ESC European Society of Cardiology

European Heart Journal (2020) **41**, 1821–1829
doi:10.1093/eurheartj/ehaa388

FASTTRACK CLINICAL RESEARCH
Prevention and epidemiology

Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy

Riccardo M. Inciardi [1†], Marianna Adamo[1†], Laura Lupi[1†], Dario S. Cani [1], Mattia Di Pasquale[1], Daniela Tomasoni [1], Leonardo Italia[1], Gregorio Zaccone[1], Chiara Tedino[1], Davide Fabbricatore[1], Antonio Curnis[1], Pompilio Faggiano[1], Elio Gorga[1], Carlo M. Lombardi[1], Giuseppe Milesi[1], Enrico Vizzardi[1], Marco Volpini [1], Savina Nodari[1], Claudia Specchia[2], Roberto Maroldi[3], Michela Bezzi[4], and Marco Metra [1*]

[1]Institute of Cardiology, ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [2]Department of Molecular and Translational Medicine, University of Brescia, Brescia Italy; [3]Institute of Radiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; and [4]Respiratory Unit, ASST Spedali Civili di Brescia, Brescia, Italy

Received 1 April 2020; revised 17 April 2020; editorial decision 25 April 2020; accepted 6 May 2020; online publish-ahead-of-print 8 May 2020

See page 1830 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa415)

Aims To compare demographic characteristics, clinical presentation, and outcomes of patients with and without concomitant cardiac disease, hospitalized for COVID-19 in Brescia, Lombardy, Italy.

Methods and results The study population includes 99 consecutive patients with COVID-19 pneumonia admitted to our hospital between 4 March and 25 March 2020. Fifty-three patients with a history of cardiac disease were compared with 46 without cardiac disease. Among cardiac patients, 40% had a history of heart failure, 36% had atrial fibrillation, and 30% had coronary artery disease. Mean age was 67 ± 12 years, and 80 (81%) patients were males. No differences were found between cardiac and non-cardiac patients except for higher values of serum creatinine, N-terminal probrain natriuretic peptide, and high sensitivity troponin T in cardiac patients. During hospitalization, 26% patients died, 15% developed thrombo-embolic events, 19% had acute respiratory distress syndrome, and 6% had septic shock. Mortality was higher in patients with cardiac disease compared with the others (36% vs. 15%, log-rank $P = 0.019$; relative risk 2.35; 95% confidence interval 1.08–5.09). The rate of thrombo-embolic events and septic shock during the hospitalization was also higher in cardiac patients (23% vs. 6% and 11% vs. 0%, respectively).

Conclusions Hospitalized patients with concomitant cardiac disease and COVID-19 have an extremely poor prognosis compared with subjects without a history of cardiac disease, with higher mortality, thrombo-embolic events, and septic shock rates.

Keywords COVID-19 • Cardiovascular disease • Pneumonia • Mortality

* Corresponding author. Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy. Tel: +39 3356460581, Email: metramarco@libero.it

† These authors contributed equally to this work.

Introduction

New pneumonia cases related to the severe acute respiratory syndrome coronavirus (SARS-CoV-2), or coronavirus disease 2019 (COVID-19), rapidly spread worldwide, establishing critical challenges for the public health and medical communities. The World Health Organization has declared COVID-19 a public health emergency of international concern, with a global estimate of laboratory-confirmed cases of 1 696 588, and 105 952 deaths as of 12 April 2020.[1]

A high proportion of COVID-19 patients have comorbidities.[2–5] Studies from China show that 15–40% of them have a history of cardiac disease[2–5] and 10–30% show laboratory signs of cardiac injury and cardiovascular involvement, associated with a more severe clinical course.[6,7] These values are probably higher in COVID-19 patients from other areas, such as Europe and the USA, because of the older age of their population. In a report from the USA, including 21 critically ill patients with COVID-19, heart failure (HF) was present in 43% of cases at baseline and complications leading to HF occurred in a third of these patients.[8] Another series of 24 patients admitted to the intensive care unit (ICU) in the Seattle area for hypoxaemic respiratory failure showed a prevalence of hypotension requiring vasopressors of 71%, with a 50% in-hospital mortality. No data regarding history of cardiovascular disease were given.[9]

Thus, although patients with a history of cardiac disease seem more likely to be infected and to have a more severe clinical course with COVID-19, their clinical characteristics and outcomes have not yet been described. In the Brescia area of the Lombardy region, North Italy, the COVID-19 outbreak has caused a major burden on healthcare services, with major changes in in-hospital medical specialties, leading to a transformation of otherwise specialized units, such as cardiology units, into specialized COVID-19 units.[10] In this report, we describe the demographic characteristics, clinical presentation, and outcomes of consecutive patients with COVID-19 and cardiac disease, and compare them with patients with COVID-19 and no history of cardiac disease, hospitalized at the same hospital during the same time interval.

Methods

Study population

The study population comprises two groups of consecutive patients hospitalized for COVID-19 pneumonia at Civil Hospitals of Brescia, Lombardy, Italy, between 4 March and 25 March 2020. The first group included all patients with a history of cardiac disease admitted to our Cardiology Unit, the second all patients with no history of cardiac disease, admitted to a COVID-19 unit of our hospital (director M.B.). All patients had a diagnosis confirmed by positive results of PCR testing of a nasopharyngeal swab. Only patients with a complete follow-up at 14 days were included.

Data collection and definitions

Demographic, clinical, laboratory, instrumental, treatment, and outcome data were extracted from the in-hospital medical records. Chronic kidney disease (CKD) was defined by the presence of an estimated glomerular filtration rate (eGFR), calculated by the CKD-EPI equation, of ≤60 mL/min/m^2. Fever was defined as axillary temperature of at least 37.5°C. The sequential organ failure assessment (SOFA) score was calculated for all patients.[11] Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition.[12]

Radiological assessments included chest radiography or computed tomography (CT). An internal radiological score was developed (see Supplementary material online, *Text S1*). Venous blood samples and arterial samples for blood gas analysis were collected at the time of hospitalization and thereafter based on clinical indications. High sensitivity troponin T (hsTnT) plasma levels were defined as normal when below the 99th percentile of normal values, e.g. 14 ng/L. N-terminal probrain natriuretic peptide (NT-proBNP) plasma levels were defined as normal when <125 pg/mL for patients aged 0–74 years and <450 pg/mL for those older.[13]

Statistical analysis

Continuous variables are expressed as mean (SD) or median [interquartile range (IQR)] values when they did not show a normal distribution. Categorical data were expressed as absolute values and proportions. Variables were compared between patients with and without concomitant cardiac disease as well as between survivors and non-survivors and between patients with different causes of inclusion in the cardiac group by using the Fisher exact test or χ^2 test for categorical variables, and the *t*-test or the Mann–Whitney U test, as appropriate, for continuous variables. The overall trend difference in laboratory markers during the hospitalization course among patients with cardiac disease, stratified by mortality, was assessed using a mixed-effects longitudinal analysis model. Survival curves were plotted using the Kaplan–Meier method and compared between patients with and without cardiac disease by the log-rank test. Analyses were performed with Stata, version 14 (Stata Corp., College Station, TX, USA). For all the statistical analyses, P <0.05 was considered significant.

Results

Characteristics on admission

Demographic and clinical features are shown in *Table 1*. Among the cardiac patients, HF, atrial fibrillation (AF), coronary artery disease (CAD), and CKD were present in 40, 36, 30, and 28% of the patients, respectively. Cardiac patients were more likely to receive chronic treatment with an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor–neprilysin inhibitor (ARNI), anticoagulants, and statins. Fever on admission was present in 42% of patients. Chest X-ray showed pneumonia in all patients. No differences were found in any variable except for a lower blood pressure in cardiac patients.

Laboratory parameters are reported in *Table 2*. The only differences between the two groups regarded higher values of serum creatinine, NT-proBNP, and hsTnT in cardiac patients. NT-proBNP plasma levels were increased in 25 of the 28 cardiac patients (88%) and in 26 of the 45 non-cardiac patients (58%) in whom they were measured. hsTnT levels were increased in 31 of the 40 cardiac patients (71%), and in 17 of 36 non-cardiac patients (47%).

In-hospital management

Data regarding in-hospital management are shown in Supplementary material online, *Table S1* and in *Table 3*. Chronic therapy with an ACEi, ARB, or ARNI was discontinued in 77% of cases because of severe hypotension. Oxygen support with FiO_2 ≥50% was needed in

Table 1 Demographic and clinical findings

Variable	Total (*N* = 99)	Cardiac disease (*N* = 53)	No cardiac disease (*N* = 46)	*P*-value
Demographics				
Age, years	67 ± 12	68 ± 12	66 ± 12	0.51
Sex (male), *n* (%)	80 (81)	45 (85)	35 (76)	0.27
Body mass index (kg/m^2) ≥30 kg/m^2, *n* (%)	18 (23)	13 (26)	5 (18)	0.41
Clinical history, *n* (%)				
Smoker	17 (20)	11 (21)	6 (18)	0.77
Hypertension	63 (64)	40 (75)	23 (51)	0.012
Dyslipidaemia	29 (30)	23 (43)	6 (13)	<0.001
Diabetes	30 (31)	16 (30)	14 (31)	0.92
Heart failure	21 (21)	21 (40)	0 (0)	<0.001
Atrial fibrillation	19 (19)	19 (36)	0 (0)	<0.001
Coronary artery disease	16 (16)	16 (30)	0 (0)	<0.001
Prior cardiac surgery	9 (9)	9 (17)	0 (0)	0.003
Prior percutaneous valve treatment	3 (3)	3 (11)	0 (0)	0.10
Chronic obstructive pulmonary disease	9 (9)	6 (11)	3 (6)	0.41
Chronic kidney disease	15 (15)	15 (28)	0 (0)	<0.001
Cancer	17 (18)	13 (24)	4 (9)	0.05
Prior ACEi/ARB/ARNI therapy	30 (31)	28 (53)	2 (4)	<0.001
Prior anticoagulant therapy	17 (18)	16 (30)	1 (2)	<0.001
Prior statin therapy	25 (26)	23 (44)	2 (4)	<0.001
Data on admission				
Temperature, °C	37.3 ± 1.0	37.3 ± 1.1	37.2 ± 0.9	0.53
Fever, *n* (%)	39 (42)	24 (46)	15 (37)	0.35
Systolic blood pressure, mmHg	132 ± 23	126 ± 23	140 ± 20	0.003
Heart rate, b.p.m.	87 ± 20	86 ± 21	90 ± 18	0.33
Oxygen saturation (ambient air), %	91 ± 89	92 ± 5	90 ± 12	0.30
PaO_2/FiO_2	273 ± 88.5	272 ± 98.5	274 ± 75	0.91
PaO_2/FiO_2 <300, *n* (%)	50 (64)	27 (61)	23 (68)	0.57
SOFA score	2.2 ± 1.2	2.2 ± 1.3	2.2 ± 0.9	0.85
COVID score peak	10.2 ± 4.4	10.9 ± 4.7	9.4 ± 3.9	0.13
Left ventricular ejection fraction, %	48 ± 14	47 ± 14	57 ± 3	0.25

Continuous variable are reported as mean ± SD.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; FiO_2, fraction of inspired oxygen; PaO_2, oxygen partial pressure at arterial gas analysis; SOFA, sequential organ failure assessment; COVID, coronavirus disease.

half of patients; non-invasive ventilation was used in 19% of patients; two patients needed intubation. Ventilatory support or intubation were excluded in seven cardiac patients and in three non-cardiac patients for their age and/or comorbidities.

Outcomes

The most frequent complications of the clinical course are shown at *Table 3* and included acute respiratory distress syndrome (ARDS), venous thrombo-embolism, arterial thrombo-embolism, and sepsis or septic shock in 19, 12, 3, and 6% of the patients, respectively. Mortality was significantly higher in cardiac compared with non-cardiac patients (35.8% vs. 15.2%; log-rank $P = 0.019$; relative risk 2.35; 95% confidence interval 1.08–5.09) (*Take home figure*). Death occurred during the hospitalization at a median time of 8 days (IQR 5–14) in cardiac patients and at a median time of 10 days (IQR 6–12) among non-cardiac patients. Causes of death of cardiac patients were ARDS in 11 patients, septic shock in five patients and acute pulmonary thrombo-embolism in the other three. Cause of death among non-cardiac patients was ARDS in all but one subject who died for pulmonary embolism. Even after excluding patients who were denied intubation due to comorbidities or age, the mortality rate remained higher in cardiac compared with non-cardiac patients (26% vs. 9%; $P = 0.039$).

Clinical, laboratory, and outcome characteristics of the overall study population stratified by mortality are reported in Supplementary material online, *Tables S2–S4*.

Clinical characteristics of survivors and non-survivors among cardiac patients

Compared with patients who were alive, those who died were older and more likely to have a history of HF, diabetes, CAD, and CKD.

Table 2 Laboratory findings of patients stratified by concomitant cardiac disease

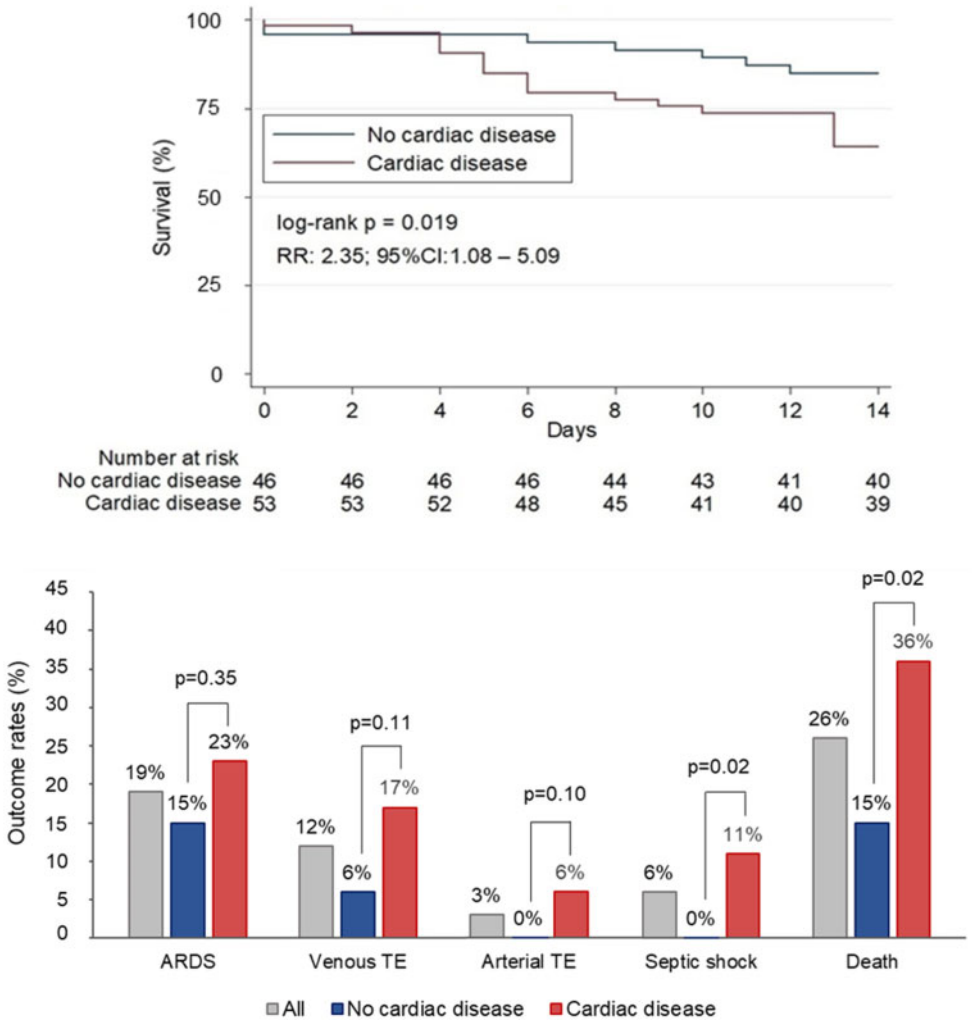
Variable	Reference range	Total (*N* = 99)	Cardiac (*N* = 53)	Non-cardiac (*N* = 46)	*P*-value
Red blood cell count, $\times 10^6$/μL	4.0–5.2	4.6 (4.0–5.0)	4.4 (3.7–4.9)	4.7 (4.3–5)	0.035
Haemoglobin, g/dL	12.0–16.0	13.8 (12.3–14.7)	13.2 (11.1–15)	13.9 (13.2–14.4)	0.45
White blood cell count, per μL	4000–10800	6620 (4870–8750)	6370 (4660–8880)	6750 (5010–8700)	0.58
Neutrophils, per μL	1500–8000	4625 (2855–6725)	4150 (2830–6650)	5108 (3170–6880)	0.64
Lymphocytes, per μL	900–4000	920 (700–1250)	850 (640–1160)	1040 (750–1290)	0.15
Platelet count, $\times 10^3$/μL	130–400	188 (155–242)	183 (155–233)	188 (158–247)	0.73
Creatinine, mg/dL	0.60–1.00	1.0 (0.9–1.3)	1.1 (0.9–1.4)	1.0 (1–1.1)	0.037
Sodium, mEq/L	136–145	137 (135–139)	137 (134–139)	138 (136–140)	0.15
Potassium, mEq/L	3.4–4.5	3.9 (3.6–4.3)	4.1 (3.6–4.4)	3.8 (3.5–4.1)	0.04
Chloride, mEq/L	98–107	99 (97–102)	99.5 (96.5–101.5)	101 (97–103)	0.23
Baseline CRP, mg/L	<5.0	65 (21–133)	50 (11–113)	99 (48–138)	0.07
Peak CRP, mg/L	<5.0	113 (65 –169)	113 (59–176)	107 (72–160)	0.9
Procalcitonin, ng/mL	<0.5	0.3 (0.1–0.8)	0.3 (0.1–1.4)	0.1 (0.1–0.2)	0.022
Ferritin, μg/L	30–400	1392 (745–2733)	1574 (745–2754)	1373 (753–2245)	0.62
D-dimer, ng/mL	<232	576 (330–985)	640 (204–1873)	573 (332–868)	0.85
High sensitivity troponin T, ng/L	<14	18 (10–43)	34 (14–105)	16 (7–21)	<0.001
NT-proBNP, pg/mL	<93	311 (107–1536)	2584 (206–4546)	180 (86–458)	<0.001
Aspartate transaminase, U/L	18–39	46 (34–68)	46 (35–63)	44 (34–69)	0.96
Alanine transaminase, U/L	10–50	34 (24–58)	31 (24–49)	41.5 (24–67)	0.06
Lactate dehydrogenase, U/L	135–225	351 (251–481)	321 (242–448)	365 (289–490)	0.15
Creatine phosphokinase, U/L	39–308	153 (64–335)	151 (64–353)	158 (64–302)	0.59
Albumin, g/L	45–52	33 (29.4–36)	35 (30–37)	32 (28–34)	0.041
Lactate, mmol/L	0.5–2.2	1.1 (0.9–1.5)	1.3 (0.9–1.6)	1.0 (0.8–1.53)	0.06

Values are reported as median (interquartile range).
CRP, C-reactive protein, NT-proBNP, N-terminal probrain natriuretic peptide.

Table 3 In-hospital management and outcomes of the study population stratified by concomitant cardiac disease

Variable	Total (*N* = 99)	Cardiac (*N* = 53)	Non-cardiac (*N* = 46)	*P*-value
Changes in ongoing treatment				
ACE/ARB/ARNI interruption, *n* (%)*	23 (77)	21 (75)	2 (100)	<0.001
Needed ventilatory support				
Oxygen support with FiO_2 <50%, *n* (%)	54 (57.4)	31 (58.5)	23 (56.1)	0.82
Oxygen support with FiO_2 ≥50%, *n* (%)	47 (50)	29 (54.7)	18 (43.7)	0.3
Non-invasive ventilation, *n* (%)	18 (19.1)	10 (18.9)	8 (19.5)	0.94
Intubation, *n* (%)	2 (2)	2 (3.8)	0 (0)	0.19
Outcomes				
Intensive care unit admission, *n* (%)	12 (12)	10 (19)	0 (0)	<0.001
Hospital length of stay, days	11.4 ± 6.5	11.8 ± 8.3	10.8 ± 3.4	0.48
ARDS, *n* (%)	19 (19)	12 (23)	7 (15)	0.35
Venous thrombo-embolism, *n* (%)	12 (12)	9 (17)	3 (6)	0.11
Arterial thrombo-embolism, *n* (%)	3 (3)	3 (6)	0 (0)	0.1
Septic shock/sepsis, *n* (%)	6 (6)	6 (11)	0 (0)	0.019
Death, *n* (%)	26 (26)	19 (36)	7 (15)	0.02

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; FiO_2, fraction of inspired oxygen; ARDS, acute respiratory distress syndrome.
*The proportion of patients who underwent ACEi/ARB/ARNI interruption was calculated relative to the number of patients on chronic therapy.



Take home figure Top: Kaplan–Meier 14-day survival rates for the patients with and without concomitant cardiac disease. Bottom: 14-day outcomes (major complications and deaths) of all patients and the patients without and with concomitant cardiac disease. ARDS, acute respiratory distress syndrome; CI, confidence interval; RR, relative risk; TE, thrombo-embolism.

Moreover, they had lower systolic blood pressure, higher SOFA score, and were more likely to have a PaO_2/FiO_2 ratio <300 mmHg at the time of hospitalization (*Figure 1*; Supplementary material online, *Table S5*).

With regard to laboratory parameters, non-survivors had lower lymphocyte count and higher serum creatinine and procalcitonin levels at the time of hospitalization. D-dimer, C-reactive protein (CRP), NT-proBNP, and hsTnT levels were numerically higher at the time of hospitalization in non-survivors compared with survivors (*Figure 2*; Supplementary material online, *Table S6*). All nine patients with normal troponin levels did not have complications or death during hospitalization. Plasma levels of sodium, potassium, and chloride tended to be lower in non-survivors vs. survivors during the whole clinical course. Platelets were lower at admission and increased during the hospitalization, reaching higher values in the subjects who died (*Figure 3*).

Non-survivors needed oxygen support with FiO_2 >50% more frequently than survivors. Among complications, ARDS and septic shock were more common in patients who died compared with those who were alive, whereas thrombo-embolic events were similar between the two groups (Supplementary material online, *Table S7*).

Primary causes of hospital admission of cardiac patients are shown in Supplementary material online, *Text S1* and *Tables S8–S10*.

Discussion

This is the first study describing the clinical characteristics and outcome of patients with a history of cardiac disease and COVID-19 pneumonia. Our results showed a high rate of in-hospital mortality and complications in cardiac patients compared with those without a history of cardiac disease. Mortality of cardiac patients was high

Factor	Died (N=19)	Alive (N=34)	SMD (95% CI)	p–value
Age (years), mean (SD)	72.3±13.5	65.5±10.2	0.59 (0.02, 1.17)	0.046
Sex (male), n (%)	17 (89.5)	28 (82.5)	0.33 (–0.62, 1.27)	0.490
Body mass index (kg/m^2) >= 30kg/m^2, n (%)	5 (27.8)	8 (25.0)	0.08 (–0.62, 0.78)	0.830
Hypertension, n (%)	13 (68.4)	27 (79.4)	–0.32 (–1.02, 0.38)	0.370
Diabetes, n (%)	9 (47.4)	7(20.6)	0.69 (0.01, 1.36)	0.042
Heart failure, n (%)	12 (63.2)	9 (26.5)	0.86 (0.20, 1.52)	0.009
Atrial fibrillation, n (%)	8 (42.1)	11(32.5)	0.23 (–0.41, 0.87)	0.480
Coronary artery disease, n (%)	9 (47.4)	7(20.6)	0.69 (0.01, 1.36)	0.042
Chronic obstructive pulmonary disease, n (%)	4 (21.1)	2 (5.9)	0.80 (–0.19, 1.79)	0.095
Chronic kidney disease (eGFR<60 mL/min/m^2), n (%)	10 (52.6)	5(14.7)	1.03 (0.31, 1.75)	0.003
History of cancer, n (%)	7 (36.8)	6 (17.7)	0.55 (–0.16, 1.26)	0.120
Prior ACEi/ARB/ARNI therapy, n (%)	8 (42.1)	20 (58.8)	–0.37 (–1.00, 0.26)	0.240
Prior anticoagulant therapy, n (%)	4 (21.1)	12 (35.3)	0.39 (–0.30, 1.08)	0.280
SOFA score, mean (SD)	3.2±1.5	1.7±0.9	1.92 (1.25, 2.59)	<0.001
LV ejection fraction (%), mean (SD)	41.6±15.1	50.2±12.7	–0.63 (–1.31, 0.06)	0.070

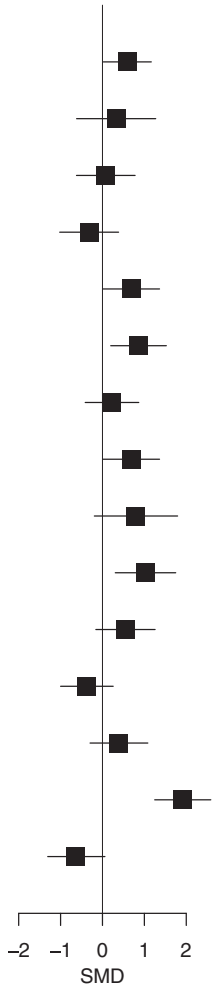


Figure 1 Clinical features of cardiac patients stratified by vital status. Standardized forest plot comparing selected clinical variables between survivors and non-survivors among cardiac patients. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; LV, left ventricular; SMD, standardized mean difference; SOFA, sequential organ failure assessment.

regardless of their main cause of hospitalization, COVID-19 pneumonia vs. acute cardiac conditions. More than a third of our cardiac patients died in hospital and more than half developed severe complications such as ARDS, septic shock, or thrombo-embolic events. Mortality and major event rates of cardiac patients were higher compared with those of non-cardiac patients admitted for COVID-19 pneumonia (36% vs. 15% for mortality and 57% vs. 21% for overall major complications). Several conditions (i.e. history of HF, severe aortic stenosis, and CKD), and laboratory abnormalities (i.e. lymphocytopenia, high levels of D-dimer, procalcitonin, TnT, and NT-proBNP on admission) were associated with poor outcomes.

The outcomes reported for our patients are worse than those reported in series from China,[2–5,7] but are consistent with those reported from the USA.[8,9] The poor outcomes of our patients were probably related to their older age and higher burden of cardiac comorbidities, as shown by the comparison with non-cardiac COVID-19 patients. Older age was consistently shown to be a major risk factor for poor outcomes[3,14,15] and/or myocardial injury.[6,7] Also a history of cardiovascular disease was associated with poorer outcomes. A higher prevalence of hypertension and CAD in non-survivors, compared with survivors, was shown by Zhou *et al.*,[3] and hypertensive patients were more likely to develop ARDS in the study by Wu *et al.*[14]

Patient selection may have influenced our results. However, we describe a series of consecutive patients admitted in a limited time interval because of COVID-19 and concomitant cardiac disease. These patients were selected at the time of their presentation to our emergency department and the reason for admission to our institute of cardiology was considered upon their concomitant cardiac disease requiring specialized treatment, regardless of whether their primary cause of hospitalization was COVID-19 pneumonia or a cardiac disorder. Consistently, the primary cause of admission had no

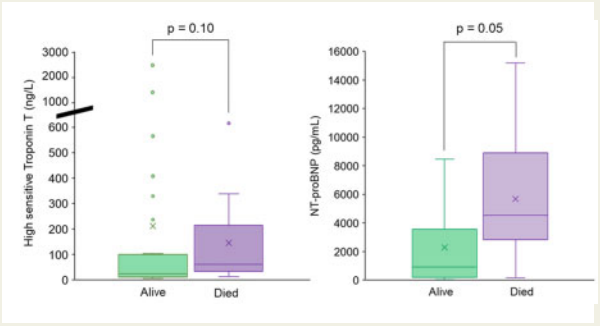


Figure 2 Cardiac biomarkers on admission among cardiac patients. Box plot showing high sensitivity troponin T and N-terminal probrain natriuretic peptide (NT-proBNP) on admission in alive (green) and dead (purple) patients.

relationship to the characteristics our cardiac patients (Supplementary material online, *Tables S8–S10*). Thus, our data point out the major impact of a clinically relevant cardiac comorbidity on the outcomes of COVID-19 patients.

The mechanism of poor outcomes in patients with COVID-19 and concomitant cardiac disease may be multiple and cannot be ascertained by our data. An exaggerated inflammatory activation with hypercytokinaemia (cytokine storm) and multiorgan failure seem to be the main mechanisms of the high mortality of COVID-19 pneumonia and ARDS.[16] This is consistent with the increase in inflammatory markers, such as CRP, D-dimer, ferritin, and interleukin plasma levels, in the patients developing ARDS and/or not surviving COVID-19 infection.[2–4,14,15,1,17] Inflammatory activation may have a prominent role in the patients with HF and/or CAD, and this may explain their susceptibility to COVID-19 and their poorer clinical course.[18,19,20]

Severe hypoxaemia, inflammatory activation, and hypotension may all contribute to myocardial injury during COVID-19, and patients with concomitant CAD or HF may be at higher risk.[21] Recent data show that cardiac injury may occur in 10–30% of unselected patients with COVID-19 and be associated with a severe clinical course and high mortality, independently of a history of cardiovascular disease.[3,6,7] More than 70% of our cardiac patients had increased hs-TnT levels, and high hsTnT levels were also found in almost half of those with a non-cardiac history, consistent with greater severity of COVID-19 patients hospitalized in our area. Plasma troponin levels tended to be higher at entry in non-survivors, compared with survivors. This difference did not reach statistical significance probably because of the small size of our study group. Consistent with previous studies,[7] our patients who had low troponin levels at the time of hospitalization had an uneventful clinical course and all survived. Similar to what was proposed for the patients with acute HF,[22] the detection of normal troponin levels at the time of hospitalization might therefore be considered as a criterion for early discharge from hospital even in a high-risk population such as our patients.

The rate of thrombo-embolic events was high in our patients, with 15% of all our patients and 23% of our cardiac patients showing major thrombo-embolic events. Such events were likely to be favoured by the marked inflammatory activation associated with COVID-19.[23] Elevated plasma levels of coagulation parameters have been associated with poorer outcomes in COVID-19 patients.[3,4,17,24] Anticoagulation was not routinely performed in our patients in sinus rhythm. However, based on such a high event rate, a wider use of anticoagulation, or at least thrombo-embolic prophylaxis, seems warranted. Better outcomes were shown with low molecular weight heparin treatment in COVID-19 patients with high D-dimer plasma levels or meeting sepsis-induced coagulopathy criteria.[25]

It is controversial whether treatment with ACEi/ARB/ARNI may favour coronavirus infection or be protective from COVID-19 pneumonia.[26–29] To date, it is considered that these drugs 'should be continued in patients in otherwise stable condition who are at risk for Covid-19.'[28] Our data indirectly support this statement as the prevalence of patients on ACEi/ARB/ARNI was similar between non-survivors and survivors. It is, however, noteworthy that 78% of our patients had to have these drugs temporarily withdrawn during the hospitalization because of persistent hypotension. High rates of hypotension were also shown in another series of critically ill patients.[9]

Antiviral and antinflammatory agents were given to our patients based on recommendations by an infective disease specialist. Many of these therapies have been associated with untoward effects in cardiac patients. Based on our observational data, it is not possible to ascertain whether they contributed to the poor outcomes of our patients. However, as similar outcomes are reported in other series of patients of similar age and with similar comorbidities,[8,9] we may consider that such poor outcomes are caused by COVID-19 and not by concomitant treatment. Despite its hypothesized untoward effects in viral pneumonia, corticosteroid therapy has been associated with more favourable outcomes in COVID-19 pneumonia in an observational study.[14]

The main limitation of our study is the relatively small size of our study group. However, the extreme burden of the COVID-19 outbreak on the healthcare system and the high major event rates of our patients offset such a limitation. A larger study group would have probably allowed more sophisticated analyses aimed at finding independent prognostic variables. Given the logistical limitations at the onset of this emerging outbreak, some laboratory data (such as troponin and NT-proBNP) were not collected in all patients. Similarly, detailed echocardiographic data were not collected. Data from larger cardiovascular populations and multiple centres are warranted. However, our data are from one of the two areas, Brescia and Bergamo, which were firstly and more severely affected by the COVID-19 outbreak in Italy.

In conclusion, patients with concomitant cardiac disease and COVID-19 have an extremely poor prognosis, compared with subjects without a history of cardiac disease, with higher mortality, septic shock, and thrombo-embolic event rates. Better prevention of COVID-19 and possibly better evidence-based treatment of COVID-19 is warranted in these patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: M.M. has received personal honoraria for participation in trial committees, advisory boards, or speeches at sponsored symposia from Abbott Vascular, Amgen, Astra Zeneca, Bayer, and Vifor Pharma. All other authors have no conflicts to declare.

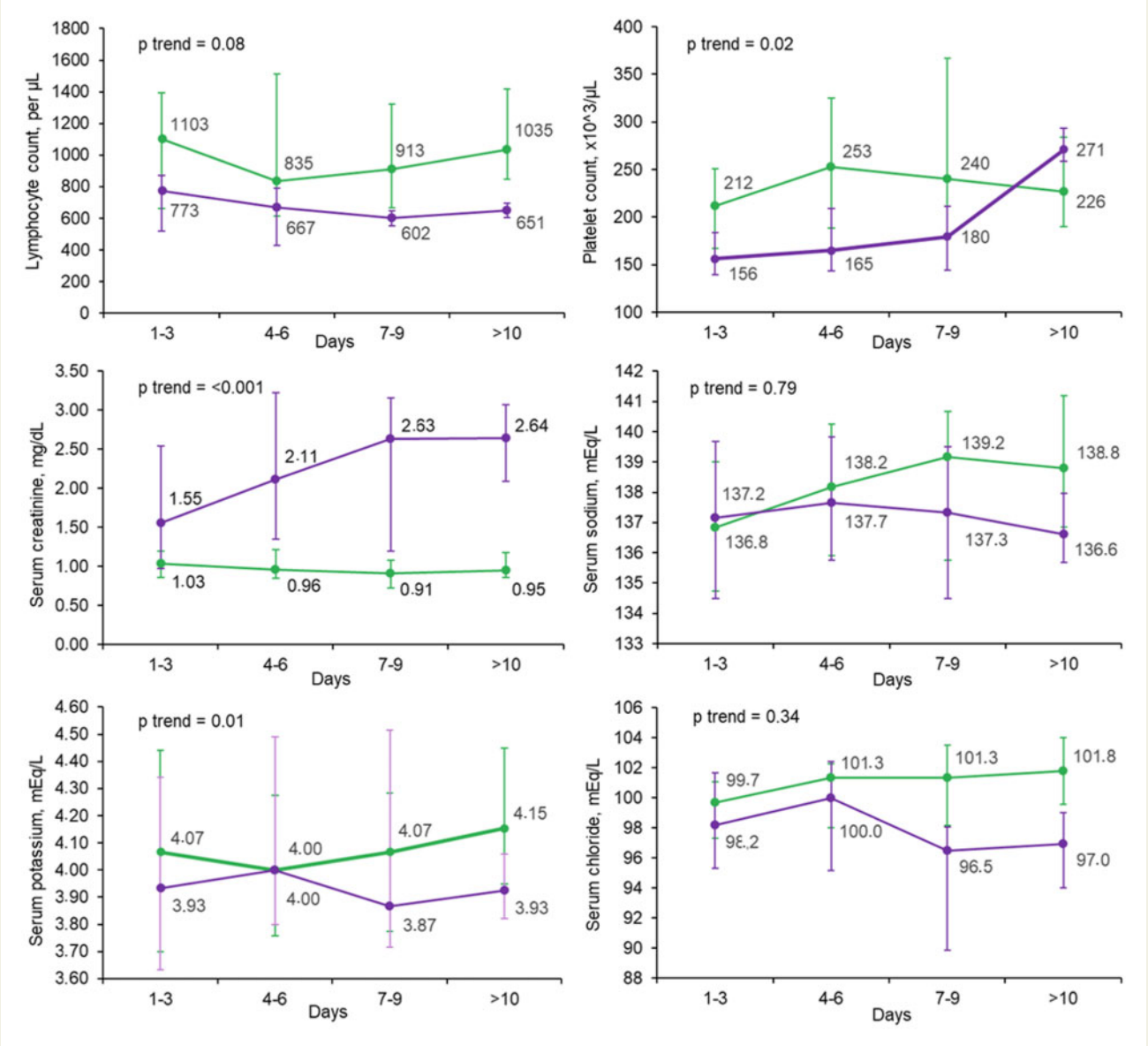


Figure 3 Temporal changes in laboratory markers during the hospitalization in cardiac patients. Median and interquartile range changes over time in lymphocytes, platelets, serum creatinine, sodium, potassium, and chloride in patients stratified by in-hospital mortality (alive, green; dead, purple).

References

1. World Health Organization. Coronavirus Disease 2019 (COVID-19): Situation Report 44. Published 4 March 2020.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;doi: 10.1056/NEJMoa2002032.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–1062.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**:497–506.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;**395**:507–513.
6. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.0950.
7. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.1017.
8. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020;doi: 10.1001/jama.2020.

9. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim M, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PM, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S, Mikacenic C. Covid-19 in critically ill patients in the Seattle region—Case Series. *N Engl J Med* 2020;doi: 10.1056/NEJMoa2004500.
10. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA* 2020;doi: 10.1001/jama.2020.4031.
11. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Crit Care* 2019;**23**: 374.
12. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;**315**: 762–774.
13. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL Jr; Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;**21**: 715–731.
14. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;doi: 10.1001/jamainternmed.2020.0994.
15. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;doi: 10.1016/S2213-2600(20)30079.
16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Healh Across Speciality Collaboration UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;**395**:1033–1034.
17. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;**368**:m1091.
18. Markousis-Mavrogenis G, Tromp J, Ouwerkerk W, Devalaraja M, Anker SD, Cleland JG, Dickstein K, Filippatos GS, Harst P, Lang CC, Metra M, Ng LL, Ponikowski P, Samani NJ, Zannad F, Zwinderman AH, Hillege HL, Veldhuisen DJ, Kakkar R, Voors AA, Meer P.The clinical significance of interleukin-6 in heart failure: results from the BIOSTAT-CHF study. *Eur J Heart Fail* 2019;**21**:965–973.
19. Liberale L, Montecucco F, Tardif JC, Libby P, Camici GG. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. *Eur Heart J* 2020; doi:10.1093/eurheartj/ehz961.
20. Lawler PR, Bhatt DL, Godoy LC, Luscher TF, Bonow RO, Verma S, Ridker PM. Targeting cardiovascular inflammation: next steps in clinical translation. *Eur Heart J* 2020; doi:10.1093/eurheartj/ehaa099.
21. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.
22. Pang PS, Teerlink JR, Voors AA, Ponikowski P, Greenberg BH, Filippatos G, Felker GM, Davison BA, Cotter G, Kriger J, Prescott MF, Hua TA, Severin T, Metra M. Use of high-sensitivity troponin T to identify patients with acute heart failure at lower risk for adverse outcomes: an exploratory analysis from the RELAX-AHF Trial. *JACC Heart Fail* 2016;**4**:591–599.
23. Glynn RJ, Ridker PM. Inflammation, venous thromboembolism, and what we can do about it. *Eur Heart J* 2018;**39**:3615–3617.
24. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;**18**:844–847.
25. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020;doi: 10.1111/jth.14817.
26. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;**17**:259–260.
27. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020;**8**:e21.
28. Vaduganathan M VO, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;**382**:1653–1659.
29. Danser AHJ, Epstein M, Batlle D. Renin–angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin–angiotensin system blockers. *Hypertension* 2020;doi: 10.1161/HYPERTENSIONAHA.120.15082.