American Heart Journal Plus: Cardiology Research and Practice 25 (2023) 100244

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Long term mortality in patients with hypertrophic cardiomyopathy – A Danish nationwide study

Mads-Holger Bang Jacobsen [a,*], Jeppe Kofoed Petersen [a], Daniel Modin [b], Jawad Haider Butt [a], Jens Jakob Thune [d], Henning Bundgaard [a], Christian Torp Pedersen [c], Lars Køber [a], Emil Loldrup Fosbøl [a], Anna Axelsson Raja [a]

[a] Dep. of Cardiology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
[b] Dep. of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Kildegårdsvej 28, 2900 Hellerup, Denmark
[c] Dep. of Clinical Research and Cardiology, Nordsjællands Hospital, Hillerød, Denmark
[d] Dep. of Cardiology, Copenhagen University Hospital, Bispebjerg-Frederiksberg, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark

ARTICLE INFO

Keywords:
Hypertrophic cardiomyopathy
Long-term mortality
Sudden cardiac death
Registry
Background population

ABSTRACT

Background: Patients with hypertrophic cardiomyopathy (HCM) are generally regarded as having increased risk of arrhythmia, stroke, heart failure, and sudden cardiac death, but reported mortality rates vary considerably and originate from selected populations.
Study objective: We aimed to investigate the long-term mortality rate in a nationwide cohort of patients with HCM compared to a matched cohort from the general Danish population.
Methods: All patients with a first-time HCM diagnosis in Denmark between January 1, 2007 and December 31, 2018 were identified through nationwide registries. In the main analysis, two visits in an outpatient clinic were required in order to increase specificity. Patients were matched to controls from the background population in a 1:3 ratio based on age, sex, selected comorbidities and date of HCM. Mortalities were compared using Kaplan Meier estimator and multivariable Cox regression models.
Results: We identified 3126 patients with a first-time diagnosis of HCM. 1197 patients had at least two visits in the outpatient clinic (43 % female, median age 63.1 [25th–75th percentile 52.1–72.1] years). All-cause mortality was significantly higher in HCM patients than in matched controls: 10-year probabilities of death were 36.4 % (95 % CI 30.2–43.5 %) for HCM patients and 19.4 % (95 % CI 16.8–22.5 %) for controls. After adjusting for additional comorbidities and medications, a diagnosis with HCM was associated with an increased mortality rate (HR 1.48 (95 % CI 1.18–1.84, $p = 0.001$)).
Conclusion: Compared to matched controls from the background population, presence of HCM was associated with a significant increase in mortality rate.

1. Introduction

Patients with hypertrophic cardiomyopathy (HCM) are generally regarded as having an increased risk of heart failure, atrial fibrillation, ventricular arrhythmia, stroke, and sudden cardiac death (SCD) compared to the background population [1–3]. However, data on mortality are conflicting. Early reports suggested that HCM was associated with a particularly unfavorable outcome, with an annual mortality rate of 6 % [4–6]. One recent, large study also found excessive mortality compared to the background population and demonstrated that young age at diagnosis and the presence of a sarcomere mutation were predictors of adverse outcomes [3]. In contrast, several recent studies have suggested a less severe natural course, which together with contemporary management strategies, including implantation of prophylactic implantable cardioverter defibrillators (ICD), have resulted in a near-normal life expectancy for patients with HCM [7–11]. The

Abbreviations: ATC, anatomical therapeutic chemical classification system; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DOAC, direct-acting oral anticoagulants; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ICD-10, International Classification of Diseases, 10th revision; PVD, peripheral vascular disease; RAS, renin-angiotensin-system; VKA, vitamin-K-antagonist.

* Corresponding author at: Dep. of Cardiology, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail address: madsholger08@hotmail.com (M.-H.B. Jacobsen).

https://doi.org/10.1016/j.ahjo.2022.100244
Received 27 September 2022; Received in revised form 18 December 2022; Accepted 18 December 2022
Available online 22 December 2022

phenotype is highly heterogenous, and since most previous studies have primarily been based on cohorts from tertiary centers with a risk of referral bias, our knowledge about the clinical course in an unselected cohort of patients with HCM is limited.

Danish nationwide registries provide an opportunity to assess outcome in patients with HCM with minimum selection bias and with significant comorbidities taken into account. Thus, we aimed to investigate long-term mortality in a nationwide cohort of patients with HCM in comparison to a matched cohort from the general Danish population.

2. Methods

2.1. Data sources and covariates

The Danish health-care system is tax-funded providing free-of-charge care to all citizens independent of health insurance. Nearly all Danish hospitals (99 % of hospital beds) are public [12]. First-degree relatives to patients with HCM are, according to national guidelines, offered, clinical and genetic assessment, which is also free-of-charge.

The presence of personal identification numbers that are unique and permanent through-out life for every Danish citizen enables identification of all citizens in the nationwide registries and allows for individual linkage between these registries. Danish registries are considered reliable and are well-validated [13–16]. The following registries were used: the Danish National Patient Registry, the Danish Civil Registration System, Danish National Prescription Registry, and the Cause of Death Register. The National Patient Registry contains information on hospital admissions and outpatient visits according to the International Classification of Diseases and surgical procedures according to the NOMESCO classification of surgical procedures. Information on vital status, sex, and date of birth and death was collected from the Danish Civil Registration System. Concomitant pharmacotherapy was obtained from the National Prescription Registry that holds information on all claimed prescriptions according to the international anatomical therapeutic chemical (ATC) classification system [17]. The use of medications was defined as at least one filled prescription up to six months prior to baseline. Information on comorbidities was obtained from ICD-8 and ICD-10 codes in the Danish National Prescription Registry (supplemental material). In addition, we identified individuals with hypertension that was not expected to explain the degree of left ventricular hypertrophy. This was defined as those claiming prescriptions for combination treatment with at least two classes of antihypertensive drugs within the last 180 days before index date, as done previously [18,19]. For controls these were non-loop diuretics, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, beta-blockers, and dihydropyridine and non-dihydropyridine calcium channel blockers. Betablockers and non-dihydropyridine calcium channel blockers were not included in the definition of antihypertensive treatment in HCM patients, since those are standard therapy for symptomatic HCM. Information on cause of death relevant in relation to the outcome analysis was found in the Cause of Death Register. In Denmark by law, registry-based research on anonymized data does not require ethical approval.

2.2. Population, study period and exposure

We included all patients with a first-time diagnosis of HCM (ICD-10 codes I42.1 or I42.2) in the Danish National Patient Registry between January 1, 2007 and December 31, 2018. The rationale for beginning the study period in 2007 was that a nationwide working group and a collaboration of outpatient clinics for inherited cardiac diseases were established in 2005, hereby bringing attention to the disease including correct diagnosis and coding of inherited cardiomyopathies. Beginning the study period in 2007 also allowed for a certain time for implementation and correction of diagnoses in patients with a general cardiomyopathy diagnosis prior to 1994 (ICD-8), minimizing the risk that they were included as first-time HCM. To increase specificity of the diagnose based on ICD codes in registers, patients were only included in the main analysis if they had at least two outpatient visits for HCM. In addition, a sensitivity analysis was conducted, including patients with at least one outpatient visit who were compared to a matched background population. Patients undergoing septal reduction therapy before January 1, 2007 were excluded. Patients were matched with controls from the Danish background population in a 1:3 ratio by the use of exposure density matching based on age, sex, comorbidities (hypertension, ischemic heart disease, diabetes mellitus, cancer and chronic obstructive pulmonary disease) and the date of HCM. In order to do so we used a greedy matching macro [20]. The study population was followed until death, emigration, or end of study period (December 31, 2018), whichever came first. Index date was defined as the second outpatient visit with a diagnosis of HCM in the main analysis in order to avoid survival bias and in the sensitivity analysis as the first and only visit. Controls were randomly assigned index dates from the cases. Controls could not have a history of HCM and were only matched upon if alive at index date.

2.3. Statistics

Baseline characteristics are presented as medians with 25th–75th percentiles, or frequencies with percentages. Comparisons of baseline characteristics between patients diagnosed with HCM and matched controls were performed by unpaired *t*-tests for normally distributed continuous variables, the Mann-Whitney *U* test (Wilcoxon rank-sum) for non-normally distributed continuous variables, and $\chi 2$ or Fisher's exact test for categorical variables. All-cause death for patients and controls is shown by cumulative incidence curves, and difference between groups was assessed using log-rank test. A Cox proportional hazard analysis adjusting for further comorbidities (atrial fibrillation, chronic renal failure, valve disease, peripheral vascular disease, stroke and liver disease), concomitant medication (statins, vitamin K antagonists and non-vitamin K antagonist oral anticoagulants (VKA and DOAC)) and calendar year was used to assess hazard ratios (HR) with 95 % confidence intervals (CI) for HCM patients compared with their matched controls using strata statement for matching. A sensitivity analysis including all patients with at least one (instead of at least two) outpatient visits for HCM was performed. Subgroup analyses were performed to compare patients having undergone septal reduction therapy and received an ICD-unit with those who did not (supplemental material). Both septal reduction therapy and ICD-implantation were included as time dependent variables. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

We identified 3126 patients with a first-time diagnosis of HCM in the period 1 January 2007 to 31 December 2018 at an average age of 63 years. For the main analysis 1838 patients were excluded since they had only one outpatient visit with a diagnosis of HCM. In addition, 91 patients were excluded, since no controls met the strict predefined matching criteria with emphasis on comorbidities believed to have an impact on outcome. This resulted in a final study population of 1197 HCM patients (Fig. 1). Table 1 shows demographic characteristics at baseline (index date which was defines as the second outpatient visit with a diagnosis of HCM) for HCM patients and matched controls, respectively. HCM patients had more comorbidities as compared to matched controls, especially with respect to HCM-related conditions, such as heart failure and atrial fibrillation. Accordingly, the use of HCM-related medications such as betablockers, calcium channel blockers and oral anticoagulants was also significantly higher in the HCM group.

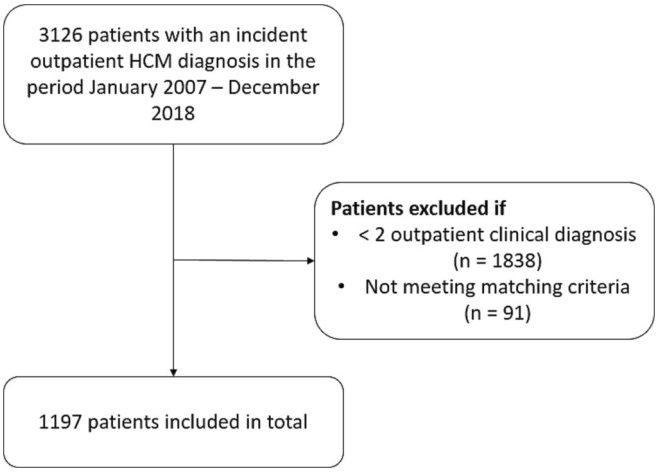

Fig. 1. Selection process. The figure illustrates the selection process by which the primary study population was reached.

Table 1
Baseline characteristics for patients with ≥2 outpatient visits for HCM and controls.

	HCM patients	Controls	P-value
Number, N	1197	3404	
Female, N (%)	514 (42.9)	1454 (42.7)	N/A
Patient age, years (IQR)	63.1 (52.1–72.1)	62.9 (51.2–71.6)	N/A
Comorbidities, N (%)			
Hypertension	272 (22.7)	672 (19.7)	N/A
Valvular disease	98 (8.2)	41 (1.2)	<0.001
Heart failure	163 (13.6)	124 (3.6)	<0.001
Stroke	79 (6.6)	168 (4.9)	0.03
Atrial fibrillation	230 (19.2)	192 (5.6)	<0.001
Ischemic heart disease	331 (27.7)	851 (25.0)	N/A
PVD	40 (3.3)	58 (1.7)	<0.001
Liver disease	27 (2.3)	48 (1.4)	0.05
Diabetes mellitus	94 (7.9)	234 (6.9)	N/A
Chronic renal failure	43 (3.6)	41 (1.2)	<0.001
Cancer	114 (9.5)	272 (8.0)	N/A
ICD	99 (8.9)	16 (0.5)	<0.001
COPD	58 (4.8)	119 (3.5)	N/A
Medications, N (%)			
Beta-blockers	729 (60.9)	542 (15.9)	<0.001
Calcium-antagonists	300 (25.1)	477 (14.0)	<0.001
Digoxin	23 (1.9)	43 (1.3)	0.1
RAS-inhibitors	469 (39.2)	844 (24.8)	<0.001
VKA	124 (10.4)	117 (3.4)	<0.001
DOAC	79 (6.6)	55 (1.6)	<0.001
Statins	420 (35.1)	910 (26.7)	<0.001
Loop diuretics	195 (16.3)	187 (5.5)	<0.001

IQR denotes interquartile range; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; HCM, hypertrophic cardiomyopathy; DOAC, direct-acting oral anticoagulants; PVD, peripheral vascular disease; RAS, renin-angiotensin-system; VKA, vitamin K-antagonist. Most but not all patients were able to be matched upon 3 controls.

3.2. Mortality after HCM diagnosis

The median follow-up time was 3.3 (25th–75th percentile 2.0–6.0) years for HCM patients and 3.5 (25th–75th percentile 2.1–6.2) years for controls. The crude mortality rate in HCM patients was significantly higher than in matched controls (Fig. 2). For HCM patients, one-, five- and 10-year rates of death were 3.0 % (95 % CI 2.1–4.1 %), 16.5 % (95 % CI 14.0–19.4 %) and 36.4 % (95 % CI 30.2–43.5 %), while the corresponding rates for matched controls were 1.7 % (95 % CI 1.3–2.2 %), 10.0 % (95 % CI 8.9–11.1 %) and 19.4 % (95 % CI 16.8–22.5 %). The unadjusted rate ratio of death compared to controls was 1.81 (95 % CI 1.50–2.18, $p = 0.001$). After adjusting for relevant comorbidities and use of medications, HCM was associated with an increased rate of all-cause death compared with the matched controls, HR 1.48 (95 % CI 1.18–1.84, p = 0.001). The unadjusted rate of death compared to controls was highest in the youngest age groups, but was significantly higher in patients compared to controls across all age groups (Fig. 3). Cardiovascular cause of death was more frequent in patients with HCM compared to matched controls (124 (68.9 %) vs. 123 (41.7 %, $p = 0.001$)).

3.3. Sensitivity analysis in patients with at least one outpatient visit

With regards to the sensitivity analysis, 211 patients were excluded since no controls met matching criteria, resulting in a final sensitivity population of 2915 HCM patients (supplemental table 2). We thus included 2915 patients with ≥1 outpatient visit (median age 64.0 [25th–75th percentile 51.7–74.2] years, 55.6 % male) (Supplemental table 2). In accordance with the main analysis, mortality rates were significantly higher in HCM patients than in matched controls. For HCM patients, one-, five- and 10-year rates of death were 4.1 % (95 % CI 3.5–4.9 %), 18.7 % (95 % CI 17.1–20.4 %) and 37.2 % (95 % CI 34.2–40.3 %), while the corresponding rates for matched controls were 1.6 % (95 % CI 1.3–1.9 %), 10.0 % (95 % CI 9.2–10.8 %) and 20.9 % (95 % CI 19.5–22.4 %) for matched controls, respectively (Fig. 4). After adjusting for relevant comorbidities and medications, HCM was associated with increased all-cause mortality (HR 1.79, 95 % CI 1.59–2.0, $p = 0.001$). To explore a possible reason for why patients were not seen more than once, we assessed mortality within one year and diagnoses related to HCM in this group of patients. Among the 1695 patients with only one outpatient visit with the HCM diagnosis, 105 (6.2 %) died within one year from first visit. Another 40 (2.4 %) had a follow-up visit with another or unspecified type of cardiomyopathy while 34 (2.0 %) had a follow-up visit with atrial fibrillation within a year from the index date and 36 (2.1 %) had an outpatient visit with a diagnosis of heart failure.

3.4. Subgroup analysis

Patients from tertiary center facilities having undergone either surgical myectomy or alcohol septal ablations ($n = 148$) during follow up and patients receiving an ICD-unit ($n = 189$) either before or after index date were compared with those who did not (supplemental material). When adjusting for relevant comorbidities and use of medication, septal reduction therapy was significantly associated to a better outcome with a HR of 0.40 ($p = 0.04$), while implantation of an ICD-unit was not associated to a significantly better outcome with a HR of 0.983 ($p = 0.92$).

3.5. Sex differences

Male HCM patients were seven years younger when diagnosed compared to female patients (median age 60.0 (25th–75th percentile 48.6–69.1 years) vs. 67.2 (25th–75th percentile 56.8–75.2 years, $p = 0.001$)) (Supplemental table 3). When including all patients with an ICD-unit, women were less likely to receive one than men (12.8 % vs. 18.0 %, $p = 0.02$). Among males with HCM, one-, five-, and 10-year mortality rates after diagnosis were 3.1 % (95 % CI 2.0–4.7 %), 14.4 % (95 % CI 11.4–18.0 %) and 31.8 % (95 % CI 24.3–40.8 %), while the corresponding rates for females with HCM were 2.8 % (1.7–4.8 %), 19.4 % (15.4–24.3 %) and 42.5 % (95 % CI 32.6–54.1 %). When adjusting for age, comorbidities and medications among HCM patients, female gender was not significantly associated with increased mortality compared to male gender (HR 1.2, 95 % CI 0.8–1.6, $p = 0.358$). Compared to their respective controls, the adjusted HR for male patients was 1.6 (95 % CI 1.2–2.2, $p = 0.004$) and the HR for female patients was 1.5 (95 % CI 1.1–2.1, $p = 0.014$).

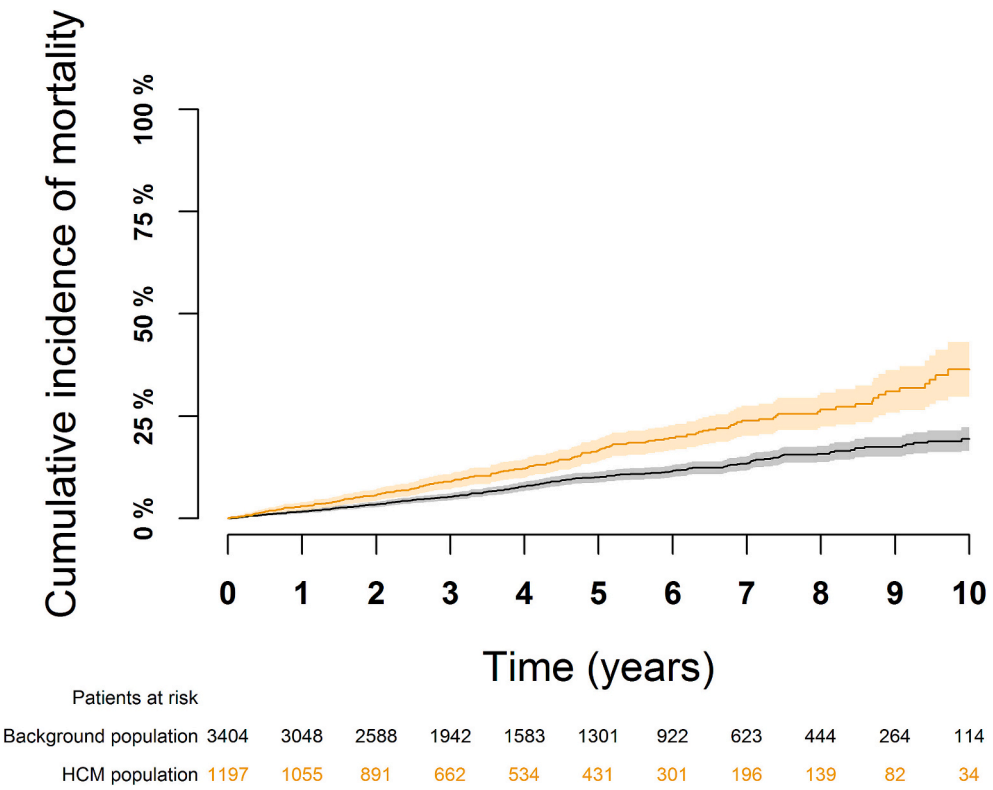

Fig. 2. Survival. The curve shows the unadjusted cumulative incidence of death in HCM patients (≥2 outpatient visits) (yellow) compared to the background population (black). The x-axis shows years after index, and the y-axis shows the cumulative incidence of death. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

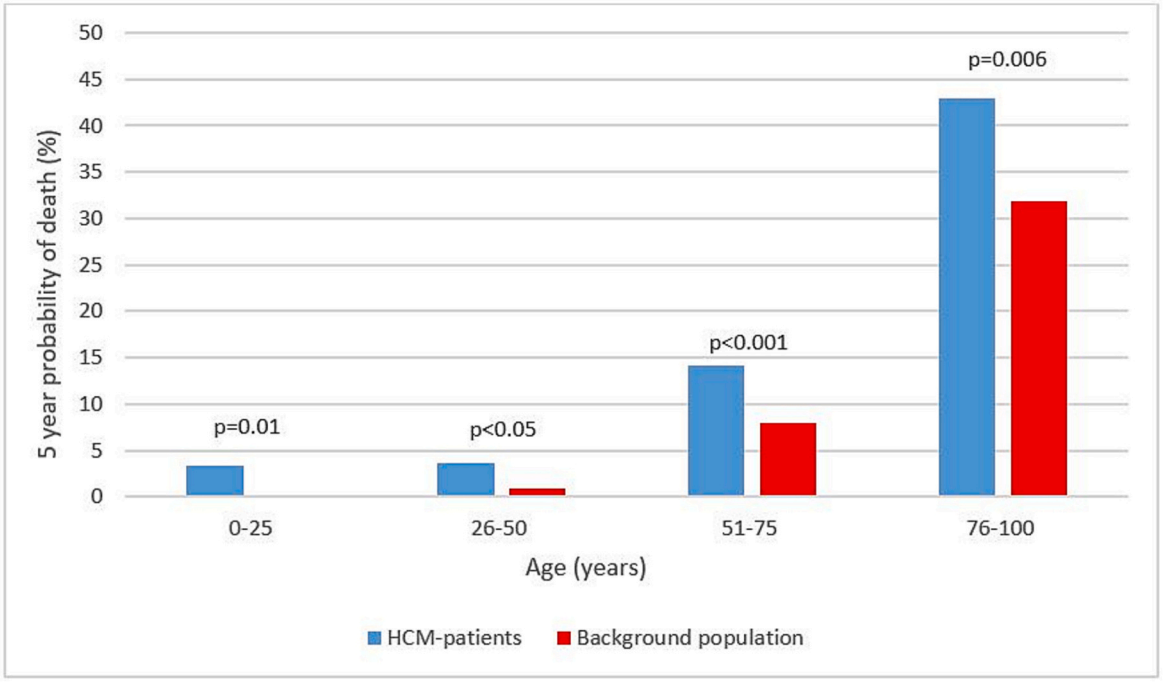

Fig. 3. Probability of death in different age groups. The figure shows the absolute risk of death in different age groups for HCM patients (blue) and the background population (red). The x-axis shows age in years at death, and the y-axis shows absolute five-year mortality rates. P are for log-rank test for difference. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In this study, we examined long-term mortality in a nationwide cohort of patients diagnosed with HCM compared to age- and sex-matched controls. There were four major findings: 1) A diagnosis with HCM was associated with a significantly higher mortality during a

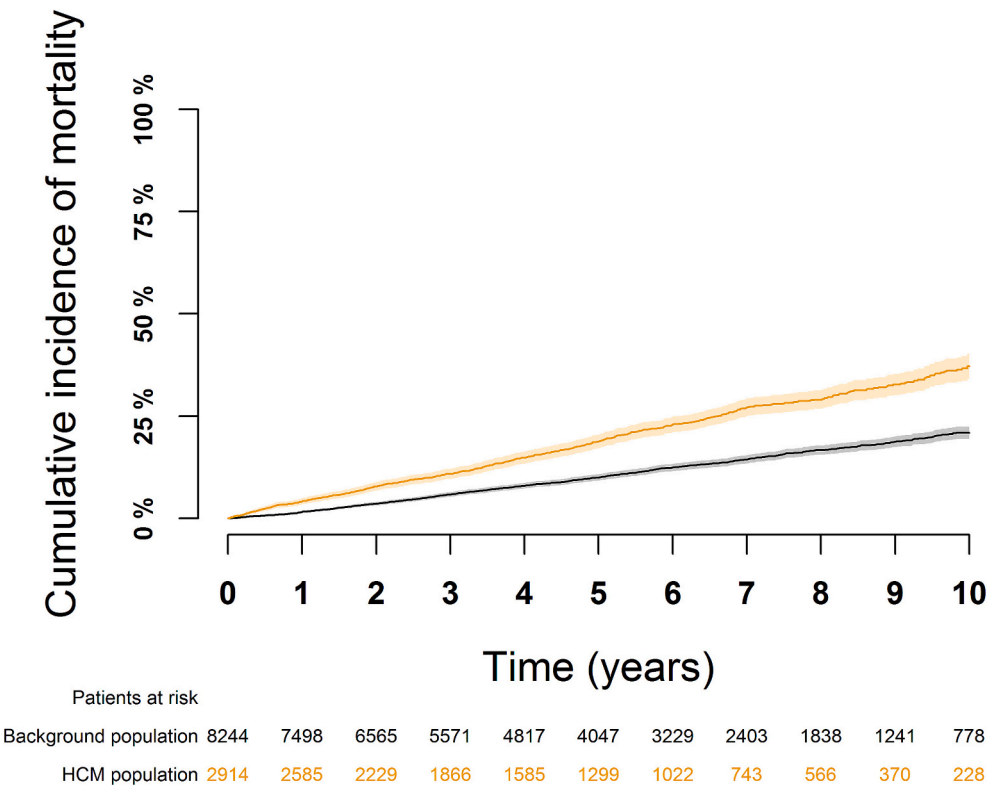

Fig. 4. Survival. The curve shows the unadjusted cumulative incidence of death in HCM patients (yellow) compared to the background population (black) in a sensitivity analysis of patients with ≥1 outpatient visit. The x-axis shows years after index, and the y-axis shows the cumulative incidence of death. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

median follow-up of 3.3 years compared with matched controls, even after adjustments for additional risk factors; 2) The increased mortality was significant across age groups; 3) The 10-year mortality rates after diagnosis of HCM at a median age of 63 years was 36 %; 4) Cardiovascular cause of death was more frequent among HCM patients than matched controls.

4.1. Mortality compared to the background population

Historically, patients with HCM have been considered to have an unfavorable prognosis with annual mortality rates of up to 6 % [21]. More recent studies investigating mortality in this population, as compared to background populations, are, however, conflicting [7–11]. It has been suggested that contemporary treatment strategies, including ICD implantation and septal reduction therapies have reduced the contemporary mortality rates to be similar to that of the background population [22]. In contrast, a cohort study from 2020 including 4893 patients from 7 different European referral centers reported significant excess mortality among HCM patients throughout the entire life course [23]. In accordance with the latter, the recent multinational Sarcomeric Human Cardiomyopathy Registry (SHaRe) found significantly increased mortality rates among HCM patients compared to an age-matched background US population.

In the present study, the mortality rates in HCM were increased as we identified a HR of 1.48 when comparing patients with HCM to controls matched on age, sex and significant comorbidities. The annual mortality rate was 3 % for HCM patients, compared to 2 % among controls. The annual mortality rates followed similar patterns to the findings from SHaRe, in which annual mortality rates were found to be 4 % in the age group 60–69 years [3]. In the present study, the mortality rates in HCM patients were increased compared to the background population across all age groups and, also in accordance with the SHaRe study, the relative mortality difference was most pronounced in the youngest age groups.

However, the population in our study was older than in previous studies. We included data from 2007 to 2018 and the older age at diagnosis may reflect a trend of increasing age at diagnosis over time demonstrated in recent literature [7,24]. Increasing awareness of the disease, family screening strategies identifying asymptomatic individuals as well as more sensitive and widespread use of diagnostic tools such as echocardiography may explain the trend. The nationwide setting, as opposed to studies from high-volume centers may also contribute to the difference in age. With this in mind, SHaRe did demonstrate that a majority of HCM-related complications occurred later in life, peaking between 50 and 70 years of age. Another important difference that must be kept in mind when comparing the results with the findings from ShaRe is that the HCM population in our study was compared not only to an age-matched background population but was matched also on significant comorbidities.

Previous studies have also investigated the cause of death among patients diagnosed with HCM, finding that the majority of patients (54.6 %–68.5 %) died from cardiovascular events [7,9,10]. Our study shares these findings as we found that 68.9 % of HCM patients, a number that was significantly higher than for matched controls (41.7 %), died from cardiovascular cause.

4.2. Subgroup analysis

Patients diagnosed at older ages have a higher risk of an overall adverse outcome dominated by heart failure, while the risk of malignant ventricular arrhythmias is very low in patients diagnosed >60 years of age [3]. The older age at diagnosis in our cohort may explain why septal reduction therapy but not the implantation of an ICD was associated to better survival in our cohort.

The ICD utilization was somewhat lower than reported in recent literature [25]. Unquestionably, this reflects an overall more conservative approach in European countries compared to the US. In addition,

specific to our study, the lower implantation rate most likely reflects an older age at diagnosis, resulting in a lower risk score according to the ESC 2014 HCM risk SCD algorithm.

4.3. Comparison of outcome in men and women

Sex differences in HCM have been assessed and debated in several studies [26–30]. In a nationwide setting, we found that women were diagnosed with HCM at a seven year older age than men, which is consistent with previous findings [26–30]. While it is agreed that women are diagnosed at a later age than men, results on adverse outcomes are not uniform. We observed higher unadjusted mortality rates after diagnosis in women, but when adjusting for age, comorbidities and medications among HCM patients, gender was not significantly associated with mortality. Some studies have reported equal mortality rates among men and women, while others have reported that female sex is associated with higher mortality, with one explanation being that women at time of diagnosis are more severely affected [26–30]. Again, previous studies have primarily represented single center experiences and the discrepancy in survival may be explained by selection bias, where women typically are referred to centers later than men [29]. In addition, we know from the literature that women diagnosed with acute myocardial infarction are less likely to receive invasive procedures such as ICDs for primary and secondary prevention of SCD, potentially leading to a higher burden of adverse events [31]. Our study corroborates these findings in the context of HCM as we reported higher utilization of ICDs in men than women.

One study showed that female sex was only a risk factor in patients below the age of 50 years [27]. Older age in our study compared to previous studies from tertiary centers may thus partially explain equal mortality rates between males and females.

4.4. Limitations

As an observational, registry-based study based on ICD-10 codes in the Danish National Registries, some limitations must be considered. Firstly, diagnosis of HCM can be difficult and requires exclusion of other causes of left ventricular hypertrophy, including mimics such as Fabry and amyloid, making room for erroneous diagnoses. The positive predictive value of the ICD-10 codes for HCM in the Danish National Patient Registry has, however, been shown to be 90 % for first time HCM [13]. We sought to enhance specificity by only including patients with a minimum of two outpatient visits for HCM in the main analysis. A consistent result when including patients with only at least one outpatient visit in a sensitivity analysis is also reassuring. Secondly, we acknowledge that the nationwide, registry-based approach limits our ability to characterize the cohort in detail. E.g., data on degree of outflow tract obstruction, medical doses and genetics were not available and we were unable to look into the more specific causes of death and the predictors of these outcomes. Besides, due to our limited diversity with a population consisting of mainly White patients, results may not be extrapolated to other populations. Thirdly, our matching approach for controls may underestimate the impact of HCM on mortality since receiving a comorbidity diagnosis requires controls to seek regular medical care. Fourth, and last, even by comparing with an age, sex -and comorbidity-matched background population and using adjusted analyses, several confounders may still be present.

5. Conclusion

Compared to matched controls from the background population, diagnosis with HCM was associated with a significant increase in mortality. Thus, even in the light of contemporary management strategies, including refined risk stratification and implantation of ICDs for the prevention of SCD, the relative burden of disease in HCM is substantial. This finding challenges recent suggestions of HCM patients having a normal life expectancy.

CRediT author statement

Mads-Holger Bang Jacobsen: Methodology, Software, Analysis, Investigation, Writing - Original draft. **Jeppe Kofoed Petersen**: Software, Analysis, Writing - Reviewing and Editing. **Daniel Modin**: Software, Writing - Reviewing and Editing. **Jawad Haider Butt**: Software, Writing - Reviewing and Editing. **Jens Jakob Thune**: Writing - Reviewing and Editing. **Henning Bundgaard**: Writing - Reviewing and Editing. **Christian Torp Pedersen**: Writing - Reviewing and Editing. **Lars Køber**: Writing - Reviewing and Editing. **Emil Loldrup Fosbøl**: Writing - Reviewing and Editing, Resources, Analysis. **Anna Axelsson Raja**: Project administration, Analysis, Conceptualization, Supervision.

Funding

The study was supported by Rigshospitalet Research Council. The funder had no part in the design of the study, the collection, analysis, or interpretation of data or publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100244.

References

[1] P.M. Elliott, et al., 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC), Eur. Heart J. 35 (39) (2014) 2733–2779.
[2] B.J. Maron, Clinical course and management of hypertrophic cardiomyopathy, N. Engl. J. Med. 379 (7) (2018) 655–668.
[3] C.Y. Ho, et al., Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe), Circulation 138 (14) (2018) 1387–1398.
[4] P.M. Shah, The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy, Circ. Res. 35 (2) (1974) p. suppl II:179-95.
[5] W. McKenna, et al., Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features, Am. J. Cardiol. 47 (3) (1981) 532–538.
[6] W.J. McKenna, J.E. Deanfield, Hypertrophic cardiomyopathy: an important cause of sudden death, Arch. Dis. Child. 59 (10) (1984) 971–975.
[7] F. Cecchi, et al., The italian registry for hypertrophic cardiomyopathy: a nationwide survey, Am. Heart J. 150 (5) (2005) 947–954.
[8] W. Ahmed, et al., Hypertrophic cardiomyopathy in the saudi arabian population: clinical and echocardiographic characteristics and outcome analysis, J. Saudi Heart Assoc. 26 (1) (2014) 7–13.
[9] M.S. Maron, et al., Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 67 (12) (2016) 1399–1409.
[10] N. Cardim, et al., The Portuguese registry of hypertrophic cardiomyopathy: overall results, Rev. Port. Cardiol. 37 (1) (2018) 1–10.
[11] N. Songsirisuk, et al., Modes of death and clinical outcomes in adult patients with hypertrophic cardiomyopathy in Thailand, BMC Cardiovasc. Disord. 19 (1) (2019) 1.
[12] <The Danish Health Care System.pdf>.
[13] J. Sundbøll, et al., Positive predictive value of cardiovascular diagnoses in the danish National Patient Registry: a validation study, BMJ Open 6 (11) (2016), e012832.
[14] H.W. Kildemoes, H.T. Sørensen, J. Hallas, The Danish National Prescription Registry, Scand. J. Public Health 39 (7 Suppl) (2011) 38–41.

[15] K. Helweg-Larsen, The Danish register of causes of death, Scand. J. Public Health 39 (7 Suppl) (2011) 26–29.
[16] M. Schmidt, L. Pedersen, H.T. Sørensen, The danish civil registration system as a tool in epidemiology, Eur. J. Epidemiol. 29 (8) (2014) 541–549.
[17] D. Gaist, H.T. Sørensen, J. Hallas, The danish prescription registries, Dan. Med. Bull. 44 (4) (1997) 445–448.
[18] T.K. Schramm, et al., Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people, Circulation 117 (15) (2008) 1945–1954.
[19] J.B. Olesen, et al., Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study, BMJ 342 (2011), d124.
[20] Biomedical Statistics and Informatics software packages, Available from, http://bioinformaticstools.mayo.edu/research/gmatch/, 2007.
[21] P.M. Elliott, et al., Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy, Heart 92 (6) (2006) 785–791.
[22] B.J. Maron, et al., How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50 years of clinical research and practice, JAMA Cardiol. 1 (1) (2016) 98–105.
[23] M. Lorenzini, et al., Mortality among referral patients with hypertrophic cardiomyopathy vs the general european population, JAMA Cardiol. 5 (1) (2020) 73–80.
[24] M. Canepa, et al., Temporal trend of age at diagnosis in hypertrophic cardiomyopathy: an analysis of the international sarcomeric human cardiomyopathy registry, Circ. Heart Fail. 13 (9) (2020), e007230.
[25] V. Nauffal, et al., Worldwide differences in primary prevention implantable cardioverter defibrillator utilization and outcomes in hypertrophic cardiomyopathy, Eur. Heart J. 42 (38) (2021) 3932–3944.
[26] I. Olivotto, et al., Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 46 (3) (2005) 480–487.
[27] Y. Wang, et al., Female sex is associated with worse prognosis in patients with hypertrophic cardiomyopathy in China, PLoS One 9 (7) (2014), e102969.
[28] J.B. Geske, et al., Women with hypertrophic cardiomyopathy have worse survival, Eur. Heart J. 38 (46) (2017) 3434–3440.
[29] E.J. Rowin, et al., Impact of sex on clinical course and survival in the contemporary treatment era for hypertrophic cardiomyopathy, J. Am. Heart Assoc. 8 (21) (2019), e012041.
[30] N.K. Lakdawala, et al., Associations between female sex, sarcomere variants, and clinical outcomes in hypertrophic cardiomyopathy, Circ. Genom Precis. Med. 14 (1) (2021), e003062.
[31] L.H. Curtis, et al., Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death, JAMA 298 (13) (2007) 1517–1524.