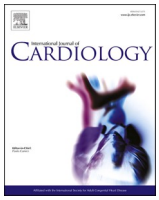
International Journal of Cardiology 434 (2025) 133350

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



High incidence of malignant arrhythmias and heart failure in patients with *RBM20*-associated cardiomyopathy: A multicenter cohort study and review of the literature

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ARTICLE INFO

Keywords:
Cardiomyopathy
Heart failure
Ventricular arrhythmias
Sudden cardiac death
RBM20 variants
Truncating variants

ABSTRACT

Background: Patients with RBM20 cardiomyopathy present with an aggressive phenotype, associated with premature malignant arrhythmias, sudden cardiac death, and progressive heart failure (HF). This study aimed to investigate genotype-phenotype correlations, clinical outcomes, and causes of death in patients with RBM20-associated cardiomyopathy and review the current literature.
Methods: The cohort included patients with cardiomyopathy harboring pathogenic (P) or likely pathogenic (LP) RBM20 variants. For survival and regression analysis, a control group matched for sex, age, and presence of left ventricular dysfunction was included. Additionally, a comprehensive literature search was conducted.
Results: Sixty-two patients (45 % male, 42 ± 15 years at presentation) were included. We found 11 truncating variants. Patients with truncating variants diagnosed with HF were older compared to patients with missense variants (mean age 62 ± 9 vs. 45 ± 14; $p = 0.01$). Over a median follow-up duration of 5.0 [1.0–10.5] years, 21 (34 %) patients reached the composite endpoint, with 19 (31 %) patients experiencing malignant ventricular arrhythmia (VA) (mean age 45 ± 15 years, 63 % males). Males exhibited higher risk for the composite endpoint (log-rank $p = 0.02$), particularly for VA (log-rank $p = 0.007$). The literature review analyzed 34 studies comprising 678 patients (53 % male). In these studies, 123 (24 %) patients experienced a VA, 58 (12 %) underwent a heart transplant or were treated with LVAD, and 52 (11 %) died.
Conclusion: This multicenter study highlights the severe phenotype associated with LP/P RBM20 variants, with a high incidence of VA, particularly in males. Additionally, this study presents 11 truncating variants mainly observed in older individuals.

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https://doi.org/10.1016/j.ijcard.2025.133350
Received 4 September 2024; Received in revised form 22 March 2025; Accepted 30 April 2025
Available online 6 May 2025

1. Introduction

Pathogenic variants in the Ribonucleic acid (RNA) Binding Motif Protein 20 (RBM20, OMIM #613171) gene have been identified as a cause of cardiomyopathy and ventricular arrhythmia (VA). RBM20 controls the post-translational splicing of multiple genes, which is disrupted by *RBM20* mutation. Most pathogenic *RBM20* variants described are missense variants resulting in a gain of function which leads to the mis-splicing of other genes, several of which, such as *Titin* (*TTN*), are also associated with cardiomyopathies. Thus, different *RBM20* variants can result in different cardiomyopathy phenotypes [1–3]. Current literature on *RBM20*-associated cardiomyopathy describes mostly dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and occasionally noncompaction cardiomyopathy (NCCM).

RBM20 has been associated with a relatively high prevalence of VA in 6.7 %–28 % of patients [4,5]. Analyzing genotype-phenotype associations combined with the clinical outcomes may provide further insights in risk factors associated with VA. Investigating genotype-phenotype correlations and clinical outcomes in *RBM20*-associated cardiomyopathies could, therefore, contribute to a more personalized approach to the risk stratification, prevention, and treatment of VA, sudden cardiac death (SCD), and heart failure (HF) in these patients.

The aim of this study was to investigate the genomic, clinical, imaging, and pathological characteristics of patients with cardiomyopathy caused by pathogenic *RBM20* variants, combined with an overview of the current literature.

2. Methods

2.1. Study population

This multicenter study enrolled 62 patients from 2013 to 2023 at multiple cardiology and clinical genetics departments. The study was approved by the relevant ethics committees and adhered to the principles set out in the Declaration of Helsinki. It included index patients and relatives with DCM or NCCM, all carrying likely pathogenic (LP) or pathogenic (P) RBM20 variants. A control group of DCM patients with heart failure was selected from the Rijnmond Heart Failure/Cardiomyopathy registry (Feb 2014 - July 2023). These patients were 1:1 matched based on sex, age at presentation (within 5 years), and LVEF $\leq$40 %. Genetic testing confirmed no LP/P variants in the control group.

2.2. Data collection

Data was collected from the initial presentation and the most recent hospital visit, retrospectively extracted from electronic medical records. The primary presentation was classified into four subgroups: HF, VA/syncope, chest pain/palpitations, and asymptomatic. The primary outcome was a composite of sustained VA, appropriate implantable cardioverter-defibrillator (ICD) therapy, heart transplantation (HTx), and cardiovascular death. Appropriate ICD therapy was defined as a device activation of either antitachycardia pacing (ATP) or shock for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Secondary outcomes included survival analysis of the composite endpoint and individual assessments of composite arrhythmia and end-stage heart failure (ESHF).

2.3. Genetic testing

Laboratory values were collected during routine diagnostic procedure and genomic DNA extracted according to standard protocols. Patients were tested for variants in at least all cardiomyopathy-related genes for DCM that were and/or currently are recommended in the core panel [6]: Genes were analyzed in one of the diagnostic laboratories either by a custom next-generation sequencing panel, or whole-exome sequencing-based testing.

Identified variants were interpreted and classified as pathogenic (class 5), likely pathogenic (class 4), uncertain clinical significance (class 3), likely benign (class 2), or benign (class 1), according to criteria established by the American College of Medical Genetics and Genomics [7]. Truncating variants (Tv) were defined as any variants that result in a shortened or incomplete transcript. Some of these transcripts may be subjected to nonsense-mediated decay (NMD) and degraded and therefore not translated into protein. This study, included only patients with either pathogenic or likely pathogenic variant in the *RBM20* gene.

2.4. Histological evaluation

The myocardial tissue of two HTx patients was available for histopathological analysis. The heart tissue was retrieved from the archive of the department of pathology of the Erasmus University Medical Center. Tissue samples were prepared using routine procedures and compared with the patients cardiac magnetic resonance imagnig (CMR) and transthoracic echocardiographic images.

2.5. Literature review

The literature review covered all original publications on RBM20 variants in cardiomyopathy patients and their clinical outcomes. On August 2nd, 2023, Embase, MEDLINE, Web of Science, and Cochrane were searched (details in Supplementary Material). Inclusion and exclusion criteria were defined beforehand, and no studies were excluded based on publication date. The search retrieved 544 studies; after removing duplicates and screening for eligibility, 34 studies were included (Fig. S1) [4,5,8–39]. The review encompassed 15 cohort studies, 18 case reports or series, and one case-control study. When considered alongside our existing cohort, the total number of patients included in the literature reaches 678.

2.6. Statistical analysis

For normally distributed data, continuous variables were presented as mean $\pm$ SD; otherwise, they were reported as median and interquartile range. Numbers and percentages were used to report categorical variables. Comparison of continuous variables between groups was done using Student *t*-test, MWU test, Kruskal-Wallis test, or ANOVA followed by Tukey's post hoc analyses, when appropriate. Chi-squared or Fisher's exact test were used to compare categorical variables between groups. The Kaplan-Meier method was used for calculating the event free survival and the Log-rank test for calculating the *p*-value between the 2 groups. A competing risk analysis was performed to correct for the lower chance of experiencing a VA after undergoing HTx in the primary combined endpoint. A stratified univariable cox regression analysis was used to investigate whether certain comorbidities modify the risk of developing the composite endpoint associated with the RBM20 variant. Statistical significance was set to be a p-value <0.05. These statistical analyses were done in SPSS version 28.0.1.0, and R version 4.3.1, using the survival package (version 3.5–7).

3. Results

This study included 62 patients with LP/P RBM20 variants from 40 families, of whom 38 patients were probands and 24 were relatives. A total of 11 patients were identified as first-degree relatives, 5 as second-degree relatives, 4 as third-degree relatives, 3 as fourth-degree relatives, and 1 for whom the degree of relationship was not ascertained. In total, 16 different *RBM20* variants were identified Table 1 summarizes the genomic position, cDNA position in transcript NM_00113463 and predicted amino acid change, with frequency of occurrence, variant classification according to ACMG guidelines, and information on previous reports of the variant. Nine *RBM20* variants were novel variants, i.e. not previously reported in the literature. Eight of the novel variants were

Table 1
Overview of RBM20 variants.

n	UCSC genomic position (hg38)	Nucleotide change	Amino acid change	Class	ACMG	Comments
1	Chr10: 110780846	c.237_298del	p.(Asn80Profs*67)	4	PVS1, PM2	Novel
1	Chr10: 110781022	c.414del	p.(Arg138Serfs*5)	4	PVS1, PM2	Novel
1	Chr10: 110781454	c.846_853del	p.(Tyr283Glnfs*14)	4	PVS1_strong, PM2	Novel
1	Chr10: 110781726	c.1118_1119del	p.(Gln373Argfs*25)	4	PVS1 PM2	Novel
2	Chr10: 110810463	c.1880 + 1G > A	p.?	4	PVS1, PM2	Prior report [34]
1	Chr10: 110812139_110812645	c.1881-139_2248del	p.(Arg627Serfs*7)	4	PVS1, PM2	Prior report [34]
37	Chr10:110812297	c.1900C > T	p.(Arg634Trp)	5	PM1, PM2, PS4, PP3, PP5	Prior report [18,20,21,29,34,37,39]
7	Chr10: 110812303	c.1906C > T	p.(Arg636Cys)	5	PM1, PM2, PP3, PS4	Prior report [37]
1	Chr10: 110812304	c.1907G > A	p. (Arg636His)	5	PM1, PM2, PP3	Prior report [14,23,27,33–35,37,39]
1	Chr10: 110812309	c.1912C > A	p.(Pro638Thr)	4	PM1, PM2, PM5	Novel
2	Chr10: 110812310	c.1913C > T	p. (Pro638Leu)	5	PS4, PP1_strong, PM2, PM1, PS3, PM5_supp	Prior report [8,12,23,34,37]
3	Chr10: 110812459	c.2062C > T	p.(Arg688*)	4	PVS1_strong, PM2, PP1_supp, PS4_supp	Prior report [22]
1	Chr10: 110812573	c.2176C > T	p.(Arg726*)	4	PVS1_strong, PS4_supp, PM2	Novel
1	Chr10: 110812756	c.2359G > T	p.(Glu787*)	4	PVS1_strong, PM2	Novel
1	Chr10: 110821306	c.2687del	p.(Glu896Glyfs*14)	4	PVS1_strong, PM2	Novel
1	Chr10: 110821537	c.2919del	p.(Ala974Glnfs*29)	4	PVS1_strong, PM2	Novel

* Amino acid changes ending with truncating variants. This is a genetic change that causes a gene to produce a shortened or incomplete transcript. Some of these transcripts will be degraded and not translated into protein.

truncating; an amino acid change (c.1912C > A) with potential impact on the three-dimensional structure. The most frequently occurring variant was c.1900C > T, which was identified in 37 patients (59 %). Of those patients, 17 were probands and 20 were relatives, all from 19 families. Eleven variants were truncating, which were identified in 14 patients. Thirteen were probands and 1 was a first degree relative.

3.1. Clinical characteristics

Table 2 displays the clinical characteristics of the total RBM20 cohort, stratified into four groups based on the primary presentation. The mean age at presentation was 42 ± 15 years, 45 % were males. DCM was the dominant cardiomyopathy phenotype, diagnosed in 60/62 (97 %) patients. ECG data showed that 23/57 (40 %) patients had atrial fibrillation or atrial flutter. In 8/57(14 %) patients bundle branch block was observed: 5/8(63 %) right bundle branch block, 2/8(25 %) left bundle branch block, and 1/8(13 %) was nonspecific.

Nineteen patients presented with HF at initial presentation (33 % male), and 15 patients presented with VA/syncope (67 % males). The HF group exhibited a significantly lower LVEF than the chest pain/palpitations and asymptomatic groups (32 ± 13 % vs. 52 ± 12 % and 45 ± 13; $p = 0.01$), but there was no significant difference in LVEF between the HF group and the VA/syncope group (32 ± 13 % vs. 40 ± 11 %; $p = 0.29$). The asymptomatic group 53 % were prescribed RAAS inhibitors for asymptomatic LV dysfunction.

Fourteen patients with truncating *RBM20* variants (Tv) were compared with those carrying non-truncating *RBM20* variants (nTv) (Supplemental Table S1a). The mean age at presentation for the Tv group was 48 ± 14 years, by trend higher than the nTv group with a mean age of 42 ± 15 years ($p = 0.08$). Notably, patients with Tv had significantly fewer family members with a history of VA compared to those in the nTv group (1/12 (8 %) vs. 26/45 (59 %); $p = 0.004$). The two NCCM patients included in this study were both male probands with a mean age of 50 years (32–67) at initial presentation, and neither had any significant comorbidities. Both patients experienced non-sustained VT (NSVT), and one patient also had an AV block. Post-HTx, explanted native heart tissues of two patients were available for histopathological analyses and were compared to the available imaging (Fig. S2). CMR of one patient revealed mid-myocardial LGE in the septum and hinge point LGE. Tissue showed mild LV hypertrophy, focal vacuolization (especially anterior), subendocardial replacement fibrosis, interstitial fibrosis, and minimal chronic inflammation, without disarray. The other patient, without CMR imaging, exhibited similar tissue characteristics, with more fibrosis but no inflammation.

3.2. Long-term clinical outcome of RBM20 variants

Follow-up data for 62 patients are presented in Table 2, reflecting a median follow-up (FU) duration of 5.0 years [IQR: 1.0–10.5]. In total 21/61 (34 %) reached the primary composite endpoint of which 9 reached the primary composite endpoint during follow-up (mean time 5.1 ± 9.2 years). Observed events were exclusively recorded in probands. Six (10 %) patients developed both ESHF and a VA, with 5 patients experiencing a VA first. Nineteen (31 %) patients experienced VA during their lifetime, and among them, 12 had their first arrhythmia during the follow-up period. Eight out of 55 patients (15 %) progressed to ESHF (Fig. 1). Thirteen males and 8 females (46 % vs. 24 %) reached the composite endpoint, with Kaplan-Meier analysis showing a significant difference between genders ($p = 0.022$) (Fig. 1b). Additionally, 12 males (43 %) experienced composite arrhythmia compared to 7 females (21 %), with a significant difference in Kaplan-Meier analysis ($p = 0.007$) (Fig. S3b). There was no significant sex difference in ESHF, and the competing risk from HTx did not affect the composite arrhythmia analysis (Fig. S3c).

In this cohort, 18/62 patients (28 %) received ICDs. Among these, 14/38 were probands (38 %) and 4/24 family members (17 %). Of those with ICDs, 44 % experienced appropriate therapy, and 22 % received inappropriate therapy. Only 1 patient (2 %) died of ESHF during follow-up, while 7 (14 %) underwent HTx. The composite endpoint was reached by 9/19 (47 %) patients with initial heart failure, 10/15 (67 %) with initial VA/syncope, and 2/20 (10 %) initially asymptomatic patients.

The age of onset HF in the nTv group was significantly lower (45 ± 14 years) than that observed in the Tv group (62 ± 9 years; $p = 0.01$; Table S1b). In the Tv group, 6/14 (43 %) reached the composite endpoint. All 6 experienced VA, and one of them experienced combined VA and ESHF. The majority of patients in the Tv group received ICDs for secondary prevention, in contrast to the nTv group (3/4, 75 % vs. 1/14, 7 %; $p = 0.05$).

3.3. RBM20 variant vs. control DCM group without genetic variants

Baseline characteristics are shown in the supplementary file (see Table S2a). In both groups 12/35 (34 %) patients underwent

Table 2
Baseline characteristics of patient with RBM20 variants per primary presentation.

Characteristics	Total (n = 62)	Heart failure (n = 19)	Ventricular arrhythmia/ syncope (n = 15)	Chest pain/ palpitations (n = 7)	Asymptomatic/ screening (n = 21)
Demographics					
Age at presentation, years	42 ± 15	47 ± 16	44 ± 10	34 ± 20	39 ± 15
Male	28/62 (45)	6/19 (33)	10/15 (67)	4/7 (57)	8/21 (38)
Ethnicity,					
Caucasian	31/35 (89)	9/12 (75)	6/6 (100)	4/4 (100)	12/13 (92)
African	2/35 (6)	1/12 (8)	0/6 (0)	0/4 (0)	1/13 (8)
Asian	0/35 (0)	0/12 (0)	0/6 (0)	0/4 (0)	0/13 (0)
Other	2/35 (6)	2/12 (17)	0/6 (0)	0/4 (0)	0/13 (0)
Comorbidities,					
Hypertension	13/58 (22)	7/18 (39)	3/15 (20)	1/7 (17)	2/18 (11)
Diabetes	4/36 (11)	2/13 (15)	1/7 (14)	0/7 (0)	1/14 (7)
Hypercholesterolemia	4/36 (11)	3/13 (23)	1/7 (14)	0/7 (0)	0/9 (0)
Cancer	3/38 (8)	1/13 (8)	2/7 (29)	0/7 (0)	0/11 (0)
Stroke	3/38 (8)	1/13 (8)	1/7 (14)	0/7 (0)	1/11 (9)
Coronary artery disease	3/38 (8)	2/13 (15)	0/7 (0)	0/7 (0)	1/11 (9)
Family history					
CMP or heart failure	47/57 (83)	11/16 (69)	11/14 (79)	7/7 (100)	18/20 (90)
SCA and/or VA	27/56 (48)	7/15 (47)	6/15 (40)	3/7 (43)	11/19 (58)
Genetic testing	20/39 (51)	4/13 (31)	2/7 (29)	2/4 (50)	12/15 (58)
Physical examination					
Height, m	173 ± 11	172 ± 7	175 ± 9	167 ± 23	175 ± 8
Weight, kg	82 ± 18	84 ± 15	86 ± 18	78 ± 33	79 ± 13
Heart rate, bpm	65 (57–79)	67 (57–79)	65 (54–76)	82 (69–89)	64 (57–73)
Systolic BP, mmHg	126 ± 16	129 ± 18	122 ± 12	136 ± 7	122 ± 16
Diastolic BP, mmHg	76 ± 10	74 ± 11	79 ± 13	79 ± 11	76 ± 9
Electrocardiography					
Sinus rhythm	32/57 (56)	10/19 (53)	6/12 (50)	4/6 (67)	12/20 (60)
Atrial fibrillation/ flutter	23/57 (40)	9/19 (47)	5/12 (42)	2/6 (33)	7/20 (35)
Paced rhythm	2/57 (4)	0/19 (0)	1/12 (8)	0/6 (0)	1/20 (5)
PQ, ms (mean ± SD)	149 ± 27	161 ± 25	141 ± 29	131 ± 18	150 ± 26
QRS, ms (mean ± SD)	109 ± 22	113 ± 22	120 ± 32	90 ± 7	102 ± 10
QTc, ms (mean ± SD)	410 ± 38	423 ± 36	413 ± 46	392 ± 55	404 ± 22
Bundle branch block	8/57 (14)	2/19 (11)	3/12 (25)	0/6 (0)	3/20 (14)
2rd degree AV block	1/57 (2)	0/19 (0)	0/12 (0)	1/6 (17)	0/20 (0)

Characteristics	Total (n = 62)	Heart failure (n = 19)	Ventricular arrhythmia/ syncope (n = 15)	Chest pain/ palpitations (n = 7)	Asymptomatic/ screening (n = 21)
Echocardiography					
LA diameter, mm	38 ± 8	45 ± 5	41 ± 6	38 ± 8	34 ± 7
LVED diameter, mm	59 ± 9	63 ± 12	57 ± 8	51 ± 6	59 ± 7
LVES diameter, mm	46 ± 17	48 ± 17	39 ± 9	38 ± 11	51 ± 20
IVS diameter, mm	8 (7–9)	8 (7–9)	8 (8–9)	10 (8–11)	8 (8–9)
PWT diameter, mm	8 (7–8)	7 (7–8)	6 (6–7)	9 (8–10)	8 (7–8)
LVEF, %	40 ± 14	32 ± 13	40 ± 11	52 ± 12	45 ± 13
TAPSE diameter, mm	27 ± 29	37 ± 56	22 ± 7	23 ± 2	24 ± 5
Severe valve disease	3/45 (7)	2/11 (18)	0/15 (0)	0/7 (0)	1/12 (5)
CMR					
LVEF	43 (26–52)	25 (21−31)	39 (35–45)	25 (13–38)	51 (49–55)
RVEF	51 (48–56)	9	49	28 (14–42)	54 (49–57)
Late gadolinium enhancement	16/37 (43)	4/8 (50)	5/12 (42)	0/3 (0)	7/14 (50)
Medication, n (%)					
Anticoagulants	15/36 (42)	10/12 (83)	2/7 (29)	1/3 (33)	2/14 (14)
Antiplatelet	4/36 (11)	1/13 (8)	2/7 (29)	0 (0)	1/14 (7)
Beta-receptor antagonist	42/59 (73)	17/18 (94)	13/15 (87)	3/6 (50)	9/19 (47)
RAAS inhibitor	36/59 (61)	14/19 (74)	11/15 (73)	1/6 (17)	10/19 (53)
MRA	19/36 (32)	11/13 (58)	5/15 (33)	0/6 (0)	3/19 (16)
Diuretics	17/59 (29)	10/19 (53)	4/15 (27)	0/6 (0)	3/19 (16)
Digoxin	2/59 (3)	1/17 (6)	1/15 (7)	0/6 (0)	0/21 (0)
Amiodarone	4/59 (7)	2/17 (12)	2/15 (13)	0/6 (0)	0/21 (0)
Calcium channel blockers	4/59 (7)	2/17 (12)	0/15 (0)	0/6 (0)	2/21 (12)
Cardiomyopathy, n (%)					
DCM	60/62 (97)	19/19 (100)	14/15 (93)	6/7 (86)	21/21 (100)
NCCM	2/62 (3)	0/19 (0)	1/15 (7)	1/7 (17)	0/21 (0)
Proband	38/62 (61)	16/19 (84)	14/15 (93)	3/7 (43)	5/21 (24)
Devices, n (%)					
CRT	6/54 (11)	3/16 (19)	2/14 (14)	0/6 (0)	1/18 (6)
ICD	18/54 (33)	8/16 (50)	7/14 (50)	1/6 (17)	2/18 (11)
Primary prevention	14/18 (78)	7/8 (88)	5/7 (71)	1/1 (100)	1/2 (50)
Secondary prevention	4/18 (22)	1/8 (12)	2/7 (29)	0/1 (0)	0/2 (0)
Outcomes, n (%)					

(continued on next page)

Table 2 (*continued*)

Characteristics	Total (n = 62)	Heart failure (n = 19)	Ventricular arrhythmia/ syncope (n = 15)	Chest pain/ palpitations (n = 7)	Asymptomatic/ screening (n = 21)
Follow-up, years	5.0 [1.0–10.5]	6.0 [1.5–18.0]	5.0 [2.0–13.0]	5.0 [3.3–9.8]	3.0 [0.5–7.0]
Invasive EP	4/31 (13)	1/13 (8)	1/6 (17)	1/3 (33)	1/9 (11)
Age first VA	45 ± 15	45 ± 15	46 ± 13	15	65
Age of onset heart failure	48 ± 14	51 ± 14	47 ± 12	15	44 ± 12
ICD appropriate therapy	8/18 (44)	4/8 (50)	3/7 (43)	0/1 (0)	1/2 (50)
ICD inappropriate therapy	4/18 (22)	2/8 (25)	2/7 (29)	0/1 (0)	0/2 (0)
Heart transplant	7/52 (14)	6/18 (33)	1/13 (8)	0/6 (0)	0/15 (0)
Cardiovascular death	1/52 (2)	0/18 (0)	1/13 (8)	0/6 (0)	0/15 (0)
Composite arrhythmia[#]	19/61 (31)	7/19 (37)	10/15 (67)	0/7 (0)	2/20 (10)
End-stage heart failure[*]	8/55 (15)	6/19 (32)	2/13 (15)	0/6 (0)	0/17 (0)
Composite endpoint[*]	21/61 (34)	9/19 (47)	10/15 (67)	0/7 (0)	2/20 (10)

[*] Continuous variables are summarised by mean ± SD or median (IQR), categorical variables are described as: n (%). AV block = atrioventricular; BP = blood pressure; CMP = cardiomyopathy; CMR = cardiovascular magnetic resonance; CRT = cardiac resynchronization therapy; DCM; dilated cardiomyopathy; EP = electrophysiology; HF = heart failure; ICD = implantable cardioverter-defibrillator; IVS: interventricular septal; LA = Left atrium; LVED = left ventricular end diastolic; LVEF = left ventricular ejection fraction; LVES = left ventricular end systolic; MRA; mineralocorticoid receptor antagonist; NCCM = noncompaction cardiomyopathy; PWT = posterior wall thickness; RAAS = renin-angiotensin-aldosterone system; RVEF = right ventricular ejection fraction; SCA = sudden cardiac arrest; TAPSE = tricuspid annular plane systolic excursion; VA = malignant ventricular arrhythmia; VT: ventricular tachycardia.
[#] Lifetime outcome.

implantation of an ICD. CMR was performed in a subset of patients (22 [63 %] in the RBM20 group and 9 [25 %] in the control group). Of these, 21 RBM20 and 5 control patients underwent LGE assessment, revealing LGE in 9 (43 %) RBM20 patients and 2 (40 %) controls. Most RBM20 patients presented with a mid-myocardial pattern (67 %), whereas subendocardial, subepicardial, and transmural patterns each occurred in one patient (11 %). In RBM20 patients with LGE, the lateral wall and inferior wall were most frequently affected (56 %), followed by the septal (44 %), and anterior (11 %) segments. Composite endpoint in 2/9 (22 %) RBM20 patients with LGE compared to 4/12 (33 %) in RBM20 patients without LGE. The median follow-up time was 3.0 [1.0–10.8] years in the *RBM20* variant group vs. 13.0 [7.0–17.0] years in the DCM control group ($p = 0.001$) (Table S2b). Kaplan-Meier analysis comparing the composite endpoint between the *RBM20* variant group and control group showed no significant difference ($p = 0.26$) (Fig. 1c).

To investigate whether certain comorbidities modify the risk of developing the composite endpoint associated with the RBM20 variant, we performed univariable stratified Cox regression analyses in the age, sex, and LV-function matched cohort (Table S3). (Quasi-) complete separation with a positive association was present in hypertensive patients, patients with a prolonged PR-interval and patients presenting with NSVT at baseline. This means that (almost) all patients with both this risk factor and an RBM20 variant developed the composite endpoint throughout the follow up, making an accurate estimation of the effect with Cox regression impossible. Contrastingly, in patients without these risk factors, the presence of an RBM20 variant was not associated with an increased risk of developing arrhythmia and/or ESHF(Table S3). There was a trend for an increased risk of developing arrhythmia and/or ESHF during follow up associated with an RBM20 variant in patients without diabetes, and patients with a normal QRS-duration at baseline, while such an effect of RBM20 could not be concluded in patients with diabetes and with a prolonged QRS-complex.

3.4. Literature review

An overview of the 34 included studies within a total of 678 patients is shown in Table 3. Summary estimates indicate that the mean age was 32 years, and 279 (53 %) of the participants were reported as male across 26 studies. The phenotypes were reported in 32 studies and included 496 DCM patients (73 %), 54 HCM patients (8 %), and 11 NCCM patients (2 %). Clinical characteristics showed that 154 (39 %) patients had HF symptoms, and 123 (24 %) patients had experienced a VA. For prevention of VA, a total of 151 (33 %) patients received an ICD. Clinical outcomes were comparable with the current study, with 58 (12 %) patients undergoing HTx or LVAD. However, mortality rates were higher in the literature (excluding current cohort) as opposed to the present cohort (12 % vs. 2 %; $p = 0.02$). When combining the current cohort and literature, 52 (11 %) patients died. Five studies exclusively involved pediatric patients ($n = 7$) with a mean age of 13 ± 2 years. [9,24,27,30,31] These pediatric patients did not experience a VA, but 75 % manifested HF, 40 % underwent HTx, and the mortality rate was 14 %. In comparison, studies exclusively focusing on adult patients ($n = 330$, current study included) reported a 23 % incidence of VA, with 35 % of patients receiving an ICD, 41 % developing HF, 11 % undergoing HTx and a mortality rate of 6 %. [5,11,12,16,18–22,28,33,34,37]

Sex-specific data were provided in several studies, comprising a total of 158 males and 157 females. Both groups had a comparable incidence of VA (males: 22 %, females: 18 %). However, ICD implantation rates were 26 % in males and 37 % in females. The prevalence of HF was 34 % in both groups. Mortality rates were 8 % in males and 7 % in females.

4. Discussion

This multicenter study aimed to investigate the genomic, clinical, imaging, and pathologic characteristics of cardiomyopathy caused by pathogenic RBM20 variants. To this end, a total of 678 cases were reviewed, comprising the results of the study and a literature review. In addition, nine novel RBM20 variants were identified. Eight of these were truncating variants. Among patients with LP/P RBM20 variants, 21 (34 %) reached the composite endpoint: 19 (31 %) had VA, 7 (15 %) experienced end-stage HF, and 1 died. Furthermore, male patients with RBM20 variants exhibited a more severe phenotype, with higher risks of malignant VA and end-stage HF. The literature review indicated a higher mortality rate than our study, despite reported younger population (42 ± 15 years vs. 32 years). Our RBM20 cohort's outcomes for composite endpoint of arrhythmia and end-stage HF were consistent with the literature. [4,5,8–39] However, our cohort showed higher of malignant VA in males rather than end-stage HF. [10,27,37]

To further analyze the *RBM20* genotype-phenotype correlation, this study compared the cohort to age, sex, and presence of LV dysfunction matched DCM control patients. By controlling for these confounding factors, the survival analysis showed no significant differences between the groups. Regression analysis suggested that certain comorbidities may modify the risk of developing the composite endpoint associated with RBM20 variants. In RBM20, patients with hypertension, prolonged PR interval and NSVT at baseline had a higher risk of the composite endpoint. This is probably attributed to the limited sample sizes. Existing studies have investigated the impact of specific risk factors on the

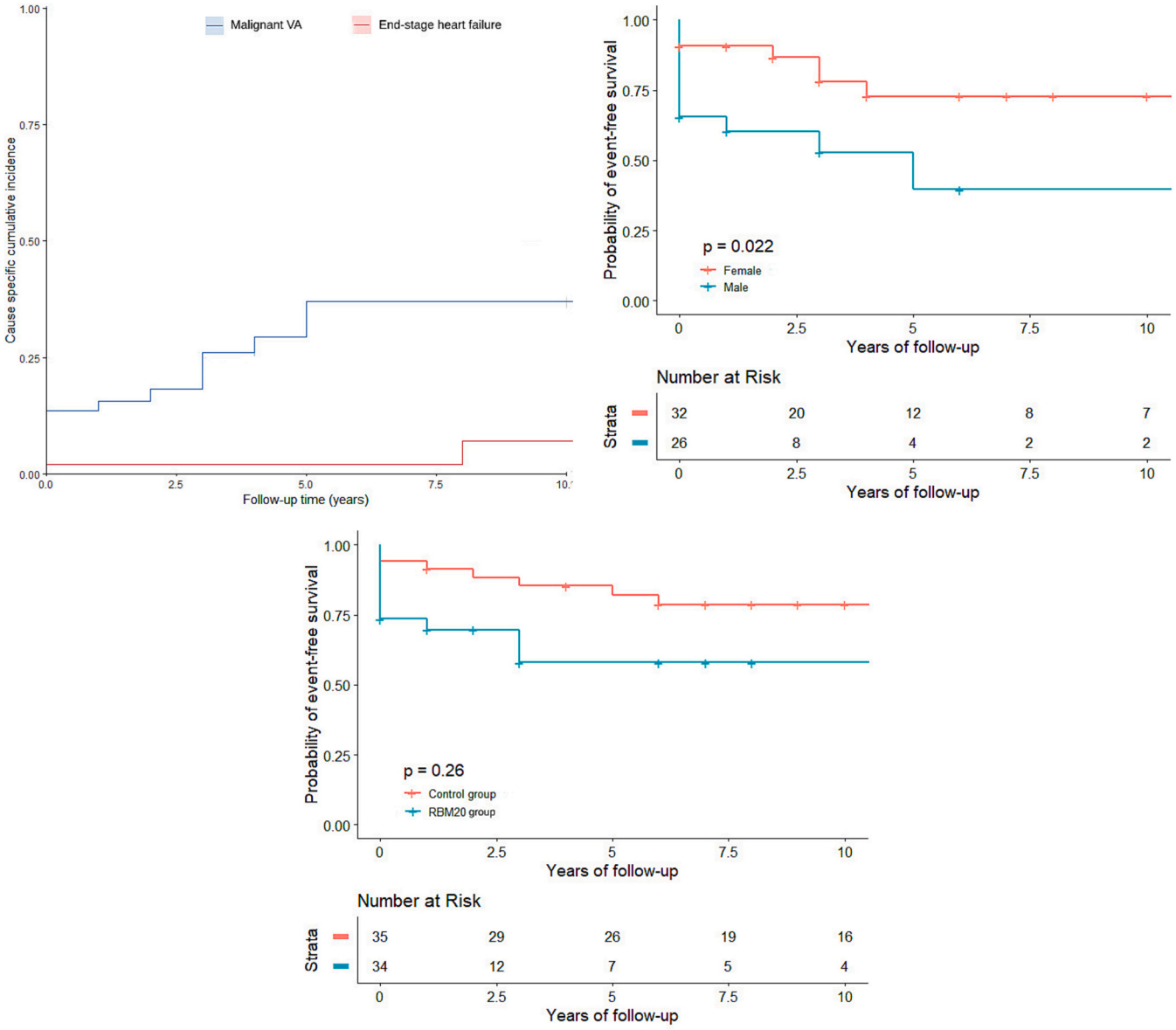

Fig. 1. a. Kaplan-Meier curve for the long-term outcome for VA vs end-stage HF in RBM20 patients.
b. Kaplan Meier curve for composite endpoint for sex in RBM20 variants.
c. Kaplan-Meier curve for composite endpoint in RBM20 vs DCM control groups.

composite endpoint in RBM20 patients, but these factors are often general population risk factors for these composite endpoints. [37] Furthermore, the regression analysis showed that LVEF does not modify the risk of developing the composite endpoint in RBM20 patients. This finding explains why the mean LVEF of 40 % in the VT/syncope primary presentation group is not a driver for VT. It also highlights the frequent overlap between VT and HF presentations.

The summary estimates of the literature review including this study resulted in 678 patients. VA had a comparable prevalence in the literature (24 %) compared to our cohort (31 %). However, the mean age in the literature was lower (32 years vs. 42 years), probably due to a higher rate of case reports. The literature estimate was 12 % mortality excluding the current study compared to 2 % mortality in this cohort ($p = 0.02$). This difference could be explained by the literature showing all-cause mortality compared to cardiovascular mortality in our cohort. In addition, 16 studies included in the literature review were case reports or case series, which are likely to describe more severe cases, which could explain the observed difference in mortality. In contrast to our study, the literature review identified RBM20 variants in patients with HCM. It is well known that RBM20 variants are predominantly associated with DCM, which supports the representativeness of our cohort. For example, the Erasmus MC which has the largest HCM outpatient clinic in the Netherlands, did not identify any likely pathogenic or pathogenic RBM20 variants in their HCM patient registry. The absence of HCM patients in our cohort may have potentially influenced the study results, although the largest population of RBM20 with HCM phenotype is reported by Dai et al. from China, raising the question of possible regional clustering [5].

Our findings highlight the significant burden of arrhythmias and HF in RBM20 variant carriers, revealing a clinical phenotype that closely resembles cardiomyopathy caused by Lamin A/C (LMNA) gene variants. Both RBM20 and LMNA mutations are linked to DCM and NCCM and are associated with a high risk of arrhythmias and HF [40–42]. Ventricular arrhythmias have been reported in 18–56 % of LMNA carriers, comparable to 31 % in our cohort [43–45]. Similarly, 15 % of RBM20 patients in our study had end-stage HF, aligning with the elevated HF risk seen in LMNA-related disease [45]. Atrial fibrillation was observed in 40 % of RBM20 carriers, consistent with the 39–61 % reported in LMNA

Table 3
Summary of papers included in the literature review.

First author year	Number of patients	Country	Type of study, quality rating	Mean age, Sex, n (%)	Phenotype (DCM/HCM/ NCCM)	RBM20 cDNA type variant	Imaging	VT/ VF, n (%)	Heart failure, n (%)	Outcome (ICD, HTX or LVAD, death) n (%)
Brauch et al. [8] 2009	44	United States	Case series 4	36 y; 22 males (50)	DCM, 1 unaffected and 4 uncertain.	c.1901G > A,c.1905G > A,c.1906C > A, c.1909A > G, c.1913C > T	Mean LVEF: 36 %	9 (25)	NA	ICD: 8 (21) HTX: 4 (11) Death: 11(20)
Millat et al.[9] 2011	1	France	Pediatric case report 5	15 y; 1 male (100)	DCM	c.1909A > G	NA	0 (0)	NA	Prevalence: 0.9 % (1/105 of DCM pts). HTX: 1
Perrot et al.[10] 2011	3	Germany	Retrospective cohort study 3	NA; NA	DCM	c.1903 T > G, c.1906C > A, c.2452G > T	NA	NA	3 (100)	ICD: 2 (3 pts. with arrhythmias).
Guo et al.[11] 2012	1	United States	Case report 5	34 y; NA	DCM	c.1903 T > G	NA	NA	1 (100)	HTX: 1.
Refaat et al.[12] 2012	8	United States	Retrospective cohort study 3	NA; 4 males (50)	DCM	c.247C > A, c.1364C > T, c.1913C > T, c.2109G > C, c.2662G > A, c.3091G > T, c.3242C > G, c.3616G > A	NA	1 (13)	1 (13)	Prevalence: 2.8 % of DCM pts. ICD: 2 pts. (1 appropriate ICD therapy) HTX: 1. RBM20 variants did not adversely affect survival or MVA in DCM
Wells et al.[13] 2013	19	United States	Retrospective cohort study 3	33.8 ± 11.5 y; NA	DCM	c.1905G > A	NA	NA	NA	HTX: 1 Death: 11 (61 %) The mean age of death or HTX was 46 ± 17 years.
Chami et al.[14] 2014	1	Canada	Case report 5	56 y; NA	DCM	c.1907G > A	LVEF: 25 %	0 (0)	1 (100)	RBM20 variant found in 1 patient, who also carried a LMNA variant.
Haas et al.[15] 2015	15	Germany	Multi-Centre prospective cohort study 2	NA; NA	DCM	NA	NA	NA	NA	ICD: 10 (66 %) odds ratio of 5.56 (1.89–16.86; $P = 0.002$) RBM20 variant patient significant predictor for ICD-carrier status in DCM.
Posafalvi et al. [39] 2015	35	The Netherlands	Prospective cohort study 2	36 ± 14 y; 3 males (38)	DCM, peripartum cardiomyopathy	c.1603G > C, c.1895G > A, c.1898C > T, c.1900C > T, c.1901G > C, c.1907G > A, c.1910G > A	LVEF:33 %	1 (10)	3 (30)	This study identified 18 novel and 5 known missense variants in 35 probands. Furthermore,10 variants were classified as LP/P. ICD: 3 HTX: 3(30) Death: 2(20)
Beqqali et al. [16] 2016	9	Denmark	Retrospective cohort study 3	56 ± 17 y; 6 males (67)	DCM	c.2737G > A	LVEF: 38 ± 15 % LVIDD: 62 ± 9 LVIDS: 50 ± 9 IVS: 9 ± 2 PWS: 9 ± 1 severe MR: 1 (11)	NA	8 (89)	ICD: 1 HTX: 1. Death: 2 this study found strongly reduced protein levels in the heart of an RBM20. Lastly, an increased sarcomere resisting length in cardiomyocytes revealed an attenuated frank-Starling mechanism.
Mendirichaga et al.[17] 2017	2	United States	Case report 5	26 y; 1 male (50)	DCM	c.2749G > A	NA	0 (0)	2 (100)	LVAD: 1 HTX: 2
Miszalski-Jamka and Jefferies et al.	5	United States	Prospective cohort study 2	NA y; NA	NCCM	NA	Mean NC/C ratio of 3.3. Mean number of affected segments 9.4.	NA	NA	No patients had neuromuscular disease.

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Table 3 (*continued*)

First author year	Number of patients	Country	Type of study, quality rating	Mean age, Sex, n (%)	Phenotype (DCM/HCM/ NCCM)	RBM20 cDNA type variant	Imaging	VT/ VF, n (%)	Heart failure, n (%)	Outcome (ICD, HTX or LVAD, death) n (%)
[4] 2017							LVEF <50 % in 2 patients. No LGE			
Yao et al.[18] 2017	1	Australia	Case report 5	52 y; 1 male (100)	DCM	c.1900C > T	LVEF: 18 %	1 (100)	1 (100)	ICD: 1 (1 appropriate shock)
Khedraki et al. [19] 2018	1	United States	Case report 5	37 y; 0 males (0)	NCCM	c.1900A > G	LVEF: 30 %	1 (100)	1 (100)	ICD: 1
Murayama et al. [20] 2018	3	Japan	Case series 4	27 ± 14 y; 3 males (100)	DCM: 2 NCCM: 1	c.1900C > T, c.3091G > T	Median LVEF of 25 % [16–30]. LVIDD: 67 ± 15 LVIDS: 59 ± 13 IVS: 10 ± 1 PWS: 10 ± 1	2 (67)	3 (100)	SCA: 1 Death: 1 The study also demonstrates that RBM20 is phosphorylated in cells and that its phosphorylation on the RS-rich region is critical for its nuclear localization.
Pantou et al. [21] 2018	6	Greece	Case series 4	31 ± 15 y; 5 males (83)	DCM: 5 HCM: 1	c.1900C > T	LVEF: 42 ± 11 LVIDD: 61 ± 12	4 (80)	3 (60)	ICD: 3 Death: 2
Zareba et al. [22] 2018	7	United States	Retrospective cohort study 3	47 ± 8 y; 5 males (71)	DCM	c.2062C > T	Variant carriers had more mid-wall fibrosis by LGE than non-carriers (19 ± 12 % vs. 12 ± 7 %), and a lower LVEF(47 ± 14 % vs. 58 ± 4 %)	1 (20)	4 (67)	ICD: 3 Death: 1
Hey et al.[23] 2019	80	Denmark	Retrospective cohort study 3	37 ± 15 y; 31 males (58)	DCM	c.1901G > A, c.1906C > A, c.1907G > A, c.1913C > T, c.2737G > A	Males had a lower mean LVEF than females: 29 ± 13 % versus 38 ± 9 %; P < 0.01)	16 (30)	NA	Penetrance RBM20: 66 % (53/80) ICD: 16 (30) HTX: 11 (35) males, 0 females (p < 0.001) Death: 6 (11) males were significantly younger at diagnosis of RBM20 than females (age, 29 ± 11 years versus 48 ± 12 years; P < 0.01;.
Kiselev et al. [24] 2019	1	Russia	Case report 5	14 y; 1 male (100)	DCM	c.2737G > A	LVEF: 19 %	0 (0)	1 (100)	LVAD: 1
Parikh et al.[25] 2019	74	United States	Retrospective cohort study 3	46 ± 17 y; NA	DCM HCM: 5 (7 %)	c.1601–1640, c.1881–1920, c.2721–2760	LVEF: 40 ± 17 % LVEDD: 56 ± 12 LGE: 11 (50)	10 (25)	NA	Composite arrhythmias (AF, NSVT, ICD, SCA): 43 % LVAD: 1 HTX: 5 Death: 3
Sielemann et al. [26] 2020	4	Germany	Retrospective cohort study 3	38 ± 14 y; 4 males (100)	DCM	NA	LVEF: 27 ± 11 LVEDD: 72 ± 7 LVEDS: 65 ± 6 FS: 9 ± 4 %	NA	NA	LVAD: 1 HTX: 3
Sun et al.[27] 2020	2	China	Case series 4	12 y; 1 male (50)	NCCM & DCM	c.1907G > A, c.1909A > G	NC/C: 3/1 LVEF: 24 % LVEDD: 69 % severe tricuspid regurgitation	0 (0)	2 (100)	Death: 1

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Table 3 (*continued*)

First author year	Number of patients	Country	Type of study, quality rating	Mean age, Sex, n (%)	Phenotype (DCM/HCM/NCCM)	RBM20 cDNA type variant	Imaging	VT/VF, n (%)	Heart failure, n (%)	Outcome (ICD, HTX or LVAD, death) n (%)
Robles-Mezcua et al.[28] 2021	8	Spain	Case series 4	55 [52–59] y; 6 males (75)	DCM: 7 (87.5) HCM: 1 (12.5)	c.154C > A, c.529A > T, c.580A > G, c.776G > T, c.1793A > C	LVEF: 43 % [31–54] LVEDD: 58 [54–64] LGE: 3 (38)	3 (38)	8 (100)	ICD: 4 (50) (1 appropriate ICD therapy)
Dai et al.[5] 2021	45	China	Case-control study 3	52 ± 12 y; 32 males (71)	HCM	NA	LVEF: 55 ± 15 % LVEDD: 49 ± 10	3 (7)	32 (71)	SCA: RBM20 variant vs. non-RBM20 variant (6.7 % vs. 0.9 %; p = 0.001) RBM20 heterozygotes had higher incidences of resuscitated cardiac arrest, recurrent NSVT and MVA.
Das et al.[29] 2021	5	India	Case report 5	26 [19–60] y; 3 males (60)	DCM	c.1900C > T	LVEF 14 %	2 (40)	NA	Death: 2
Nielsen et al. [30] 2021	1	United States	Case report 5	17 y; 0 males (0)	DCM	c.1913C > A	LVEF: 20 %	0 (0)	0 (0)	HTX: 1 Patient with RBM20 variant combined with diGeorge syndrome.
Badshah et al. [31] 2022	2	United States & Pakistan	Case report 5	12 [10–13] y; 2 males (100)	NA	c.1587C > G	NA	NA	NA	2 patients with epilepsy who are homozygous for CNTNAP2, ALG6, RBM20, and PDZD7
Garmany et al. [32] 2022	40	United States	Retrospective cohort study 3	NA; 20 males (50)	DCM	NA	NA	11 (28)	4 (10)	ICD: 14 (35) RBM20 variant patients were more likely to have a family history of sudden cardiac arrest (78 % vs 34 %; $p < 0.0001$) than TTN variant patients.
Inagaki et al. [33] 2022	2	Japan	Case report 5	55 y; 0 males (0)	HCM	c.1907G > A	LVEF: 51 % LVEDD: 58	0 (0)	1 (50)	RBM20 c.1907G > A which has been reported in DCM, could be disease causing in HCM.
Lennermann et al.[34] 2022	33	The Netherlands	Retrospective cohort study 3	47 ± 13 y; 16 males (48)	DCM	c.233A > C, c.239A > C, c.773C > T, c.1880 + 1G > A, c.1881-139_2248del, c.1898C > T, c.1901G > T, 1907G > A, c.1913C > T, c.2042A > G, c.2131C > T, c.2303C > T, c.2357A > G, c.3623C > T, c.1900C > T	All patients LVEF: 33 ± 14 % c.1900C > T LVEF: 36 ± 13 %	8 (24)	24 (73)	ICD: 12 (36)
Malakootian et al.[35] 2022	5	Iran	Case report 5	33 ± 12 y; 2 males (40)	DCM	c.1907G > A	LVEF: 48 %	1 (50)	2 (40)	Penetrance: 67 %. Death: 1
Shen et al.[36] 2022	4	China	Retrospective cohort study 3	NA; NA	DCM	NA	NA	NA	NA	The study compared nonsynonymous variants and their occurrence frequencies with population data, and found 4 variants in the RBM20 gene with risk of sporadic DCM.
Cannie et al. [37] 2023	143	12 centres in EU, 1 in Australia	Retrospective cohort study 3	36 (20–47);	DCM	c.1900C > T, c.1901G > A c.1906C > A, c.1906C > T c.1907G > A, c.1913C > T	LVEF: 48 (37–58) LVED: 55 (50–60) LGE: 17(38)	30 (22)	20 (14)	After 86 (39–178 months follow-up, at 5 year follow-up 22 % of RBM20 patients vs. 4 % idiopathic

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Table 3 (*continued*)

First author year	Number of patients	Country	Type of study, quality rating	Mean age, Sex, n (%)	Phenotype (DCM/HCM/ NCCM)	RBM20 cDNA type variant	Imaging	VT/ VF, n (%)	Heart failure, n (%)	Outcome (ICD, HTX or LVAD, death) n (%)
				71 males (50)		c.2723 T > C, c.2737G > A c.2746G > A				LV systolic dysfunction patients had reached MVA or ESHF. Risk of MVA was similar in male and female RBM20 patients. RBM20 variant carriage conferred a 6.0-fold increase in risk of MVA/ESHF.
Manai et al.[38] 2023	5	Italy	Case series 4	25 ± 15 y; NA	NA	NA	NA	NA	NA	Mean age at diagnosis was significantly lower for pathogenic variant carriers compared to VUS carriers (25 ± 15 vs 46 ± 2 y; p = 0.04). No other differences were found between pathogenic and VUS group.
Current study 2023	63	The Netherlands UK	Retrospective cohort study 3	42 ± 15y; 29 males (46)	DCM: 50 NCCM: 2	c.237_298del, c.414delG, c.846_853delTTACGGAC, c.1118_1119delAG, c.1880 + 1G > A, c.1881-139_2248del, c.1900C > T, c.1906C > T, c.1907G > A, c.1912C>, c.1913C > T, c.2062C > T, c.2176G > A,c.2359G > T, c.2919delT, c.3598G > A	LVEF: 40 ± 14 LVED: 5 9 ± 9 LVES: 46 ± 17 IVS: 8 (7–9) PWT: 8 (6–8) LGE: 16 (43)	19 (31)	29 (46)	ICD: 18 (28) HTX: 7 (22) death: 1
Summary estimates	678			32 y; 279 males (53)	DCM: 496 (73) HCM: 54 (8) NCCM: 11 (2)		LVEF: 36 %	123 (24)	154 (39)	ICD implantation: 151 (33) HTx /LVAD 58 (12) death: 52 (11)

AF = atrial fibrillation; DCM = dilated cardiomyopathy; ESHF = end-stage heart failure; HCM = hypertrophic cardiomyopathy; HTX = heart transplantation; ICD = implantable cardioverter-defibrillator; IVS = interventricular septum; LGE = late gadolinium enhancement; LP/P = likely pathogenic/pathogenic; LVAD = left ventricular assist device; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic diameter; LVIDS = left ventricular internal systolic diameter; MVA = malignant ventricular arrhythmia; NA = not available; NC/C ratio = noncompacted to compacted ratio; NCCM = noncompaction cardiomyopathy; NSVT = non-sustained ventricular tachycardia; PWS = posterior wall thickness; SCA = sudden cardiac arrest; severe MR = Severe mitral regurgitation; VT/VF = ventricular tachycardia/ventricular fibrillation; VUS = variant of unknown significance. Quality rating scheme for studies and other evidence; 1 = properly powered and conducted randomized clinical trial or systematic review with meta-analysis; 2 = well-designed controlled trial without randomization or prospective comparative cohort trial; 3 = case-control study or retrospective cohort study; 4 = case series with or without intervention or cross-sectional study; 5 = opinion of respected authorities or case reports.

[43,44,46]. However, a RBM20 and LMNA show differences in conduction disease: while AV block occurs in 32–65 % of LMNA patients, only 2 % of our RBM20 cohort had second-degree AV block or higher, and 14 % showed bundle branch block [43,44,46]. The shared features and distinct differences between RBM20 and LMNA phenotypes suggest that pathological mechanisms may overlap in these nuclear gene-related cardiomyopathies.

The most frequently identified variant was c.1900C > T, which is a recurrent variant and were all observed in Dutch patients. A previous study has demonstrated that the c.1900C > T variant patients are descendants of a single founder [47]. Furthermore, this study is the first to describe a large cohort of patients with Tv *RBM20* variants. A previous study described two patients with Tv but could not provide clear evidence of their pathogenicity [48]. The current study identified 11 truncating variants in a total of 14 patients. The age of onset was by trend higher in Tv than the nTv group (48 ± 14 years vs. 42 ± 15 years; $p = 0.08$). However 6 out of 14 (43 %) patients with a Tv experienced VA attesting to still a substantial incidence of severe outcomes in Tv.

RBM20 missense variants have been shown to cause a gain of function, whereas truncating variants may produce hypomorphic alleles, leading to a milder phenotype. [49] This could possible explain the later age of onset in patients with Tv. Additionally, since RBM20 Tv have likely been underdiagnosed and not previously recognized as being pathogenic, fewer family members of patients with Tv may have been offered genetic testing compared to family members of patients with pathogenic missense variants. A recent review highlighted the RS-domain of RBM20 and included the C.1900C > T variant, which show gain-of-function effect and are phenotypically pathogenic [50]. This suggests that the Tv described in this study, are associated with a less severe phenotype than nTv.

4.1. Limitations

Participating centers were all specialist cardiomyopathy units leading to potential referral bias. The population numbers were limited so that only 35 out of 62 could be matched with the control group, thereby precluding multivariable cox analyses. This made it difficult to look for subgroups within RBM20 patients with an increased risk of VA and end-stage HF. The control group underwent genetic testing over multiple years, leading to variations in the gene panels used.

5. Conclusions

In this multicenter cohort, we describe 62 patients, with 16 *RBM20* variants, including 11 protein truncating variants. Truncating variant patients developed HF at older age, and frequently experienced VA. Male patients showed a more aggressive phenotype with increased risk for malignant VA and end-stage HF than female patients. Lastly, this study found a lower mortality rate than the literature.

CRediT authorship contribution statement

Martijn Tukker: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Wouter P. te Rijdt:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Ahmad S. Amin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **Deborah J. Morris-Rosendahl:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Data curation. **Alexander Hirsch:** Writing – review & editing, Supervision, Data curation. **Yael Ben-Haim:** Writing – review & editing, Validation, Project administration. **Arjan C. Houweling:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Amanda Varnava:** Writing – review & editing, Resources. **Elijah R. Behr:** Writing – review & editing. **Matthew Edwards:** Writing – review & editing, Project administration, Investigation, Data curation. **Alexander Vanmaele:** Writing – review & editing, Writing – original draft, Formal analysis. **Aida Hajdarpasic:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Jan von der Thusen:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Investigation, Formal analysis. **Michelle Michels:** Writing – review & editing, Data curation. **Rudolf A. de Boer:** Writing – review & editing, Supervision, Software, Resources, Conceptualization. **Marjon A. van Slegtenhorst:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Kadir Caliskan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Funding

None.

Declaration of competing interest

A. Hirsch received a research grant and consultancy fees from GE Healthcare and speaker fees from GE Healthcare, Bayer, and Bristol Myers Squibb. He is also a member of the medical advisory board of Medis Medical Imaging Systems and was MRI corelab supervisor of Cardialysis BV until 2022. The institution of Dr. De Boer has received research grants and/or fees from Alnylam, AstraZeneca, Abbott, Bristol-Myers Squibb, NovoNordisk, and Roche; Dr. de Boer has had speaker engagements with and/or received fees from and/or served on an advisory board for Abbott, AstraZeneca, Bristol Myers Squibb, NovoNordisk, Roche, and Zoll; Dr. de Boer received travel support from Abbott and NovoNordisk. A Manohar acknowledges support from the American Heart Association (AHA 24POST1187968). A. Owens reports consulting for Alexion, Avidity, Bayer, Bristol Myers Squibb, Cytokinetics, Edgewise, Imbria, Corvista, BioMarin, Lexeo, Tenaya, Stealth and research grant to the institution from BMS.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133350.

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