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Published in:
ESC Heart Failure

DOI:
10.1002/ehf2.14073

ESC HEART FAILURE
ESC Heart Failure ()
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14073

ORIGINAL ARTICLE

Blood-based biomarkers for the prediction of hypertrophic cardiomyopathy prognosis: a systematic review and meta-analysis

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Abstract

Aims Hypertrophic cardiomyopathy (HCM) is the most prevalent monogenic heart disease. HCM is an important cause of sudden cardiac death and may also lead to outflow tract obstruction and heart failure. Disease severity is highly variable and risk stratification remains limited. Therefore, we aimed to review current knowledge of prognostic blood-based biomarkers in HCM.

Methods and results A systematic literature search was performed on PubMed, Embase, and the Cochrane library to identify studies assessing plasma or serum biomarkers for outcomes involving malignant ventricular arrhythmia, outflow tract obstruction, and heart failure. Risk of bias was assessed using the QUIPS tool. Meta-analyses were performed using the random effects method. A total of 26 unique cohort studies assessing 42 biomarkers were identified. Overall risk of bias was moderate. Thirty-two biomarkers were significantly associated to an HCM outcome in at least one study (nine biomarkers in at least two studies). In pooled analyses, cardiovascular mortality was predicted by N-terminal prohormone of brain natriuretic peptide (hazard ratio [HR] 5.38 per log[pg/mL], 95% confidence interval [CI] 2.07–14.03, $P < 0.001$, $I^2 = 0\%$) and high-sensitivity C-reactive protein (HR 1.30 per μg/mL, 95% CI 1.00–1.68, $P = 0.05$, $I^2 = 78\%$), all-cause mortality by low-density lipoprotein cholesterol (HR 0.63 per μmol/mL, 95% CI 0.49–0.80, $P < 0.001$, $I^2 = 0\%$), and a combined congestive heart failure, malignant ventricular arrhythmia, and stroke outcome by high-sensitivity cardiac troponin T (pooled HR 4.19 for ≥0.014 ng/mL, 95% CI 2.22–7.88, $P < 0.001$, $I^2 = 0\%$). Quality of evidence was low–moderate.

Conclusions Several blood-based biomarkers were identified as predictors of HCM outcomes. Additional studies are required to validate their prognostic utility within current risk stratification models.

Keywords Hypertrophic cardiomyopathy; Prognosis; Heart failure; Sudden cardiac death; Biomarker; Systematic review

Received: 13 March 2022; Revised: 7 June 2022; Accepted: 27 June 2022
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Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of the ventricular wall not explained by abnormal loading conditions. It is primarily caused by pathogenic variants in genes encoding proteins in the cardiac sarcomere.[1,2] The prevalence of HCM is estimated at 1:500 worldwide,[3] making it the most common monogenic heart disease. HCM is a major cause of sudden cardiac death (SCD)[4] and may also lead to left ventricular outflow tract (LVOT) obstruction, atrial fibrillation (AF) and thromboembolic stroke, and end-stage heart failure (HF).[1] However, clinical severity is highly variable

with a low overall mortality in HCM patients,[5] highlighting the need for risk stratification.

Currently, use of risk stratification models, such as the European Society of Cardiology HCM Risk-SCD calculator, is recommended to identify patients whom may benefit from a prophylactic implantable cardioverter-defibrillator (ICD).[1,2,6,7] However, these models still have room for improvement in order to minimize the number of patients experiencing SCD who do not fulfil criteria for ICD implantation and to limit ICD implantations in patients who will not develop malignant ventricular arrhythmia (MVA).[7] Moreover, there are no established prognostic models for LVOT obstruction and HF in HCM patients.

Serum and plasma biomarkers are indicators of biological processes[8] extracted from blood and objectively measured using laboratory techniques. They are routinely used in diagnosis and management of patients with HF and myocardial infarction, including brain natriuretic peptide (BNP) or N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and high-sensitivity cardiac troponin I/T (hs-cTnI/hs-cTnT), respectively.[9,10] Likewise, these biomarkers have been assessed in HCM,[11] as well as other biomarkers related to cardiac stress, fibrosis, inflammation, endothelial function, coagulation and platelet aggregation, apoptosis, and energy metabolism.[12] However, no comprehensive overview of the prognostic utility of these biomarkers currently exists and their level of evidence has not yet been systematically assessed.

In this systematic review and meta-analysis, we provide an overview of prognostic serum and plasma biomarkers in HCM and assess the available evidence, focusing on outcomes involving MVA, LVOT obstruction and HF.

Methods

Search strategy

Two complementary systematic searches were performed on PubMed, Embase, and the Cochrane library on 11 October 2021. The first was aimed at including studies assessing a variety of biomarkers using broad search terms, that is, hypertrophic cardiomyopathy and biomarker, including abbreviations and synonyms. The second search focused on identifying studies involving specific biomarkers, with search terms including hypertrophic cardiomyopathy and specific biomarker names, for example, BNP and uric acid. The search terms are provided in Supporting Information, *Table S1*. Reference lists of included articles and previously published reviews were screened for additional relevant studies. References were managed using EndNote (Version X7, Thomson Reuters now Clarivate Analytics, Philadelphia, PA, USA, 2013).

Study eligibility and definitions

Studies were assessed for eligibility by two independent authors (M. J. and S. A.) using Rayyan QCRI (Qatar Computing Research Institute, Ar-Rayyan, Qatar, available at https://rayyan.qcri.org/). Discrepancies were resolved through discussion.

Cohort studies were considered eligible for inclusion when ≥1 plasma or serum biomarker, obtained from a peripheral (venous) blood sample, was associated to one or more predefined HCM-related outcomes. The outcomes of interest were HF, MVA, and LVOT obstruction. Additionally, composite endpoints including surrogate endpoints for HCM progression, including AF, unexplained syncope, non-sustained ventricular tachycardia (nsVT), ICD implantation, thromboembolic stroke, and all-cause mortality, alongside components of our co-primary outcomes were included. Eligible statistical parameters included means or medians of continuous biomarker values, odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs). Details on study eligibility and definitions are provided in Supporting Information, Methods.

Studies were assessed for potential cohort overlap by examining study sites and inclusion periods. When a biomarker was associated to the same outcome in multiple studies with potential cohort overlap, only the result from the study with the largest sample size was included.

Quality assessment

The Quality in Prognostic Studies tool[13] was used to assess the risk of bias of individual studies. Using this tool, studies were systematically categorized into 'low', 'moderate', and 'high' bias risk across six predefined areas important to observational prognostic studies (i.e. study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). Study quality was assessed by two independent authors (M. J. and S. A.), and discrepancies were resolved through discussion.

Statistical analysis

Missing summary data were calculated where applicable, as described in Supporting Information, Methods. Data are presented as means ± standard deviations, adjusted means (standard error), medians (interquartile range), or counts (percentages). Quantitative assessment consisted of meta-analyses of studies reporting HR and adjusted HR (aHR) to allow comparison of studies with different follow-up durations. Pooled analyses were performed on unadjusted HR with reported 95% confidence intervals (CIs) using an inverse variance, random effects model. The I^2 index

DOI: 10.1002/ehf2.14073

was used to assess statistical heterogeneity, with a value <25% indicating low, 25–75% indicating moderate, and >75% indicating high degrees of heterogeneity.[14] Analyses were conducted in Review Manager Version 5.4 (The Cochrane Collaboration, 2020).

Results

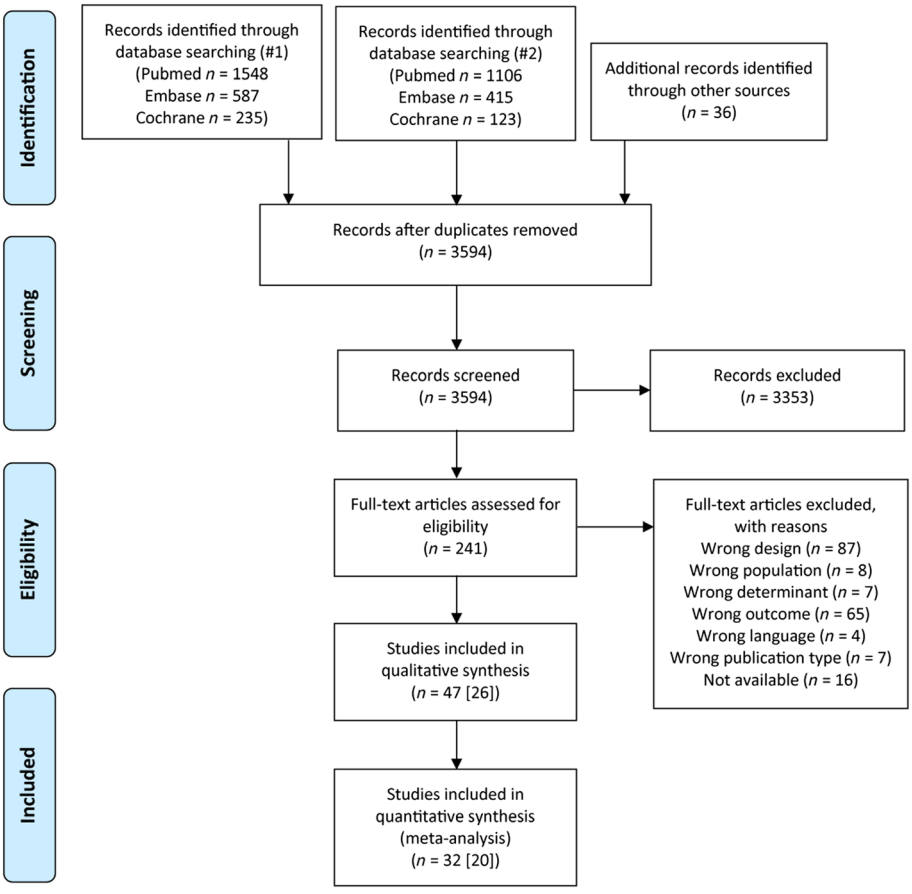
A flow diagram of study inclusion is provided in *Figure 1*.[15] In total, 48 studies published between June 2001 and August 2021 were included in the qualitative assessment. An overview of the included studies is provided in *Table 1*; detailed inclusion and exclusion criteria and biomarker platforms are provided in Supporting Information, *Table S2*. The full reference list is provided in Supporting Information, References. An overview of the studies excluded during full-text assessment and the reason for exclusion is provided in Supporting Information, *Table S3*.

After screening for potential cohort overlap, 26 unique studies were identified. Hereafter, only totals of studies without potential overlap are reported with references of overlapping studies indicated with a forward slash (/). The median cohort size was 116 subjects (interquartile range 93–411) and the median follow-up duration was 3.8 years (interquartile range 2.1–6.1 years).

Specific HF, MVA, and LVOT obstruction outcomes were assessed in 14 studies; combinations with surrogate endpoints were assessed in three studies. An overview of the biomarkers assessed for specific HCM outcomes and combinations with surrogate endpoints is provided in *Table 2*.

Combined HCM progression outcomes (composite endpoints of HF, MVA, and/or LVOT obstruction) were described in four studies. Combinations of combined HCM progression outcomes and surrogate endpoints were reported in 19 studies. An overview of the biomarkers assessed for combined HCM progression outcomes and combinations with surrogate endpoints is provided in *Table 3*.

Figure 1 Study inclusion flow diagram. Flow diagram[15] of study inclusion showing the reasons for exclusion during full-text screening. The numbers within square brackets indicate the number of studies without potential cohort overlap.



DOI: 10.1002/ehf2.14073

Table 1 Overview of included studies

Study (reference)	Design	Domain	*N* subjects	Age (years)	Follow-up (years)	Biomarker(s)	Outcome(s)
Aizawa 2019 (S1)	Retrospective monocentre	HCM	434	59.1 ± 13.9	8.4 ± 6.7	BNP, creatinine, eGFR	Systolic dysfunction
Ayca 2015 (S2)	Prospective monocentre	HCM (outpatient) excluding ACE-inhibitor treatment	49	38 ± 22	1.5	BNP, TGF-β1	Congestive HF MVA Congestive HF/MVA/surrogate End-stage HF/MVA/surrogate
Begue 2020 (S3)	Consecutive multicentre	HCM (outpatient)	357	52 (36–65)	1.9 (1.1–2.5)	MR-proANP, NT-proBNP	Congestive HF/MVA/surrogate
Bi 2021 (S4)	Consecutive monocentre	HOCM undergoing myectomy	55	45.9 ± 14.8	3.7 (3.5–3.9)	PICP/ICTP ratio MMP-2/TIMP1 ratio	Congestive HF/MVA/surrogate
Coats 2013 (S5)	Prospective monocentre	HCM	847	53 ± 15 ≥ 16	3.5 (2.5–4.5)	NT-proBNP	End-stage HF MVA End-stage HF/MVA/surrogate
D'Amato 2013 (S6)	Consecutive monocentre	HCM (outpatient) excluding LVEF < 50%	183	50 ± 17	3.9 ± 2.8	NT-proBNP	Congestive HF/systolic dysfunction/surrogate End-stage HF/MVA/surrogate
Ekizler 2019 (S7)	Retrospective consecutive monocentre	HCM (inpatient)	411	51.9 ± 15.1	6.0 (5.0–8.0)	Creatinine, glucose, haemoglobin, HDL-cholesterol, hs-CRP, lymphocyte, monocyte, neutrophil, platelet and white blood cell count, monocyte : HDL-cholesterol ratio, TSH, uric acid	End-stage HF/MVA/surrogate
Gastl 2020 (S8)	Retrospective monocentre	HCM (outpatient) undergoing CMR excluding ICD/pacemaker	91	49.9 ± 16.8	3.4 ± 2.6	hs-cTnT	Congestive HF/systolic dysfunction MVA/surrogate
Geske 2013 (S9)	Retrospective monocentre	HCM	772	52 ± 16	1.7 ± 1.9	BNP	SRT SRT/end-stage HF/MVA/surrogate End-stage HF/MVA/surrogate
Gommans 2021 (S10)	Prospective consecutive multicentre	HCM (outpatient) with hs-cTnT measurement	135	54 ± 14	5.0 (4.9–5.1)	Hs-cTnT	Congestive HF/MVA/surrogate
Hamada 2016 (S11)	Prospective monocentre	HCM excluding HF, LVEDD ≥ 50 mm, LVFS < 30%, atrial fibrillation, notched R wave on ECG	77	54 ± 12	17.8 ± 4.0	CK-MB	Congestive HF End-stage HF MVA

(*Continues*)

Table 1 (continued)

Study (reference)	Design	Domain	*N* subjects	Age (years)	Follow-up (years)	Biomarker(s)	Outcome(s)
Hasler 2016 (S12)	Retrospective consecutive monocentre	HCM (outpatient)	91	40 ± 18 range 18–79	11.5 range 0.5–35	Hs-cTnT	Congestive HF/systolic dysfunction MVA Congestive HF/systolic dysfunction/MVA/surrogate
Hu 2016 (S13)	Prospective monocentre	HCM	107	[52.4 ± 15.1]	Range NA–7	Galectin-3	Congestive HF/MVA/surrogate
Imazu 2020 (S14)	Retrospective consecutive monocentre	HCM after HF hospitalization	25	65 (52–69)	[5.3]	BNP eGFR Indoxyl sulfate	Congestive HF/MVA/surrogate
Kitaoka 2001 (S15)	Consecutive monocentre	HCM excluding systolic dysfunction and severe mitral regurgitation due to chordal rupture	46	[59 ± 13]	2.1 ± 0.9	ANP	HF (not defined)/MVA/surrogate
Kitaoka 2010 (S16)	Retrospective monocentre	HCM	41	57 ± 15	3.2 ± 0.7	BNP, MMP-2, MMP-9, TIMP1	Congestive HF
Kitaoka 2011 (S17)	Retrospective monocentre	HCM excluding LVFS $< 25\%$	130	60 ± 16	3.7 ± 1.7	BNP	Congestive HF/MVA/surrogate
Kitaoka 2012 (S18)	Retrospective monocentre	HCM	36	55 ± 14	4.8 ± 1.4	BNP, eGFR, tenascin-C	Congestive HF
Kubo 2011 (S19)	Consecutive monocentre	HCM	167	61.4 ± 15.5 range 9–88	3.2 ± 1.5	BNP and cTnI	Congestive HF/MVA/surrogate
Kubo 2013 (S20)	Retrospective consecutive monocentre	HCM	183	61.2 ± 15.3 range 13–88	4.1 ± 2.0	Hs-cTnT	Congestive HF MVA Congestive HF/MVA
Kubo 2020 (S21)	Retrospective consecutive monocentre	HCM with serial echocardiography excluding LVEF $< 50\%$	157	59.9 ± 14.2	6.3 ± 2.8	Hs-cTnT	Systolic dysfunction
Maczynska-Mazuruk 2019 (S22)	Prospective monocentre	HCM (inpatient and outpatient)	603	44 ± 17	2.3 ± 1.2	NT-proBNP	Congestive HF MVA End-stage HF/MVA/surrogate
Minami 2018 (S23)	Retrospective consecutive monocentre	HCM	346	51.2 ± 15.5	8.4 (4.2–12.5)	BNP	MVA
Miyaji 2016 (S24)	Consecutive monocentre	HCM	116	65.6 ± 15.2	1.6 (0.6–2.4)	BNP	Congestive HF/MVA/surrogate
Murakami 2004 (S25)	Prospective	HCM	55	57 ± 10	8.8 ± 4.2	Homeostasis model assessment insulin resistance	Congestive HF End-stage HF MVA
Mutlu 2006 (S26)	Prospective consecutive	HCM	80	47.0 ± 17.3	1.6 ± 0.8, range 0.1–2.5	NT-proBNP	Congestive HF/MVA/surrogate
Ozyilmaz 2018 (S27)	Prospective consecutive multicentre	HCM with uric acid measurement excluding prior SRT	115	45.5 (IQR NA), range 18–79	2.6 ± 1.1	Uric acid	MVA MVA/surrogate

(*Continues*)

Table 1 (continued)

Study (reference)	Design	Domain	*N* subjects	Age (years)	Follow-up (years)	Biomarker(s)	Outcome(s)
Pieroni 2007 (S28)	Consecutive monocentre	HCM excluding HOCM	40	42 ± 8	5.9 ± 0.56	BNP	Systolic dysfunction
Sahin 2017 (S29)	Retrospective	HCM excluding acute congestive HF and LVEF < 50%	60	42.7 ± 13.3	2	Copeptin, NT-proBNP	Congestive HF End-stage HF/MVA Congestive HF/MVA/ surrogate
Scott 2019 (S30)	Retrospective multicentre	HCM (3 cohorts)	373 8565 9573	56.7 ± 19.3 58.4 ± 18 61.5 ± 15.8	NA	Monocyte count	End-stage HF/MVA/ surrogate
Shirotani 2020 (S31)	Retrospective consecutive monocentre	Apical HCM with BNP measurement	144	[52.3 ± 13.7]	8.9 (4.2–12.7)	BNP	Congestive HF/MVA/ surrogate
Siriwardena 2018 (S32)	Prospective monocentre	HCM (outpatient)	111	52 ± 16 NA (42–63) range 18–86	6.2 ± 3.4, 6.9 (3.1–9.6)	BNP	Congestive HF/MVA/ surrogate
Song 2019 (S33)	Retrospective consecutive monocentre	HOCM undergoing myectomy	758	46.1 ± 13.8	2.6 (1.3–4.8)	NT-proBNP	End-stage HF/MVA/ surrogate
Song 2020 (S34)	Monocentre	HOCM undergoing myectomy	125	[49.2 ± 3.73]	NA	Galectin-3, soluble ST2	End-stage HF/MVA/ surrogate
Sugiura 2019 (S35)	Retrospective consecutive monocentre	HCM excluding with 2011 ACCF/AHA guideline SCD risk factors	93	57.7 ± 13.1	4.7 (2.9–7.5)	BNP	MVA
Wang 2017 (S36)	Retrospective consecutive monocentre	HCM	245	48.5 ± 12.9	3 (2–5)	Big endothelin-1	Congestive HF End-stage HF MVA End-stage HF/MVA/ surrogate
Wang 2020a (S37)	Retrospective consecutive monocentre	HCM (inpatient)	454	57.5 (46.0–67.0)	3.8 (IQR NA) range 0.1–9.4	eGFR, glucose, LDL-cholesterol, triglycerides, uric acid	End-stage HF/MVA/ surrogate
Wang 2020b (S38)	Retrospective multicentre	HOCM undergoing myectomy with diabetes	67	50.1 ± 13.8	2.3 (1.1–4.4)	eGFR, NT-proBNP	End-stage HF/MVA/ surrogate
Wang 2021a (S39)	Retrospective consecutive monocentre	HOCM undergoing myectomy	867	47.9 (37.0–56.0)	2.9 ± 1.4	Haemoglobin, LDL-cholesterol, NT-proBNP, red blood cell distribution width	End-stage HF/MVA/ surrogate
Wang 2021b (S40)	Retrospective consecutive monocentre	HCM with albumin levels and lymphocyte counts	393	57.0 (46.0–66.0)	4.8 (2.4–6.8)	Prognostic nutritional index (10 × albumin [g/ dL] + 5 × lymphocyte count [nL])	End-stage HF/MVA/ surrogate
Yang 2018 (S41)	Retrospective monocentre	HCM	98	58.3 ± 13.9	1.4 ± 0.8	Haemoglobin LDL NT-proBNP	Congestive HF

(*Continues*)

Table 1 (continued)

Study (reference)	Design	Domain	*N* subjects	Age (years)	Follow-up (years)	Biomarker(s)	Outcome(s)
Yildiz 2018 (S42)	Prospective multicentre	HCM (outpatient) excluding NYHA III/IV	87	38.4 ± 12.7	2	Red blood cell distribution width BNP, creatinine, intelectin-1	Congestive HF MVA End-stage HF/MVA Congestive HF/MVA/ surrogate
Yoshihisa 2019 (S43)	Prospective consecutive monocentre	HCM (inpatient and outpatient)	93	[63.0 ± 13.9]	2.8 ± 1.7 range 0.04–7.9	Soluble neprilysin	Congestive HF/MVA End-stage HF/MVA/ surrogate
Zen 2005 (S44)	Prospective monocentre	Dilated HCM (LVEDD ≥ 55 mm, LVEF ≤ 50%) outpatient	11	57 ± 10	1.8 ± NA, range 0.7–2.8	Soluble Fas	Congestive HF
Zhang 2018 (S45)	Consecutive monocentre	HOCM (inpatient) excluding amiodaron treatment	756	51.15 ± 12.87 ≥ 16	3.7 ± 1.5	Creatinine, free T3 and T4, NT-proBNP, TSH	End-stage HF/MVA/ surrogate
Zhu 2015 (S46)	Monocentre	HCM	588	51.2 ± 13.7 range 15–87	5.2 ± 2.4	Uric acid	Congestive HF MVA Congestive HF/MVA End-stage HF/MVA/ surrogate
Zhu 2017 (S47)	Prospective monocentre	HCM	490	51.6 ± 13.6 range 15–87	3.7 ± 2.0	Hs-CRP	End-stage HF MVA End-stage HF/MVA/ surrogate

ANP, atrial natriuretic peptide; BNP, ventricular (brain or B-type) natriuretic peptide; CK-MB, creatine (phospho)kinase MB isoform; CRP, C-reactive protein; cTnI/cTnT, cardiac troponin I/T; eGFR, estimated glomerular filtration rate; G+P−, genotype-positive phenotype-negative; HCM, hypertrophic cardiomyopathy; HDL, high-density lipoprotein; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; ICTP, C-terminal telopeptide of type I collagen; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVH, left ventricular hypertrophy; MMP, matrix metallopeptidase (metalloproteinases); MR-proANP, midregional pro-atrial natriuretic peptide; MVA, malignant ventricular arrhythmia; NA, not available; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SRT, septal reduction therapy (i.e. alcohol septal ablation and/or myectomy); T3, triiodothyronine; T4, thyroxine; TGF, transforming growth factor; TIMP, TIMP (tissue inhibitor of metalloproteinases) metallopeptidase inhibitor 1; TSH, thyroid-stimulating hormone.

Overview of the studies included in the qualitative assessment. References are provided in Supporting Information, References. HCM-related inclusion and exclusion criteria are summarized as the domain. Ages and follow-up durations are provided as reported by the original authors, shown as mean ± standard deviation, median (interquartile range), and/or range; if patients were excluded according to age and no range was provided, the age thresholds are provided. Outcomes are categorized in accordance with the definitions provided in our Methods section.

Table 2 Overview of biomarkers analysed for specific outcomes

Biomarker	Congestive heart failure		Systolic dysfunction		End-stage heart failure		Malignant ventricular arrhythmia		Septal reduction therapy	
Big endothelin-1	+ (n = 207)	(S36)			+ (n = 245)	(S36)	− (n = 245)	(S36)		
BNP	+ (n = 98)	(S41)	2− (n = 474)	(S1, S28)			2+ (n = 439)	(S23, S35)	+ (n = 471)	(S9)
	− (n = 41)	(S16)								
CK-MB	+ (n = 77)	(S11)			+ (n = 77)	(S11)	+ (n = 77)	(S11)		
Copeptin	+ (n = 60)	(S29)								
Creatinine			− (n = 434)	(S1)						
eGFR	− (n = 36)	(S18)	+ (n = 434)	(S1)						
Haemoglobin	+ (n = 98)	(S41)								
Hs-CRP					+ (n = 490)	(S47)	+ (n = 490)	(S47)		
Hs-cTnT	+ (n = 183)	(S20)	+ (n = 157)	(S21)			2− (n = 274)[d]	(S12, S20)		
	− (n = 91)[a]	(S12)								
Insulin resistance	− (n = 55)	(S25)			− (n = 55)	(S25)	+ (n = 55)	(S25)		
Intelectin-1	+ (n = 87)	(S42)					− (n = 87)	(S42)		
Mean corpuscular volume	− (n = 98)	(S41)								
MMP-2	+ (n = 41)	(S16)								
MMP-9	− (n = 41)	(S16)								
NT-proBNP	2+ (n = 663)	(S22, S29)			+ (n = 847)	(S5)	2− (n = 1450)	(S5, S22)		
	+ (n = 183)[b]	(S6)								
Red blood cell distribution width	+ (n = 98)	(S41)								
Soluble Fas	+ (n = 11)[c]	(S44)								
Tenascin-C	+ (n = 36)	(S18)								
TGF-β1	− (n = 49)	(S2)					− (n = 49)	(S2)		
TIMP1	+ (n = 41)	(S16)								
Uric acid	+ (n = 588)	(S46)					2+ (n = 690)[d]	(S27, S46)		

BNP, ventricular (brain or B-type) natriuretic peptide; CK-MB, creatine (phospho)kinase MB isoform; CRP, C-reactive protein; cTnI/-T, cardiac troponin I/T; eGFR, estimated glomerular filtration rate; hs, high-sensitivity; MMP, matrix metallopeptidase (metalloproteinases); NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TGF, transforming growth factor; TIMP1, TIMP (tissue inhibitor of metalloproteinases) metallopeptidase inhibitor 1.

Overview of the biomarkers reported in studies assessing specific hypertrophic cardiomyopathy (HCM) endpoints (and surrogate endpoints). Combined congestive and end-stage heart failure outcomes are grouped under congestive heart failure. The results are indicated as a plus sign (+) for studies reporting statistically significant coefficients (adjusted means, odds ratios, relative risks, or hazard ratios) or a minus sign (−) for studies reporting coefficients that did not reach statistical significance. The number of studies (counting potentially overlapping studies as one) is indicated by the number in front of the plus or minus sign; studies assessing outcomes including surrogate endpoints are indicated separately. Subject totals and references are provided within brackets, only taking the largest study when there was potential overlap.

[a]Outcome also included systolic dysfunction.

[b]Outcome also included systolic dysfunction, atrial fibrillation, and stroke.

[c]Only included patients with dilated HCM (with systolic dysfunction).

[d]Was predictive of a composite endpoint of malignant ventricular arrhythmia and non-sustained VT; Gastl 2020 (S8, not shown due to potential overlap with Hasler 2016 [S12]) for hs-cTnT and Ozyilmaz 2018 (S27, which also showed predictive utility for an outcome restricted to malignant ventricular arrhythmia) for uric acid.

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DOI: 10.1002/ehf2.14073

Table 3 Overview of biomarkers analysed for combined outcomes

Biomarker	Congestive HF, MVA		End-stage HF, MVA		Congestive HF, MVA, surrogate outcomes		Cardiovascular mortality		All-cause mortality	
ANP					+ (n = 46)	(S16)				
Big endothelin-1							+ (n = 245)	(S36)		
BNP					+ (n = 130)	(S17)			+ (n = 772)	(S9)
					+ (n = 144)[a]	(S31)				
					+ (n = 116)[b]	(S24)				
					+ (n = 111)	(S32)				
					+ (n = 87)	(S42)				
					− (n = 25)[c]	(S14)				
BNP and cTnI					+ (n = 167)	(S19)				
CK-MB									+ (n = 77)	(S11)
Copeptin			− (n = 60)[b]	(S29)	+ (n = 60)[b]	(S29)				
Creatinine					− (n = 87)	(S42)	− (n = 411)	(S7)	+ (n = 756)	(S45)
eGFR					− (n = 25)[c]	(S14)	− (n = 454)	(S37)	+ (n = 454)	(S37)
									+ (n = 67)[d, e]	(S38)
Free T3									+ (n = 756)	(S45)
Free T4									− (n = 756)	(S45)
Galectin-3					− (n = 107)	(S13)			+ (n = 125)[d]	(S34)
Glucose							2− (n = 865)	(S7, S37)	+ (n = 454)	(S37)
Haemoglobin							− (n = 411)	(S7)	− (n = 867)[d]	(S39)
							− (n = 867)[d]	(S39)		
HDL-cholesterol							− (n = 411)	(S7)		
Hs-CRP							2+ (n = 901)	(S7, S47)		
Hs-cTnT	+ (n = 183)	(S20)			2+ (n = 318)	(S10, S20)				
					− (n = 91)	(S12)				
Indoxyl sulfate					+ (n = 25)[c]	(S14)				
Intelectin-1			+ (n = 87)	(S42)	+ (n = 87)	(S42)				
LDL-cholesterol							− (n = 454)	(S37)	+ (n = 454)	(S37)
									+ (n = 867)[d]	(S39)
Lymphocyte count							− (n = 411)	(S7)		
MMP-2 : TIMP1 ratio					− (n = 55)	(S4)				
Monocyte count							+ (n = 411)	(S7)	+ (n = 9573)	(S30)
Monocyte : HDL-cholesterol ratio							+ (n = 411)	(S7)		
MR-proANP					+ (n = 357)	(S3)				
Neutrophil count							− (n = 411)	(S7)		
NT-proBNP			− (n = 60)[b]	(S29)	+ (n = 357)	(S3)	+ (n = 1030)	(S5, S6)	+ (n = 847)	(S5)
					+ (n = 80)	(S26)	+ (n = 867)[d]	(S39)	+ (n = 603)[b]	(S22)
					+ (n = 60)[b]	(S29)			+ (n = 867)[d]	(S39)
Platelet count							− (n = 411)	(S7)		
PICP : ICTP ratio					+ (n = 55)	(S4)				
Prognostic nutritional index							+ (n = 537)	(S40)	+ (n = 537)	(S40)
Red blood cell distribution width							+ (n = 867)	(S39)	+ (n = 867)	(S39)
Soluble neprilysin	− (n = 93)	(S43)							− (n = 93)	(S43)
Soluble ST2									+ (n = 125)[d]	(S34)
TGF-β1					+ (n = 49)	(S2)			− (n = 49)	(S2)
Triglycerides							+ (n = 454)	(S37)	+ (n = 454)	(S37)

(*Continues*)

Table 3 (continued)

Biomarker	Congestive HF, MVA	End-stage HF, MVA	Congestive HF, MVA, surrogate outcomes	Cardiovascular mortality	All-cause mortality
TSH				− (n = 411) (S7)	− (n = 756) (S45)
Uric acid	+ (n = 588) (S46)			2+ (n = 1042) (S37, S46)	+ (n = 454) (S37)
				− (n = 411) (S7)	
				− (n = 411) (S7)	
White blood cell count					

ANP, atrial natriuretic peptide; BNP, ventricular (brain or B-type) natriuretic peptide; CK-MB, creatine (phospho)kinase MB isoform; CRP, C-reactive protein; cTnI/-T, cardiac troponin I/T; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; ICTP, C-terminal telopeptide of type I collagen; LDL, low-density lipoprotein; MMP, matrix metallopeptidase (metalloproteinases); MR-proANP, midregional pro-atrial natriuretic peptide; MVA, malignant ventricular arrhythmia; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PICP, propeptide of procollagen type I; T3, triiodothyronine; T4, thyroxine; TGF, transforming growth factor; TIMP1, TIMP (tissue inhibitor of metalloproteinases) metallopeptidase inhibitor 1; TSH, thyroid-stimulating hormone.

Overview of the biomarkers reported in studies assessing composite endpoints involving HF, MVA, and surrogate endpoints. The results are indicated as a plus sign (+) for studies reporting statistically significant coefficients (P-value for odds ratios, relative risks, or hazard ratios < 0.05) and a minus sign (−) for studies reporting coefficients that did not reach statistical significance (P-value ≥ 0.05). If multiple studies assessed a biomarker using the same outcome, the number of studies (counting potentially overlapping studies as one) is indicated by the number in front of the plus or minus sign. Subject totals and references are provided within brackets, only taking the largest study when there was potential cohort overlap. Outcomes including different surrogate endpoints are reported separately; surrogate endpoints are specified in Supporting Information, *Table S9*.

[a]Restricted to patients with apical hypertrophic cardiomyopathy.

[b]After adjustment (no unadjusted effect measures reported).

[c]Restricted to patients hospitalized for HF.

[d]Restricted to patients undergoing myectomy.

[e]Restricted to patients with diabetes.

A total of 20 studies were eligible for quantitative analysis. Forest plots of the reported HRs are provided in Supporting Information, *Figure S1*.

Quality assessment

The results of the risk of bias assessment are shown in *Figure 2*. Overall, the risk of bias was moderate, determined by moderate to high risks of bias in patient selection due to retrospective designs and incomplete descriptions of participation of eligible patients, the sampling frame and recruitment ('study participation'), inadequate description of patients lost to follow-up, lack of description of planned follow-up visits and attempts of retrieving outcome data of patients who dropped out ('study attrition'), lack of adjustment to confounders using multivariable analysis ('study confounding'), and use of statistical models not suited to data censored at variable follow-up durations and selective reporting ('statistical analysis and reporting').

Heart failure

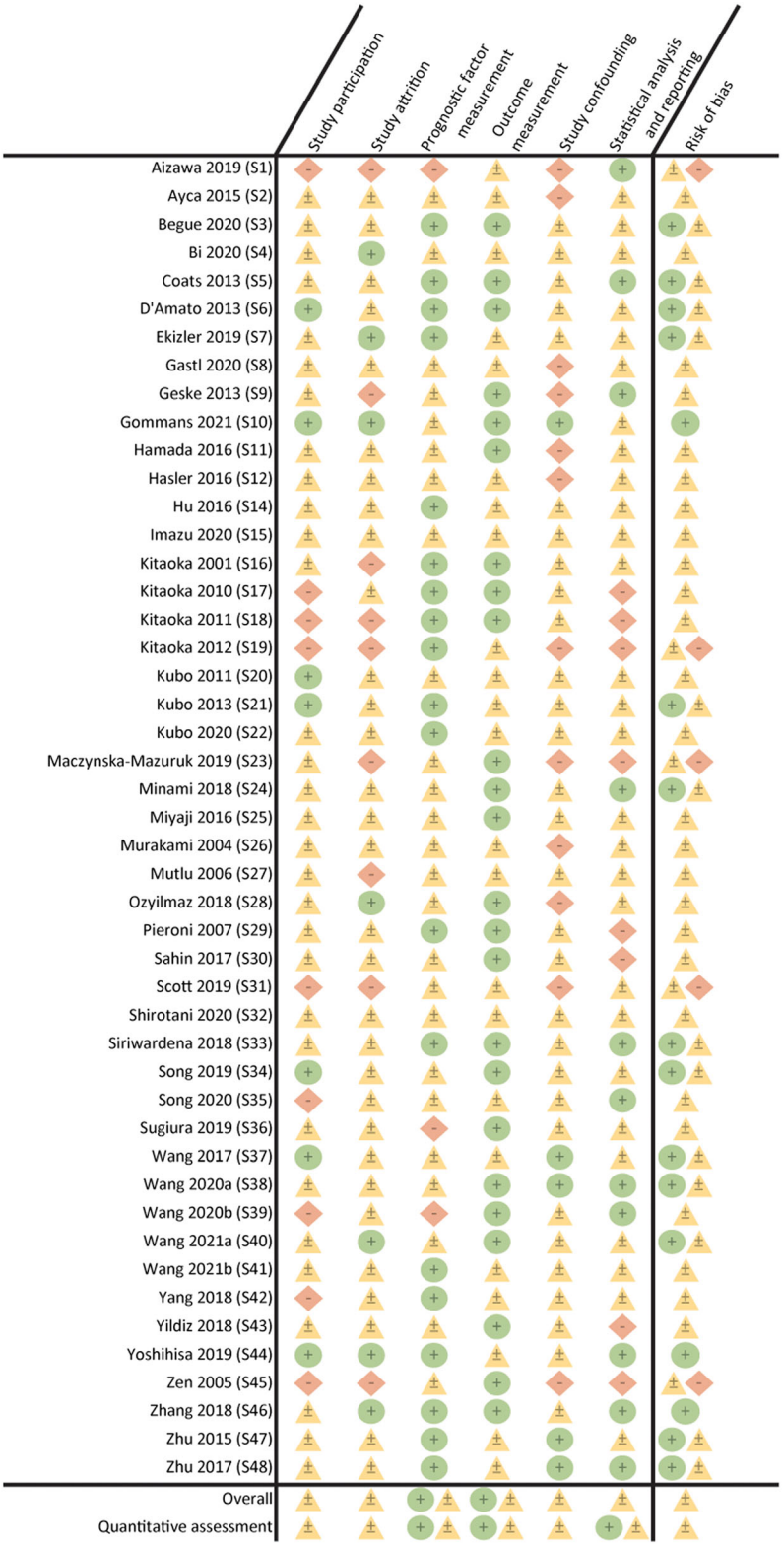
Heart failure outcomes were assessed in a total of 12 studies (n = 3242), as detailed in Supporting Information, *Table S4*. Congestive HF was assessed in seven studies. The median incidence rate of congestive HF was 3.5%/year (2.3–3.5%/year; n = 1293), and 35%/year in one study examining HCM patients in the dilated phase (n = 11).[S11, S20, S22, S41, S42, S44, S46] Three studies assessed systolic dysfunction (n = 631), occurring at rates of 0.49%, 1.3%, and 4.2%/year.[S1, S21, S28] One study combined congestive HF and systolic dysfunction (n = 91), occurring at a rate of 0.19%/year.[S12] Three studies assessed end-stage HF (n = 1414), occurring at rates of 0.77%, 0.78%, and 1.2%/year.[S5, S11, S47] One study combined congestive HF and systolic dysfunction with AF and stroke (n = 183), occurring at a rate of 9.4%/year.[S6]

BNP and NT-proBNP were assessed in a total of eight studies. In three out of four studies, BNP or NT-proBNP predicted congestive HF.[S16, S22, S29, S41] BNP did not predict systolic dysfunction in two studies.[S1, S28] NT-proBNP predicted end-stage HF in one study[S5] and a composite endpoint of congestive HF, systolic dysfunction, AF, and stroke in another.[S6]

High-sensitivity cardiac troponin T was assessed in two studies. In one, hs-cTnT predicted congestive HF and systolic dysfunction.[S20/S21] In the other, it predicted a combined congestive HF and systolic dysfunction outcome.[S12]

Estimated glomerular filtration rate (eGFR) did not predict congestive HF in one study,[S18] but did predict systolic dysfunction in another.[S1] Biomarkers associated to congestive HF in separate studies were big endothelin-1,[S36] creatine kinase MB isoform (CK-MB),[S11] copeptin,[S29] haemoglobin,[S41] intelectin-1,[S42] matrix metallopeptidase-2,[S16] red blood cell

Figure 2 Risk of bias assessment. Review authors' judgement regarding risk of bias for each included study, assessed using the Quality in Prognostic Studies tool.[13] Green circles with a plus sign (+) indicate low risks of bias, yellow triangles with a plus–minus sign (±) indicate moderate risks of bias, and red diamonds with a minus sign (−) indicate high risks of bias.



DOI: 10.1002/ehf2.14073

distribution width,[S41] soluble Fas in dilated HCM,[S44] tenascin-C,[S18] tissue inhibitor of metalloproteinases 1,[S16] and uric acid.[S46] End-stage HF was predicted by big endothelin-1, CK-MB, and high-sensitivity C-reactive protein (hs-CRP).[S11, S36, S47]

Seven studies were included in the quantitative assessment, but only BNP and NT-proBNP were assessed in two or more studies. One study identified BNP as a predictor of congestive HF (HR 1.039 per pg/mL, 95% CI 1.019–1.060, $P < 0.001$),[S41] but BNP did not predict systolic dysfunction in another (HR 1.001 per pg/mL, 95% CI 1.000–1.002, $P = 0.13$).[S1] NT-proBNP predicted congestive HF after adjustment for unreported variables (aHR 1.76 for tertile 2–3 vs. tertile 1, 95% CI 1.03–3.0, $P = 0.037$),[S22] end-stage HF (HR 3.03 per log[fmol/mL], 95% CI 1.99–4.60, $P < 0.001$),[S5] and a combined endpoint of congestive HF, systolic dysfunction, AF, and stroke (HR 2.73 per log[pg/mL], 95% CI 1.67–4.4, $P < 0.01$).[S6] No pooled analyses were performed as outcomes differed in all of these studies.

Malignant ventricular arrhythmia

Malignant ventricular arrhythmia were assessed in nine studies ($n = 2943$), as detailed in Supporting Information, *Table S5*. MVA occurred at a median rate of 1.1%/year (0.52–1.5%/year).[S5, S11, S12, S20, S22, S23, S27, S35, S46] Two studies also combined MVA with nsVT, occurring at rates of 15% and 8.0%/year.[S8, S27]

BNP predicted MVA in two studies, including one study restricted to subjects without risk factors of MVA established by the 2011 American College of Cardiology Foundation/American Heart Association HCM guidelines.[S23, S35] NT-proBNP was not predictive in two studies.[S5, S22] Hs-cTnT did not predict MVA in two studies,[S12, S20] but did predict a combined endpoint of MVA and nsVT in one.[S8] Uric acid predicted MVA in two studies,[S27, S46] as well as a combined endpoint of MVA and nsVT.[S27] CK-MB, hs-CRP, and insulin resistance predicted MVA in one study each.[S11, S25, S47]

BNP, hs-CRP, and uric acid remained predictive of MVA after adjustment for risk factors of MVA, including family history of SCD, unexplained syncope, and maximum wall thickness (as well as nsVT for BNP and hs-CRP and LVOT obstruction for hs-CRP and uric acid).[S23, S46/S47]

Quantitative assessment included five studies. Only BNP was assessed in two (or more) studies included in quantitative assessment, predicting MVA in both (HR 5.89 for >312 pg/mL, 95% CI 2.99–11.6, $P < 0.001$; HR 1.035 per 10 pg/mL, 95% CI 1.005–1.065, $P = 0.023$, respectively).[S23, S35] However, pooled analyses were not possible due to differences in modelling strategies. Additionally, NT-proBNP was assessed in one study, showing a trend towards predicting MVA (HR 1.54 per log[fmol/mL], 95% CI 0.91–2.60, $P = 0.111$).[S5]

Outflow tract obstruction

Only one study was identified, detailed in Supporting Information, *Table S7*. Patients underwent septal reduction therapy at a rate of 8.6%/year ($n = 471$, with no prior procedures or planned within 30 days). Higher BNP levels were associated with lower survival free of septal reduction therapy (3 year Kaplan–Meier estimate per tertile: 88.5% [95% CI 81.2–93.3], 74.2% [63.9–82.3%], and 67.8% [57.5–76.7%], log-rank $P = 0.001$).[S9]

Composite endpoints

An overview of the biomarkers assessed for combined HCM progression outcomes and combinations with surrogate endpoints is provided in *Table 3*. Event rates are listed in Supporting Information, *Table S8*.

Composite endpoints of HF and MVA were assessed in three studies, as detailed in Supporting Information, *Table S9*. Hs-cTnT and uric acid were significantly associated to composite endpoints of congestive HF and MVA in one study each.[S20, S46] Intelectin-1 was found to predict a composite endpoint of end-stage HF and MVA in one study.[S42]

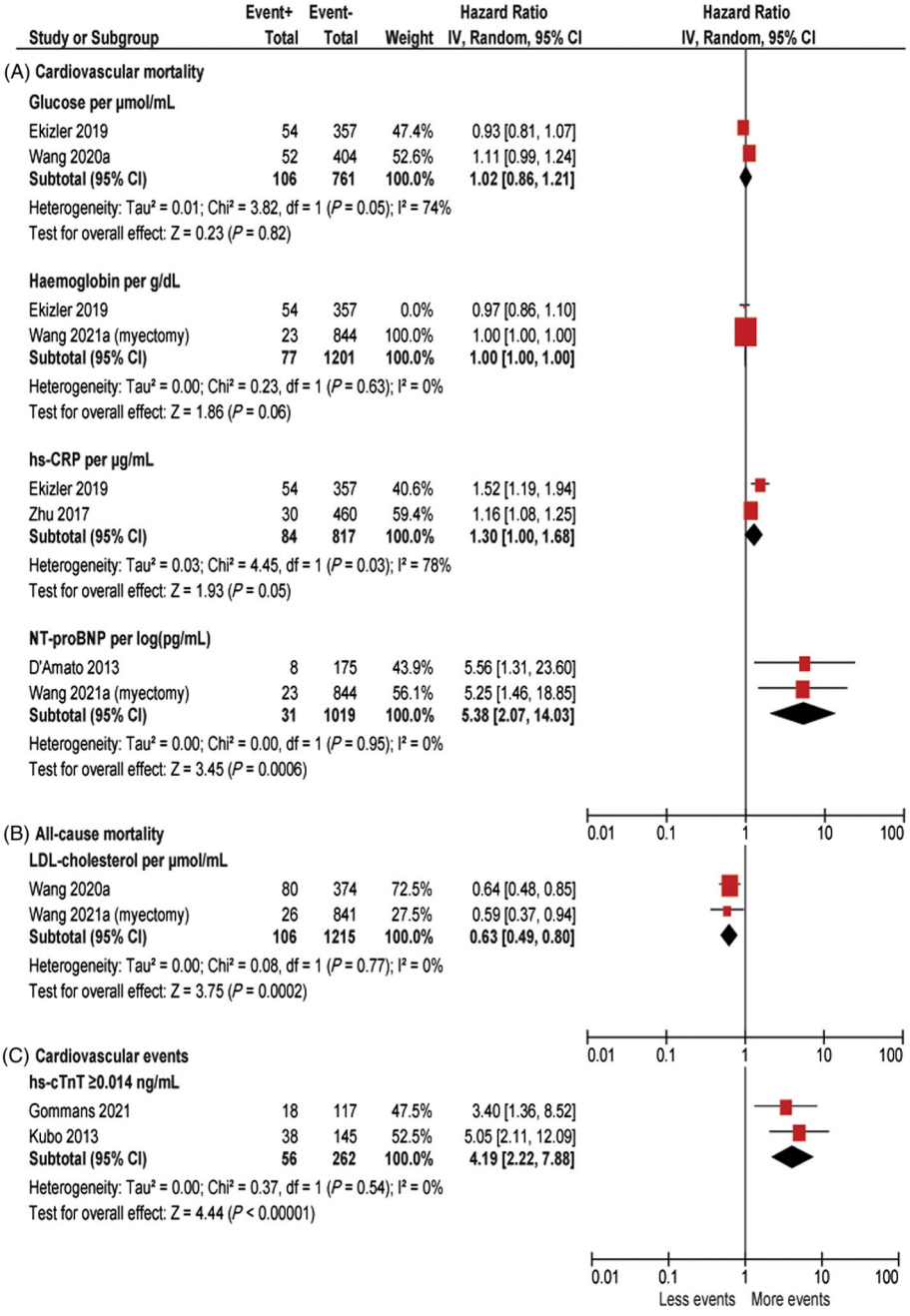
Composite endpoints of HF, MVA, and surrogate endpoints were assessed in 20 studies, of which one additionally assessed a composite endpoint including septal reduction therapy. Studies are detailed in Supporting Information, *Table S10*.

Cardiovascular mortality occurred at a rate of 1.3%/year (1.1–2.1%/year) in five studies ($n = 2762$).[S5–S7, S33/S36/S39/S46/S47, S37/S40] Three studies identified NT-proBNP as a prognostic biomarker for cardiovascular mortality,[S5, S6, S39] and hs-CRP was predictive in two studies.[S7, S47] Uric acid showed conflicting results in three studies.[S7, S37, S46] Big endothelin-1, monocyte count, monocyte to high-density lipoprotein-cholesterol ratio, prognostic nutritional index, red blood cell distribution width, and triglycerides were associated to cardiovascular mortality in separate studies.[S7, S36/S39, S37/S40]

All-cause mortality occurred at a rate of 2.3%/year (1.5–3.3%/year) in nine studies ($n = 3533$).[S2, S5, S9, S11, S22, S30, S34/S38/S39/S45, S37/S40, S43] Three studies indicated NT-proBNP as a predictor of all-cause mortality.[S5, S22, S39] BNP likewise predicted all-cause mortality in one study, as well as a combined endpoint of septal reduction therapy and all-cause mortality.[S9] Low-density lipoprotein (LDL)-cholesterol and eGFR predicted all-cause mortality in two studies.[S37, S38, S39] CK-MB, creatine, free T3, galectin-3, glucose, monocyte count, prognostic nutritional index, red blood cell distribution width, soluble ST2, triglycerides, and uric acid were associated to all-cause mortality in separate studies.[S11, S30, S34/S39/S45, S37/S40]

Other combined outcomes including congestive HF, MVA, and surrogate endpoints were assessed in 12 studies. BNP

Figure 3 Pooled analyses. Forest plots of the hazard ratios eligible for pooled analysis, stratified per biomarker. Outcomes included (A) cardiovascular mortality, (B) all-cause mortality, and (C) cardiovascular events (congestive heart failure, malignant ventricular arrythmia, and stroke). Pooled analyses were performed using an inverse variance, random effects model. The I^2 index was used to assess statistical heterogeneity. CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IV, inverse variance; LDL, low-density lipoprotein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.



predicted a variety of outcomes in five out of six studies,[S14, S17, S24, S31, S32, S42] as did NT-proBNP in three studies.[S3, S26, S29] Hs-cTnT was predictive in two out of three studies.[S10, S12, S20] Atrial natriuretic peptide (ANP), combined assessment of BNP and cTnI, indoxyl sulfate, intelectin-1, midregional proANP, propeptide of procollagen type I/C-terminal telopeptide of type I collagen ratio, and transforming growth factor β1 associated to combined congestive HF, MVA, and surrogate endpoints in separate studies.[S2/S29/S42, S3, S4, S14, S16/S19, S26]

Quantitative assessment included 18 studies assessing composite HCM endpoints (including surrogate outcomes).

DOI: 10.1002/ehf2.14073

Pooled analyses could be performed for five biomarkers, as shown in *Figure 3*. Cardiovascular mortality was predicted by NT-proBNP (pooled HR 5.38 per log[pg/mL], 95% CI 2.07–14.03, $P < 0.001$, $I^2 = 0\%$). Hs-CRP likewise predicted cardiovascular mortality, but with significant heterogeneity between studies (pooled HR 1.30 per μg/mL, 95% CI 1.00–1.68, $P = 0.05$, $I^2 = 78\%$). Glucose did not predict cardiovascular mortality (pooled HR 1.02 per μmol/mL, 95% CI 0.86–1.21, $P = 0.82$, $I^2 = 74\%$). All-cause mortality was predicted by LDL-cholesterol (pooled HR 0.63 per μmol/mL, 95% CI 0.49–0.80, $P < 0.001$, $I^2 = 0\%$). Cardiovascular events (congestive HF, MVA, and stroke) were predicted by hs-cTnT (pooled HR 4.19 for ≥0.014 ng/mL, 95% CI 2.22–7.88, $P < 0.001$, $I^2 = 0\%$). Other analyses could not be pooled due to differences in modelling strategies (use of cut-off values and/or data transformations, e.g. log-transformation) and outcomes.

Discussion

In this systematic review and meta-analysis, we performed a systematic search to identify plasma and serum biomarkers predicting outcomes involving HF, MVA, and LVOT obstruction in patients with HCM. Twenty-six unique studies were identified that associated biomarkers to at least one of these endpoints. In total, 32 biomarkers were significantly associated to an HCM outcome in at least one study, of which BNP, eGFR, hs-CRP, hs-cTnT, LDL-cholesterol, monocyte count, NT-proBNP, red blood cell distribution width, and uric acid associated in at least two studies. Pooled analyses confirmed NT-proBNP, hs-CRP, hs-cTnT, and LDL-cholesterol as prognostic biomarkers in HCM.

BNP and its prohormone NT-proBNP are produced by ventricular cardiomyocytes in response to increased wall stress.[16] Both BNP and NT-proBNP are established diagnostic and prognostic biomarkers for congestive HF[9]; natriuretic peptides have been shown to be the best predictors of incident HF.[17] Although concentrations of BNP and NT-proBNP react differently to concomitant conditions such as AF and renal function, their utility to predict mortality in patients with HF and reduced ejection fraction has been shown to be similar.[18] Natriuretic peptides likely reflect haemodynamic stress in HCM, correlating to several of its hallmarks, including wall thickness, LVOT obstruction, echocardiographic indices of left ventricular filling pressures, and extent of late gadolinium enhancement.[11,19]

In this systematic review, BNP and NT-proBNP consistently predicted composite endpoints of HF, MVA, and surrogate endpoints such as cardiovascular and all-cause mortality,[S3, S5, S6, S9, S17, S22, S24, S26, S29/S42, S31, S32, S39] except for one underpowered study.[S25] In addition, multiple studies indicated NT-proBNP as a predictor for specific HF outcomes,[S5, S6, S22, S29] but results were conflicting for BNP.[S1, S16, S28, S41] Conversely, BNP was shown to predict MVA[S23, S35] while results were negative for NT-proBNP.[S5, S22] This may have resulted from differences in modelling strategies and study populations, as well as lack of power in one study on NT-proBNP due to a lower event rate. Therefore, the prognostic utility for specific HF and MVA endpoints requires further investigation.

High-sensitivity C-reactive protein is a non-specific marker of inflammation[20] and has previously been shown to predict cardiovascular disease and HF in both high-risk and general populations.[21,22] Increased levels of hs-CRP and other inflammatory biomarkers have been found in HCM patients, and inflammatory responses are hypothesized to modulate myocardial fibrosis in HCM.[12,23] In this systematic review, hs-CRP predicted cardiovascular mortality[S7, S47]; however, its utility in predicting specific HF and MVA events was only assessed in one study.[S47] Monocytes also play an integral role in inflammation and atherosclerosis.[24] In HCM, monocyte count significantly associated with all-cause mortality in one study that confirmed the predictive effects across three potentially overlapping cohorts,[S30] and with cardiovascular mortality in another study.[S7] Taken together, these findings suggest that non-specific inflammatory pathways impact prognosis of HCM patients, despite HCM not primarily being an inflammatory disease.

High-sensitivity cardiac troponin T, a marker of myocardial injury,[10] is postulated to result from subendocardial ischaemia, myocyte turnover, and fibrosis in HCM. Hs-cTnT correlates to wall thickness, as well as (but to lesser degrees than natriuretic peptides) to echocardiographic indices of left ventricular filling pressure.[11] Additionally, hs-cTnT levels are increased in subjects with extensive late gadolinium enhancement.[25] In this systematic review, hs-cTnT showed conflicting results for specific and combined HF and MVA outcomes.[S8/S12, S10, S20/S21] However, our pooled analysis did reveal hs-cTnT as a predictor of cardiovascular events, warranting further analysis. Similarly, LDL-cholesterol and eGFR predicted all-cause mortality,[S37, S39] but LDL-cholesterol was not shown to predict other HCM outcomes and results for eGFR were inconsistent. Both studies on red blood cell distribution width were positive but assessed different outcomes, that is, cardiovascular and all-cause mortality in one study and congestive HF in the other. Therefore, these markers require further validation.

Uric acid is the final product of purine metabolism[26] and has previously been associated to HF.[27] The role of uric acid in HCM pathogenesis remains poorly understood, but it is hypothesized to reflect xanthine oxidase activity, which may increase due to changes in cardiac energy metabolism and result in inflammation and oxidative stress.[28] In HCM, studies were inconsistent on prediction of cardiovascular mortality[S7, S37, S46]; results could not be pooled due to heterogeneity in cut-off values. Of note, one of the studies indicated a U-shaped relationship between uric acid levels and

cardiovascular mortality,[S37] which may have contributed to the inconsistent results between studies. Taken together with the indications of uric acid as a predictor of specific MVA and HF outcomes,[S27, S46] this warrants further analysis of uric acid as a prognostic marker for HCM.

The ability of BNP, hs-CRP, and uric acid to predict MVA were retained after adjustment for most of the 2011 American College of Cardiology/American Heart Association guideline SCD risk factors.[29] However, these findings have not yet been validated in other studies and did not encompass all risk factors included in current guidelines, that is, the 2014 European Society of Cardiology *HCM-risk SCD calculator*[6] and the 2019 Enhanced American College of Cardiology/American Heart Association strategy.[7] Therefore, future studies are required to assess whether integration of these biomarkers into contemporary models will improve risk stratification. Furthermore, as event rates in HCM are low, ranging from 8.6%/year for septal reduction therapy, 3.5%/year for congestive HF, 0.78%/year for end-stage HF, to 1.1%/year for MVA, future efforts should preferably consist of multicentre studies, such as the *Hypertrophic Cardiomyopathy Registry*[30] and our *BIO FOr CARe* study (*Biomarkers of hypertrophic cardiomyopathy development and progression in Dutch carriers of truncating MYBPC3 variants*).[31]

Our systematic review identified a plethora of biomarkers suggested by single, predominantly monocentre studies. This included biomarkers related to known mechanisms of HCM pathophysiology, including natriuretic peptides (ANP and midregional proANP)[S3, S16] and markers of myocardial injury (CK-MB and tenascin-C),[S11, S18] fibrosis (big endothelin-1, matrix metallopeptidase-2, propeptide of procollagen type I/C-terminal telopeptide of type I collagen ratio, soluble ST2, and tissue inhibitor of metalloproteinases 1),[S4, S16, S34, S36] and inflammation (intelectin-1).[S42] However, validation studies are required to establish the prognostic utility of these biomarkers.

Left ventricular outflow tract obstruction was only investigated in one study; therefore, more studies are required to validate the utility of biomarkers to predict this outcome. Furthermore, the included studies frequently exhibited moderate to high risks of bias in study participation, study attrition, study confounding, and statistical analysis and reporting. Additionally, there was marked heterogeneity in outcomes, cut-off values, and data transformations, limiting possibilities for pooled analyses. Due to these two concerns, the overall quality of evidence was deemed to be low–moderate. Consequently, the use of blood-based biomarkers to guide ICD implantation is currently not recommended, particularly as their incremental value above current risk stratification models remains unclear. However, there is evidence that BNP and NT-proBNP in particular, but also hs-CRP, uric acid, and hs-cTnT, may identify HCM patients with worse general prognosis, for whom intensification of follow-up frequency and medical treatment is likely justified.

Many of the biomarkers identified in this systematic review are known markers of cardiovascular disease. Although these may be of prognostic value as signs of ongoing structural heart disease and pathophysiological changes, they do not inform us of the molecular processes causing the phenotypical heterogeneity in HCM patients, and by extension genotype-positive phenotype-negative family members. Several proteomics and metabolomics studies have been performed to discover biomarkers for the mechanisms underlying HCM, identifying markers linked to hypertrophy and fibrosis (aldolase fructose-bisphosphate A-peptide, glutathione S-transferase omega 1-peptide, Ras suppressor protein 1-peptide, talin 1-peptide, thrombospondin 1-peptide, and c-KIT) and a marker of inflammation (complement C3-peptide).[32–35] However, these studies were limited by cross-sectional designs and not fully representative control groups such as healthy or hospital controls, instead of asymptomatic HCM patients or genotype-positive phenotype-negative family members. Therefore, prospective studies in HCM patients and/or genotype-positive phenotype-negative family members are required. Such studies would be invaluable in the identification of biomarkers for disease progression as well as potential treatment targets.

Conclusions

This systematic review and meta-analysis provides a comprehensive overview of prognostic plasma and serum biomarkers of HCM prognosis. BNP, NT-proBNP, hs-CRP, hs-cTnT, and uric acid were identified as predictors of HCM outcomes. However, further research is required to establish their prognostic utility for specific HF and MVA outcomes and to evaluate their value when incorporated in current risk stratification models. Several other markers have been suggested in single studies but require further validation. The overall quality of studies included in this review was low–moderate. Therefore, future prospective studies should address concerns regarding study participation, attrition, confounding, and statistical analysis and use uniform outcome definitions and strategies for modelling biomarkers.

Funding

This work was supported by the Netherlands Cardiovascular Research Initiative: An initiative with the support of the Dutch Heart Foundation (Hartstichting) (CVON2014-40 DOSIS; Dutch Cardiovascular Alliance 2020B005 DOUBLE DOSE to F.W.A., J.P.v.T., J.v.d.V., M.M., and R.A.d.B.; CVON2015-12 eDETECT to F.W.A. and J.P.v.T.), Dutch Heart Foundation (Dekker 2015T041 to A.F.B. and M.J.), Netherlands Organization for Sciences-ZonMW (VICI

91818602 to J.v.d.V.), and University College London Hospitals National Institute for Health Research Biomedical Research Centre (to F.W.A.).

Conflict of interest

None declared.

Supporting information

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

Table S1: Search strategy.
Table S2: Reported in-/exclusion criteria and biomarker platforms.
Table S3: Excluded studies & reason for exclusion.
Table S4: Biomarkers for heart failure.
Table S5: Biomarkers for malignant ventricular arrhythmia.
Table S6: Biomarkers for outflow tract obstruction.
Table S7: Event rates of composite endpoints (including surrogate endpoints).
Table S8: Biomarkers for composite endpoints.
Table S9: Biomarkers for composite endpoints including surrogate endpoints.
Figure S1: Quantitative analysis endpoints.

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DOI: 10.1002/ehf2.14073