Original Article

Coronavirus disease 2019 in patients with cardiovascular disease: clinical features and implications on cardiac biomarkers assessment

Luca Arcari[a], Michelangelo Luciani[b], Luca Cacciotti[a], Mariateresa Pucci[a], Maria Beatrice Musumeci[c], Lorenzo Pietropaolo[d], Valerio Spuntarelli[b], Andrea Negro[b], Giovanni Camastra[a], Enrico Bentivegna[b], Giuseppe Marazzi[e], Cinzia Sighieri[d], Gerardo Ansalone[a], Claudio Santini[d], Paolo Martelletti[b], Massimo Volpe[c] and Luciano De Biase[e]

Introduction **Previous cardiovascular disease (CVD) and myocardial involvement are common in coronavirus disease-19 (COVID-19). We investigated relationships between CVD, cardiac biomarkers and outcome in COVID-19.**

Methods **We analyzed $n = 252$ patients from a multicenter study and provided comparison according to the presence or absence of underlying CVD. Cardiac biomarkers high-sensitivity Troponin [upper reference of normality (URN) 35 pg/ml for Troponin I and 14 pg/ml for Troponin T] and natriuretic peptides (Nt-pro-B-type natriuretic peptide, URN 300 pg/ml and B-type natriuretic peptide, URN 100 pg/ml) were both available in $n = 136$.**

Results **Mean age was 69 ± 16 years (56% men, 31% with previous CVD). Raised hs-Troponin and natriuretic peptides were detected in 36 and 50% of the cases respectively. Age, chronic obstructive pulmonary disease, hemoglobin, hs-Troponin and natriuretic peptides were independently associated with underlying CVD ($P < 0.05$ for all). Compared with the normal biomarkers subgroups, patients with isolated hs-Troponin elevation had higher in-hospital mortality (31 vs. 4%, $P < 0.05$), similar CVD prevalence (15 vs. 11%) and trend towards higher D-dimer (930 vs. 397 ng/ml, $P = 0.140$). Patients with both biomarkers elevated had higher age, D-dimer, CVD and in-hospital mortality prevalence compared with other subgroups (all $P < 0.05$ for trend). Outcome analysis revealed previous CVD [model 1: OR 2.72 (95% CI 1.14–6.49), $P = 0.024$. model 2: OR 2.65 (95% CI 1.05–6.71), $P = 0.039$], hs-Troponin (log_{10}) [OR 2.61 (95% CI 1.21–5.66), $P = 0.015$] and natriuretic peptides (log_{10}) [OR 5.84 (95%CI 2.43–14), $P < 0.001$] to be independently associated with in-hospital mortality.**

Conclusion **In our population, previous CVD was part of a vulnerable phenotype including older age, comorbidities, increased cardiac biomarkers and worse prognosis. Patients with isolated increase in hs-Troponin suffered higher mortality rates despite low prevalence of CVD, possibly explained by higher COVID-19-related systemic involvement.**

J Cardiovasc Med 2021, **22**:000–000

Keywords: B-type natriuretic peptide, cardiovascular disease, coronavirus disease 2019, prognosis, troponin

[a]Covid-Cardiology Unit, Madre Giuseppina Vannini Hospital, [b]Internal Medicine Unit, [c]Cardiology Unit, Clinical and Molecular Medicine Department, Faculty of Medicine and Psychology, Sapienza University of Rome, [d]Covid-Internal Medicine Unit, Madre Giuseppina Vannini Hospital and [e]Covid Unit, Heart Failure Unit, Clinical and Molecular Medicine Department, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy

Correspondence to Luca Arcari, Department of Cardiology, Madre Giuseppina Vannini Hospital, Via di Acqua Bullicante 4, 00177, Rome, Italy
Tel: +39 624291425; e-mail: luca_arcari@outlook.it

Received 11 February 2021 **Revised** 8 May 2021
Accepted 7 August 2021

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection featuring variable systemic involvement and significant mortality.[1] Age and comorbidity burden are both predictors of hospital admission in COVID-19 patients,[2] whereas previous cardiovascular disease (CVD) has been associated with worse prognosis.[3–5] Notwithstanding, the relationship between COVID-19 and CVD could be seen as bi-directional,[6] as cardiac involvement detected in the course of the disease is not uncommon even in CVD naive patients. Cardiac biomarker abnormalities, namely elevated high sensitivity Troponin (hs-Troponin) and natriuretic peptides, have been described and linked to adverse outcome[7–11] where reasons for their increase in COVID-19 are not fully elucidated, ranging from myocardial infarction to myocarditis, systemic inflammation and hypoxia.[12–16] Cardiac biomarker levels are influenced by the presence of underlying CVD, as conditions, such as atrial fibrillation or heart failure may be per se the reason for increased hs-Troponin or natriuretic peptides.[17,18] However, the influence of previous CVD on cardiac biomarker assessment in COVID-19 has been poorly investigated to date. Lombardi *et al.*[8] showed that elevated hs-Troponin portended higher mortality

DOI:10.2459/JCM.0000000000001252

risk in patients with COVID-19 either in the presence or absence of known CVD. Fewer data are available for natriuretic peptides. The aim of the present study was to investigate clinical characteristics and laboratory findings, including hs-Troponin and natriuretic peptides assessment, in a cohort of patients with COVID-19 pneumonia enrolled in a multicenter ongoing study,[15] in order to further clarify relationships between underlying CVD, cardiac biomarkers increase and outcome in this population.

Methods

Detailed description of patients' enrollment and data acquisition at our institutions (Mother Giuseppina Vannini Hospital and S. Andrea Hospital, both in Rome, Italy) have been previously reported.[15] As of 15 December 2020, the population consists of $n = 265$ patients with COVID-19 pneumonia enrolled during the pandemic peaks in the Lazio region, Italy, cousin the transitory activation of COVID-19-dedicated wards (15 March to 30 April and from 1 November to 15 December 2020; no new admissions in between-peak periods). For the purpose of the present study, we included $n = 252$ in the final analysis ($n = 11$ excluded because of other prominent acute clinical conditions leading to index hospital admission, including $n = 5$ myocardial infarction, $n = 2$ Takotsubo syndrome, $n = 2$ myocarditis as confirmed by cardiac MRI,[19] $n = 2$ stroke, $n = 2$ acute decompensated heart failure). All clinical, laboratory and arterial blood gas data were recorded within 24 h upon admission. As previously described,[15] natriuretic peptide values were reported as factor of guideline-suggested URN[20] increase to provide unified analysis between centers using different assays (Vannini hospital: Nt-pro-B-type natriuretic peptide (BNP) with guideline-defined cut-off value <300 pg/ml. S. Andrea hospital: with guidelines defined cut-off value <100 pg/ml). Hs-Troponin T (normal value <14 pg/ml) and hs-Troponin I (normal value <35 pg/ml) were assessed at Vannini and S. Andrea hospital, respectively. Previous CVD was defined as a composite of atrial fibrillation, coronary artery disease, heart failure and stroke.[15] History of CVD and ongoing medical therapy was assessed at hospital admission by the accepting physician. Hs-Troponin was available in $n = 229$ patients, natriuretic peptides in $n = 146$; concomitant and timely assessment of both hs-Troponin and natriuretic peptides was performed in $n = 136$ patients. For the purpose of the study, we identified subgroups with and without previous CVD as well as with different cardiac biomarkers levels (both biomarkers negative, isolated hs-Troponin increase, isolated natriuretic peptides increase, both biomarkers elevated) and provided analysis for comparisons.

Chi-square, Fisher exact test, Mann–Whitney *U* test or Kruskall–Wallis test as appropriate was used to compare groups stratified by CVD and cardiac biomarkers results. Between-group differences were assessed by post hoc analysis with Bonferroni correction. Biomarkers values were reported as $\log_{10}$-transformed in regression analysis to yield an approximate normal distribution. Univariable and multivariable logistic regression analyses were used to investigate factors independently associated with CVD and in-hospital mortality. All variables with *P* less than 0.2 at univariable analysis were included in the multivariable models. Collinearity between independent variables was assessed using correlation matrix. We assumed a correlation closer than ±0.6 as a proxy of significant collinearity between variables[21] that were thus not included within the same multivariable model; variables meeting these criteria were age, hs-Troponin ($\log_{10}$) and natriuretic peptides ($\log_{10}$factor × URN) for which three separate multivariable models were built. All analyses were carried out using SPSS software version 25; a two-tailed *P* less than 0.05 was considered statistically significant. The study complied with the Declaration of Helsinki and received approval from Sapienza University Ethic Committee no. CE_5773_2020. Outcome data were updated on 31 January 2020.

Results

Baseline characteristics

Baseline clinical and demographic findings in $n = 252$ patients included in the study are summarized in Table 1. Mean age was 69 ± 16 years and 56% were men. Comorbidities were common in our population; more than half of the patients had known hypertension and $n = 77$ (31%) had preexisting CVD (12% atrial fibrillation, 11% coronary artery disease, 9% heart failure, 7% stroke). Venous blood samples analysis revealed increase in median CRP (5.7 mg/dl, normal value <0.5 mg/dl) and D-dimer (561 ng/ml FEU, normal value <500 ng/ml FEU). We detected raised troponin (identified by value >URN) in 36% of the cases, whereas in 14% of the patients, the increase was beyond three times the respective URN. Natriuretic peptides values were elevated in 50% of the cases. On arterial blood gas analysis, mean PaO_2 was 77 ± 26 mmHg and median PaO_2/FIO_2 310 (interquartile range 244–371). In-hospital mortality rate in our population was 18% ($n = 44$).

Characteristics of population according to underlying cardiovascular disease

On subgroup analysis, patients who had previous CVD were older (77 vs. 66 years old), with higher prevalence of CKD and COPD (10 vs. 4% and 25 vs. 13%, respectively) and lower mean hemoglobin (11.8 vs. 12.9 mg/dl), whereas they more often were on cardiac medications. Hs-Troponin (29 vs. 10 pg/ml) and natriuretic peptides (5 vs. 0.5 factor × URN increase) were significantly elevated in patients with CVD, where PaO_2/FIO_2 was lower (290 vs. 323). A 2.5-fold increase of in-hospital mortality was observed amongst patients with CVD (30 vs. 12%).

Table 1 Baseline clinical characteristics and laboratory findings in the overall population and in patients with and without previous cardiovascular disease

Variable	Overall ($n=252$)	No previous CVD ($n=175$)	Previous CVD ($n=77$)	*P*
Age	69 ± 16	66 ± 16	77 ± 11	**<0.001**
Sex (male) (%)	142 (56)	97 (55)	45 (58)	0.657
Coexistent conditions				
Hypertension (%)	143 (57)	86 (49)	57 (74)	**<0.001**
Dyslipidemia (%)	47 (19)	23 (13)	24 (31)	**0.001**
Diabetes (%)	45 (18)	30 (17)	15 (19)	0.655
Previous CVD (%)	77 (31)	–	–	–
Atrial fibrillation (%)	31 (12)	–	–	–
Coronary artery disease (%)	29 (11)	–	–	–
Heart failure (%)	24 (9)	–	–	–
Stroke (%)	17 (7)	–	–	–
CKD (%)	15 (6)	7 (4)	8 (10)	**0.046**
COPD (%)	41 (16)	22 (13)	19 (25)	**0.015**
Cancer (%)	17 (7)	12 (7)	5 (6)	0.907
Previous treatments				
Ace-inhibtor/ARB therapy (%)	93 (37)	51 (29)	42 (54)	**<0.001**
Beta-blocker (%)	55 (22)	21 (12)	34 (44)	**<0.001**
Furosemide (%)	35 (14)	8 (5)	27 (35)	**<0.001**
Atiplatelet (%)	62 (25)	12 (7)	50 (65)	**<0.001**
Oral anticoagulant (%)	29 (11)	0 (0)	29 (27)	**<0.001**
Laboratory tests				
Hb (mg/dl)	12.6 ± 2	12.9 ± 2	11.8 ± 2	**<0.001**
WBC ($\times 10^9$/l)	7 (5.1–10.2)	7 (5.2–10.4)	6.7 (4.3–9.2)	0.863
Neutrophil ($\times 10^9$/l)	4.7 (3.2–7.3)	4.7 (3.2–7.6)	4.9 (3.2–6.7)	0.682
Lymphocyte ($\times 10^9$/l)	0.98 (0.7–1.4)	1 (0.7–1.4)	0.94 (0.6–1.4)	0.241
Creatinine (mg/dl)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.4)	0.414
Platelet ($\times 10^9$/l)	213 (160–283)	213 (167–280)	210 (133–294)	0.863
CRP (mg/dl)	5.7 (1.6–10.5)	5.5 (1.3–10.3)	6.4 (2.1–13.3)	0.151
D-dimer (FEU)	561 (301–1080)	530 (280–1044)	729 (324–1372)	**0.029**
Hs-Troponin (pg/ml) (available in $n=229$)	14 (6–34)	10 (5–22)	29 (14–80)	**<0.001**
Hs-Troponin > URN (available in $n=229$)	81 (36)	45 (28)	36 (55)	**<0.001**
Hs-Troponin > 3 × URN (available in $n=229$)	31 (14)	14 (9)	17 (26)	**0.001**
NP (factor × URN) (available in $n=146$)	0.95 (0.32–4.8)	0.5 (0.25–2.4)	5 (1, 40)	**<0.001**
NP > URN (available in $n=146$)	73 (50)	32 (33)	41 (82)	**<0.001**
Blood gas analysis				
pH	7.46 ± 0.6	7.45 ± 0.06	7.47 ± 0.06	0.151
pO_2 (mmHg)	77 ± 26	78 ± 28	75 ± 21	0.468
pCO_2 (mmHg)	36 ± 6	36 ± 6	36 ± 8	0.731
PaO_2/FIO_2	310 (244–371)	323 (254–377)	290 (196–351)	**0.028**
In-hospital outcome				
In-hospital death (%)	44 (18)	21 (12)	23 (30)	**0.001**

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; FEU, fibrinogen equivalent unit; Hb, hemoglobin; NP, natriuretic peptide; URN, upper reference of normality; WBC, white blood cells. Bold indicates $P<0.05$.

Multivariable logistic regression analysis identified the following variables to be independently associated with underlying CVD (Table 2): age [model 1: OR 1.05 (95% CI 1.02–1.07), $P<0.001$], COPD [model 1: OR 2.5 (95% CI 1.05–5.11), $P=0.038$], Hb [model 1: OR 0.84 (95% CI 0.71–0.99), $P=0.039$; model 2: OR 0.8 (0.67–0.96), $P=0.014$], hs-Troponin ($\log_{10}$) [model 2: OR 2.47 (95% CI 1.37–4.48), $P=0.003$], natriuretic peptides ($\log_{10}$) [model 3: OR 4.56 (95% CI 2.4–8.66), $P<0.001$].

Characteristics of population according to cardiac biomarkers

Table 3 depicts characteristics of the $n=136$ patients with available assessment of both hs-Troponin and natriuretic peptides stratified by cardiac biomarker results; specifically $n=56$ had normal cardiac biomarkers levels, $n=13$ had increased hs-Troponin only, $n=23$ had increased natriuretic peptides only and $n=44$ had elevation of both biomarkers. A stepwise increase in age was observed between groups ($P<0.001$ for trend, depicted in Fig. 2a), whereas prevalence of CVD was significantly higher in groups including patients with positive vs. negative natriuretic peptides ($P<0.001$ for trend, depicted in Fig. 2b). D-dimer was significantly increased in the group with cardiac biomarkers both elevated (depicted in Fig. 2c), but not when compared with the group with hs-Troponin only positive; furthermore, a trend towards higher D-dimer in lone hs-Troponin increase as compared with the normal cardiac biomarkers subgroup was detected (930 vs. 397 ng/ml, $P=0.140$). When compared with the subgroup of patients with cardiac biomarkers both normal, in-hospital mortality was significantly higher in patients with elevated hs-Troponin (mortality rate of 31 and 36% in patients with normal and elevated natriuretic peptides, respectively vs. mortality rate of 4% in patients with cardiac biomarkers both normal, $P<0.05$ for both) but

Table 2 Univariable and multivariable logistic regression analysis for factors associated with previous cardiovascular disease (top) and univariable and multivariable logistic regression analysis for factors associated with in-hospital mortality (bottom)

Previous CVD

	Univariable		Multivariable model 1		Multivariable model 2		Multivariable model 3	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.06 (1.03–1.08)	**<0.001**	1.05 (1.02–1.07)	**<0.001**	–	–	–	–
Sex (male)	1.13 (0.66–1.95)	0.657	–	–	–	–	–	–
COPD	2.3 (1.16–4.57)	**0.017**	2.31 (1.05–5.11)	**0.038**	NS	NS	NS	NS
Creatinine	1.12 (0.89–1.4)	0.324	–	–	–	–	–	–
Hb (g/dl)	0.75 (0.65.0.86)	**<0.001**	0.84 (0.71–0.99)	**0.039**	0.8 (0.67–0.96)	**0.014**	NS	NS
CRP (log_{10})	1.54 (0.99–2.42)	0.057	NS	NS	NS	NS	NS	NS
D-dimer (log_{10})	1.76 (0.92–3.34)	0.086	NS	NS	NS	NS	NS	NS
Hs-Troponin (log_{10})	3.21 (1.87–5.53)	**<0.001**	–	–	2.47 (1.37–4.48)	**0.003**	–	–
NP factor × URN (log_{10})	4.64 (2.57–8.39)	**<0.001**	–	–	–	–	4.56 (2.4–8.66)	**<0.001**
PaO_2/FIO_2 (per 10-point increase)	0.97 (0.94–0.99)	**0.017**	NS	NS	NS	NS	NS	NS

In-hospital mortality

	Univariable		Multivariable model 1		Multivariable model 2		Multivariable model 3	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.075 (1.04–1.11)	**<0.001**	1.08 (1.04–1.13)	**<0.001**	–	–	–	–
Sex (male)	1.15 (0.59–2.22)	0.687	–	–	–	–	–	–
COPD	1.96 (0.89–4,28)	0.094	NS	NS	NS	NS	NS	NS
Cancer	0.61 (0.13–2.77)	0.521	–	–	–	–	–	–
Lymphocyte ($\times 10^9$/l)	0.27 (0.11–0.63)	**0.003**	NS	NS	NS	NS	NS	NS
Creatinine	1.33 (1.04–1.7)	**0.025**	NS	NS	NS	NS	NS	NS
Previous CVD	3.12 (1.6–6.09)	**0.001**	2.72 (1.14–6.49)	**0.024**	2.65 (1.05–6.71)	**0.039**	NS	NS
Hb (g/dl)	0.79 (0.67–0.92)	**0.003**	NS	NS	NS	NS	NS	NS
CRP (log_{10})	2.42 (1.25–4.67)	**0.008**	NS	NS	NS	NS	4.06 (1.04–15.9)	**0.044**
D-dimer (log_{10})	2.37 (1.11–5.05)	**0.025**	NS	NS	NS	NS	NS	NS
Hs-Troponin (log_{10})	5.03 (2.6–9.71)	**<0.001**	–	–	2.61 (1.21–5.66)	**0.015**	–	–
NP factor × URN (log_{10})	3.94 (2.14–7.27)	**<0.001**	–	–	–	–	5.84 (2.43–14)	**<0.001**
PaO_2/FIO_2 (per 10-point increase)	0.93 (0.90–0.96)	**<0.001**	0.94 (0.89–0.98)	**0.007**	0.95 (0.90–0.99)	**0.047**	NS	NS

Bold indicates *P* less than 0.05. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; Hb, hemoglobin; NP, natriuretic peptide; URN, upper reference of normality; WBC, white blood cells.

not in those with normal hs-Troponin and elevated natriuretic peptides (mortality rate 17%) (Fig. 2d).

Outcome analysis

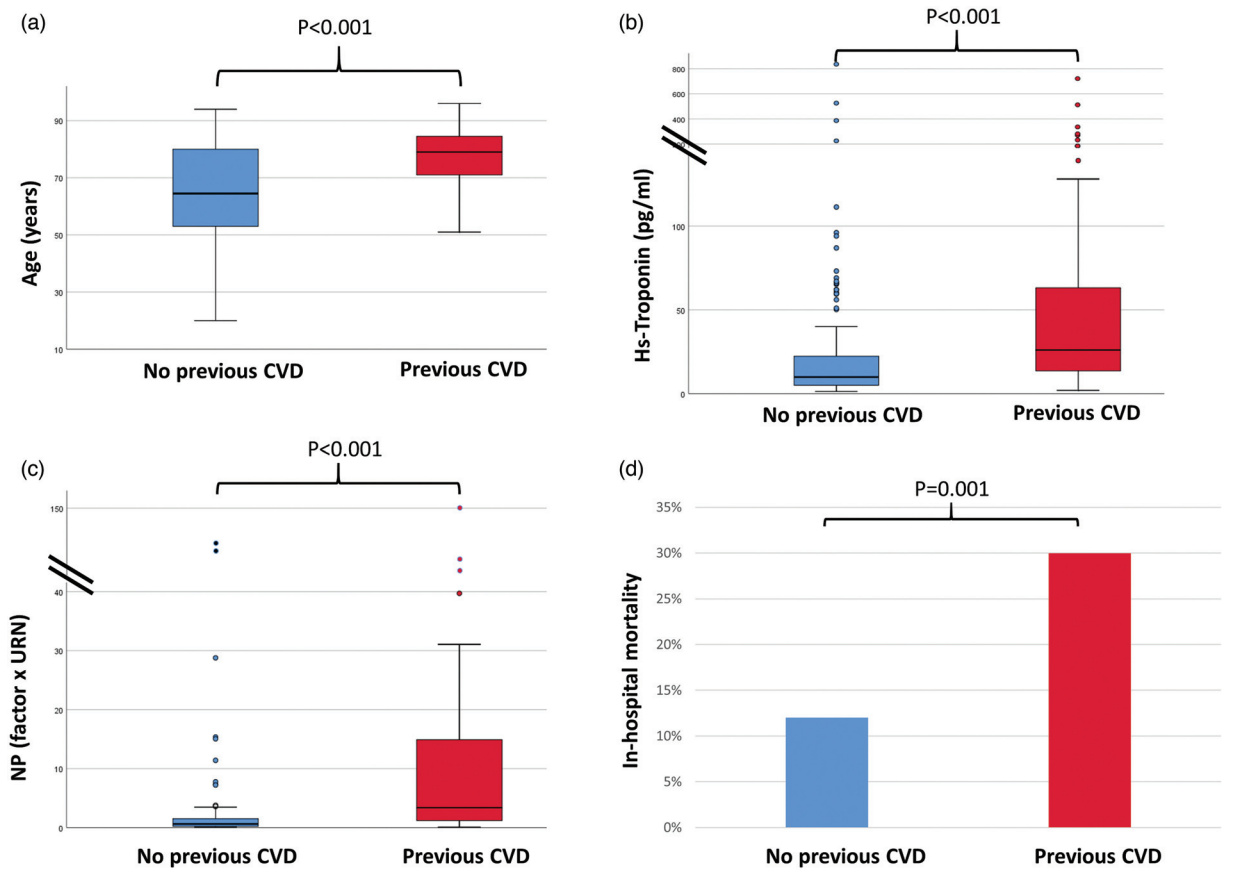
Univariable and multivariable analysis for factors associated with in-hospital mortality are depicted in Table 2. Variables independently associated with a worse outcome included: age [model 1: OR 1.08 (95% CI 1.04–1.13), $P < 0.001$], previous CVD [model 1: OR 2.72 (95% CI 1.14–6.49), $P = 0.024$; model 2: OR 2.65 (95% CI 1.05–6.71), $P = 0.039$], CRP (model 3: OR 4.06 (95% CI 1.04–15.9), $P = 0.044$], hs-Troponin (log_{10}) [model 2: OR 2.61 (95% CI 1.21–5.66), $P = 0.015$], natriuretic peptides (log_{10}) [model 3: OR 5.84 (95% CI 2.43–14), $P < 0.001$] and PaO_2/FIO_2 (per 10-point increase) [model 1: 0.94 (95% CI 0.89–0.98), $P = 0.007$; model 2: OR 0.95 (95% CI 0.90–0.99), $P = 0.047$].

Discussion

Main findings of the present study are as follows: patients with underlying CVD are characterized by increased cardiac biomarker levels, older age and clustering of comorbidities, such as anemia and COPD; a limited subgroup of patients with COVID-19 pneumonia, characterized by relatively low prevalence of underlying CVD, presents with increased hs-Troponin, normal natriuretic peptides and worse outcome; previous CVD, increasing hs-Troponin and natriuretic peptides were all independently associated with higher in-hospital mortality.

We found patients with COVID-19 and underlying CVD to be older and having higher prevalence of comorbidities including COPD, anemia and chronic kidney disease. However, the CRP level did not differ between groups, whereas differences regarding PaO_2/FIO_2 (lower in patients with CVD) and D-dimer (higher in patients with CVD) were not significant after multivariable analysis. This is in keeping with findings from others,[6] suggesting that the higher mortality rate in this vulnerable subset of patients might be highly influenced by underlying pre-existing conditions rather than more severe COVID-19 pneumonia at hospital admission. Hs-Troponin and natriuretic peptides were both significantly higher in patients with than without underlying CVD. Furthermore, patients with both cardiac biomarkers elevated were elderly, with higher prevalence of CVD as well as in-hospital mortality. Hence, the prognostic value retained by these biomarkers might be partly explained by their

Fig. 1



Boxplots and bar graph show significantly higher age (a), hs-Troponin (b), and natriuretic peptides (c) and in-hospital mortality rate (d) in patients with underlying CVD.

ability for identifying the vulnerable subset of older and comorbid patients, in whom their increase is partly explained by underlying comorbidities.[17,22,23]

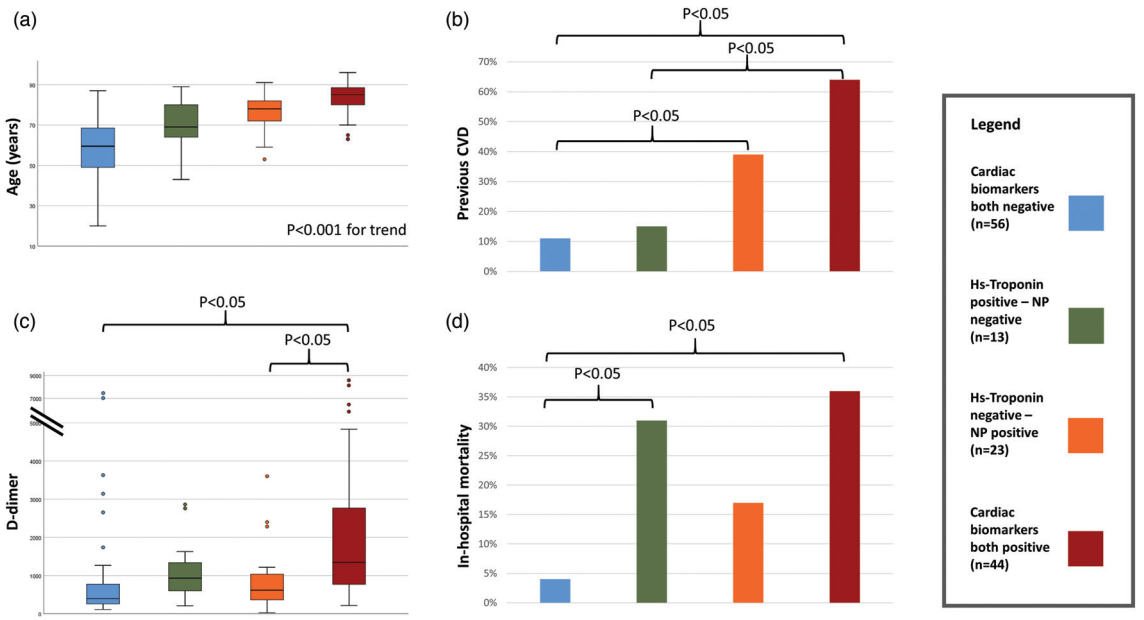
In accordance with previous literature,[7] we observed hs-Troponin and natriuretic peptides to be highly correlated with each other, whereas the majority of patients with abnormal cardiac biomarkers showed increased levels of both. Notwithstanding, smaller subgroups of the study population had isolated increases in either hs-Troponin or natriuretic peptides, displaying peculiar patterns. Patients with a lone increase in hs-Troponin had a similar prevalence of underlying CVD albeit a significantly higher mortality rate and trend towards higher D-dimer levels, whereas patients with a lone increase in natriuretic peptides had a higher prevalence of CVD but not significantly higher mortality as compared with patients with cardiac biomarkers both within normal ranges of normality. Several hypotheses could be made to explain myocardial injury unrelated to underlying CVD in the course of COVID-19. In particular, some studies have reported that an excessive host inflammatory response may cause multiorgan damage.[24] The imbalance between NF-KB vs. interferon activity during the flogistic cascade promotes the development of myocardial inflammation with variable extension, through direct and indirect effects on monocyte migration.[25] Moreover, cytokine storm also induces vascular remodeling and thrombosis phenomena, accelerating hypoxia-related damage.[11] All these mechanisms could in the end lead to myocardial inflammation, detected by cardiac MRI with tissue mapping in a consistent proportion of patients with recovered COVID-19, with its extent related to the hs-Troponin but not the NT-pro-BNP level.[16] Lombardi *et al.*[8] showed that patients with COVID-19, elevated hs-Troponin and no previous CVD had similar mortality to patients with previous CVD and nonelevated hs-Troponin, suggesting that COVID-19-related myocardial injury can be a marker of more severe disease and worse outcome. Indeed, a more conspicuous cytokine storm and a multiorgan involvement[26] might contribute to the higher mortality rate observed in this subgroup. Such a manifestation is not uncommon in COVID-19, where the onset of any organ dysfunction increases the risk of complications and mortality.[27]

Table 3 Baseline clinical characteristics and laboratory findings in subgroup of patients with variable cardiac biomarkers results

Variable	Cardiac biomarkers both negative ($n=56$)	Hs-Troponin positive – NP negative ($n=13$)	Hs-Troponin negative – NP positive ($n=23$)	Cardiac biomarkers both positive ($n=44$)	*P*
Age	$58\pm15^{b,c,d}$	$70\pm13^{a,d}$	77 ± 9^{a}	$83\pm8^{a,b}$	**<0.001**
Sex (male) (%)	34 (61)	11 (85)	12 (52)	23 (52)	0.149
Coexistent conditions					
Hypertension (%)	25 (45)[d]	8 (61)	14 (61)	35 (79)	0.005
Dyslipidemia (%)	9 (16)	5 (38)	4 (17)	8 (18)	0.314
Diabetes (%)	7 (12)	1 (8)	4 (17)	12 (27)	0.196
Previous CVD (%)	6 (11)[c,d]	2 (15)[d]	9 (39)[a]	28 (64)[a,b]	**<0.001**
Atrial fibrillation (%)	0 (0)[c,d]	0 (0)	4 (17)[a]	14 (33)[a]	**<0.001**
Coronary artery disease (%)	4 (7)	1 (8)	5 (22)	11 (26)	**0.049**
Heart failure (%)	0 (0)[c]	0 (0)	1 (4)	12 (27)[a]	**<0.001**
Stroke (%)	2 (4)	1 (8)	1 (4)	5 (12)	0.443
CKD (%)	0 (0)[c,d]	0 (0)	3 (13)[a]	8 (19)[a]	**0.004**
COPD (%)	7 (12)	2 (15)	4 (17)	9 (21)	0.731
Cancer (%)	3 (5)	0 (0)	3 (13)	2 (5)	0.342
Laboratory tests					
Hb (mg/dl)	$13.5\pm1.5^{c,d}$	12.5 ± 2	11.7 ± 1.7^{a}	11.4 ± 1.9^{a}	**<0.001**
WBC ($\times 10^9$/l)	6.6 (4.9–9.2)	5.7 (5.3–10.5)	8.3 (5.9–16)	7.8 (5.8–11)	0.066
Neutrophil ($\times10^9$/l)	4.6 (3.1–7.2)	3.9 (3.3–5.9)	4.8 (3.3–9)	5.5 (4–9.3)	0.209
Lymphocyte ($\times10^9$/l)	0.98 (0.61–1.35)	1.1 (0.96–1.78)	1.1 (0.5–1.7)	0.8 (0.6–1.3)	0.311
Creatinine (mg/dl)	0.8 (0.7–0.9)[d]	1 (0.9–1.3)	1.1 (0.7–1.3)	1 (0.8–1.7)[a]	**<0.001**
Platelet ($\times10^9$/l)	225 (188–276)	222 (158–278)	210 (138–273)	192 (149–295)	0.706
CRP (mg/dl)	5 (1–9)[d]	5.5 (2.6–11.7)	5.4 (4.3–11.8)	7.6 (3.4–19.6)[a]	**0.027**
D-dimer (ng/ml FEU)	397 (252–774)[d]	930 (553–1481)	616 (344–1072)[d]	1346 (670–2820)[a,c]	**<0.001**
Blood gas analysis					
pH	7.45 ± 0.06	7.5 ± 0.1	7.44 ± 0.09	7.46 ± 0.07	0.069
pO_2 (mmHg)		78 ± 20	68 ± 9	75 ± 17	73 ± 23
pCO_2 (mmHg)	37 ± 5	34 ± 6	37 ± 7	35 ± 7	0.344
PaO_2/FIO_2	305 (242–382)	316 (288–333)	328 (203–385)	271 (150–328)	0.075
In-hospital outcome					
In-hospital death	2 (4)[b,d]	4 (31)[a]	4 (17)	16 (36)[a]	**<0.001**

Bold indicates *P* less than 0.05 for trend. ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; FEU, fibrinogen equivalent unit; Hb, hemoglobin; NP, Natriuretic peptide; URN, upper reference of normality; WBC, white blood cells. [a] *P* less than 0.05 vs. Cardiac biomarkers both negative group. [b] *P* less than 0.05 vs. Hs-Troponin-positive–NP-negative group. [c] *P* less than 0.05 vs. Hs-Troponin-negative–NP-positive group. [d] *P* less than 0.05 vs. Cardiac biomarkers both positive group.

Fig. 2



Boxplots and bar graphs show stepwise increase in age among cardiac biomarkers subgroups (a). CVD prevalence was significantly higher in patients with elevated natriuretic peptides only (b). Patients with both cardiac biomarkers significantly elevated had a higher D-dimer level as compared with patients with normal hs-Troponin, but not when compared with patients with isolated hs-Troponin increase (c). Groups with both cardiac biomarkers increased and isolated hs-Troponin increase (but not those with isolated natriuretic peptides increase) had significantly higher in-hospital mortality rates as compared with patients with normal cardiac biomarkers (d).

Taken together, these findings support the hypothesis that isolated elevation of hs-Troponin, especially in the absence of any CVD, might represent higher COVID-19-related systemic involvement, where isolated natriuretic peptides increase could be more related to preexisting cardiac vulnerability given by underlying CVD. When hs-Troponin and natriuretic peptides are both elevated, often acute myocardial injury, CVD, severe inflammation and comorbidities coexist in the same patient, leading to the highest rate of in-hospital mortality.

Our findings could potentially carry clinical implications. Irrespective of the underlying mechanisms, previous CVD and elevated cardiac biomarkers in our study were independently associated with increased in-hospital mortality. Hence, all measures available to improve prognosis in this vulnerable subset of patients should be considered, including preventive measures, such as precocious vaccination in CVD patients and a lower threshold for hospitalization whenever infected. Furthermore, our data support an integrated reading of hs-Troponin and natriuretic peptide values in relation to the presence of underlying CVD, in order to provide a more comprehensive interpretation of cardiac biomarker results. Patients with COVID-19 represent a heterogeneous and highly comorbid population, in which prompt identification of an acute heart failure rather than more severe COVID-19 status with larger systemic involvement might help in guiding clinical management.

Limitations

The present study should be read in light of several limitations, including its retrospective nature, limited sample size, especially of subgroups with cardiac biomarker assessment, noncritical care setting and geographic specificity, which might reduce generalizability of our findings. Associations that we observed must be cautiously interpreted as hypothesis-generating only, not allowing cause–effect relationships to be established. In our study, we only detected a trend towards higher D-dimer levels in patients with lone hs-Troponin increase, in the context of limited subgroup size influencing statistical power. Assessment of CVD and ongoing medical treatments was determined at the clinical level; hence we acknowledge that collected data might be partly incomplete because of patients' carelessness or inability in self-reporting medical history as well as to the presence of underlying asymptomatic and undetected CVD. Cause of death has not been systematically investigated in our population; furthermore, autopsies, as well as comprehensive evaluation of thromboembolic phenomena (including microvessel thrombosis), were not routinely performed preventing us from confirming the hypothesis as to whether the subgroup of patients with COVID-19 and isolated hs-Troponin increase was characterized by higher inflammatory[28] or thrombotic[24] drivers. Finally, the number of patients who died in hospital was relatively low, and statistical overfitting might have occurred.

Conclusion

In conclusion, in our COVID-19 population, we found a common occurrence of underlying previous CVD, which was part of a vulnerable phenotype, including older age, comorbidities, increased cardiac biomarkers and worse prognosis. Patients with isolated increase in hs-Troponin suffered increased mortality, despite the low prevalence of CVD, possibly explained by higher COVID-19-related systemic involvement.

Conflicts of interest

There are no conflicts of interest.

References

1 Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**:497–506.
2 Petrilli CM, Jones SA, Yang J, *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; **369**:m1966.
3 Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe Massimo M. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian society of hypertension. *Hypertension* 2020; **76**:366–372.
4 Wang L, He W, Yu X, *et al.* Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020; **80**:639–645.
5 Inciardi RM, Adamo M, Lupi L, *et al.* Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. n.d. 2020; **41**:1821–1829
6 Tomasoni D, Inciardi RM, Lombardi CM, *et al.* Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. *Eur J Heart Fail* 2020; **22**:2238–2247.
7 Guo T, Fan Y, Chen M, *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**:811–818.
8 Lombardi CM, Carubelli V, Iorio A, *et al.* Association of troponin levels with mortality in Italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. *JAMA Cardiol* 2020; **5**:1274–1280.
9 Gao L, Jiang D, Wen XS, *et al.* Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res* 2020; **21**:83.
10 Zuin M, Rigatelli G, Zuliani G, Bilato C, Zonzin P, Roncon L. Incidence and mortality risk in coronavirus disease 2019 patients complicated by acute cardiac injury: systematic review and meta-analysis. *J Cardiovasc Med* 2020; **21**:759–764.
11 Zhao BC, Liu WF, Lei SH, *et al.* Prevalence and prognostic value of elevated troponins in patients hospitalised for coronavirus disease 2019: a systematic review and meta-analysis. *J Intensive Care* 2020; **8**:88.
12 Tomasoni D, Italia L, Adamo M, *et al.* COVID-19 and heart failure: from infection to inflammation and angiotensin stimulation: searching for evidence from a new disease. *Eur J Heart Fail* 2020; **22**:957–966.
13 Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019 (COVID-19): possible mechanisms. *J Card Fail* 2020; **26**:470–475.
14 Inciardi RM, Lupi L, Zaccone G, *et al.* Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**:819–824.
15 Arcari L, Luciani M, Cacciotti L, *et al.* Incidence and determinants of high-sensitivity troponin and natriuretic peptides elevation at admission in hospitalized COVID-19 pneumonia patients. *Intern Emerg Med* 2020; **15**:1467–1476.
16 Puntmann VO, Carerj ML, Wieters I, *et al.* Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**:1265–1273.
17 Januzzi JL, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J* 2012; **33**:2265–2271; https://doi.org/10.1093/eurheartj/ehs191.

18 Noubiap JJ, Sanders P, Nattel S, Lau DH. Biomarkers in atrial fibrillation: pathogenesis and clinical implications. *Card Electrophysiol Clin* 2021; **13**:221–233.
19 Camastra G, Ciolina F, Arcari L, Danti M, Cacciotti L. Heart and lung involvement detected by native T1 and T2 mapping magnetic resonance imaging in a patient with coronavirus disease-19. *Eur Hear J Cardiovasc Imaging* 2021; **22**:e90.
20 Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**:2129–2200.
21 Tay R. Correlation, variance inflation and multicollinearity in regression model. n.d.
22 Søyseth V, Bhatnagar R, Holmedahl NH, *et al.* Acute exacerbation of COPD is associated with fourfold elevation of cardiac troponin T. *Heart* 2013; **99**:122–126.
23 Turan A, Cohen B, Rivas E, *et al.* Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Br J Anaesth* 2021; **126**:94–101.
24 Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020; **142**:68–78.
25 Epelman S, Liu PP, Mann DL. Role of innate and adaptive immune mechanisms in cardiac injury and repair. *Nat Rev Immunol* 2015; **15**:117–129.
26 Oudit GY, Kassiri Z, Jiang C, *et al.* SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest* 2009; **39**:618–625.
27 Potere N, Valeriani E, Candeloro M, *et al.* Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Crit Care* 2020; **24**:389.
28 Thachil J. All those D-dimers in COVID-19. *J Thromb Haemost* 2020; **18**:2075–2076.