Time to diagnosis in hypertrophic cardiomyopathies and the association with adverse outcomes post-diagnosis

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Introduction

- Hypertrophic cardiomyopathy (HCM) is a cardiac disease (which may have a genetic cause), characterized by disorganized architecture of the myocardium and left ventricular hypertrophy and can involve left ventricular outflow tract obstruction, with obstructive and non-obstructive subtypes[1]
- The prevalence of HCM can vary, with one estimate at 1 in 500; this is likely to be an underestimate owing to a proportion of patients being asymptomatic or having non-specific symptom burden[2]
- Patients with HCM can have variable symptomatic burden and outcomes, from asymptomatic disease with normal life expectancy, to heart failure or even sudden cardiac death (SCD)[3]
- Other symptoms include shortness of breath, light-headedness, chest pain, and palpitations, which are often associated with ventricular and supraventricular arrhythmias[4]
- The pathway to diagnosis often includes genetic screening or examination of family history when a patient presents with cardiovascular (CV)-related symptoms (e.g. within a primary care setting or accident and emergency). Given that initial symptoms are common to many other conditions, patients often have to navigate through multiple layers of the healthcare system and can be misdiagnosed before diagnostic tests – such as echocardiograms or cardiac magnetic resonance imaging – are performed to confirm a diagnosis of HCM[5]
- There is a lack of research investigating the association of delayed time to diagnosis (TTD) and outcomes at and after diagnosis

Objectives

- The objective of this study is to analyze the TTD following referral and its association with time to adverse clinical outcomes post-diagnosis in a single specialist center in the UK

Methods

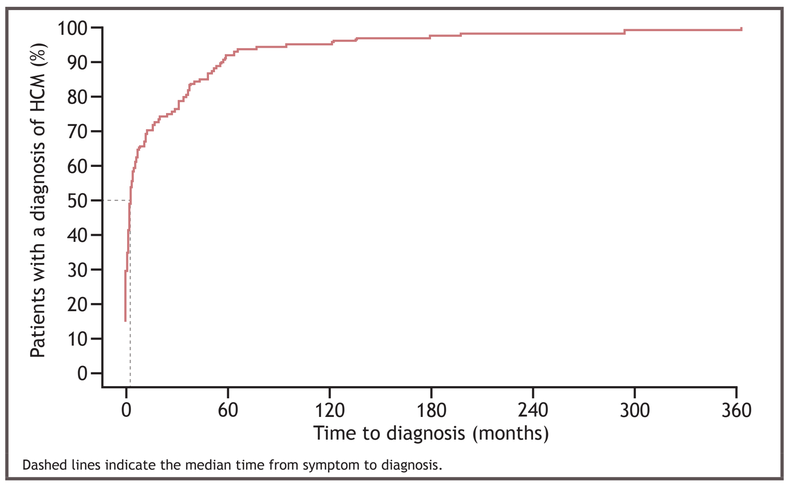
- A retrospective, chart review study was performed that utilized internal patient records from adults (≥ 18 years) diagnosed with HCM and its subtypes within the University Hospital Coventry and Warwickshire (UHCW) NHS Trust, a large tertiary teaching hospital in the UK
- Adult patients diagnosed with HCM between 2008 and 2022 were included
- The study was conducted in accordance with the International Society of Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices
- Data extraction was performed by research nurses employed by the UHCW NHS Trust and data were obtained from an internal electronic patient records system. Patient clinical letters were reviewed manually and relevant information was extracted. Efforts were made to obtain relevant patient records from other trusts, where applicable. All relevant information was abstracted and compiled into a database used for these analyses. Validation was performed on a select random subset of patient records through adjudication
- The index date, per patient, was the date at which 2 independent clinicians identified an event that they agreed triggered the referral pathway to diagnosis; this event was referred to as the trigger event (e.g. exertional dyspnea or palpitations). TTD was defined as the time from the index date to diagnosis of HCM or its subtypes
- Patients with a TTD lower than the median were included in the early diagnosis subgroup, and patients with a TTD later than the median were included in the late diagnosis subgroup

Results

Baseline characteristics and time to diagnosis

- A total of 167 patients met the study inclusion criteria; 128 patients had a clinically agreed trigger event and were included in the study cohort. The other 39 patients were excluded because a trigger event could not be defined (n = 31), data were missing (n = 3), or because they moved out of the care of the UHCW NHS Trust (n = 5)
- Of the 128 patients, 62.5% were male, 79.7% were White, and the mean (standard deviation; SD) age at diagnosis was 56.8 (15.4) years (**Table 1**)
- Unlike other studies, the majority (58.6%) of patients had the non-obstructive HCM phenotype[6]
- Median TTD was 2.62 (interquartile range: 0.10–26.37) months (**Figure 1**), with 31.3% and 25.8% of patients with a TTD of greater than 1 and 2 years, respectively. Less than 10% of patients had a TTD of greater than 5 years, up to a maximum of 30 years
- When stratifying by patient's TTD, females were significantly more likely to receive a late diagnosis than males (46.9% vs 28.1%, *P* = 0.028)

Figure 1. Kaplan-Meier plot of TTD (between trigger event and HCM diagnosis)



Dashed lines indicate the median time from symptom to diagnosis.

Table 1. Baseline characteristics of the study cohort with a trigger event, overall and stratified by median TTD

	All patients (n = 128)	Early diagnosis[a] (n = 64)	Late diagnosis[a] (n = 64)	*P* value[b]
Sex, n (%)				
Male	80 (62.5)	46 (71.9)	34 (53.1)	**0.028**
Female	48 (37.5)	18 (28.1)	30 (46.9)	
Phenotype, n (%)				
Obstructive	53 (41.4)	26 (40.6)	27 (42.2)	0.858
Non-obstructive	75 (58.6)	38 (59.4)	37 (57.8)	
Ethnicity,[c] n (%)				
White British	99 (78.6)	48 (77.4)	51 (79.7)	0.760
White Other	3 (2.4)	2 (3.2)	1 (1.6)	
Asian	12 (9.5)	4 (6.5)	8 (12.5)	
Black	6 (4.8)	5 (8.1)	1 (1.6)	
Other	6 (4.8)	3 (4.8)	3 (4.7)	
Age at diagnosis (years)				
N	128	64	64	0.162[d]
Mean (SD)	56.8 (15.4)	54.4 (17.6)	59.2 (12.54)	
Median (LQ, UQ)	56.5 (46.0, 68.0)	55.5 (41.0, 68.0)	60.0 (52.0, 67.8)	
Minimum - Maximum	19 - 86	19 - 86	29 - 86	
Smoking status, n (%)				
Status recorded?	124	61	63	0.617
Non-smoker	68 (54.8)	36 (59.0)	32 (50.8)	
Ex-smoker	35 (28.2)	15 (24.6)	20 (31.7)	
Smoker	21 (16.9)	10 (16.4)	11 (17.5)	
BMI at diagnosis (kg/m^2)				
N	64	36	28	0.107[d]
Mean (SD)	31.0 (6.57)	29.7 (5.38)	32.8 (7.56)	
Median (LQ, UQ)	30.3 (26.7, 33.8)	29.6 (25.4, 32.4)	31.6 (26.8, 36.0)	
Minimum - Maximum	21 - 50.9	21 - 47.2	22.3 - 50.9	
BMI category at diagnosis, n (%)				
BMI recorded?	64	36	28	0.572
Normal	13 (20.3)	9 (25.0)	4 (14.3)	
Overweight	17 (26.6)	9 (25.0)	8 (28.6)	
Obese	34 (53.1)	18 (50.0)	16 (57.1)	
Family history of HCM, n (%)				
History recorded?	83	42	41	0.231
Yes	21 (25.3)	13 (31.0)	8 (19.5)	
No	62 (74.7)	29 (69.0)	33 (80.5)	
Family members screened, n (%)				
Screening status recorded?	69	40	29	0.826
Yes	37 (53.6)	21 (52.5)	16 (55.2)	
No	32 (46.4)	19 (47.5)	13 (44.8)	
Family history of SCD or SCA, n (%)				
History recorded?	94	47	47	0.636
Yes	24 (25.5)	13 (27.7)	11 (23.4)	
No	70 (74.5)	34 (72.3)	36 (76.6)	

[a]Stratified by ± median TTD of 2.62 months; [b]Chi-squared test unless specified otherwise; [c]The ethnicity of 2 patients was not recorded; [d]Mann-Whitney U test.
Bold indicates significance at *P* < 0.05.
BMI, body mass index; LQ, lower quartile; SCA, sudden cardiac arrest; SCD, sudden cardiac death; TTD, time to diagnosis; UQ, upper quartile.

Clinical presentation at time of diagnosis

- A significant association for late versus early diagnosis was observed in both setting of and reason for diagnosis (*P* < 0.001 and *P* = 0.007, respectively). Patients who received a later diagnosis (vs early) were more likely to be diagnosed as an outpatient (92.1% vs 44.4%) and referred based on a cardiovascular trigger event (93.8% vs 76.6%) (**Table 2**)
- Late diagnosis was also associated with presentation of presyncope (34.4% vs 18.8%; *P* = 0.045), syncope (20.3% vs 7.8%; *P* = 0.042) and palpitations (31.3% vs 15.6%; *P* = 0.037)
- Conversely, early diagnosis (vs late) was more likely to be incidental after presenting for another reason (17.2% vs 4.7%) and accounted for all observed out-of-hospital cases of cardiac arrest (9.4% vs 0.0%; *P* = 0.028)
- Overall, ≥ 90% of patients were assigned New York Heart Association (NYHA) class I or II at presentation of symptoms or at diagnosis, of which approximately half were NYHA class I, with no association to TTD

Figure 2. Kaplan-Meier plots of time from diagnosis to (A) hospitalization and (B) death (stratified by median TTD)

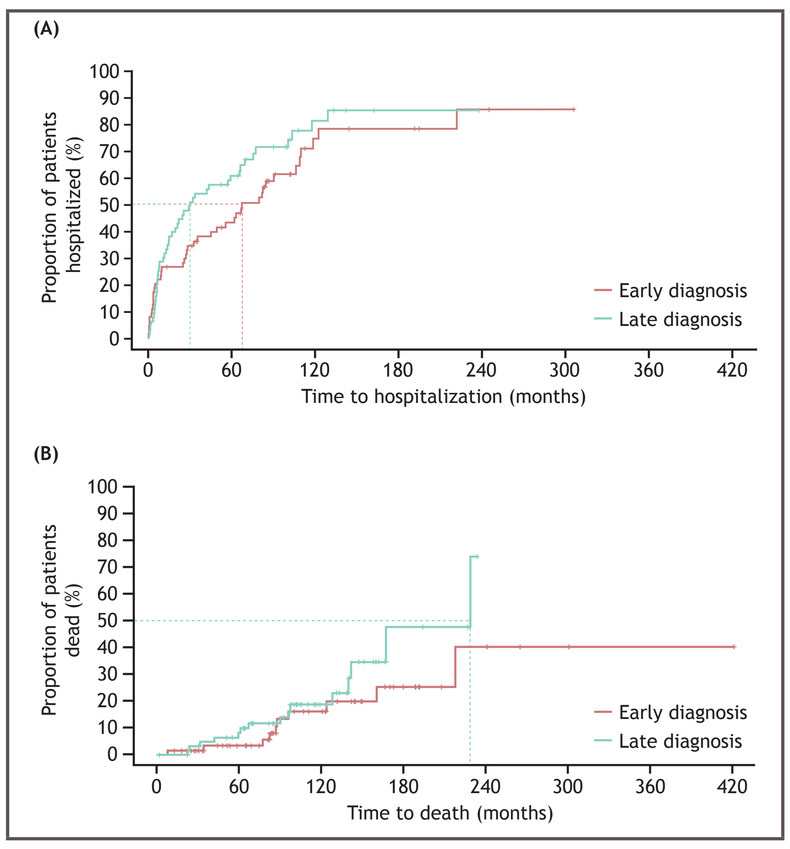


Table 2. Clinical presentation at time of diagnosis, overall and stratified by median TTD

	All patients (n = 128)	Early diagnosis[a] (n = 64)	Late diagnosis[a] (n = 64)	*P* value[b]
Setting of diagnosis, n (%)				
Setting recorded?	126	63	63	**< 0.001**
Outpatient	86 (68.3)	28 (44.4)	58 (92.1)	
Inpatient	40 (31.7)	35 (55.6)	5 (7.9)	
Reason for diagnosis, n (%)				
Reason recorded?	128	64	64	**0.007[c]**
Cardiovascular symptoms	109 (85.2)	49 (76.6)	60 (93.8)	
Family screening	5 (3.9)	4 (6.3)	1 (1.6)	
Incidental finding	14 (10.9)	11 (17.2)	3 (4.7)	
Clinical presentation at diagnosis, n (%)				
Chest pain	64 (50.0)	35 (54.7)	29 (45.3)	0.289
Shortness of breath	53 (41.4)	21 (32.8)	32 (50.0)	**0.048**
Systolic murmur	44 (34.4)	17 (26.6)	27 (42.2)	0.063
Presyncope	34 (26.6)	12 (18.8)	22 (34.4)	**0.045**
Palpitations	30 (23.4)	10 (15.6)	20 (31.3)	**0.037**
Syncope	18 (14.1)	5 (7.8)	13 (20.3)	**0.042**
Peripheral swelling	8 (6.3)	2 (3.1)	6 (9.4)	0.273[c]
Fatigue	6 (4.7)	4 (6.3)	2 (3.1)	0.680[c]
Out-of-hospital cardiac arrest	6 (4.7)	6 (9.4)	0 (0)	**0.028[c]**
Psychiatric symptoms	3 (2.3)	2 (3.1)	1 (1.6)	1.000[c]
Other	27 (21.1)	15 (23.4)	12 (18.8)	0.516
NYHA class at first symptoms, n (%)				
Class recorded?	100	50	50	0.552[c]
Class I	56 (56.0)	27 (54.0)	29 (58.0)	
Class II	38 (38.0)	21 (42.0)	17 (34.0)	
Class III	6 (6.0)	2 (4.0)	4 (8.0)	
Class IV	0 (0)	0 (0)	0 (0)	
NYHA class at diagnosis, n (%)				
Class recorded?	100	50	50	0.356
Class I	45 (45.0)	26 (52.0)	19 (38.0)	
Class II	45 (45.0)	19 (38.0)	26 (52.0)	
Class III	10 (10.0)	5 (10.0)	5 (10.0)	
Class IV	0 (0)	0 (0)	0 (0)	

[a]Stratified by ± median TTD of 2.62 months; [b]Chi-squared test unless specified otherwise; [c]Fisher's exact test.
Bold indicates significance at *P* < 0.05.

Time to diagnosis and association with time to adverse clinical outcomes post-diagnosis

- The time between diagnosis and an adverse clinical outcome (including hospitalization and death) was shorter in patients who received a late diagnosis (vs early) (**Figure 2**)
- Patients with a later diagnosis after the appearance of first symptoms had a shorter time to hospitalization (hazard ratio [HR]: 1.52; *P* = 0.097) and age-adjusted death (HR: 2.44; *P* = 0.050), based on a Cox regression model

Limitations

- The study includes data from a single center in the UK Midlands; as such, generalizability to other regions or settings cannot be guaranteed
- As a retrospective study, the results are dependent on the quality of data that has been recorded and as such, has limitations similar to other studies involving retrospective data extraction
- Data were compiled by 2 research nurses, and this involved the interpretation of data within patient notes. Although validation was performed by blinded cross-checking and alignment of a select series of extractions, interpretation in some cases may have been inconsistent owing to subjectivity
- Trigger events in the study were based on clinicians' agreement of patient records and, as such, is entirely dependent on a patient's full history being recorded. It is likely that some patients presented at an earlier point than the first recorded entry, especially where referral or patient information provided to the UHCW NHS Trust was limited and, as such, TTD is likely to be an underestimate
- A median time was used to define a 'late' diagnosis; this is specific to the cohort in question. Expert agreement on what constitutes a 'late' diagnosis should be sought

Conclusions

- Within this study, later TTD from presentation was associated with a shorter time to adverse clinical outcomes and death
- Those who received an early diagnosis were also more likely to have received a diagnosis incidentally, with severe presentations at diagnosis, such as chest pain or out-of-hospital cardiac arrest
- Consistent with other studies, females were more likely to receive a diagnosis later than males, highlighting a key inequity that needs addressing[7]
- This study is one of the first to highlight in this patient population, that the TTD of HCM can be substantial, and that improved diagnostic pathways and clinical management are crucial to improve patient outcomes at the time of and following diagnosis

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Disclosures

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