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 91131 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

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 fulfill 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 HCM4,5 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 del 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) ≥ 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 as 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 χ² 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, 55.4 ± 16.6 years old, \( P = 0.0003 \)), had higher percentage of comorbidities including hypertension (11, 64.7% vs. 108, 55.4 ± 16.6 years old, \( P = 0.0003 \)), had higher percentage of comorbidities including hypertension (11, 64.7% vs. 108, 55.4 ± 16.6 years old, \( P = 0.0003 \)).
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. 21, 20.2%, $P = 0.001$).
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
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: 2189–2198 DOI: 10.1002/ehf2.13964
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), \( P = 0.060 \)]. 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...
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. 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, 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 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.

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

| Death | OR | sig. (P) |
|-------|----|---------|
| Whole cohort | 3.46 (3.31–3.61) | <0.0001 |
| Age (10) | 2.03 (1.82–2.27) | <0.0001 |
| HCM vs. controls | 1.70 (0.98–2.91) | 0.0600 |
| Age <= 80 years only | 3.59 (3.33–3.88) | <0.0001 |
| Age (10) | 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.
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. 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.

Acknowledgements

We want to thank all patients and their relatives for their collaboration. A full list of the investigators of the SHaRe and Dilema registries is provided in Appendix S1.

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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.

Funding

The project was funded by a grant from the Instituto de Salud Carlos III (ICSIII, COV20 00420). We should state that the SHaRe registry has been supported by an unrestricted grant from MyoKardia/Bristol Myers Squibb.

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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