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Title page

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

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Abstract

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

Methods and results: 305 patients (age 56.6±16.9 years old, 191 [62.6%] males) with HCM and SARS-Cov-2 infection were enrolled. The control group consisted of 91,131 **infected** individuals. Endpoints were (1) SARS-CoV-2 related mortality, and (2) severe clinical course **(death or 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: 8 (2.6%) of respiratory failure, 4 (1.3%) of heart failure, 2 (0.7%) suddenly and 3 (1.0%) due to other SARS-CoV-2 related complications. Covariates associated with mortality in the multivariable were age [OR per 10-years increase 2.25 (95%CI: 1.12-4.51), p=0.0229], baseline NYHA class [OR per 1 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 to 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 out-flow 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 to** (i) to describe the natural history of SARS-CoV-2 infection in patients with HCM compared to a control group **of SARS-CoV-2 individuals over a 12 months period** and (ii) to identify predictors of adverse events in patients with HCM and SARS-CoV-2 infection.

Methods

Registry Design & 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 2nd 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 on-line 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 participants centres is summarized in **supplementary table 1**.

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 8th March 2020

till 2nd of February 2021 was obtained from the Subdirección General de Tecnologías de la Información (SGTI) 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 31st August 2021 were included in the registry. In the control group, 1,687 deaths attributed or related to SARS-CoV-2 infection (1,259 died during hospital admission), and 214 deaths 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, COPD), 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, 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 intensive care unit (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 t-student or non-parametric test where appropriate. Categorical variables were reported as counts and percentages. Among-group comparisons 2x2 were made using a chi-square test or Fisher's exact test if any expected cell count was less than five.

A stepwise multivariable logistic regression analysis was performed to analyze the relationship between patient characteristics and mortality. We included all candidate covariates and those with $p<.10$ in a univariate analysis. A significance level of .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%CI's 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%] males, 114 [37.4%] females) 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 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 (ARB), 40 (13.1%) on angiotensin converting enzyme inhibitors (ACEi), 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), ARBs (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 maxLVWT, 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**) (**Supplementary table 2**). 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 to 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 to 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, 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) (Supplementary **table 3**). 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 heart failure, 2 (0.7%) sudden deaths and 1 (0.3%) other cardiac related death. Eight (2.6%) died of respiratory failure and 2 (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 9 patients (2.9%; **including** 5 outpatients, 3 ICU and **1 non-ICU inpatient**). There were 3 (1.0%) strokes (2 ICU patients and 1 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), 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-obesity (70, 82.3% vs 132, 65.6%, p=0.005), **compared to 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 47, 22.3%, p=0.002) or prior atrial fibrillation (28, 31.5% vs 43, 20.4%, p=0.039). Compared to 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 on **table 2**. The only covariates associated with a severe COVID-19 course in the multivariable model were age [OR per 10-years increase 1.67 (95%CI: 1.00-2.78), p=0.0483], and baseline NYHA class [OR per 1 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 on **table 2, were** covariates associated with mortality. In the multivariable analysis, age [OR per 10-years increase 2.25 (95%CI: 1.12-4.51), p=0.0229], baseline NYHA class [OR per 1 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: 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). There were 7,502 (8.2%) who required hospital admission and 1,687 (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 4 times more common in the HCM than control cohort (n=91 or 29.8% vs. n=7,502 or 8.2%, p<.0001). HCM patients were older (56.6 ± 16.9 vs 39.6 ± 21.8 years, p<.0001), **more often males** (n=191 or 62.6% vs n=43,317 or 47.5%, p<.0001) compared to 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=1,687 or 1.9% [95%CI: 1.87-1.90], p<.001) (figure 3).

In a multivariable model comparing death rates among HCM and control patients, age [OR per 10-years increase 3.46 (95%CI: 3.31-3.61), p<.0001] and male sex [OR 2.03 (95%CI: 1.82-2.27), p<.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 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 5-fold. LVSD and LVOTO were associated with 7.7 and 5.6-fold increases in mortality, respectively. When compared to a control cohort **of individuals in the general population**, the presence of HCM conferred a 4-fold **(2.4 adjusted by age and gender)** higher likelihood of hospital admission and a 3-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 class 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, 2 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 edema 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**.

LVSD 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** heart failure, sudden death, 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, heart failure 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 hemodynamic deterioration or** shock.

~~Poor functional state captured by NYHA status likely integrates numerous physiologic factors associated with decreased cardiorespiratory and metabolic reserve which render patients more vulnerable to SARS-CoV-2 infection. Importantly, it was the baseline NYHA functional class which was prognostic. This could be obscured at the time of hospitalization for SARS-CoV-2 infection where patients are generally unwell. Accordingly, ascertainment of NYHA status prior SARS-CoV-2 infection should be sought in order to identify patients at increased risk of complications.~~

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, and 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 to 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 statement

None to declare. 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.

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Figures legends

Figure 1. Distribution of the percentage of HCM patients with SARS-Cov-2 regarding care setting (upper chart) and proportion of sex by care setting (lower chart).

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

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

Table 1. Baseline characteristics of patients requiring hospitalization

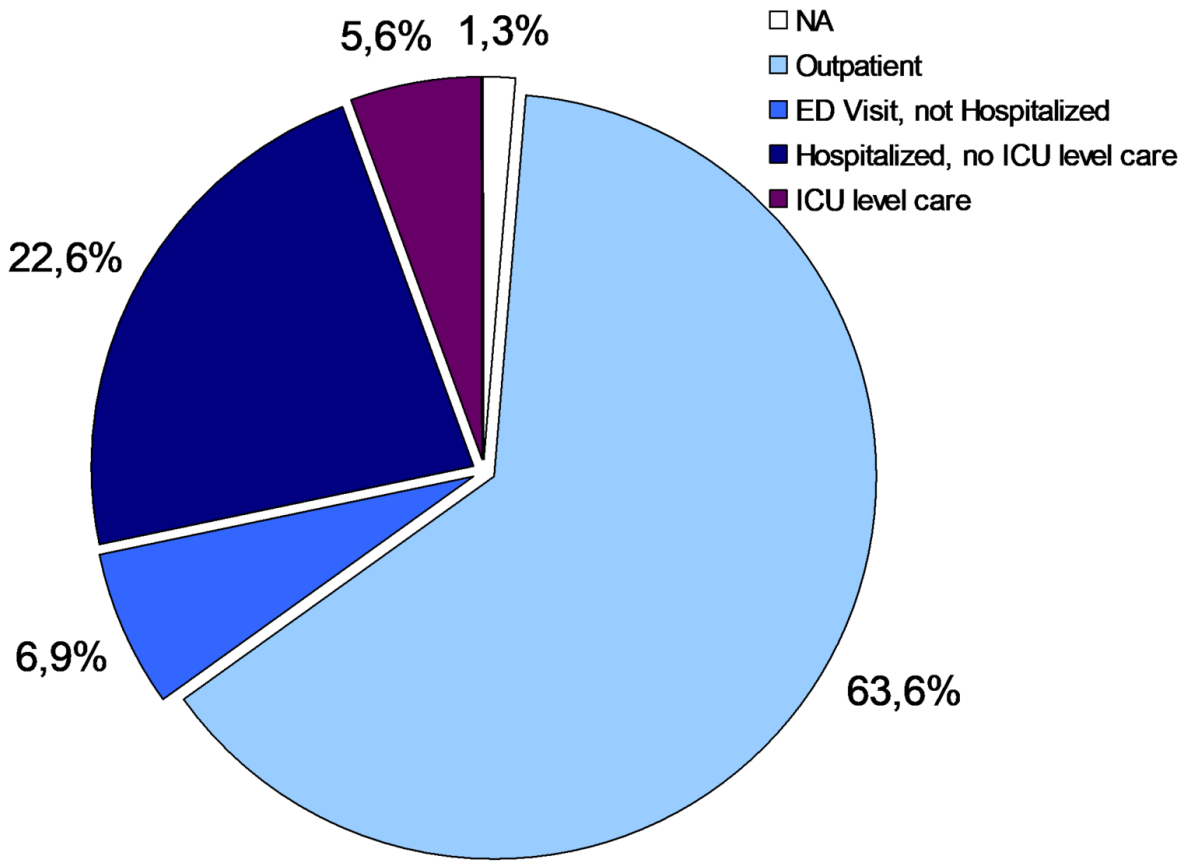
Table 2. Multivariable analysis of the predictors of ICU admission and death

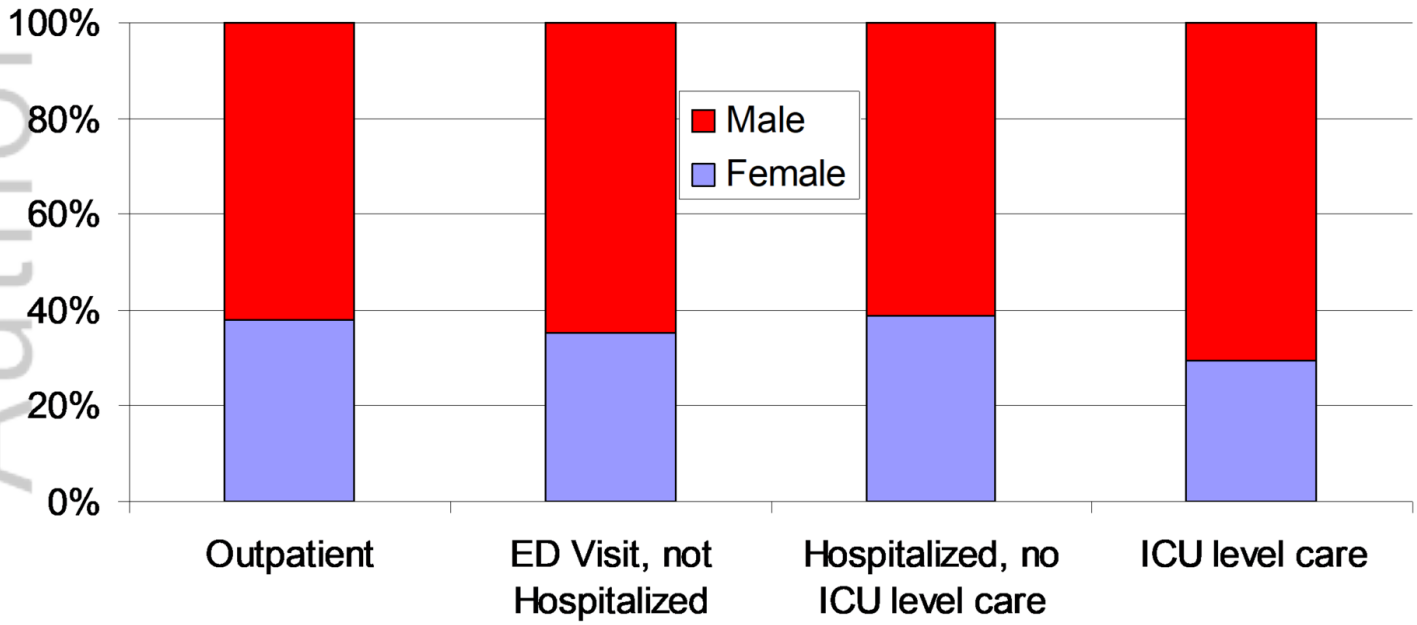
Table 3. HCM vs control, age and sex adjusted analysis of mortality

Supplementary table 1. Supplementary table 1: List of participating centres

Supplementary table 2. Characteristics of hospitalized patients with adverse clinical course (ICU admission or hospital death)

Supplementary Table 3. Comparison of patients who survived to those who died





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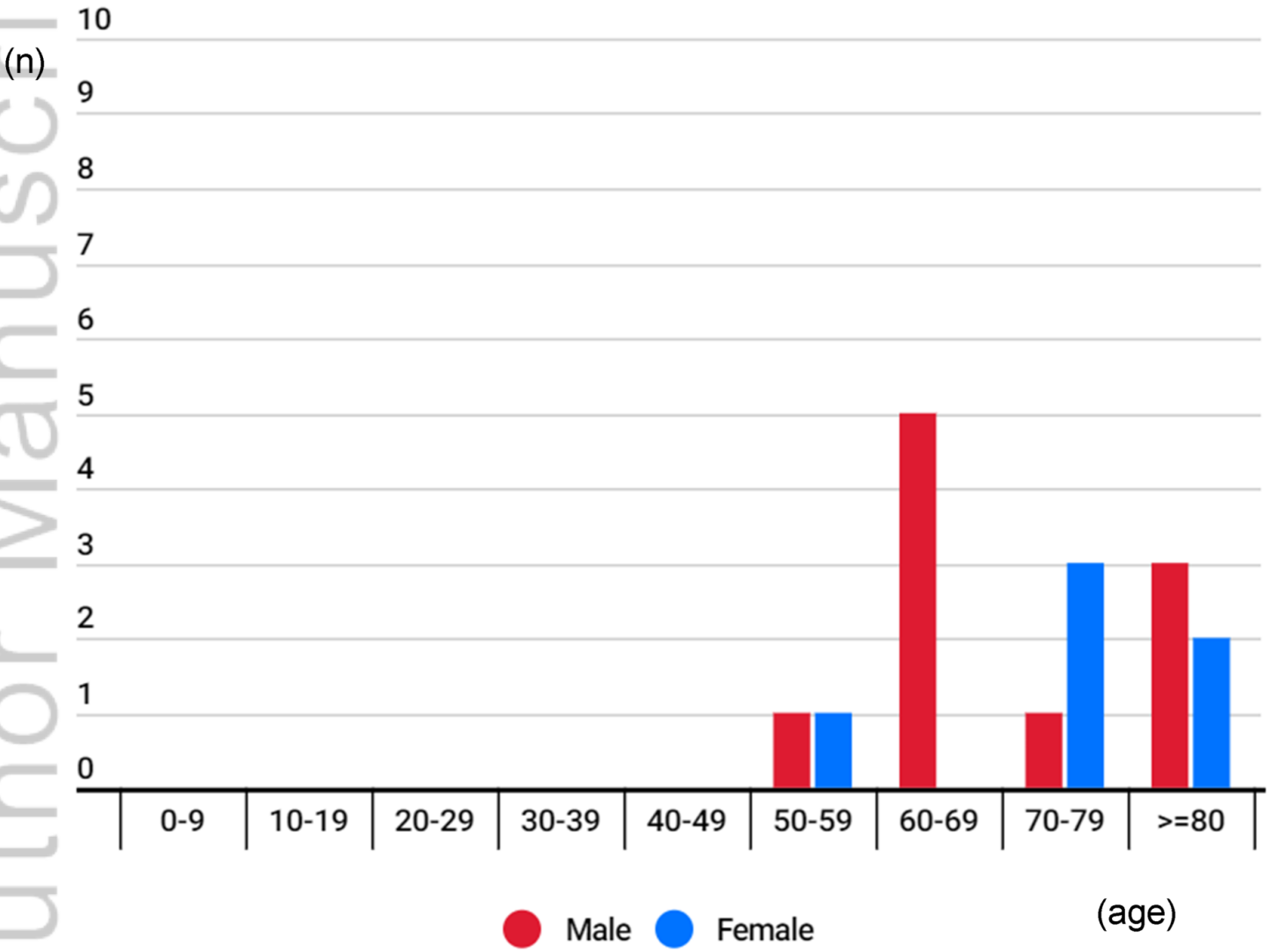

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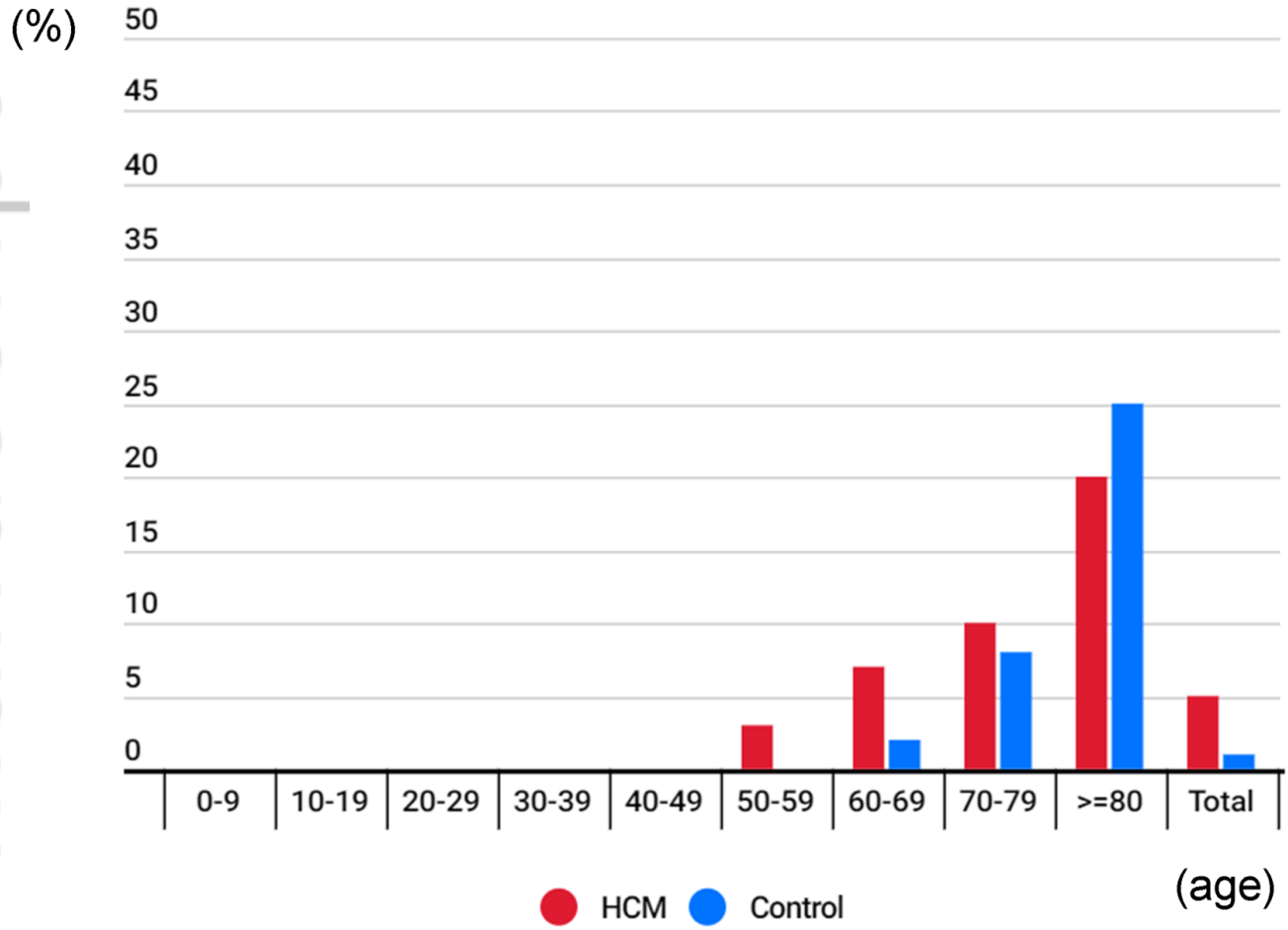

	HCM			Control		
Age	**Cases**	**Deaths**	**% Deaths (95% CI)**	**Cases**	**Deaths**	**% Deaths (95% CI)**
0-9	0	0	---	8583	1	0.01 (0.01 - 0.01)
10-19	4	0	0 (0 - 0)	11,114	3	0.03 (0.03 - 0.03)
20-29	22	0	0 (0 - 0)	13,287	5	0.04 (0.04 - 0.04)
30-39	27	0	0 (0 - 0)	13,166	8	0.06 (0.06 – 0.06)
40-49	41	0	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)

EHF2_13964_Figure3 death HCM vs controls FINALcorrected.tif