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ORIGINAL ARTICLE

Impact of SARS-Cov-2 infection in patients with hypertrophic cardiomyopathy: results of an international multicentre registry

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Abstract

Aims To describe the natural history of SARS-CoV-2 infection in patients with hypertrophic cardiomyopathy (HCM) compared with a control group and to identify predictors of adverse events.

Methods and results Three hundred and five patients [age 56.6 ± 16.9 years old, 191 (62.6%) male patients] with HCM and SARS-Cov-2 infection were enrolled. The control group consisted of 91 131 infected individuals. Endpoints were (i) SARS-CoV-2 related mortality and (ii) severe clinical course [death or intensive care unit (ICU) admission]. New onset of atrial fibrillation, ventricular arrhythmias, shock, stroke, and cardiac arrest were also recorded. Sixty-nine (22.9%) HCM patients were hospitalized for non-ICU level care, and 21 (7.0%) required ICU care. Seventeen (5.6%) died: eight (2.6%) of respiratory failure, four (1.3%) of heart failure, two (0.7%) suddenly, and three (1.0%) due to other SARS-CoV-2-related complications. Covariates associated with mortality in the multivariable were age {odds ratio (OR) per 10 year increase 2.25 [95% confidence interval (CI): 1.12–4.51], P = 0.0229}, baseline New York Heart Association class [OR per one-unit increase 4.01 (95%CI: 1.75–9.20),

P = 0.0011], presence of left ventricular outflow tract obstruction [OR 5.59 (95%CI: 1.16–26.92), *P* = 0.0317], and left ventricular systolic impairment [OR 7.72 (95%CI: 1.20–49.79), *P* = 0.0316]. Controlling for age and sex and comparing HCM patients with a community-based SARS-CoV-2 cohort, the presence of HCM was associated with a borderline significant increased risk of mortality OR 1.70 (95%CI: 0.98–2.91, *P* = 0.0600).

Conclusions Over one-fourth of HCM patients infected with SARS-Cov-2 required hospitalization, including 6% in an ICU setting. Age and cardiac features related to HCM, including baseline functional class, left ventricular outflow tract obstruction, and systolic impairment, conveyed increased risk of mortality.

Keywords Hypertrophic cardiomyopathy; COVID-19; SARS-CoV-2 infection; Heart failure; Registry; Prognosis

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A complete list of the Investigators [on behalf of the Dilema International Cardiomyopathy and Heart Failure Registry and international SHaRe (Sarcomeric Human Cardiomyopathy Registry) Investigators group] is provided in Appendix S1.

Introduction

One of the characteristics of SARS-CoV-2 infection is the high variability of clinical presentation and outcome. Underlying cardiac disease, including heart failure (HF), is associated with increased SARS-CoV-2-related mortality.[1,2] To date, however, assessment of SARS-CoV-2 outcomes in specific causes of HF, such as cardiomyopathies, is limited.

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, with an estimated prevalence of 1 in 500 in the adult population.[3,4] HF in HCM may be associated with left ventricular outflow tract obstruction, diastolic dysfunction, and less frequently, systolic dysfunction.[5] Moreover, atrial fibrillation and ventricular tachyarrhythmias are an important source of morbidity and mortality.[5,6]

The prognosis of SARS-CoV-2 infection in HCM patients, who are often young and otherwise do not fulfil high-risk criteria for SARS-CoV-2-related outcomes, is unknown. This potentially includes predisposition to SARS-CoV-2-related complications as well as exacerbation of underlying cardiac disease. The relative rarity of HCM mandates multicentre studies on a large scale to address this issue. Thus, in the present, dedicated registry, we aimed (i) to describe the natural history of SARS-CoV-2 infection in patients with HCM compared with a control group of SARS-CoV-2 individuals over a 12 month period and (ii) to identify predictors of adverse events in patients with HCM and SARS-CoV-2 infection.

Methods

Registry design and patients

We solicited participating centres to report all patients with a diagnosis of HCM[3,4] and demonstration SARS-CoV-2 infection by antigen or PCR tests. Selected centres were either established cardiomyopathy clinics or inherited cardiac disease units. A total of 29 centres from Europe (*n* = 182), North America (*n* = 75), and South America (*n* = 48) were included. Centres were requested to report the full spectrum of consecutive SARS-CoV-2 cases, from mild to severe, including outpatient and hospitalized individuals. Patients were enrolled over a 12 month period, from early in the SARS-CoV-2 pandemic, in February 2020 to 2 February 2021.

The study was approved by each local Ethics Committee, and where required (in view of the anonymized, retrospective nature of the study), informed consent was obtained prior to data collection. All diagnostic or therapeutic procedures were left to the discretion of the treating physician. A dedicated online software was developed for the study (Dilemma SL Solutions) in order to capture data in the desired format and utilized at 79% of the sites.

Patient population

The participating sites identified patients through regular query of the electronic medical records for the results of SARS-CoV-2 infection and cross reference with active HCM registries. This was supplemented by direct communication to and from providers at the time of SARS-CoV-2 infection diagnosis, and review of SARS-CoV-2 history at the time of scheduled and unscheduled clinical encounters. Contribution from participant centres is summarized in Supporting Information, *Table S1*.

For the mortality analysis, a control group consisting of all consecutive individuals diagnosed with SARS-CoV-2 infection in the Region of Murcia, Spain, from 8 March 2020 till 2 February 2021 was obtained from the Subdirección General de Tecnologías de la Información of the Servicio Murciano de Salud.[7] A total of 91 131 from a cohort of 96 394 SARS-CoV-2-infected individuals with available follow-up information up to 31 August 2021 were included in the registry. In the control group, 1687 deaths were attributed or related to SARS-CoV-2 infection (1259 died during hospital

admission), and 214 deaths were not attributed to SARS-Cov-2 infection. Baseline demographics and vital status, but not comorbidities and medications, were available for all control patients.

Clinical variables and outcomes

Recorded variables included the care setting [outpatient, hospitalization, intensive care unit (ICU) admission], demographics, comorbidities (hypertension, diabetes, obesity, smoking, coronary artery disease, chronic obstructive pulmonary disease), baseline HCM-related variables [rhythm, presence of left ventricular outflow tract obstruction (LVOTO) $\geq$ 30 mmHg, maximal left ventricular wall thickness (max LVWT), left ventricular ejection fraction (LVEF), arrhythmias, and cardiac medications], and SARS-CoV-2-related characteristics (symptoms, admission tests, diagnosis of pneumonia, respiratory failure, medications, and outcome). Left ventricular systolic dysfunction (LVSD) was defined by the presence of LVEF $<$ 55%.

The following endpoints were assessed in the study:

1 SARS-CoV-2-related mortality: death caused by or precipitated by SARS-CoV-2 infection.
2 Severe clinical course: defined as SARS-CoV-2-related mortality or need for ICU admission.

Incident HCM-related outcomes, including new onset of atrial fibrillation, ventricular arrhythmias, shock, stroke, and cardiac arrest, were also recorded.

Statistical analysis

Continuous variables were reported as mean ± SD. Among-group comparisons were made using a Student's *t*-test or non-parametric test where appropriate. Categorical variables were reported as counts and percentages. Among-group comparisons 2 × 2 were made using a χ^2 test or Fisher's exact test if any expected cell count was less than five.

A stepwise multivariable logistic regression analysis was performed to analyse the relationship between patient characteristics and mortality. We included all candidate covariates and those with $P < 0.10$ in a univariate analysis. A significance level of 0.1 was required to allow a variable into the model, and a significance level of 0.05 was required to stay in the model. Annual rates together with their 95%CIs were estimated.

A two-sided *P* value of $<$0.05 was considered as statistically significant. All analyses were performed using SPSS statistical software Version 24.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients with HCM and SARS-CoV-2 infection

A total of 305 patients (aged 56.6 ± 16.9 years old, 191 [62.6%] male patients, 114 [37.4%] female patients) with prior HCM diagnosis developed SARS-Cov-2 infection. The majority of patients were White (274; 90.3%). Comorbidities were common: 120 (39.3%) had hypertension, 43 (14.1%) were diabetic, 42 (13.8%) were smokers, and 95 (31.1%) were obese. Of these 305, 90 (29.9%) were hospitalized, including 69 (22.9%) receiving non-ICU level care and 21 (7.0%) treated in an ICU (*Table 1*, *Figure 1*).

Key baseline HCM characteristics included max LVWT 19.2 ± 4.9 mm, LVOTO in (23.3%) and prior history of paroxysmal, persistent, or permanent atrial fibrillation in 92 (33.1%). At baseline, most patients exhibited New York Heart Association (NYHA) class I functional status (*n* = 158, 57%) prior to SARS-CoV-2 infection with 90 and 29 patients (32.5%, 10.4%) with NYHA II and III/IV effort intolerance, respectively.

Cardiac medications prior to infection included 189 patients (62.0%) on beta-blockers, 71 (23.3%) on angiotensin II receptor blockers, 40 (13.1%) on angiotensin-converting enzyme inhibitors, 76 (24.9%) on anticoagulation, and 82 (26.9%) on loop diuretics.

In comparison with women, men with SARS-CoV-2 infection were younger (54.8 ± 15.0 vs. 58.6 ± 19.3 years old, *P* = 0.076), with less hypertension (65, 34.8% vs. 55, 49.1%, *P* = 0.014) and lower utilization of medications including beta-blockers (109, 58.3% vs. 77, 68.8%, *P* = 0.07), angiotensin II receptor blockers (36, 19.3% vs. 34, 30.4%, *P* = 0.028) and loop diuretics (39, 20.9% vs. 40, 35.7%, *P* = 0.0005) despite similar mean max LVWT, proportion of LVOTO, and NYHA functional class at baseline.

Outcomes

Of the 90 HCM patients hospitalized with SARS-CoV-2 (*Table 1*), 29 (32.6%) developed a severe clinical course (defined as death or ICU requirement) (*Table S2*). HCM patients with severe course more often developed pneumonia (22, 75.9% vs. 33, 54.1%, *P* = 0.048), acute respiratory distress (9, 31.0% vs. 2, 3.3%, *P* = 0.0005), and shock (7, 24.1% vs. 0, 0.0%, *P* $<$ 0.0001), compared with those without severe SARS-CoV-2 infection.

There were 17 (5.6%) HCM patients who died during or as a consequence of SARS-Cov-2 infection. These were significantly older compared with survivors (70.2 ± 10.9 vs. 55.4 ± 16.6 years old, *P* = 0.0003), had higher percentage of comorbidities including hypertension (11, 64.7% vs. 108,

Table 1 Baseline characteristics of patients requiring hospitalization

		Outpatient	Admission	Total	sig (*P*)
n		211 (70.1)	90 (29.9)	301 (100)	-
Age		52.7 (16.9)	64.2 (13.1)	56.1 (16.7)	<0.0001
Sex	Female	80 (37.9)	31 (36.9)	111 (37.6)	0.9
	Male	131 (62)	53 (63.1)	184 (62.4)	0.9
Registry	Dilema	156 (73.9)	67 (74.4)	223 (74.1)	0.9
	Share	55 (26.0)	23 (25.6)	78 (25.8)	0.9
Race	Other or not reported	7 (3.3)	11 (12.2)	18 (6.0)	-
	White	199 (94.3)	73 (81.1)	272 (90.3)	0.1
	Black	3 (1.4)	6 (6.7)	9 (3.0)	-
	Asian	2 (0.9)	0 (0)	2 (0.7)	-
Care setting[a]	ICU level care	0 (0)	21 (23.3)	21 (7.0)	<0.0001
HTN		70 (33.1)	48 (53.3)	118 (60.8)	0.001
Diabetes		24 (11.3)	19 (21.1)	43 (14.3)	0.027
CAD		2 (0.9)	3 (3.3)	5 (1.7)	0.16
Tobacco		31 (14.6)	11 (12.2)	42 (14.0)	0.6
COPD		15 (7.1)	9 (10.1)	24 (8.0)	0.4
BMI category	Normal	69 (34.3)	15 (17.4)	84 (29.3)	0.004
	Overweight	70 (34.8)	41 (47.7)	111 (38.7)	0.04
	Obesity	62 (30.8)	30 (34.9)	92 (32.1)	0.5
NYHA class	I	128 (64.6)	29 (37.2)	157 (56.9)	-
	II	64 (32.3)	26 (33.3)	90 (32.6)	-
	III	6 (3.1)	16 (20.5)	22 (8.0)	-
	IV	0 (0)	7 (9.0)	7 (2.5)	<0.0001
Beta-blocker		131 (62.1)	56 (62.2)	187 (62.1)	0.9
Loop diuretic		47 (22.2)	35 (38.9)	82 (27.2)	0.003
Anticoagulant		48 (22.7)	28 (31.1)	76 (25.2)	0.1
ACEi		24 (11.3)	14 (15.6)	38 (12.6)	0.3
ARB		47 (22.2)	24 (26.7)	71 (23.6)	0.4
ARNi		3 (1.4)	4 (4.4)	7 (2.3)	0.2
max LVWT		19.2 (5.1)	19.1 (4.4)	19.1 (4.8)	0.9
LVOT obstruction		60 (30.1)	31 (40.8)	91 (33.1)	0.09
LVEF %		65.4 (7.2)	62 (11.9)	64.4 (9.1)	0.016
LVEF interval	<35%	0 (0)	6 (7.2)	6 (2.2)	-
	35–54%	4 (2.1)	7 (8.4)	11 (4.0)	-
	≥55%	186 (97.9)	70 (84.3)	256 (93.8)	<0.0001
LVSD		4 (2.1)	13 (15.7)	17 (6.2)	<0.0001
LVEDd		44.5 (7.7)	45.1 (8.3)	44.7 (7.8)	0.6
Rhythm	Atrial fibrillation	43 (20.3)	28 (31.1)	71 (23.6)	0.045
	Ventricular pacing	1 (0.4)	3 (3.3)	4 (1.3)	0.08

ACEi, angiotensin converter enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension; ICU, intensive care unit; LVEDd, left ventricular end diastolic diameter (mm); LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVSD, left ventricular systolic dysfunction (LVEF < 55%); obesity ≤ 30 kg/m^2; overweight ≥ 25 and <30; max LWT: maximal left ventricular wall thickness (mm); NYHA class, New York Heart Association dyspnoea class.
[a]Information on care setting (outpatient/hospitalization) was missing in four individuals.

37.6%, P = 0.026) and diabetes (6, 35.3% vs. 37, 12.9%, P = 0.021) and were more frequently hospitalized (n = 17, 100.0% vs. n = 71, 24.7%, $P < 0.0001$) (*Table S3*). They also were symptomatically more limited at baseline (NYHA III–IV 9, 52.9% vs. 20, 6.9%, $P < 0.0001$) and with a higher frequency of prior atrial fibrillation (8, 47.1% vs. 62, 21.6%, P = 0.032). *Figure 2* presents the age and sex distribution of patients with HCM who died of SARS-Cov-2. Out of the total 17 (5.6%) deaths, there were 4 (1.3%) due to HF, 2 (0.7%) sudden deaths, and 1 (0.3%) other cardiac-related death. Eight (2.6%) died of respiratory failure and two (0.7%) from other SARS-CoV-2-related complications.

Non-fatal HCM-related complications coincident with SARS-Cov-2 infection included atrial fibrillation and stroke, in nine patients (2.9%; including five outpatients, three ICU, and one non-ICU inpatient). There were three (1.0%) strokes (two ICU patients and one outpatient), all in the context of new onset atrial fibrillation. None of the 34 patients with an ICD (11.1%) had appropriate discharges.

Characteristics of HCM patients experiencing adverse outcomes

Hospitalized patients were older (64.3 ± 13.2 vs. 52.7 ± 16.9 years, $P < 0.0001$) and had a higher burden of hypertension (47, 52.8% vs. 70, 33.2%, P = 0.001), diabetes (19, 21.3% vs. 24, 11.4%, P = 0.02), and overweight or obesity (70, 82.3% vs. 132, 65.6%, P = 0.005), compared with outpatients. Hospitalized patients were also more likely to have NYHA III–IV effort intolerance (23, 29.9% vs. 6, 3.0%, $P < 0.0001$), treatment with loop diuretics (35, 39.3% vs.

Figure 1 Distribution of the percentage of hypertrophic cardiomyopathy patients with SARS-Cov-2 regarding care setting (upper chart) and proportion of sex by care setting (lower chart). ICU, intensive care unit.

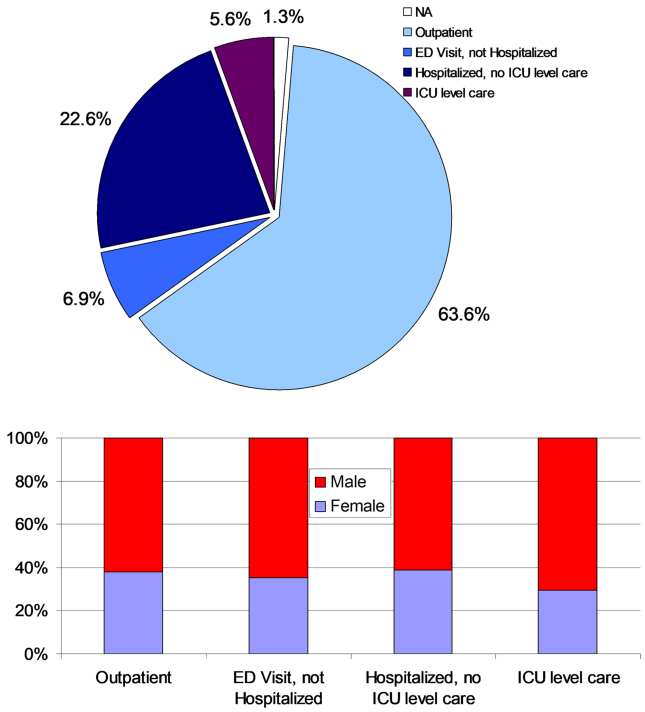
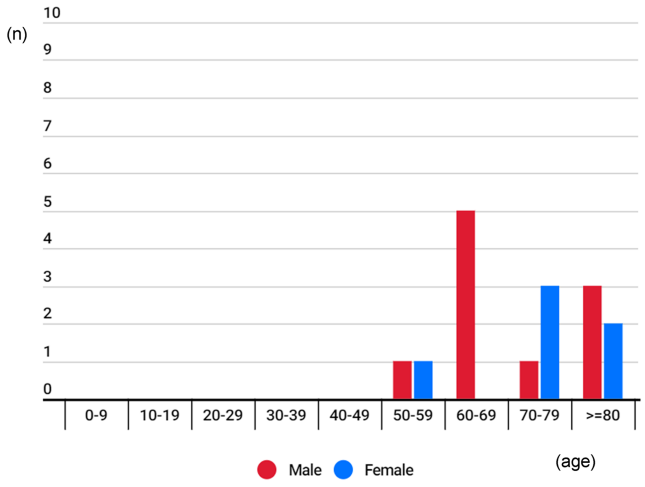


Figure 2 Distribution of the number of patients with hypertrophic cardiomyopathy-related and SARS-CoV-2-related death by age interval and sex.



47, 22.3%, $P = 0.002$), or prior atrial fibrillation (28, 31.5% vs. 43, 20.4%, $P = 0.039$). Compared with HCM patients not requiring hospitalization, admitted patients had significantly lower LVEF (62.0% ± 12.0% vs. 65.4% ± 7.3%, $P = 0.018$), although with similar max LVWT and proportion of LVOTO.

Patients who required ICU stay or died had a higher percentage of LVOTO (13, 59.1% vs. 19, 34.5%, $P = 0.048$) and baseline NYHA III–IV effort intolerance (14, 63.6% vs. 9, 16.3%, $P = 0.0002$). The odds associated with risk factors for severe clinical course (ICU or hospital death) were

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Table 2 Multivariable analysis of the predictors of ICU admission and death

		Univariable		Mutivariable	
ICU/Death		OR	sig. (*P*)	OR	sig. (*P*)
Age (10)		1.65 (1.25–2.17)	0.0004	1.67 (1.00–2.78)	0.0483
Sex	Male	1.1 (0.47–2.58)	0.8283		
HTN		2.08 (0.96–4.50)	0.0631		
Diabetes		3.22 (1.35–7.66)	0.0082		
Tobacco		1 (0.33–3.05)	0.9954		
COPD		0.83 (0.19–3.73)	0.8098		
BMI category	Overweight/Obese	6.29 (1.46–27.08)	0.0136		
	Obese	1.36 (0.61–3.01)	0.4503		
NYHA class		5.53 (3.06–9.98)	<0.0001	4.9 (2.40–10.02)	<0.0001
Beta-blocker		1.38 (0.61–3.14)	0.4449		
Loop diuretic		2.4 (1.10–5.25)	0.0281		
Anticoagulant		1.17 (0.50–2.77)	0.7181		
ACEi		1.17 (0.50–2.77)	0.4481		
ARB		1.04 (0.43–2.55)	0.9310		
ARNi		3.91 (0.72–21.13)	0.1131		
max LVWT		1.04 (0.96–1.13)	0.3407		
LVOT Obstruction		3.24 (1.33–7.9)	0.0097	3.18 (0.98–10.38)	0.0552
LVEF		0.93 (0.90–0.97)	0.0001		
LVEF interval		0.22 (0.10–0.47)	0.0001		
LVSD		7.8 (2.69–22.61)	0.0002	6.43 (0.96–43.06)	0.0551
LVEDd		1 (0.95–1.06)	0.9325		
Rhythm	Atrial fibrillation	1.57 (0.68–3.62)	0.2928		
		Univariable		Mutivariable	
Death		OR	sig. (*P*)	OR	sig. (*P*)
Age (10)		1.95 (1.33–2.87)	0.0007	2.25 (1.12–4.51)	0.0229
Sex	Male	1.07 (1.03–1.11)	0.9943		
HTN		3.04 (1.09–8.45)	0.0332		
Diabetes		3.69 (1.29–10.56)	0.0152		
Tobacco		1.36 (0.37–4.96)	0.6387		
COPD		1.61 (0.35–7.48)	0.5460		
BMI category	Overweight/Obese	3.26 (0.73–14.57)	0.1221		
	Obese	1.15 (0.41–3.22)	0.7867		
NYHA class		5.6 (2.82–11.13)	<0.0001	4.01 (1.75–9.2)	0.0011
Beta-blocker		0.81 (0.30–2.19)	0.6785		
Loop diuretic		3.36 (1.25–9.03)	0.0163		
Anticoagulant		2.25 (0.83–6.15)	0.1123		
ACEi		0.87 (0.19–3.97)	0.8613		
ARB		1.01 (0.32–3.20)	0.9861		
ARNi		7.52 (1.35–42.00)	0.0215		
max LVWT		1.04 (0.94–1.15)	0.4568		
LVOT obstruction		3.93 (1.28–12.08)	0.0171	5.59 (1.16–26.92)	0.0317
LVEF		0.94 (0.90–0.98)	0.0020		
LVEF interval		0.25 (0.11–0.56)	0.0007		
LVSD		8.57 (2.59–28.31)	0.0004	7.72 (1.20–49.79)	0.0316
LVEDd		1.02 (0.95–1.09)	0.6251		
Rhythm	Atrial fibrillation	3.23 (1.20–8.71)	0.0208		

ACEi, angiotensin converter enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension; ICU, intensive care unit; LVEDd, left ventricular end diastolic diameter (mm); LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVSD, left ventricular systolic dysfunction (LVEF < 55%); obesity ≤ 30 kg/m^2; overweight ≥ 25 and <30; max LWT: maximal left ventricular wall thickness (mm); NYHA class, New York Heart Association dyspnoea class.

examined in univariate and multivariate models and are presented in *Table 2*. The only covariates associated with a severe COVID-19 course in the multivariable model were age [OR per 10 year increase 1.67 (95%CI: 1.00–2.78), *P* = 0.0483] and baseline NYHA class [OR per one-unit increase 4.90 (95%CI: 2.40–10.02), *P* < 0.0001]. There was a borderline significant relationship of both LVOTO [OR 3.18 (95%CI: 0.98–10.38), *P* = 0.0552] and systolic impairment [OR 6.43 (95%CI: 0.96–43.06), *P* = 0.0551] with severe clinical course.

Also presented in *Table 2* were covariates associated with mortality. In the multivariable analysis, age [OR per 10 year increase 2.25 (95%CI: 1.12–4.51), *P* = 0.0229], baseline NYHA class [OR per one-unit increase 4.01 (95%CI: 1.75–9.20), *P* = 0.0011], LVOTO [OR 5.59 (95%CI: 1.16–26.92), *P* = 0.0317], and systolic impairment [OR 7.72 (95%CI:

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1.20–49.79), P = 0.0316] were all associated with increased mortality.

Analysis of SARS-CoV-2-related mortality in HCM vs. control population

We compared mortality among HCM patients to a contemporary cohort of 91 131 consecutive patients diagnosed with SARS-CoV-2 infection in the general population (mean age 39.6 ± 21.8 years old, 47.5% male patients). There were 7502 (8.2%) who required hospital admission and 1687 (1.9%) deaths. The time from SARS-CoV-2 diagnosis to death was 2.0 ± 2.6 months (median 0.80 months, [0.51, 2.29]).

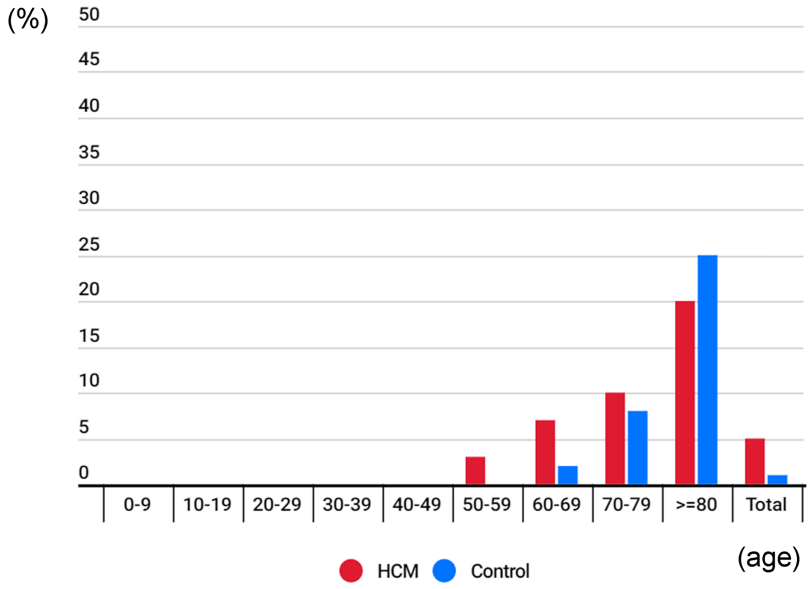
Although ascertainment methods differed, hospital admissions were almost four times more common in the HCM than control cohort (n = 91 or 29.8% vs. n = 7502 or 8.2%, $P < 0.0001$). HCM patients were older (56.6 ± 16.9 vs. 39.6 ± 21.8 years, $P < 0.0001$), more often male patients (n = 191 or 62.6% vs. n = 43 317 or 47.5%, $P < 0.0001$) compared with the control cohort. Mortality was 3.0-fold higher in the HCM cohort (n = 17 or 5.6% [95%CI: 4.97–6.22] vs. n = 1687 or 1.9% [95%CI: 1.87–1.90], $P < 0.001$) (*Figure 3*).

In a multivariable model comparing death rates among HCM and control patients, age [OR per 10 year increase 3.46 (95%CI: 3.31–3.61), $P < 0.0001$] and male sex [OR 2.03 (95%CI: 1.82–2.27), $P < 0.0001$] were significantly associated with mortality (*Table 3*). The presence of HCM was associated with borderline increase in mortality [OR 1.70 (95%CI: 0.98–2.91), P = 0.0600]. However, when the analysis was limited to patients younger than 80 years, risk associated with a diagnosis of HCM became significant [OR 2.24 (95%CI: 1.21–4.12), P = 0.0099].

Discussion

In this international study representing 29 centres, we have prospectively examined the impact of SARS-CoV-2 infection

Figure 3 Percentage of SARS-CoV-2-related death by age interval for patients with HCM and controls. HCM, hypertrophic cardiomyopathy.



	HCM			Control		
Age	**Cases**	**Deaths**	**% Deaths (95% CI)**	**Cases**	**Deaths**	**% Deaths (95% CI)**
0-9	0	0	---	8583	1	0.01 (0.01 - 0.01)
10-19	4	0	0 (0 - 0)	11,114	3	0.03 (0.03 - 0.03)
20-29	22	0	0 (0 - 0)	13,287	5	0.04 (0.04 - 0.04)
30-39	27	0	0 (0 - 0)	13,166	8	0.06 (0.06 – 0.06)
40-49	41	0	0 (0 - 0)	15,671	24	0.15 (0.15 – 0.16)
50-59	65	2	3.08 (2.33 - 3.83)	13,206	72	0.55 (0.54 - 0.55)
60-69	81	6	7.41 (5.82 - 8.99)	7,589	181	2.39 (2.33 - 2.44)
70-79	39	4	10.26 (7.14 - 13.37)	4,458	359	8.05 (7.82 - 8.26)
>=80	25	5	20.00 (12.84 - 27.16)	4,057	1,034	25.49 (24.8 - 26.18)
Total	304	17	5.59 (4.97 - 6.22)	91,131	1,687	1.85 (1.84 - 1.86)

Table 3 HCM vs. control, age, and gender adjusted analysis of mortality

Death	OR	sig. (*P*)
Whole cohort		
Age (10)	3.46 (3.31–3.61)	<0.0001
Sex (male)	2.03 (1.82–2.27)	<0.0001
HCM vs. controls	1.70 (0.98–2.91)	0.0600
Age ≤ 80 years old only		
Age (10)	3.59 (3.33–3.88)	<0.0001
Sex (male)	2.12 (1.80–2.50)	<0.0001
HCM vs. controls	2.24 (1.21–4.12)	0.0099

HCM, hypertrophic cardiomyopathy; OR, odds ratio.

on patients with HCM. Advanced age and key markers of HCM disease severity—as can be obtained with by clinical history and echocardiogram—were associated with hospitalization, ICU admission, or death.[2] In particular, for every class increase in NYHA functional state risk of death increased nearly five-fold. LVSD and LVOTO were associated with 7.7-fold and 5.6-fold increases in mortality, respectively. When compared with a control cohort of individuals in the general population, the presence of HCM conferred a four-fold (2.4 adjusted by age and gender) higher likelihood of hospital admission and a three-fold (1.7 adjusted by age and gender) increase in mortality, which was evident in all but the oldest patients (>80 years). Overall, 5% of HCM patients in this series died, which may have reflected an older cohort enriched with classes III–IV symptoms and relevant comorbidities. The majority of the deaths were SARS-Cov-2 respiratory related, which may have been aggravated by underlying heart disease including, two patients who died suddenly. Incident atrial fibrillation was the most common non-fatal HCM complication related to SARS-CoV-2 infection, affecting 3% of infected patients whereas ICD discharges were not observed.

Characteristics of HCM patients experiencing adverse SARS-CoV-2 outcomes

Similar to studies conducted in the broader population, we identified that advanced age was a strong risk factor for adverse SARS-CoV-2 outcomes. Specific to the HCM population, we observed that traditional markers of disease severity, LVOTO, LVSD, and NYHA functional class, have poor prognostic values.[5] In the specific case of outflow tract obstruction, adverse outcomes may be related to the dynamic changes in loading conditions that accompany critical illness. A decrease in preload related to diminished appetite, fever, or other gastrointestinal symptoms, coupled with a decrease in afterload due to the vasoplegia of sepsis could worsen the hemodynamic severity of LVOTO. In the setting of associated pneumonia and critical illness, worsening LVOTO may precipitate pulmonary oedema and further complicate acute respiratory failure. Thus, baseline assessment and monitoring of LVOTO may be crucial in HCM patients with clinical worsening in the context of SARS-CoV-2 infection. In obstructive patients, management should include continuation of baseline medical therapy, if appropriate, associated with judicious use of crystalloid infusion and vasopressors to prevent hemodynamic deterioration.

Left ventricular systolic dysfunction is an adverse complication presenting in ~8% of HCM patients,[5,8] associated with a substantial increase in risk of virtually all HCM-related complications (e.g. death, advanced HF, sudden death, and atrial fibrillation). In this context, it is not surprising that HCM patients with LVSD may incur increased risk of SARS-CoV-2-related death. In contrast to LVOTO, however, HF in these patients may be exacerbated by expansion of intravascular volume. Moreover, in the event of septic shock, patients with systolic dysfunction may not be able to mount a compensatory increase in cardiac output necessary to maintain tissue perfusion. Thus, the required strategy in these patients is based on judicious diuresis and use of beta agonists in case of haemodynamic deterioration or shock.

Overall, the present findings are in keeping with recent reports that patients with cardiovascular comorbidities are more likely to develop an adverse course due to SARS-Cov-2 infection[8–12] and support aggressive and systematic implementation of SARS-Cov-2 prophylaxis and management options in HCM patients, particularly in the presence of high-risk features.

Limitations

There are inherent limitations to retrospective studies based on multicentre registries. The magnitude of the pandemic and subsequent lockdown led to heterogeneity of clinical data, due to differential access of patients to medical care depending on local policies. Data collection was based on the interview of patients/relatives and the review of available medical records. Although data collection was implemented homogeneously over a short time-course, there was not a standardized protocol of examinations at each participating site. Standard COVID-19 outcomes scores could therefore not be evaluated.

Similar to other published HCM studies, this cohort is predominantly middle age, White, and male with characteristic morphology and associated comorbidities. In addition, we cannot exclude a selection bias towards the most severe cases (admitted patients were more likely to be identified by their doctors/investigators). In this regard, the proportion of hospitalized patients in the centres with higher enrolment rate was 25.9%, while intermediate enrolment centres had a 42.9% and lower enrollers a 33.3%. Alternatively, HCM patients followed in specialty centres may have been more likely to be offered earlier admission through established access to specialty care.

In contrast to general population series of SARS-CoV-2, male sex and comorbidities were not predictors of adverse course or mortality in our study.[13] However, our sample size is limited and there is no a priori reason to suspect these covariates are unimportant for patients with HCM. The control group might not be representative of the general population SARS-CoV-2 mortality in other geographical areas. Importantly, SARS-Cov-2 vaccination was not recorded. However, the impact of vaccination on our results is very low as enrolment finished just as vaccines became available, with less than 2% of the population fully vaccinated by the end of study period.

Conclusions

Patients with HCM and SARS-Cov-2 patients are more likely to require hospitalization and die, compared with the general population, particularly in presence of older age, worse functional class, LVOTO, and systolic impairment. These data suggest the need for aggressive and systematic implementation of prophylactic measures for SARS-Cov-2 in patients with inherited cardiac disease.

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Conflict of interest

Elias Grande, Carlos Peña, and Lorenzo Monserrat work for a Dilemma SL company and made substantial contributions to the study. They participated in development of the eCRF, in the revision, and in the approval of the manuscript. The rest of the authors declared no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. List of participating centres.
Table S2. Characteristics of hospitalized patients with adverse clinical course (ICU admission or hospital death).
Table S3. Comparison of patients who survived to those who died.
Appendix S1. Full list of authors.

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