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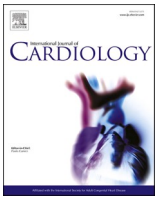

Heart failure and co-morbidities confer a negative prognosis in COVID-19 infection☆

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ABSTRACT

Background: Since early reports, it has been shown that cardiovascular (CV) diseases, including heart failure (HF), represent a risk factor for infection, hospital admissions and mortality from COVID-19. The COVID-19 pandemics has been of major importance in Italy and in the Lombardy Region. Aims of this study were to compare COVID-19 infection in HF and No-HF subjects, and to quantify among HF patients the risk for COVID-19 infection and all-cause mortality.

Methods: All consecutive patients (98,549) with at least one hospital discharge of HF (primary diagnosis) during January 1st, 2015, to December 31st, 2019, were identified in the Lombardy Region Database (>10 million inhabitants), and compared with No-HF subjects (394,104 with a lower age limit 40 years), randomly chosen in a 4:1 proportion among hospitalized patients.

The whole cohort of cases of COVID-19 infection, laboratory-confirmed by RT-PCR, aged >40 years, diagnosed from the beginning of the epidemic on 21 February 2020 to 1 October 2020 was studied. The study outcomes were: occurrence, hospitalization, and death in COVID-19 cases.

Results. Incidence of COVID-19 increased with age in both HF ($p < 0.001$) and No-HF patients ($p < 0.001$); cases (and incidence rates, IR) were 8,648 (IR = 29.653 × 100.000) in HF and 14,256 (IR = 10.195) and in No-HF ($p < 0.001$); hospital admissions were 4,974 (IR = 14.970) and 4,943 (IR = 3.484), respectively (p ⟨0001); deaths were 7,650 (IR = 5.368) and 18,368 (IR = 56.921), respectively ($p < 0.001$); the incidence rate ratio (IRR) was 2.909 (95 % C.I. 2.908–2.909) for infection ($p < 0.001$), 4.297 (95 % C.I. 4.296–4.297) for hospital admission ($p < 0.001$), and 10.603 (95 % C.I.10.602–10.604) for mortality ($p < 0.001$). The excess IRR for mortality varied from 25.001 (95 % C.I. 24.971–25.032) for the age decade 40–49 to 1.925 (95 % C.I. 1.923–1.926) for the age decade 100–109. Among HF patients, age (OR = 1.087, 95 % C.I.1.05–1.088), male sex (OR = 1.27, 95 % C.I. 1.23–1.31), number of hospital admissions for HF during the period 2015–2019 (OR = 2.22, 95 % C.I. 2.11–2.33), co-morbidities (OR = 1.33, 95 % C.I. 1.32–1.35), or Charlson Index (OR = 1.21, 95 % C.I.

Abbreviations: CV, Cardiovascular; HF, Heart failure; MERS, Middle East respiratory syndrome; SARS, Severe acute respiratory syndrome.

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1.20–1.22), were risk factors for both infection and all-cause mortality at univariable and at multivariable analysis.

Conclusion: Infections, hospital admissions, and mortality for COVID-19 increased with age and male sex were more frequent in HF than in No-HF patients. Among HF patients, age and sex, number of hospital admissions for HF, co-morbidities, were risk factors for both infection and mortality. These data are of relevance for prioritizing interventions for prevention of infection, and for assistance to patients with COVID-19, and to inform management of future pandemics.

1. Introduction

Since early reports on the COVID-19 pandemics, the crucial role of the cardiovascular (CV) system was established, with significant differences from previous viral pandemics such as SARS and MERS [1]. First, COVID-19 was reported to affect the CV system, causing myocardial infarction and heart failure (HF), and these events were linked to a bad prognosis [2]. Second, small and large studies indicated that any CV disease (hypertension, myocardial infarction, heart failure, HF) was more frequent among COVID patients than among controls, and conferred a worse prognosis, especially when multi-morbidity was present [2–10]. The role of HF in favoring COVID-19 infection, and its role as a negative prognostic index of COVID-19 infection, have been shown, but have not been analyzed in detail [2–10]. Also, the possible combined effect of different degrees of HF together with co-morbidities has been only partially analyzed [11–13].

The COVID-19 pandemics has been of major importance in Italy and, in particular, in the Lombardy Region [9,12,13]. Therefore, we aimed at evaluating in the Lombardy Region, in a sample of about 100,000 subjects with HF and 400,000 hospitalized subjects without HF, the role of HF in COVID-19 infection during the first wave of pandemics (period January 1, 2020–October 1, 2020). In particular, we aimed at evaluating, in patients with COVID-19 infection the role of different degrees of HF on the rate of infection, of hospitalizations, and of death, and its interplay with co-morbidities. The first part of this study was devoted to compare HF and No-HF subjects of the Lombardy Region for COVID-19 infection, hospital admissions and mortality. The second part of the study was devoted to the quantification of the risk for COVID-19 infection and mortality in HF patients.

2. Materials and methods

2.1. Methods

The study was approved by the Ethics Committee of IRCCS MultiMedica. The choice of the period (January 1, 2020 - October 1, 2020) was due to the fact that up to December 2020, no vaccine against COVID-19 was available in Italy. The National Health System (NHS) of Italy covers virtually all hospital admissions and in-hospital medical and surgical procedures, and covers or contributes to outpatient medical, diagnostic and pharmaceutical expenses of all residents [14–16]. The Administrative Database of Lombardy Regional Health Authority contains all such information of its more than ten million residents. In particular, since 1988, the Lombardy database retains, for each subject who receives NHS assistance: 1) demographic and administrative data; 2) hospital discharge database that, for all patients admitted to regional public and private hospitals, includes admission and discharge dates and up to six discharge diagnoses coded according to the International Classification of Disease, Clinical Modification, ninth version (ICD-9-CM); 3) outpatient drug prescriptions partially or totally reimbursable by the NHS, coded with the Anatomical Therapeutic Chemical (ATC) classification system; 4) outpatient visits; 5) outpatient laboratory and diagnostic procedures; 6) co-payment exemption database, including underlying conditions and the release and expiry dates of cost exemptions granted for related health-care services (e.g., drugs prescriptions, laboratory exams, and medical visits), (exemptions).

Therefore, together with hospital admissions, exemptions codes can be considered a proxy of a specific chronic disease. For each patient, the various databases are linked by a single identification code. This procedure has already been employed and validated in previous studies [14–16]. For the purpose of this study, we obtained permission from Lombardy Regional Health Authority to access the database, using anonymized procedures.

Patients with HF were defined on the basis of previous hospital discharge diagnosis of HF (primary diagnosis). We first accessed the database of all consecutive HF patients from January 1st 2015 to December 31st 2019, according to the following criteria: a) HF hospital discharge diagnosis corresponding to ICD-9-M codes: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.XX, as primary discharge diagnosis; (b) comorbidities, identified according to "exemption codes", and/or outpatient drug prescriptions relative to the therapeutic classes: (e.g, antidiabetic drugs). Control subjects were then randomly chosen from the Lombardy Regional Database in a 4:1 proportion, among patients without cardiac disease, i.e. among subjects never having been hospitalized for HF, nor having exemption codes or drug prescriptions relative to HF. Both patients and controls of either sex had to be resident in the Lombardy Region since at least six years, to be aged 40 years and older, alive at the date of January 1, 2020. The lower age limit for both patients and controls was set at 40 years. HF patients and control No-HF patients were divided in age decades because mean and median age were different, with no attempt to match for age and sex.

These data were used to calculate number of HF patients, number of HF re-hospitalizations during the previous five years, number and type of comorbidities (HF patients and control subjects). From number and frequency of admissions and re-admissions during the period 2015–2019, we built an arbitrary re-hospitalization index as follows: Level 0 = no hospital admissions for HF (no-HF patients); Level 1 = 1 hospital admission for HF (index event); Level 2 = 1 hospital admission for HF 2015–2019 + 1 new hospital re-admission at any time prior to 2019; Level 3 = 1 hospital admission for HF 2015–2019 + 1 new hospital re-admission in 2019 (i.e., last year); Level 4 = 1 hospital admission for HF 2015–2019 + more than 1 new hospital re-admissions in 2019.

The information analyzed in this study about COVID-19 was retrieved from additional routinely collected regional healthcare COVID-19 surveillance database, including demographic characteristics of cases, date of diagnosis, and possible occurrence of COVID-19-related death, hospitalization, and intensive care unit (ICU) admission.

We identified, from the regional COVID-19 integrated surveillance databases, the whole cohort of cases of COVID-19 infection laboratory-confirmed by RT-PCR (COVID-19 cases), aged >40 years and diagnosed from the beginning of the epidemic on 21 February 2020 to 1 October 2020. The cohort was followed until 1 November 2020, thus accounting for at least 30 days of follow-up.

2.2. Exposure, outcomes, and confounders

The study outcomes were the occurrence, hospitalization, and all-cause death in COVID-19 cases laboratory-confirmed by RT-PCR. The following variables were considered as potential confounders: gender, age, Charlson comorbidity index (CCI), based on hospitalizations in the previous five years and modified to exclude HF in the score (categorized

Table 1
Details of patients with heart failure (HF) and control subjects (without HF).

	No-HF	%	HF	%	p value
Subjects	394,104		98,549		
Sex (M/W)	(185,946/208,158)		(50,952/47,597)		*<0.0001*
Age (years, mean ± SD)	61.95 ± 13.67		79.64 ± 11.05		*<0.0001*
Decade 40–49 years [number and age (years ± SD)]	86,601 (45.25 ± 2.54)	21.97	1,417 (45.93 ± 2.44)	1.44	
Decade 50–59 years [number and age (years ± SD)]	106,519 (54.40 ± 2.82)	27.03	4,826 (55.26 ± 2.77)	4.89	
Decade 60–69 years [number and age (years ± SD)]	80,712 (64.28 ± 2.88)	20.47	10,485 (65.18 ± 2.83)	10.64	
Decade 70–79 years [number and age (years ± SD)]	67,494 (74.15 ± 2.84)	17.12	24,025 (74.99 ± 2.87)	24.38	
Decade 80–89 years [number and age (years ± SD)]	42,719 (83.69 ± 2.77)	10.84	40,291 (84.48 ± 2.82)	40.88	
Decade 90–99 years [number and age (years ± SD)]	9,704 (92.65 ± 2.44)	2.46	17,066 (92.77 ± 2.43)	17.31	
Decade >100 years [number and age (years ± SD)]	355 (102.06 ± 2.52)	0.09	439 (101.17 ± 1.71)	0.44	
Drugs in use					
C01A - C01B - C01D C02A C02C –cardiovascular drugs	20,772	5.27	46,020	47.69	*<0.0001*
C03C - diuretics	15,322	3.89	68,681	69.69	*<0.0001*
C03D - C03E diuretics associated with potassium sparing drugs	8,264	2.10	37,272	37.83	*<0.0001*
C07A - Beta blockers	57,290	14.54	70,477	71.51	*<0.0001*
C08C - C08D calcium antagonists	37,463	9.50	25,378	25.75	*<0.0001*
C09A - C09B - ACE-inhibitors	63,135	16.02	42,660	43.29	*<0.0001*
C09C - C09D – ARB antagonists	62,018	15.74	30,507	30.96	*<0.0001*
C10A - lipid lowering drugs	65,212	16.55	46,013	46.69	*<0.0001*
B01A –antiplatelet drugs and anticoagulants	61,245	15.54	77,557	78.70	*<0.0001*
A10A – Insulin and analogues	6,448	1.64	12,984	13.18	*<0.0001*
A10B – Oral antidiabetic drugs	26,224	6.65	20,258	20.56	*<0.0001*
R03A – Aerosol adrenergic drugs	24,726	6.27	18,995	19.27	*<0.0001*
R03B – Aerosol drugs for pulmonary diseases	22,795	5.78	20,628	20.93	*<0.0001*

as 0, 1–2, 3, and > 3) [17,18], total number of prescriptions for any drugs in the previous year, prior use (at least one prescription in the previous year) of drugs [cardiovascular drugs (diuretics, beta-blockers, calcium channel antagonists, ACE-inhibitors, ARB antagonists, antiarrhythmics), anti-platelet drugs and anticoagulants, lipid-lowering drugs, insulin and oral agents for diabetes, drugs for pulmonary disease] history of diabetes, cardiovascular disease, myocardial infarction, chronic obstructive pulmonary disease, liver disease, diabetes, hypertension, chronic renal failure, cerebrovascular disease, peripheral vascular disease, and cancer. Details of drugs under use are reported in Table 1, and comorbidities are reported in Table 2. All-cause mortality data were obtained; live subjects were censored on the conventional date of December 31, 2020. Subjects without information about vital status at that date, migrated subjects, and subjects who could not be retrieved, were excluded.

2.2.1. Sample size and power calculation

Based on the known prevalence of HF in the Lombardy Region (ICD9 021.428), 1.5 %, we estimated a total 100,000 HF subjects and 400,000 subjects without heart diseases as controls, to assess the frequency of COVID-19 infections, hospitalizations, and deaths in HF and in No-HF subjects.

2.3. Statistical analysis

Data are presented as mean ± standard deviation for continuous variables plus 95 % C.I., and as frequencies and percentages for categorical and binary variables. Statistical analysis was carried out using SAS Software v. 9.4 and R open-source programming language. Preprocessing procedures were carried out using the R data-table package. Significant differences between groups were reported at the alpha level of 0.05. Wilcoxon and chi-square tests were performed to evaluate and confirm significant differences or the ordering in the distributions of continuous and categorical variables, respectively, in the two groups (all *p* values have been reported). For categorical variables, percentages have been computed by column. Univariate and multivariable logistic regression models were implemented to evaluate the association between comorbidities and HF severity with death status at 31st December 2020. Multivariable models were adjusted for age and sex. To avoid collinearity, number of comorbidities and Charlson index were used alternatively. Charlson index and number of comorbidities were evaluated without inclusion of HF. This manuscript was prepared following

Table 2
Distribution of co-morbidities in subjects without (No-HF) and with Heart Failure (HF).

Population	393,749	98,110		
Disease	**No-HF**	**HF**	*Ratio*	*p*
Diabetes	34,642	32,958	3.95	<0.001
Kidney diseases	4,038	19,853	19.49	<0.001
AMI	3,766	11,934	19.68	<0.001
Cancer	29,498	13,373	1.49	<0.001
COPD	2,024	6,587	13.88	<0.001
Peripheral vascular disease	2,691	6,679	14.07	<0.001
Cerebrovascular disease	8,358	14,341	6.43	<0.001
Charlson index (1 to 3)	31,972	45,228	7.245	<0.001
No associated disease	321,881	33,238	0.515	<0.001

AMI = acute myocardial infarction; COPD = Chronic obstructive pulmonary disease.
The ratio refers to percentage of HF over the percentage of no-HF, for each comorbidity.

the guidelines of the STROBE statement [19].

3. Results

We retrieved data from 98,549 HF patients and 394,104 controls. Table 1 and Table 2 yield a picture of subjects in the study; Table 1 shows that the use of several drugs was significantly more frequent in HF patients than in controls. Comorbidities for HF patients and control patients are shown in Table 2. All comorbidities were significantly more frequent in HF subjects than in controls at any age decade, as it was for Charlson Index that was always higher in HF than in control patients. Therefore, subjects without any co-morbidity were more frequent among non-HF than among HF subjects at any age decade. Incident cases of COVID-19 were 14,256 (incidence rate, IR 10.195 × 100.000, 95 % 10.195–10.196) in 394,104 control subjects, and 8,648 (IR 29.653, 29.651–29.655) in 98,549 HF subjects ($p < 0.001$). Incidence of COVID-19 increased progressively and significantly with advancing age in HF patients and in control patients, being significantly higher in HF patients for any age decade, except in the decade 100–109 years, and the incidence rate ratio (IRR) was approximately two-fold higher for HF patients for any age decade, except in the decade 100–109 years (Table 3 A).

Hospital admissions (4,943, IR 3.484, 95 % C.I. 3.484–3.484) and 4,974, (IR 14.970, 95 % C.I. 14.969–14.972), respectively increased significantly with advancing age in HF subjects and in control subjects, being significantly higher in HF subjects for most age decade, except in the decade 100–109 years, and the incidence rate ratio was approximately two folds for any age decade, except for the decade 100–109 years (Table 3B). As expected, all-cause deaths 7,650 (IR 5.368, 95 % C.I. 5.368–5.369) and 18,368 (IR 56.921, 95 % C.I. 56.918–56.923), respectively significantly increased with advancing age both in HF subjects and in control subjects, but with a different pattern, being up to 25-fold (IRR 25.001 95 % C.I. 24.971–25.032) higher for HF patients in the decade 40–49 years and decreasing thereafter to approximately two folds in the age decades 90–99 years (IRR 1.866, 95 % C.I. 1.866–1.866) and 100–109 years (IRR 1.92, 95 % C.I. 1.923–1.926) (Table 3C).

Risk for COVID-19 infection is shown Table 4; compared to control subjects the unadjusted IRR was 2.318 (95 % C.I. 2.300–2.336), and the adjusted IRR varied between 1.3740 (95 % C.I. 1.368–1.379) and 1.3731 (95 % C.I. 1.369–1.377).

The frequency of hospital admissions for HF in the previous 5 years was also of importance, conferring a progressively higher value for the IRR of COVID-19 infection (Table 4, IRR 1.594, 95 % C.I. 1.587–1.600); this indicates that both co-morbidities and frequency of hospital admission for HF increase the risk for infection.

First hospitalizations for COVID-19 are shown in Fig. 1; from the left panel it appears that the greatest frequency of admissions was between April and June 2020; from the right panel it appears that the frequency of admissions was greater in HF than in non-HF especially during that period.

In HF subjects the risk of all-cause mortality increased together with the number of hospital admissions for HF during the period 2015–2019, the number of comorbidities, and Charlson Index (Table 5). Univariable and multivariable logistic models indicate that in HF subjects age (OR = 1.08, 95 % C.I. 1.08–1.09), number of hospital admissions (OR = 2.22, 95 % C.I. 2.11–2.33), comorbidities (OR = 1.33, 95 % C.I. 1.32–1.35), or Charlson Index (OR = 1.21, 95 % C.I. 1.20–1.22), and male sex (OR = 1.27, 95 % C.I. 1.23–1.31), were risks factors for mortality, indicating that during the period considered both co-morbidities and frequency of hospital admission for HF increase the risk of all-cause death (Table 6).

4. Discussion

The COVID-19 pandemic overwhelmed health systems, resulting in a surge in excess deaths. To understand the impact of the COVID-19 pandemic on mortality, sex- and age-specific excess all-cause mortality was evaluated in 20 countries, during 2020 [20,21]. Interestingly, all-cause mortality up to August 2020 was higher than in previous years in some, but not all, participating countries. Geographical location, seasonality, and overall health organization of each country, as well as the prompt application of high-stringency control measures, may explain the observed variability in mortality changes. In sex-specific analyses, excess mortality was higher in males than females, and greater in oldest age groups [21]. The mean of excess mortality in 2020 was around 1.5 for countries like Italy; the population incidence of COVID-19 had the greatest positive relationship with excess mortality, and health economics variables (government revenue and government effectiveness) were the most protective against excess mortality [20,21].

Hospital admissions for all major non-COVID-19 disease groups decreased during national lockdowns compared with the pre-pandemic baseline period, and mortality rates were higher overall and for patients admitted to hospital with conditions such as respiratory diseases, cancer, pneumonia, and sepsis [22].

Patients with cardiovascular diseases have been particularly affected by the limitations imposed by the pandemic. A significant decrease in

Table 3
Incidence of COVID-19 infections (A), hospital admissions (B), and all-cause death (C) of subjects in the study by decades of age in 2020 in No-Heart Failure and Heart Failure patients. Absolute numbers, percentages and 95 % C.I. Absolute numbers and incidence and mortality crude rates are shown. On the right. Incidence rate ratios for infections, hospital admissions, and all-cause death of subjects are reported.

A. Incidence of COVID-19 infections

Number (M/F)	No-heart failure		Heart failure		
Age (years)[a]	394,104 (185,946/208,159)		98,549 (50,952/47,597)		
	61.95 ± 13.67		79.64 ± 11.05		
Decades of age (years)	Subjects	COVID-19 (IR)	Subjects	COVID-19 (IR)	COVID-19 (IRR) (95 % C.I.)
Decade 40–49	86,601	2,228 (7.123)	1,417	67 (13.457) *	2.033
95 % C.I.		7.123–7.124		13.447–13.467	(2.021–2.045)
Decade 50–59	106,519	3,685 # (9.603)	4,826	307 (18.337) *	1.800
95 % C.I.		9.602–9.604		18.330–18.343	(1.795–1.810)
Decade 60–69	80,712	2,778 # (9.595)	10,485	700 # (19.813) *	1.889
95 % C.I.		9.594–9.597		19.808–19.817	(1.881–1.892)
Decade 70–79	67,494	2,438 # (10.196)	24,025	1,862 # (24.231) *	2.028
95 % C.I.		10.195–10.198		24.228–24.235	(2.024–2.031)
Decade 80–89	42,719	3,200 # (15.370)	40,291	3,797 # (23.655) *	1.899
95 % C.I.		15.368–15.372		23.645–23.663	(1.869–1.901)
Decade 90–99	9,704	2,220 # (31.007)	17,066	1,886 # (46.439) *	1.467
95 % C.I.		31.001–31.014		46.432–46.445	(1.465–1.469)
Decade 100–109	351	41 # (48.968)	439	33 # (38.690) §	0.800
95 % C.I.		48.921–49.015		38.648–38.732	(0.799–0.801)
Totals IR	*394,104*	*14,256 (10.195)*	*98,549*	*8,648 (29.653)* *	2.909
95 % C.I.		10.195–10.196		29.651–29.655	(2.908–2.909)

B. Incidence of hospitalisations

Number (M/F)	No-heart failure		Heart failure		
Age (years)[a]	394,104 (185,946/208159)		98,549 (50,952/47597)		
	61.95 ± 13.67		79.64 ± 11.05		
Decades of age (years)	Subjects	Hospital (IR)	Subjects	Hospital (IR)	Hospital (IRR) (95 % C.I.)
Decade 40–49	86,601	435 (1.380)	1,417	27 (5.320) *	*3.854*
95 % C.I.		1.380–1.381		5.313–5.326	(3.849–3.859)
Decade 50–59	106,519	929 # (2.401)	4,826	134 (7.815) *	*3.255*
95 % C.I.		2.400–2.401		7.811–7.820	(3.254–3.257)
Decade 60–69	80,712	994 # (3.408)	10,485	425 # (11.658) *	*3.426*
95 % C.I.		3.407–3.409		11.655–11.662	(3.425–3.427)
Decade 70–79	67,494	1,235 # (5.098)	24,025	1,243 (15.330) *	*3.007*
95 % C.I.		5.097–5.098		15.328–15.333	(3.007–3.008)
Decade 80–89	42,719	1,075 # (7.179)	40,291	2,332 # (17.379) *	*2.421*
95 % C.I.		7.177–7.180		17.377–17.381	(2.420–2.421)
Decade 90–99	9,704	268 # (8.530)	17,066	706 # (14.252) *	*1.671*
95 % C.I.		8.527–8.533		14.249–14.256	(1.670–1.672)
Decade 100–109	351	7 # (6.706)	439	7 (5.984) §	*0.892*
95 % C.I.		6.690–6.721		5.970–5.999	(0.890–0.895)
Totals IR	*394,104*	*4,943 (3.484)*	*98,549*	*4,974 (14.970)* *	*4.297*
95 % C.I.		3.484–3.484		14.969–14.972	(4.296–4.297)

C. Incidence of all-cause mortality.

Number (M/F)	No-heart failure		Heart failure		
Age (years) [a]	394,104 (185,946/208,159)		98,549 (50,952/47,597)		
	61.95 ± 13.67		79.64 ± 11.05		
Decades of age (years)	Subjects	Death (MR)	Subjects	Death (MR)	Death (IRR) (95 % C.I.)
Decade 40–49	86,601	89 (0.282)	1,417	36 (7.044) *	25.001
95 % C.I.		0.282–0.282		7.037–7.052	(24.971–25.032)
Decade 50–59	106,519	336 # (0.865)	4,826	163 (9.412) *	10.884
95 % C.I.		0.865–0.865		9.408–9.417	(10.877–10.890)
Decade 60–69	80,712	624 # (2.125)	10,485	692 # (18.738) *	8.820
95 % C.I.		2.124–2.125		18.734–18.742	(8.817–8.823)
Decade 70–79	67,494	1,580 # (6.484)	24,025	2,871 # (34.938) *	5.389
95 % C.I.		6.483–6.485		34.934–34.942	(5.388–5.390)
Decade 80–89	42,719	2,919 # (1.938)	40,291	8,472 # (65.156) *	33.623
95 % C.I.		1.938–1.938		65.151–65.160	(33.619–33.628)
Decade 90–99	9,704	2,009 # (63.655)	17,066	5,934 # (118.776) *	*1.866*
95 % C.I.		63.646–63.664		118.767–118.786	(1.866–1.866)
Decade 100–109	351	93 # (88.447)	439	200 # (170.249) *	*1.925*
95 % C.I.		88.390–88.504		170.174–170.324	(1.923–1.926)

(*continued on next page*)

Table 3 (*continued*)

C. Incidence of all-cause mortality.					
Number (M/F)	No-heart failure		Heart failure		
Age (years) [a]	394,104 (185,946/208,159)		98,549 (50,952/47,597)		
	61.95 ± 13.67		79.64 ± 11.05		
Decades of age (years)	Subjects	Death (MR)	Subjects	Death (MR)	Death (IRR) (95 % C.I.)
Totals MR	*394,104*	*7,650 (5.368)*	*98,549*	*18,368 (56.921)* *	*10.603*
95 % C.I.		5.368–5.369		56.918–56.923	(10.602–10.604)

MR = mortality rate x per 100,000 person-years; HF = heart failure; IRR are calculated on crude rates.
IR = incidence rate x per 100,000 person-years; HF = heart failure; Hospital = Hospital Admission. IRR are calculated on crude rates. [a]mean ± standard deviation; * = $p < 0.001$ vs no-heart failure; § = $p < 0.05$ vs no-heart failure;
# $p < 0.005$ vs decade 40–49 for hospitalization for both No-Heart Failure and Heart Failure.

Table 4
Incident cases and incidence rate ratio of COVID-19 in Heart Failure patients and in Non-Heart Failure patients.

Incident cases of COVID-19	Incidence rate ratio (95 % CI) *HF* vs *no-HF*	*p*-value
Unadjusted model	2.3180 (2.3000; 2.3361)	<0.001
Adjusted for age class, sex, Charlson's comorbidity index*	1.3740 (1.3682; 1.3798)	<0.001
Adjusted for age class, sex, Charlson's comorbidity index*, dyslipidemia, hypertension	1.3731 (1.3693; 1.3769)	<0.001
Adjusted for age class, sex, Charlson's comorbidity index*, dyslipidemia, hypertension and frequency of HF admissions		
Level 1 (1 hospital admission for HF)	1.2812 (1.2775; 1.2849)	<0.001
Level 2 (1 hospital admission for HF 2015 + hospital admission (after the 1st) before 2019)	1.3235 (1.3189; 1.3281)	<0.001
Level 3 (1 hospital admission for HF 2015–2015 + 1 hospital admission (after the 1st) in 2019)	1.4637 (1.4574; 1.4699)	<0.001
Level 4 (1 hospital admission for HF 2015–2015 + more than 1 hospital admission (after the 1st) in 2019)	1.5939 (1.5874; 1.6004)	<0.001

* Charlson's Comorbidity Index was assessed without HF item.

the number of patients with cardiovascular diseases seeking medical attention for acute coronary syndromes and a parallel increase in out-of-hospital sudden deaths has been demonstrated during lockdown in many countries. Limitations in access to care have also impacted the management of chronic non-communicable diseases having negatively influenced lifestyle behaviors, diet, and medication adherence, which are the foundations of medical management. During COVID-19 pandemic hospitalization for STEMI significantly decreased, although to a smaller extent than initially reported [23], NSTACS hospitalizations also decreased significantly worldwide [24]. In Italy, several medications for chronic conditions have been restricted to hospital only dispensation or prescription with regions having the power to select centers that may prescribe life-saving medications for HF patients, like proprotein convertase subtilisin/kexin type 9 inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like petide-1 receptor agonists, sacubitril/valsartan, and oral anticoagulants [25,26].

In this study, performed retrospectively in Lombardy Region during the first wave of COVID-19 pandemics, we found that COVID-19 infections, hospital admissions, and all-cause mortality increased with age, and were all more frequent among subjects with HF than among No-HF subjects. Moreover, we found that age, degree of HF and co-morbidities were associated with greater risk of COVID-19 infection

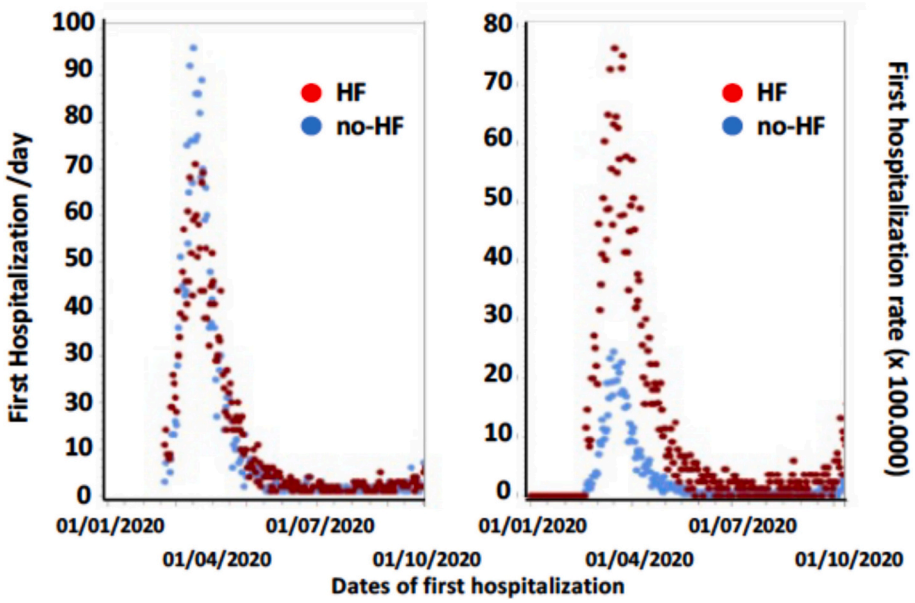

Fig. 1. Hospital admissions for COVID-19 during the period 1.1.2020 to 1.10.2020. On the left: first daily admissions for patients with and without HF On the right: first admissions for patients with and without HF (incidence rate x 100.000)

Table 5
Univariate analysis for mortality in patients with Heart Failure (HF).

A.	NUMBER OF HF ADMISSIONS			
	Alive	Dead	% dead	p value
1	51,755	16,094	23.73	< 0.0001
2	11,500	4,592	28.54	
3	4,250	2,707	38.91	
4	4,529	3,122	40.81	

B.	CO-MORBIDITIES			
	Alive	Dead	% dead	p value
0	30,932	8,197	20.95	< 0.0001
1	21,460	8,297	27.89	
2	10,142	5,367	36.41	
3	4,015	2,637	39.64	
4	1,417	1,117	44.08	
5	446	416	48.26	
6	105	119	53.13	
7	22	37	62.71	

C.	CHARLSON INDEX			
	Alive	Dead	% dead	p value
0	30,932	8,197	22.33	< 0.0001
1	15,465	5,400	25.89	
2	10,425	4,911	32.02	
3	5,609	3,238	36.60	
4	2,843	1,883	39.84	
5	1,457	995	40.58	
6	784	621	44.20	
7	340	298	46.71	
8	398	320	44.57	
9	144	164	53.25	
10	87	68	43.87	
11	28	45	61.64	
12	17	29	63.04	
13	11	15	56.79	

D.	SEX			
	Alive	Dead	% dead	p value
Females	34,237	13,360	28.07	< 0.0001
Males	37,797	13,155	25.82	

A = as a function of number of HF admissions, B = as a function of number of comorbidities.
C = as a function of Charlson Index, D = as a function of sex.

and all-cause mortality, both at univariable and at multivariable analysis. In particular, the number of specific admissions for HF during the previous 5-years period, was a risk factor for both infection and all-cause mortality. Due to its scope (very large database, PCR-confirmed COVID-19 diagnosis) this study is of importance for quantification of the health conditions of HF and No-HF subjects as risk of infection and of prognosis. In fact, previous small to large studies, or even meta-analyses, had shown that age, HF, as well as the general health status, predispose to infection and mortality [2–13,27–32]. However, previous studies, with one exception [7], did not dissect the role of different degrees of HF and of co-morbidities in the main events, e.g., infection and all-cause mortality. For instance, we found that the adjusted the risk of COVID-19 infection differed between HF and No-HF subjects and increased in HF subjects as a function of specific admissions for HF during the previous 5-years period. The risk of mortality was higher in HF than in No-HF patients, with an overall IRR 10.603, that however varied between 25.001 for the age decade 40–49 years, to 33.623 for the age decade 80–89 years, to 1.866 and 1.925 for the age decades 90–99 years and 100–109 years, respectively. The number of previous admissions for HF was of paramount importance in determining the risk for mortality, more than doubling when going from 1 admission to 4 admissions for HF during the previous 5 years; the independent role of previous admissions for HF was maintained in the multivariable analysis, appearing more important than Charlson Index or number of co-morbidities.

4.1. Limitations

There are strengths and limitations to this study. At difference from other large studies, both age at death and date of death were available in downloaded data, and participants who died with COVID-19 after the study end date would have been recorded as alive in the present analyses, and deaths are susceptible to errors in coding or data entry.

In principle, there might be error in proper HF coding when patient information is translated to ICD codes; however, in this respect we previously addressed the issue of correctness of HF discharge diagnosis in Italy, and found that sensitivity, specificity, positive predictive power, and negative predictive power all ranged between 90 and 96 % [33,34].

In this study, the Charlson comorbidity index was calculated on available data since 2015, and we could not determine if the patient was still suffering of those conditions. Some comorbidities may be under-reported, and for instance, the presence of obesity is not routinely specified in databases in Italy; for this reason we could not consider obesity among risk factors for infection, hospital admission and death, but obesity (especially when associated with diabetes) is considered a strong risk factor for an unfavorable prognosis in COVID-19 infection [35], and we observed that, contrary to previous pandemics (SARS and H1N1 influenza), obesity is linked to greater likelihood of admission to ICU [36].

In addition, we could not document HF severity in our patients, as NYHA classification is not usually reported in hospital discharge charts, but the fact that specific admissions for HF occurred more often in some HF patients is in favor of the feeling that the number of specific admissions for HF is a marker of severity of HF [37]. It is of interest that, compared with the clinician-assigned NYHA class, other indexes were recently found to detect meaningful change in health status over time, and with more prognostic value than changes in NYHA class, such as the patient-reported KCCQ-OS [38]. Of note, in a comparable cohort [39], it we have recently shown that among HF patients, the number of co-morbidities and the number of specific admissions for HF are closely related each-other.

Previous studies have evaluated the relationships between viral infections and the CV system, with smaller sample sizes than the present study. In SARS and MERS, pre-existing CV diseases (ischemic heart disease, cardiomyopathy) were associated with a worse prognosis [1].

Viral illness can damage myocardial cells through several mechanisms including direct damage by the virus, systemic inflammatory responses, destabilized coronary plaque, and aggravated hypoxia [1]. Cardiac injury can in turn aggravate pneumonia and increase the severity of symptoms. Therefore, patients with cardiovascular disease account for a large proportion of deaths from COVID-19, and from SARS and MERS. Since the entry into the organism through the ACE system of the three viruses [1] is similar, the greater infectivity of COVID-19 is probably the cause of the greater mortality.

Also several types of influenza (H1N1) are more severe in HF patients [40,41], especially when associated with COVID-19 infection [42]: on the other side, H1N1 can induce fulminant mycocarditis, leading to acute HF [43], and antibody titers to influenza A vaccine strains wane to below seroprotective levels in HF patients compared to normal controls [44]. Finally, the Respiratory syncytial virus (RSV) infection can trigger HF exacerbations, increasing morbidity and mortality [45],

With the exception of studies comparing incidence of viral disease (RSV, COVID-19 and its variants, influenza) in HF patients [46,47], studies focused on incidence of COVID-19 in naive HF patients did not appear in the literature after 2022 [27–32].

Studies thereafter have shown that several treatments have been diversely effective in reducing the death toll of COVID-19 in the

Table 6
Univariate and multivariable logistic models for mortality in patients with heart failure (HF).

	OR (95 % cl)	p-value
Univariate logistic model for the association between number of HF admissions and mortality		
1 HF admission	1.00 (reference)	<0.0001
2 HF admissions	1.28 (1.24–1.34)	<0.0001
3 HF admissions	2.05 (1.95–2.16)	<0.0001
4 HF admissions	2.22 (2.11–2.33)	<0.0001
Univariate logistic model for the association between age, Charlson index, number of comorbidities, and mortality		
Age (years)	1.087 (1.085–1.088) *	
Charlson index	1.21 (1.20–1.22)	<0.0001
Number of comorbidities	1.33 (1.32–1.35)	<0.0001
Multivariable logistic model 1		
2 vs 1 HF admissions	1.16 (1.11–1.21)	<0.0001
3 vs 1 HF admissions	1.76 (1.67–1.86)	<0.0001
4 vs 1 HF admissions	1.99 (1.89–2.10)	<0.0001
Charlson index	1.22 (1.21–1.23) *	<0.0001
Age	1.089 (1.087–1.091) *	<0.0001
Sex (male vs female)	1.27 (1.23–1.31)	<0.0001
Multivariable logistic model 2		
	OR (95 % cl)	p-value
2 vs 1 HF admissions	1.14 (1.10–1.19)	<0.0001
3 vs 1 HF admissions	1.74 (1.64–1.84)	<0.0001
4 vs 1 HF admissions	1.97 (1.86–2.07)	<0.0001
Number of comorbidities	1.34 (1.32–1.36) *	<0.0001
Age	1.088 (1.086–1.090) *	<0.0001
Sex (male vs female)	1.28 (1.24–1.32)	<0.0001

*OR was calculated for 1 unit increase.
OR = Odds Ratio; CI = confidence interval.
Number of HF admissions.
Level 1 = 1 hospital admission for HF 2015–2019.
Level 2 = 1 hospital admission for HF 2015–2019 + 1 hospital re-admission before 2019.
Level 3 = 1 hospital admission for HF 2015–2019 + 1 hospital re-admission in 2019.
Level 4 = 1 hospital admission for HF 2015–2019 + more than 1 hospital re-admissions in 2019.

community. For instance, although a greater mortality was observed with omicron variants vs delta variants in Massachusetts [48], influenza vaccination decreases COVID-19 infection, but not hospitalisations of all-cause mortality [49]. In the meanwhile, treatments improved with the systematic use of anticoagulation, and the use, when needed, of systemic steroids [50] and of ventilation [51].

COVID-19 vaccination significantly improves prognosis in HF patients, as well as long-COVID occurrence [52], in spite of possible incidence of vaccine-induced myocarditis [53]. Of note, although public health approaches changed throughout the pandemic, the clinical characteristics and outcomes of HF patients were consistent across different waves [54], and for patients hospitalized in the subsequent waves, a more rapid optimization of medical therapy was observed during hospitalization.

The lesson is that particular attention should be devoted to prevent collateral cardiovascular damage during public health emergencies [54], and there is the need for early viral detection in HF patients (be it COVID-19, RSV, or influenza) to implement preventive measures and reduce severe disease outcomes [1,45,50].

5. Conclusion

COVID-19 infections, hospital admissions, and all-cause mortality increased with age and were all more frequent among subjects with HF (HF subjects) than among No-HF subjects. More, we found that age, degree of HF and co-morbidities were associated with greater risk of COVID-19 infection and all-cause mortality, both at univariate and at multivariable analysis. In particular, the number of specific admissions for HF during the previous 5-years period, was a risk factor for both infection and all-cause mortality. These data are of relevance for prioritizing interventions for prevention of infection, and for assistance to patients with COVID-19, and to inform management of future

pandemics.

Data access, responsibility, and analysis

AEP and ET had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The datasets presented in this article are not readily available because the data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Lombardy Region upon reasonable request. Requests to access the datasets should be directed to https://www.regione.lombardia.it.

CRediT authorship contribution statement

Antonio E. Pontiroli: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Giuseppe Ambrosio:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Olivia Leoni:** Writing – review & editing, Software, Resources, Methodology, Investigation, Data curation. **Marco Forlani:** Writing – review & editing, Validation, Resources, Methodology, Formal analysis. **Barbara Antonelli:** Writing – review & editing, Resources, Project administration, Methodology, Investigation. **Edoardo Gronda:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Alberto Palazzuoli:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Francesco Bandera:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Giuseppe Galati:** Writing – review & editing, Supervision, Methodology, Investigation. **Elena Tagliabue:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Data curation.

Declaration of competing interest

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