.73-2.23)	0.39
Coronary artery disease	Yes vs No	2.29 (1.65-3.17)	<0.001	1.20 (0.67-2.14)	0.55
COPD	Yes vs No	1.79 (1.16-2.76)	0.009	1.41 (0.72-2.75)	0.32
CKD	Yes vs No	2.78 (2.00-3.84)	<0.001	1.09 (0.56-2.10)	0.81
Treatment before hospitalization					
ACE-i/ARBs/ARNI	Yes vs No	1.33 (0.92–1.92)	0.125	-	-
Mineralcorticoids	Yes vs No	1.30 (0.73 – 2.30)	0.37	-	-
Beta-blockers	Yes vs No	1.97 (1.42 – 2.69)	< 0.001	-	-
Direct oral anticoagulants	Yes vs No	1.70 (1.01 – 2.85)	0.046	-	-
Warfarin	Yes vs No	1.24 (0.70-2.19)	0.456	-	-
Statins	Yes vs No	1.93 (1.39 – 2.67)	<0.001	-	-
Baseline findings					
Heart rate	+5 bpm	1.01 (0.99 – 1.02)	0.088	-	-
Oxygen saturation	+5%	0.84 (0.77 - 0.90)	<0.001	0.97 (0.94-0.99)	0.010
Laboratory measurements					
PaO_2/FiO_2	+5 mmHg/%	0.98 (0.97-0.99)	0.002	0.98 (0.97-0.99)	<0.001
Red blood cell count	+ 1 $x10^6$/µL	0.68 (0.55 – 0.86)	0.001	-	-
Hemoglobin	+ 1 g/l	0.91 (0.85 – 0.98)	0.015	0.94 (0.84-1.06)	0.33
Hematocrit	+ 1 %	0.97 (0.95 – 0.99)	0.038	-	-
Lymphocytes count	+1000 U/µL	0.92 (0.88–0.95)	<0.001	0.95 (0.90-1.00)	0.067
Platelets count	+ 1 $x10^3$/µL	0.99 (0.99 – 0.99)	0.016	-	-

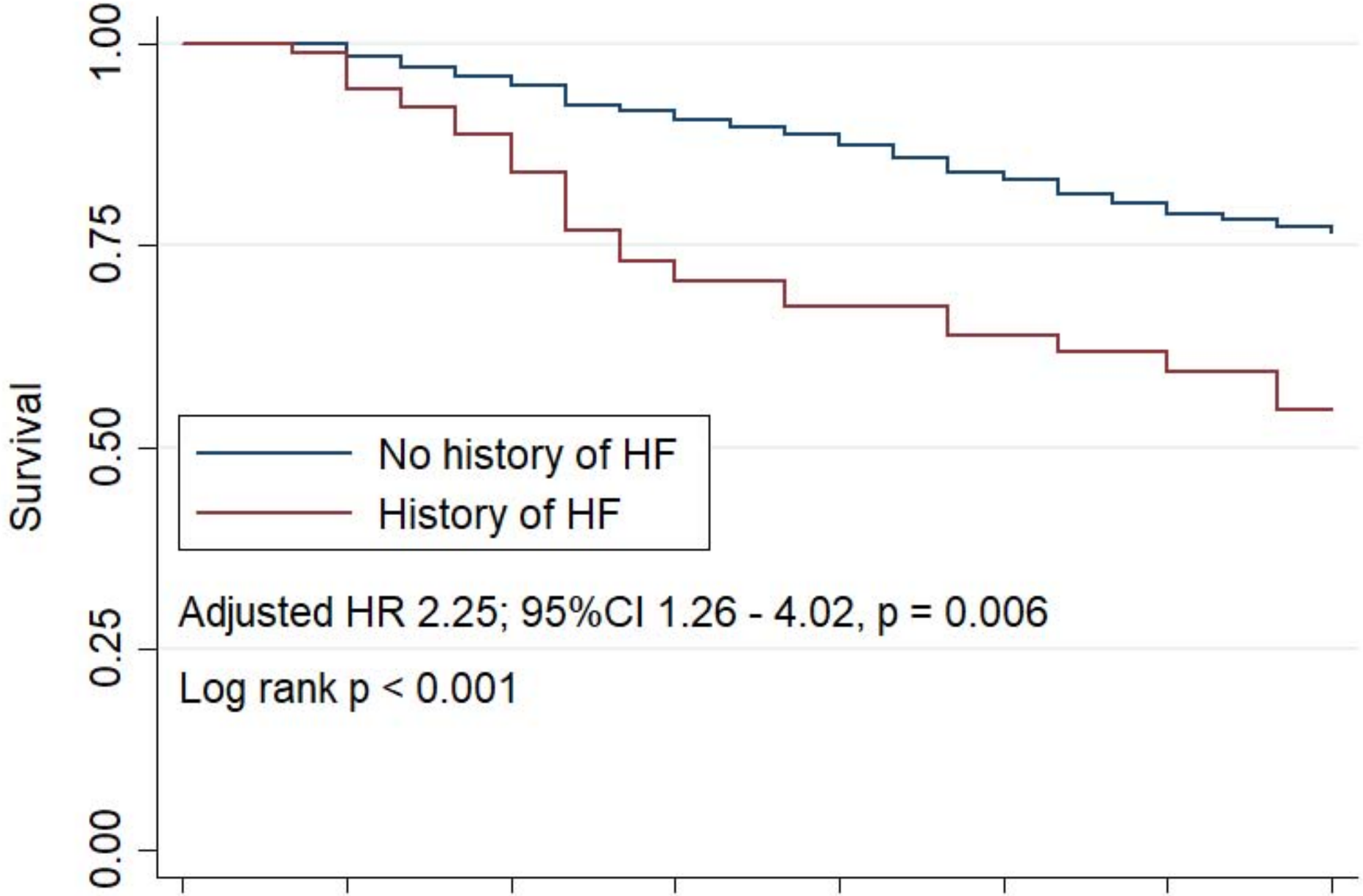
Creatinine	+ 1 mg/dl	1.12 (1.05 – 1.20)	0.001	-	-
eGFR (CKD-EPI)	+10 ml/min	0.98 (0.98-0.99)	<0.001	0.99 (0.98-1.01)	0.60
CRP on admission	+ 1 mg/dl	1.01 (1.01-1.01)	<0.001	1.00 (0.99-1.00)	0.16
Procalcitonin	+1 ng/ml	1.00 (0.98 – 1.02)	0.77	-	-
Troponin	Elevated vs Normal	3.22 (2.26-4.58)	<0.001	1.57 (0.97-2.54)	0.067
NT-proBNP	1 log U increase	1.38 (1.19 – 1.56)	<0.001	-	-
D-dimer	1 log U increase	1.37 (1.18 - 1.58)	< 0.001	-	-
Aspartate transaminase	+1	1.00 (0.99 – 1.01)	0.93	-	-
Albumin	+1	0.92 (0.66 – 1.28)	0.64	-	-
INR	+1	1.23 (1.04 – 1.45)	0.018	-	-

*HR and 95% CIs are reported only for those variables entered into the main multivariable model.
Legend: ACE-i, angiotensin-converting enzyme -inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/m2); CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; INR, International Normalized Ratio; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; PaO_2, oxygen partial pressure at arterial gas analysis.

Table 4. Univariate and multivariable Cox regression model for death adding in-hospital medications to the main model (N=404 for hydroxychloroquine and corticosteroids; N=364 for heparin)

	Univariate analysis		Multivariable analysis*	
Medication	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Hydroxychloroquine	0.45 (0.32-0.65)	<0.001	0.60 (0.33-1.11)	0.106
Lopinavir/Ritonavir	1.14 (0.81-1.60)	0.453	-	-
Darunavir/Ritonavir	0.76 (0.52-1.10)	0.149	-	-
Tocilizumab	0.76 (0.47-1.21)	0.244	-	-
Corticosteroids	0.60 (0.44-0.82)	0.001	0.46 (0.29-0.74)	0.001
Antibiotics	1.31 (0.73-2.36)	0.371	-	-
Heparin	0.57 (0.41-0.81)	<0.001	0.41 (0.25 – 0.67)	< 0.001

*The variables significant at univariate analysis were entered into the main model including age, sex, history of heart failure, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, hyperdyslipidaemia, chronic kidney disease, PaO2/FiO2, oxygen saturation, troponin, C-reactive protein, lymphocytes count, haemoglobin and eGFR.



Number at risk								
No history of HF	602	601	553	467	388	313	254	210
History of HF	90	89	76	57	43	32	26	23