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Original article

Joint effect of heart failure and coronary artery disease on the risk of death during hospitalization for COVID-19

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ABSTRACT

Aims: heart failure (HF) and coronary artery disease (CAD) are independent predictors of death in patients with COVID-19. The adverse prognostic impact of the combination of HF and CAD in these patients is unclear.
Methods and results: we analysed data from 954 consecutive patients hospitalized for SARS-CoV-2 in five Italian Hospitals from February 23 to May 22, 2020. The study was a systematic prospective data collection according to a pre-specified protocol. All-cause mortality during hospitalization was the outcome measure.
Mean duration of hospitalization was 33 days. Mortality was 11% in the total population and 7.4% in the group without evidence of HF or CAD (reference group). Mortality was 11.6% in the group with CAD and without HF (odds ratio [OR]: 1.6, $p = 0.120$), 15.5% in the group with HF and without CAD (OR: 2.3, $p = 0.032$), and 35.6% in the group with CAD and HF (OR: 6.9, $p<0.0001$).
The risk of mortality in patients with CAD and HF combined was consistently higher than the sum of risks related to either disorder, resulting in a significant synergistic effect ($p<0.0001$) of the two conditions. Age-adjusted attributable proportion due to interaction was 64%. Adjusting for the simultaneous effects of age, hypotension, and lymphocyte count did not significantly lower attributable proportion which persisted statistically significant ($p = 0.0360$).
Conclusion: The combination of HF and CAD exerts a marked detrimental impact on the risk of mortality in hospitalized patients with COVID-19, which is independent on other adverse prognostic markers.

Introduction

Since the initial coronavirus (SARS-CoV-2) outbreak in the province of Wuhan, China, more than 50 million people have been infected so far, causing unnerving impact on routine patient care and leading to significant excess of morbidity and mortality worldwide [1].

Coronavirus-related syndrome (COVID-19) is known to be associated with life-threating interstitial pneumonia, but SARS-CoV-2-related cardiac involvement is now acknowledged to be part of the wide spectrum of COVID-19 [2,3]. Moreover, the prevalence of cardiovascular comorbidities in patients hospitalised for SARS-CoV-2 is not negligible, spanning from 2% to 42% of cases and being associated with a more than two-fold risk of in-hospital death [4,5].

In this evolving clinical scenario, there is a need of scientific knowledge on prognostic factors for adverse outcome in patients with COVID-19 [6]. In this context, the United States Centers for Disease Control and Prevention (CDC) has created a list of established and possible risk factors that have been associated with severe disease [1].

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Among established risk factors, history of heart failure (HF) and coronary artery disease (CAD) have been included as heart conditions at increased risk of severe illness and death [1].

Although an interaction between these two conditions may be postulated in the general population of HF patients [7], their joint effect on the risk of death among COVID-19 patients remains to be explicitly examined using data collected in a prospective fashion.

Thus, the main aim of the present study was to investigate the distinct and the potential synergy of HF and CAD on the risk of death in patients hospitalized for COVID-19.

Methods

We analysed data from consecutive patients hospitalized from February 23 to May 22, 2020 in 5 hospitals of the Lombardy region and belonging to the Maugeri Care and Research Institutes Network [2,8].

Diagnosis of viral infection was confirmed in all patients by RNA reverse-transcriptase-polimerase-chain-reaction (RT-PCR) assays from nasopharyngeal swab specimens [9].

Notably, our study was not a retrospective collection of clinical notes of patients hospitalized for COVID-19, but rather a pre-designed protocol with subsequent prospective collection of data [2]. The protocol was approved by the Ethical Committee of our Institution and patients gave their written informed consent to participate [2].

Demographic, laboratory, and clinical management data were collected at admission and throughout the entire in-hospital stay. The presence of comorbidities was defined according to documented medical history, as collected by investigators at study site-level, including interrogation of electronic health record data of the Lombardy region.

All clinical evaluations were performed by attending physicians during the clinical interview and through interrogation of medical records. Comorbidities (including type II diabetes, chronic kidney disease, dyslipidemia, hypertension, CAD, and HF) were defined according to current Guidelines [10-16].

More specifically, HF patients were identified according to history of a symptomatic syndrome, as graded according to the New York Heart Association (NYHA) functional classification, or prior hospitalization for acute heart failure requiring intravenous therapy (diuretics, inotropes or vasodilators) [10].

History of CAD was defined by at least one of the following criteria: 1) presence of any epicardial coronary vessels with >75% stenosis tested on coronary angiography; 2) history of acute coronary syndrome; 3) coronary revascularization (either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) [16].

The study outcome was all-cause mortality during hospitalization.

Statistical analysis. Analyses were performed using Stata, version 16 (StataCorp LP, College Station, TX, USA) and R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria). We expressed continuous variables as mean ± standard deviation (SD) and the categorical variables as proportions. We analysed differences in proportions between groups using the χ^2 test. Mean values of variables were compared by independent sample *t*-test.

We evaluated the effect of prognostic factors on mortality by univariable and multivariable logistic regression analyses. The odds ratios (ORs) from the univariable and multivariable analyses and their corresponding two-sided 95% confidence intervals (CI) were derived from the regression coefficients in the logistic models.

We tested the prognostic impact of several variables which proved a significant influence on mortality in this setting. They included: age (years) [17,18]; history of diabetes (yes/no) [18]; history of hypertension (yes/no) [19]; history of dyslipidaemia (yes/no) [19], history of CAD (yes/no) [20], history of HF (yes vs no) [21], history of chronic kidney disease (yes/no) [18], respiratory failure requiring mechanical ventilation or noninvasive ventilation during hospitalization (yes/no) [19], hemoglobin levels (1 g/dL) [22], absolute lymphocyte count (1000/mcl) [19,20], platelet count (1000/mcL) [19], and severe hypotension occurred during hospitalization and requiring inotropic support (yes/no) [19].

We modeled a multivariable model using the covariates which yielded statistical significance in the univariable analysis. To include predictors in the multivariable model, we used Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) to compare different multivariable models based on their fit to the data. We also calculated the receiver-operating characteristic (ROC) curves for survival models.

We investigated the interactions between covariates according to established methods [23,24]. In particular, the estimated biologic interaction, defined as the interdependent effect of two or more causes to produce disease, was computed from the proportion of risk in the doubly exposed group resulting from the interaction itself [24].

Analyses were performed using a significance level of α=0.05 (2-sided).

Results

A total of 954 patients were admitted for COVID-19 during the study period and included in the final analysis. The demographic and clinical features of study population are reported in **Table 1**. The average length of in-hospital stay was 33 ± 17 days. The prevalence of HF and CAD was 11% and 17%, respectively. When compared with patients without HF, those with a history of HF were older ($p<0.0001$), and had a higher prevalence of comorbidities including type II diabetes mellitus ($p = 0.0030$), chronic kidney disease ($p<0.0001$), CAD ($p<0.0001$), hypertension ($p = 0.0229$), and dyslipidaemia ($p = 0.0001$). Similarly, compared with patients without CAD, those with a history of CAD had a higher prevalence of chronic kidney disease (13% vs 6.0%, $p = 0.002$), type II diabetes mellitus (36% vs 22%, $p<0.0001$), hypertension (71% vs 58%, $p = 0.001$), and dyslipidaemia (52% vs 20%, $p<0.0001$).

Patients with history of HF had lower lymphocyte ($p = 0.0052$) and platelet count ($p<0.0001$).

During hospitalization, severe hypotension ($p = 0.019$) occurred more frequently among patients with HF (**Table 1**). Overall, incidence of death was 11%.

Age, hypertension, severe hypotension, lymphocytopenia, and low

Table 1
Main features of patients included in the analysis.
Legend: CAD=coronary artery disease; CKD=chronic kidney disease; DM=diabetes mellitus.

Variable	Overall		Heart Failure	
	(*N* = 954)	No (*N* = 851)	Yes (*N* = 103)	**p value**
Age, years	72 ± 13	71 ± 14	78 ± 9	<0.00001
Male sex (%)	57	57	53	0.5553
Body mass index (Kg/m^2)	27 ± 6	26 ± 5	28 ± 7	0.0674
Hypertension (%)	60	59	71	0.0229
Dyslipidemia (%)	24	22	40	0.0001
Type II DM (%)	25	23	37	0.0030
CAD (%)	17	14	44	<0.0001
CKD (%)	7	6	20	<0.0001
Cancer. (%)	11	10	17	0.0791
Noninvasive ventilation (%)	22	22	21	0.962
Mechanical Ventilation (%)	6	7	2	0.078
Severe hypotension (%)	7	6	15	0.0019
Hemoglobin (g/dl)	12 ± 2	12 ± 2	11 ± 2	0.2111
Lymphocyte count (1,000/μL)	1.579 ± 1.17	1.613 ± 1.22	1.308 ± 0.72	0.0005
Platelet count, x 10^3 (μL)	265 ± 106	270 ± 105	225 ± 99	0.0001
Platelet count <150,000/μL, (%)	11	10	23	0.0001
Length of in-hospital stay (days)	33 ± 17	34 ± 17	29 ± 20	0.0004

platelet count recorded during in-hospital stay, pre-existing HF and known history of CAD were associated with an increased risk of death (all $p<0.05$, Table 2).

Nonetheless, adjustment for age had a stronger effect on the risk of adverse outcome ameliorating the prognostic impact of some covariates.

Table 2
Results of univariable analyses exploring predictors of in-hospital death.

Variable	Comparison	Odds ratio (95% CI)	p value
Age	5 years	1.59 (1.40–1.81)	<0.0001
Female sex	Yes vs. No	0.73 (0.47–1.12)	0.145
Dyslipidemia	Yes vs. No	1.08 (0.67–1.76)	0.743
Diabetes	Yes vs. No	1.37 (0.86–2.19)	0.189
Hypertension	Yes vs. No	1.68 (1.05–2.69)	0.030
Coronary Artery Disease	Yes vs. No	2.54 (1.58–4.07)	<0.0001
Heart Failure	Yes vs. No	3.69 (2.21–6.17)	<0.0001
Chronic Kidney Disease	Yes vs. No	1.51 (0.72–3.16)	0.272
Cancer	Yes vs. No	1.09 (0.56–2.12)	0.796
Noninvasive ventilation	Yes vs. No	0.99 (0.59–1.66)	0.962
Mechanical Ventilation	Yes vs. No	0.30 (0.10–1.24)	0.097
Severe hypotension	yes vs. no	2.49 (1.33–4.67)	0.004
Hemoglobin	1 g/dl	0.92 (0.81–1.03)	0.150
Lymphocyte count	1,000/μL	0.37 (0.24–0.57)	<0.0001
Platelet count	10,000/μL	0.73 (0.58–0.93)	0.011

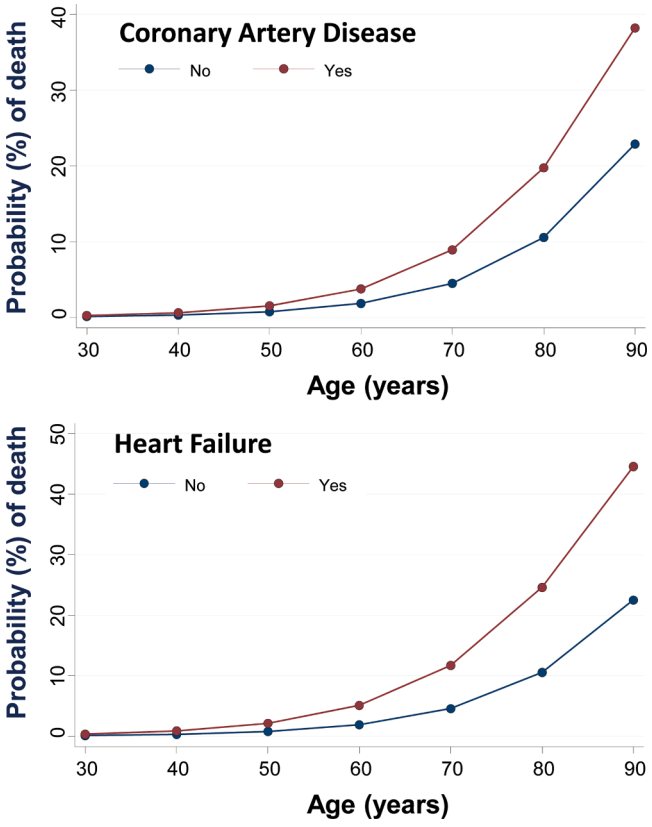

Fig. 1. Probability (%) of in-hospital death according to age in patients with and without coronary artery disease and heart failure (all $p<0.05$).

Indeed, only history of HF ($p<0.0001$), CAD ($p = 0.003$, Fig. 1), lymphocyte count ($p = 0.001$), and severe hypotension ($p<0.0001$) remained statistically significant when controlled for age. When forcing all these covariates in the same multivariable model (AIC=456, BIC=484, and ROC area=0.82 [95% CI: 0.77–0.86]), both HF (OR=1.9 [95% CI: 1.0–3.5], $p = 0.039$) and CAD (OR=1.9 [95% CI: 1.1–3.3], $p = 0.024$) were associated with an increased risk of death (Table 3).

To explore interactions between covariates, we stratified the total population into four mutually exclusive groups according to the presence or absence of HF or CAD. Crude rate of in-hospital mortality was 7.4% in the group of patients without HF or CAD (Fig. 2). Mortality was 11.6% in the group with evidence of CAD but no evidence of HF, 15.5% in the group with HF but no evidence of CAD and it raised to 35.6% in the group with coexistence of CAD and HF (OR=6.9 [95% CI: 3.5–13.5], $p<0.0001$, Fig. 2). Of note, risk for in-hospital death in those who were affected by both disorders was much higher than the sum of risks related to either disorder (HF or CAD), excluding an additive interaction between HF and CAD ($p = 0.291$). Conversely, this resulted in a significant synergistic effect ($p<0.0001$) of the two conditions and in a significant age-adjusted attributable proportions due to interaction (64%, 95% CI: 28%−98%, $p = 0.0005$ – Fig. 3, left panel). Adjusting for the simultaneous effects of age, hypotension, and lymphocyte count (Fig. 3, right panel) did not significantly lower attributable proportion which persisted statistically significant ($p = 0.0360$).

No other significant interactions between covariates were documented.

Discussion

The present study provides novel data supporting the detrimental impact of the coexistence of HF and CAD on short-term mortality in patients with COVID-19.

Some reports have recently evaluated the detrimental prognostic effect of CAD or HF in patients with COVID-19 [4,17,18,20,25-27], including monocentre [26] and multicentre [27] studies from Italy. However, never before the joint effect of these 2 conditions has been assessed in a prospective fashion. More specifically, our study is the first one investigating the potential synergism between HF and CAD on short-term risk of mortality among COVID-19 patients and extending previous data from general population studies of patients with HF [28, 29]. A recent analysis of a Registry from Sweden showed that CAD is a powerful and independent predictor of death in patients with non-valvular HF [7]. Since patients were followed for a median of 2.4 years, [7] the impact of the combination between HF and CAD in the short-term remained unclear.

Results of our analysis suggest that COVID-19 might act as a destabilizing factor accelerating the adverse impact of the coexistence of HF and CAD.

HF and CAD both portended a significant impact on adverse outcome and exerted a synergistic effect with regard to the risk of death. Specifically, the proportion of the risk in the doubly exposed group that is due to the interaction itself was 64% (Fig. 3). Notably, when additionally adjusting for other prognostic factors (age [26,30], hypotension occurring during hospitalization [20,21], and lymphocyte count [20]), this synergistic effect retained its statistical significance. Of note, age had a stronger effect on the risk of adverse outcome ameliorating the

Table 3
Multivariable model exploring factors associated with all-cause mortality.

Variable	Comparison	Odds ratio	Standard error	z	P>|z|	95% Confidence interval
Age	5 years	1.57	0.120	5.89	0.000	1.35 to 1.82
Severe hypotension	Yes vs No	3.20	1.220	3.06	0.002	1.52 to 6.76
Lymphocyte count	1000/μL	0.53	0.115	−2.93	0.003	0.35 to 0.81
Heart Failure	Yes vs No	1.90	0.594	2.06	0.039	1.03 to 3.51
Coronary Artery Disease	Yes vs No	1.88	0.528	2.26	0.024	1.09 to 3.26

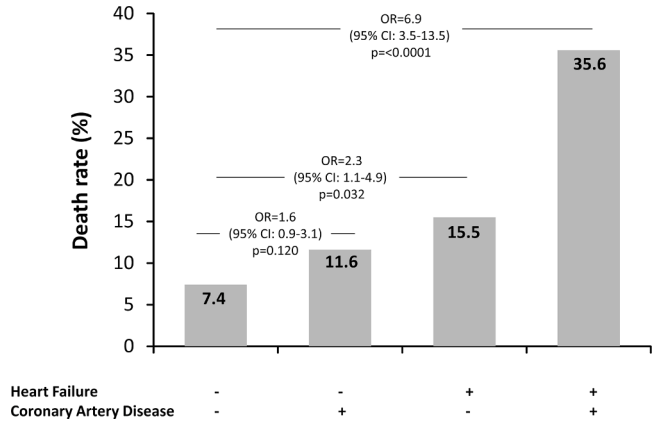

Fig. 2. Crude rates of in-hospital mortality in the four mutually exclusive groups defined by the presence or absence of heart failure and coronary artery disease. Absence of the two conditions was set as reference for the computation of the risk of death.
Legend: CI=confidence interval; OR=odds ratio.

prognostic impact of some covariates. Conversely, sex did not refine risk stratification in our study population ($p = 0.145$), showing a similar distribution between groups identified by the presence or absence of HF or CAD ($p = 0.090$).

In this context, a bi-faced mechanism for the occurrence of acute coronary events in an acute systemic viral infection has been hypothesized [31]. It includes both the rapid formation of new coronary plaques, along with acute plaque change in pre-existing plaques, and direct myocardial injury secondary to acute systemic viral infection [31].

Although acute respiratory distress syndrome and septic shock have been described as major in-hospital death causes in these patients [4,27], COVID-19 is also associated with a wide spectrum of clinical manifestations, including cardiac involvement [27,30,32] due to the enhanced systemic inflammation (cytokine storm) [3], thromboembolic complications [33], and direct myocardial cytopathic effect [34] during viral infection.

Furthermore, the expression of SARS-CoV-2 receptors on pericytes and cardiomyocytes in failing human hearts may potentially explain microvascular dysfunction and worsening HF in patients with known coronary and structural heart disease [35,36].

Taken together, these observations suggest that the powerful systemic inflammation occurring during SARS-CoV-2 infection, the myocardial involvement, and the ensuing haemodynamic impairment might act in synergy with pre-existent coronary disease and play a pivotal role as the leading cause of death in patients with HF.

Although the lungs are believed to be the site at which SARS-CoV-2 replicates, infected patients show the involvement of several organs, including heart and vessels. In other words, the clinical spectrum of COVID-19 is not limited to local pneumonia, but rather represents a multisystem illness with involvement of different organs and potential for systemic complications [37-39].

From a practical point of view, the presence of multimorbidity identifies patients at risk for severe COVID-19 [2,36-41]. In this context, our results suggest that prompt recognition at admission of HF and CAD as comorbidities might be helpful to identify patients at increased risk of death, therefore warranting a more intensive clinical monitoring management.

Nonetheless, the impact of the coexistence of HF and CAD on short-term mortality, a finding of considerable clinical interest, remains to be fully elucidated. Further studies are needed to investigate the pathophysiological role of SARS-CoV-2 in these high-risk patients.

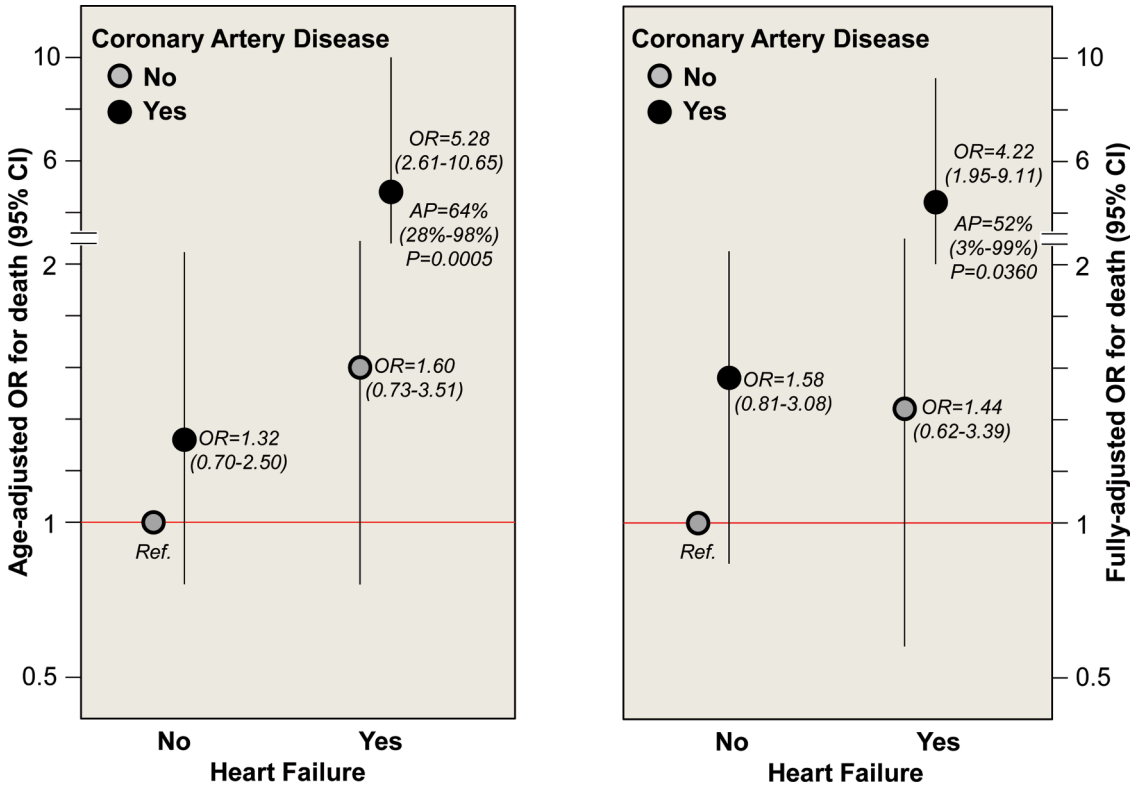

Fig. 3. Prognostic models exploring the joint effect of heart failure and coronary artery disease. The proportion of the risk in the doubly exposed group that is due to the interaction itself (attributable proportion) is also reported. The full model was adjusted by age, occurrence of severe hypotension during hospitalization, and lymphocyte count.
Legend: AP=attributable proportion; CI=confidence interval; OR=odds ratio.

Limitations

The present analysis investigated the prognostic role of HF and its complex interplay with CAD in a large prospective cohort of patients hospitalised for COVID-19.

We analysed data from consecutive patients hospitalized in 5 hospitals of the Lombardy region. Thus, our study population should not be considered as representative of all the regional COVID-19 patients [42].

Although Garcia et al. [21] recently reported no prognostic differences in terms of in-hospital mortality according to left ventricular ejection fraction, in our study no echocardiographic parameters of systolic function were available.

Furthermore, underlying causes of HF, pre-clinical CAD, anatomic coronary complexity, prior incomplete coronary revascularization, and levels of cardiac biomarkers (including troponin and natriuretic peptides) during hospitalization were not routinely collected.

Author-Disclosure-Form

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We confirm that:

1 The manuscript submitted represents original work and has not been previously published or simultaneously submitted elsewhere for publication.
2 The manuscript has been read and approved by all authors.
3 None of the authors of this study has financial or other reasons that could lead to a conflict of interest.

Declaration of Competing Interest

none declared.

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