Clinical Research in Cardiology (2019) 108:1297–1308
https://doi.org/10.1007/s00392-019-01465-3

ORIGINAL PAPER

Clinical and genetic insights into non-compaction: a meta-analysis and systematic review on 7598 individuals

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Received: 31 January 2019 / Accepted: 19 March 2019 / Published online: 12 April 2019

Abstract

Background Left ventricular non-compaction has been increasingly diagnosed in recent years. However, it is still debated whether non-compaction is a pathological condition or a physiological trait. In this meta-analysis and systematic review, we compare studies, which investigated these two different perspectives. Furthermore, we provide a comprehensive overview on the clinical outcome as well as genetic background of left ventricular non-compaction cardiomyopathy in adult patients.

Methods and results We retrieved PubMed/Medline literatures in English language from 2000 to 19/09/2018 on clinical outcome and genotype of patients with non-compaction. We summarized and extensively reviewed all studies that passed selection criteria and performed a meta-analysis on key phenotypic parameters. Altogether, 35 studies with 2271 non-compaction patients were included in our meta-analysis. The mean age at diagnosis was the mid of their fifth decade. Two-thirds of patients were male. Congenital heart diseases including atrial or ventricular septum defect or Ebstein anomaly were reported in 7% of patients. Twenty-four percent presented with family history of cardiomyopathy. The mean frequency of neuromuscular diseases was 5%. Heart rhythm abnormalities were reported frequently: conduction disease in 26%, supraventricular tachycardia in 17%, and sustained or non-sustained ventricular tachycardia in 18% of patients. Three important outcome measures were reported including systemic thromboembolic events with a mean frequency of 9%, heart transplantation with 4%, and adequate ICD therapy with 15%. Nine studies investigated the genetics of non-compaction cardiomyopathy. The most frequently mutated gene was *TTN* with a pooled frequency of 11%. The average frequency of *MYH7* mutations was 9%, for *MYBPC3* mutations 5%, and for *CASQ2* and *LDB3* 3% each. *TPM1, MIB1, ACTC1*, and *LMNA* mutations had an average frequency of 2% each. Mutations in *PLN, HCN4, TAZ, DTNA, TNNT2*, and *RBM20* were reported with a frequency of 1% each. We also summarized the results of eight studies investigating the non-compaction in altogether 5327 athletes, pregnant women, patients with sickle cell disease, as well as individuals from population-based cohorts, in which the presence of left ventricular hypertrabeculation ranged from 1.3 to 37%.

Conclusion The summarized data indicate that non-compaction may lead to unfavorable outcome in different cardiomyopathy entities. The presence of key features in a multimodal diagnostic approach could distinguish between benign morphological trait and manifest cardiomyopathy.

Keywords Left ventricular non-compaction · Genetic background · Clinical outcome

Introduction

Non-compaction or cardiac hypertrabecularization is an increasingly recognized phenotype characterized by an increase in the non-compacted myocardium layer, prominent ventricular trabeculations, and deep intertrabecular recesses [1]. Using the current definitions of this morphological trait of myocardial structure, left ventricular non-compaction (LVNC) can be found in a broad spectrum ranging from completely healthy volunteers to severely diseased patients,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-019-01465-3) contains supplementary material, which is available to authorized users.

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as congenital condition presenting immediately after birth or as a phenotype acquired later during life [1–12]. These observations result in considerable uncertainties in classifying individuals with myocardial non-compaction in clinical practice. The European Society of Cardiology (ESC) and American Heart Association (AHA) do not provide guidelines on the diagnosis and treatment of LVNC, but categorize it as "unclassified cardiomyopathy" (ESC) or "genetic cardiomyopathy" (AHA) [13, 14].

Several studies have evaluated clinical aspects, genetics, and outcome of LVNC patients in smaller cohorts, generating a heterogeneous landscape of knowledge. Sequencing analyses, for instance, revealed a complex genetic architecture of the disease with mutations functionally affecting diverse genes. An autosomal dominant (AD) inheritance occurs more commonly than X-linked or autosomal recessive (AR) patterns, which is similar to other cardiomyopathy forms [15]. In the most contemporary studies, about 32–59% of LVNC cases could be explained by a pathogenic variant and the above-mentioned inheritance patterns [11, 16, 17]; the frequency of mutations in the different genes, however, is still unclear. The same is true for the incidence of complications observed in individuals with LVNC.

The aim of the current investigation was to provide a comprehensive view on the clinical presentation, outcome and the genetic background of adult individuals with LVNC by meta-analyzing and reviewing the available literature. The summarized data provide indicators for stratifying and prognosticating affected patients.

Methods

Study design and electronic literature search strategy

We searched PubMed/Medline for studies published in English language from 2000 to 19/09/2018 for the terms "noncompaction cardiomyoathy", "noncompaction myocardium", "noncompacted cardiomyopathy", "noncompacted myocardium", "non-compaction cardiomyopathy", "non-compaction myocardium", "non-compacted cardiomyopathy", "non-compacted myocardium", "left ventricular non-compaction", "hypertrabeculation", "spongy myocardium", or "honeycomb myocardium". We also carefully reviewed reference lists of original publications and review articles for missing studies. 1543 studies met our inclusion criteria. We first selected the publications by reading the abstracts and performed the final selection by reading full articles. To mention some excluded studies: 682 case reports, 5 clinical studies, 31 editorials, 1 guideline, 265 letters, 3 books and documents, 167 reviews, and 3 systematic reviews were excluded. Furthermore, articles were excluded if they had other cardiomyopathies than LVNC in focus, were non-human investigations, included duplicates or pediatric patients. Also studies with obviously high risk of bias in multiple areas, those with inappropriate study design or statistical methodology were excluded. In addition, we reviewed and summarized the results of eight studies investigating LVNC in healthy adults or population-based cohorts (four studies), in adult athletes (two studies), in pregnant women and in patients with sickle cell disease (one study each).

Selection of articles, data extraction and quality assessment

Of the 1543 identified articles, 1448 were excluded on the basis of review of the title and abstract (Suppl. Figure 1). Two reviewers (FS and AA) independently assessed full texts of 95 remaining manuscripts. Disagreements between reviewers were resolved by a third expert (EK). From 35 identified studies [11, 12, 15–46], data were extracted including author, year, sample size, age, gender, sequencing method, frequency of documented mutations, prevalence of ECG abnormalities, ICD therapy, heart transplantation (HTx), congenital heart disease (CHD), family history of cardiomyopathies, neuromuscular disorders (NMD), and thromboembolic events.

For gender and mean age at disease onset, 22 studies were included. For frequency of mutated genes in LVNC patients 9, for conduction disease 15, for supraventricular tachycardia (SVT) 17, for ventricular tachycardia (VT) 19, for NMD and HTx 8 studies each, for systemic thromboembolism 14, for family history of cardiomyopathies 11, for appropriate ICD therapy 5, and for CHD 4 studies were included.

Statistical analysis

The meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (*PRISMA*) [47]. We implemented random effects meta-analyses for all outcomes. The models were adjusted for binary and continuous variables, respectively. If no standard deviation (SD) was available for continuous outcomes, but minimum and maximum, the SD was estimated as SD = range/4 [48]. We estimated I^2 to quantify heterogeneity. R (version 3.4.3) and the package "meta" (version 4.9-1) was used to implement the models [49].

Results

To comprehensively analyze phenotypes and genotypes of LVNC, we performed a systematic review and meta-analysis. Altogether, after excluding redundant and pediatric

cohorts, 43 studies with 7598 adult individuals could be extracted. These studies were published between 2000 and 19th of September 2018. Thirty-five studies investigated LVNC in 2271 patients and included cohorts from Switzerland, Austria, USA, Japan, UK, Turkey, Italy, Netherlands, Germany, France, China, Spain, South Africa, and Senegal. From these, five used Chin criteria for the diagnosis of LVNC, 22 used Jenni criteria, three studies used Stöllberger criteria, and three studies implemented Petersen criteria. LVNC was diagnosed in Kohli et al. based on Chin, Jenni or Stöllberger criteria, in Stähli et al. based on Chin and Jenni criteria, in Peters et al. based on Jenni and Stöllberger criteria, and in van Waning et al. based on Jenni and Petersen criteria. In Sedaghat-Hamedani et al., LVNC was diagnosed if all three Jenni, Stöllberger, and Petersen criteria were fulfilled. Nine studies performed genetic analyses, from which 6 used Sanger sequencing and 3 Next Generation Sequencing (NGS). Whereas Sedaghat-Hamedani et al. performed whole exome sequencing, Tian et al. used a panel of 10 genes and van Waning et al. a panel of 45 cardiomyopathy-associated genes (Suppl. Table 1).

Eight studies were reviewed investigating the prevalence of an LVNC phenotype in obviously healthy individuals (four studies), adult athletes (two studies), pregnant women (one study), and in patients with sickle cell disease (one study), in altogether 5327 individuals (Suppl. Table 2).

Clinical findings and outcome in LVNC patients

Twenty-two studies, including 1750 LVNC patients, showed the mean age at diagnosis to be 45.7 years (95% CI 43.5–47.8) (Fig. 1a). Similar to other genetic cardiomyopathies, the male proportion was higher. Sixty-two percent of the patients (analyzed in 22 studies including 1746 patients) were male (95% CI 58–66%) (Fig. 1b).

Congenital heart diseases (CHD) were reported in four studies investigating 571 LVNC patients (Fig. 2a and Suppl. Figure 2A). Tian et al. reported a frequency of 5.26%, including one patient with atrial septal defect (ASD), one with ventricular septal defect (VSD), and one with Ebstein anomaly with ASD. Van Waning et al. reported six ASD, three VSD, two Ebstein anomaly, two bicuspid aortic valves, and one aortic coarctation in their cohort. The two patients with Ebstein anomaly carried likely pathogenic mutations in *MYH7* gene. No mutations were found in the remaining 12 patients. Stähli et al. reported a frequency of 12% LVNC in CHD patients. In this study, the prevalence of LVNC was the highest in patients with Ebstein anomaly, followed by aortic coarctation, tetralogy of Fallot, and uni- or bicuspid aortic valves [33]. Features resembling non-compaction were also reported in three patients with Ebstein anomaly in a report by Attenhofer Jost et al. [50].

Twenty-four percent of the patients (screened in 11 studies with altogether 897 LVNC patients) presented with positive family history for cardiomyopathies (95% CI 16–34%) (Fig. 2a and Suppl. Figure 2B). Interestingly, pedigrees of the LVNC index patients included relatives with LVNC, DCM, and/or HCM. The coincidence of neuromuscular diseases in LVNC patients was not investigated in all studies. The mean frequency (reported in 8 studies) was 5% with large variability (95% CI 1–22%), mostly due to high frequency of this comorbidity in Stöllberger et al. (Fig. 2a and Suppl. Figure 2C). Patients in this study were specifically scheduled for a neurologic investigation including blood, cerebrospinal fluid investigation, and, if indicated, a nerve biopsy. In case a myopathy was suspected, a screening program for myopathy including muscle enzymes, electromyography, and muscle biopsy was also initiated [16].

Heart rhythm abnormalities were described in most studies. Conduction diseases (AV blockage or bundle branch blocks) were investigated in 15 studies, including 1319 LVNC patients, and showed a mean frequency of 26% (95% CI 21–32%), with Oechslin et al. reporting the highest frequency in their cohort (12% with right bundle branch block and 44% with left bundle branch block) (Fig. 2a and Suppl. Figure 3A) [12]. Supraventricular tachycardia (SVT) showed a mean frequency of 17% (95% CI 13–21%) (Fig. 2a and Suppl. Figures 3B). Sustained VT (sVT) had a mean frequency of 8% (95% CI 3–22%) and 17 studies (986 patients) reported a mean frequency of sustained or non-sustained VT to be 20% (95% CI 14–28%) (Fig. 2a and Suppl. Figures 4A and 4B). All these heart rhythm abnormalities were either reported at first presentation or occurred during the follow-up period. Interestingly, some families with distinct gene mutations showed predominantly one specific type of arrhythmia, such as sick sinus node disease in *HCN4* carriers [51].

Three important clinical events were reported in LVNC patients: (1) systemic thromboembolic events, (2) heart transplantation, and 3 appropriate ICD therapiey. Systemic thromboembolic events including transient ischemic attacks (TIA), stroke, pulmonary embolism, or mesenteric infarction were reported in 14 studies with 1064 patients. The mean frequency was 9% (95% CI 7–12%) (Fig. 2a and Suppl. Figure 5A). In 22 of these patients, this was even the reported reason for the referral and led to diagnosis of LVNC. Impaired systolic function and sluggish blood flow are hypothesized to cause thrombus formation in deep intertrabecular recessus of the left ventricle (Fig. 2b).

Heart failure at presentation was a common finding with 42.7%, and the mean LV-EF at presentation was 37%. The mean rate of heart transplantation was 4% (95% CI 2–7%) (Fig. 2a and Suppl. Figure 5B). This did not include the

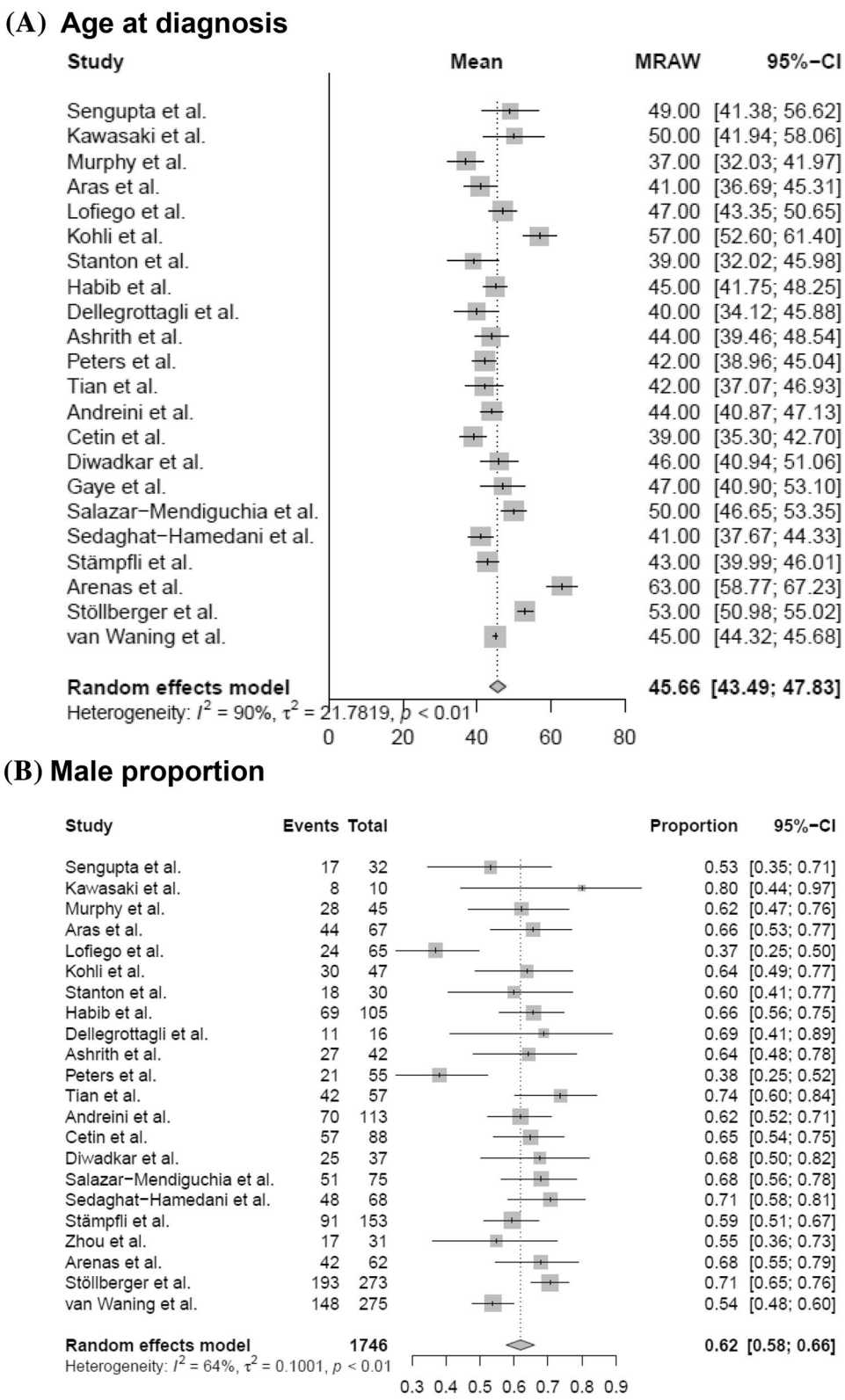

Fig. 1 Forest plot of mean age at LVNC diagnosis and male proportion in adult patients. **a** The mean age at diagnosis in LVNC patients is mid of their fifth decade of life. **b** Sixty-two percent of LVNC patients are male. *CI* confidence interval

patients who were listed for heart transplantation but died before having been transplanted. Fifteen percent of LVNC patients carrying ICD received appropriate ICD therapy (95% CI 7–29%) (Fig. 2a and Suppl. Figure 5C).

LVNC in asymptomatic individuals

Altogether 5327 individuals without apparent cardiovascular diseases were examined for the presence of LVNC. Different

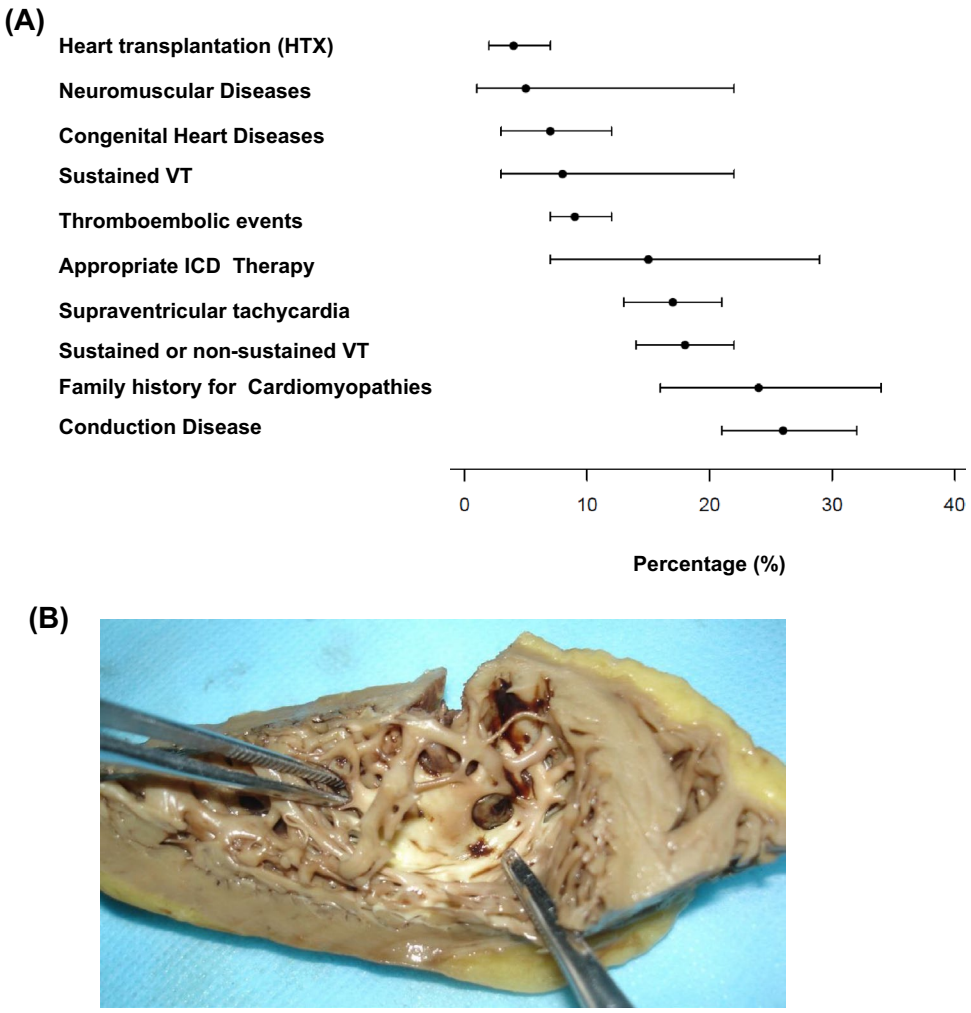

Fig. 2 Summary of relevant clinical findings and outcome in LVNC patients. **a** Relevant clinical findings, ECG abnormalities, and clinical outcome in LVNC patients **b** Thrombus formation in deep intertrabecular recessus in a 37-year-old male patient with LVNC

imaging-based diagnostic criteria for LVNC were applied, and the studies could confirm the presence of non-compacted myocardial regions in 1.3–37% of cases. Caselli et al. and Luijkx et al. investigated adult healthy athletes. Whereas Caselli et al. detected LVNC in 1.4% of 2501 athletes by implementing Jenni criteria, Luijkx et al. showed this to be as high as 21% by applying Petersen criteria [5, 6]. Four studies reported LVNC in population-based cohorts [7–10]. Cumulatively, the reported frequency had a mean of 16% (95% CI 6–33%) (Fig. 3). The study by Weir-McCall et al. showed a prevalence of 1.3–12.6% LVNC depending on the imaging-based classiciation and concluded that LVNC is an anatomical phenotype rather than distinct cardiomyopathy. Interestingly, the inclusion criteria for this study were a natriuretic peptide (BNP) level greater than the population median and patients meeting several imaging criteria had a significantly lower ejection fraction, both questioning the conclusion of the study that LVNC is only an anatomical

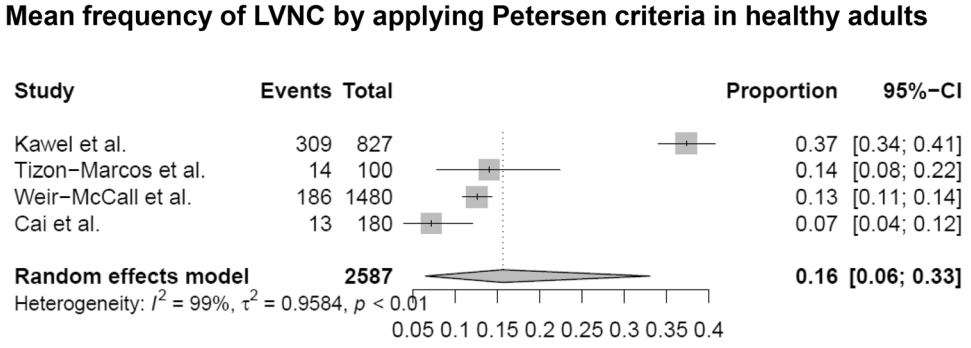

Fig. 3 Forest plot of reported mean frequency of LVNC by applying Petersen criteria in healthy adults. The mean frequency of LVNC is healthy adults according to Petersen criteria was 16% (95% CI 6–33%). *CI* confidence interval

feature [9]. By applying both Chin and Jenni criteria, Gati et al. showed an increase in the non-compacted to compacted layer (NC/C) ratio in 7.8% of pregnant women during the pregnancy. This hypertrabeculation showed complete regression in all but 5 women after the pregnancy. In a follow-up time of 24 ± 3 months, none developed abnormal systolic or diastolic functions or symptoms of heart failure [3]. In another study, Gati et al. showed that up to 20.8% of patients with sickle cell disease fulfilled Chin criteria for LVNC with only 5% showing an impaired LV function. Using both Chin and Jenni criteria, the percentage of their patients showing LVNC decreased to be 8.1% [52].

Genetics of LVNC

Altogether, nine studies investigated the frequency of gene mutations in LVNC patients. However, only in two studies, more than 20 genes were investigated in parallel, which hinders the analysis of detection sensitivity [11, 46, 53]. Also, the classification of pathogenicity of identified variants was differently performed, with only 1 study applying ACMG criteria [11]. The most frequently mutated gene was *TTN*, screened in 343 LVNC patients, showing a pooled frequency of 11% (95% CI 4–29%). Interestingly, TTN-interacting proteins are also among the LVNC disease causes, such as Nebulette or RBM20 [11]. Here, *RBM20* and truncating *TTN* variants were often reported to lead to worse outcome. Four studies with 451 patients screened for mutations in *MYH7*, resulting in a mutation frequency of 9% (95% CI 6–14%). Four studies screened for *MYBPC3* mutations and reported a frequency of 5% (95% CI 3–8%). For *LDB3*, 3 studies tested 196 LVNC patients and reported a pooled frequency of 3% (95% CI 1–8%). *CASQ2* had also a frequency of 3% (95% CI 1–9%). *TPM1, MIB1, ACTC1*, and *LMNA* had a frequency of 2% each in the LVNC patients. Mutations in *PLN, HCN4, TAZ, DTNA, TNNT2*, and *RBM2* were reported with a frequency of 1% each (Fig. 4, Suppl. Figure 6–9). Three studies separated frequency of mutations in *MYH7* between patients with and without family history for CMP. Whereas Klaassen et al. and Tian et al. showed no differences between the frequency of mutations in this gene between the two groups, the two cases with *MYH7* mutations from Sedaghat-Hamedani et al. had both a positive family history (Suppl. Table 3).

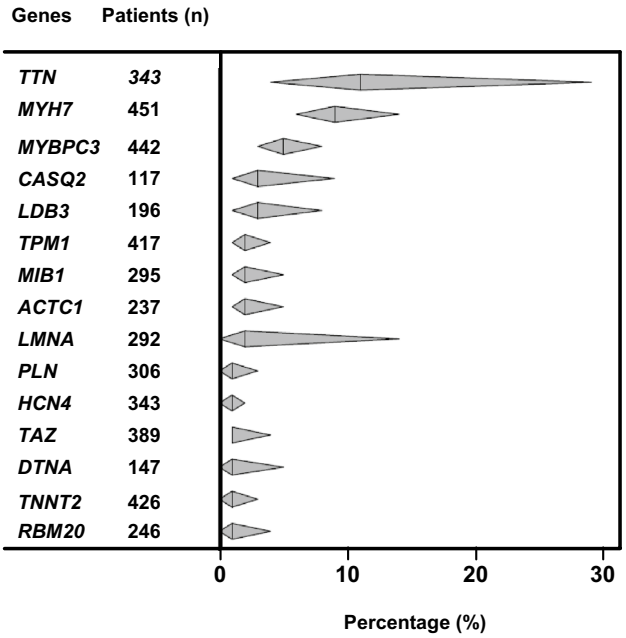

Fig. 4 Summary of forest plots of mutation frequencies in LVNC genes. The most frequently mutated genes were *TTN* (11%), *MYH7* (9%), and *MYBPC3* (5%); followed by *LDB3* and *CASQ2* (3% each), *LMNA, ACTC1, MIB1*, and *TPM1* (2% each). The frequency of mutations in *RBM20, TNNT2, DTNA, TAZ, HCN4*, and *PLN* were 1% each

Discussion

It is an ongoing and controversial debate whether left ventricular non-compaction and hypertrabeculation are pathological conditions with worse prognosis or benign morphological traits. To provide objective measures about the clinical presentation and prognosis of individuals with non-compaction, we performed this meta-analysis and show the considerable morbidity of LVNC presenting with signs or symptoms of cardiovascular disease. Our data reflect the findings in altogether more than 7500 individuals from clinical studies fulfilling scientific quality criteria and also provide comprehensive information on the genetic architecture of LVNC. Hence, the presented results can be regarded to be representative.

Towbin et al. characterized the broad phenotypic expressivity of LVNC and defined typical subtypes including benign LVNC with preserved systolic and diastolic function, dilated LVNC, hypertrophic LVNC, restrictive LVNC, and LVNC with arrhythmia [4]. It is also evident that LVNC is not necessarily present from birth, as shown in studies of athletes or pregnant women. Here, the phenotype seen in imaging can occur later in life and can also completely revert. Whether such individuals have a genetically distinct background or increased risk for development of manifest disease is currently not known. Zemrak et al., however, reported no clinically important deteriorations in healthy adults with hypertrabeculations 10 years after their first investigation by Kawel et al. [7, 54]. The presence of left ventricular hypertrabeculation in cohorts with no apparent cardiovascular diseases ranges from 1.3 to 37%. This lack of consistency might be due to applying different imaging criteria, with Petersen's criteria resulting in higher prevalence estimates. Also, differentiating trabeculae from papillary muscle, tendon or thrombi can be challenging in some cases

[8]. Another reason might be different percentages of black ethnicity in studies (0–100%), as ethnicity has been proposed to be an important determinant of myocardial response to increased loading conditions [52]. From these aggregated information, we and others derived a concept summarized in Fig. 5.

Similar to dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), LVNC is more frequent in male sex. In this meta-analysis, the prevalence of male patients was 62%. Stöllberger et al. observed no differences in age at diagnosis, symptoms, prevalence of NMD, ECG abnormalities, or mortality rate between males and females [56]. The reason why non-compaction cardiomyopathy or any other cardiomyopathy is identified more often in males than females is still unknown. A protective effect of sex hormones for symptom development in females or higher penetrance of gene mutations in males may play a role. It may be also that females with heart failure symptoms refer less often to cardiologists and are thus less often diagnosed [56]. Hypertrabeculation per se seems not to be depending on gender, since population-based studies indicate a balanced distribution in asymptomatic individuals (females: 1.4%, males: 1.1%) [9]. Hence, our finding of a male predominance

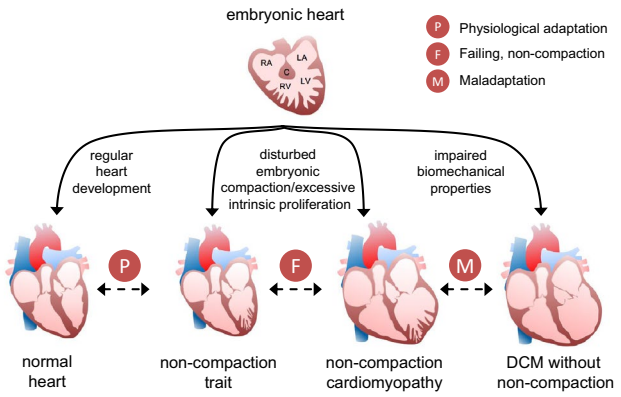

Fig. 5 Non-compaction trait vs. non-compaction cardiomyopathy. The physiological compaction process of the myocardium takes place in embryonic weeks 5–8. In case of disturbed myocardial compaction or excessive intrinsic proliferation, a non-compaction with hypertrabeculation results. During physiological adaptation (P), e.g., in competitive athletes, a non-compaction phenotype can arise de-novo and is not necessarily associated with worse prognosis. However, failing of the structurally altered myocardium can be observed in some cases (F). Heart failure, arrhythmia, and embolism are more frequently observed in the failing state (here called 'cardiomyopathy' instead of 'trait'). Pre-existing cardiac diseases (e.g., dilated cardiomyopathy, aortic regurgitation, ischemic heart disease) can result in secondary maladaptive non-compaction patterns (M). Positive family history for cardiomyopathies or sudden cardiac death, abnormal exercise test, syncope, symptoms of heart failure, elevated cardiac biomarkers, abnormal ECG or arrhythmia, and recurrent systemic embolisms are some hints for pathological state. *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle, *c* dorsal endocardial cushion. Inspired by Oechslin et al. [55]

throughout almost all published studies on LVNC patients indicates that there are additional factors that discriminate the course from asymptomatic hypertrabeulation to overt cardiomyopathy.

Congenital heart disease was reported in 7% of patients with LVNC. The LVNC phenotype in patients with CHD may either reflect a primary abnormality in the early myocardial development and can originate from the same gene mutation or it might be the result of hemodynamic changes such as pressure overload secondary to CHD. Thus, it might be highly relevant to compare phenotype and genotype of LVNC patients with and without CHD in future studies to better understand the series of events leading to the development of LVNC.

In the pooled dataset, about one-fifth of LVNC patients presented with ventricular arrhythmias, which is a remarkable risk factor. The high amount of fibrosis contributing to a mechanically less competent heart muscle architecture in non-compacted areas may play a role [53]. As such, Nucifora et al. observed late gadolinium enhancement (LGE) in 55% of patients with LVNC [57]. Also, the genetic causes of LVNC might contribute, with mutations in *TTN, LMNA, RBM20*, and other genes known to be causes of arrhythmia having a high prevalence in the investigated cohorts. It is still unknown whether or not patients with LVNC benefit from electrophysiology studies and catheter ablation. Taking into account the thin compacted myocardial layer, complication rates by catheter ablation and also after ICD-implantation may be increased. In the pooled dataset, 15% of LVNC patients who underwent ICD implantation for primary or secondary prevention had appropriate ICD shocks. Furthermore, Bertini et al. found that patients with DCM and hypertrabeculations showed better LV reverse remodeling after cardiac resynchronization therapy (CRT) compared to those DCM patients without hypertrabeculation [58]. Interestingly, the chance of being CRT-responder and showing LV reverse remodeling was higher the more non-compacted segments were observed in a patient [58]. Altogether, these suggest that ICD or CRT-D implantation should be considered a valid therapy.

The rate of systemic thromboembolism, including stroke and TIA, was 9% in this meta-analysis. Heart failure is associated with a prothrombotic status leading to an increased incidence of LV thrombi, ischemic strokes and other arterial and venous thromboembolic events [59]. There is still insufficient evidence for recommending initiation of anticoagulation in patients with non-ischemic heart failure and sinus rhythm. Impaired systolic function and deep intertrabecular recessus might increase the risk of thrombus formation by sluggish blood flow [2]. In one of our recent studies, 10.3% of LVNC patients had systemic embolism. This seems to occur independently of atrial fibrillation (AF) since 4.5% of patients without AF at baseline or during follow-up

developed systemic embolism. However, paroxysmal AF could not be excluded in these patients for certain [11]. Only prospective trials can provide evidence on the usefulness of primary prophylactic anticoagulation.

Twenty-four percent of LVNC patients in our pooled data had positive family history for cardiomyopathies. In 38–59% of patients with LVNC, mutations in genes with cardiac function could be identified [11, 46, 53]. Similar to other cardiomyopathies, autosomal dominant inheritance is more common than X-linked or autosomal recessive inheritance [2, 60] and *TTN, MYH7*, and *MYBPC3* are the most frequently mutated genes in these patients. LVNC patients with mutations in cardiac genes develop left ventricular systolic dysfunction more often, have higher number of non-compacted segments, and show more late gadolinium enhancement (LGE) as well as neuromuscular diseases [11, 46, 53]. Due to small cohort sizes, there are still insufficient data for genotype–phenotype correlations. However, some studies could report 'red flags' for distinct genotype-phenotype associations. For instance, Schweizer et al. reported that the symptom complex of sinus bradycardia and hypertrabeculation is associated with *HCN4* mutations [51]. This finding could be confirmed by independent groups and in a number of families [61, 62]. While patients with *LMNA, RBM20*, and truncating Titin variants (*TTNtv*) seem to have unfavorable outcomes, patients with *MYH7* mutations could have lower risk for cardiovascular events [11, 46]. This could also be observed in DCM patients, but not in patients with hypertrophic cardiomyopathy (HCM) [63, 64]. The mechanisms how the gene mutations translate into a LVNC phenotype are still not fully understood. In case of *TTN*, it is known that normal Titin structure and function are required for proper sarcomere assembly, force transmission, molecular signalling via associated proteins and sarcomere elasticity and that disturbances in these mechanisms might lead to manyfold molecular events, as shown by inhibition of major signalling pathways involving transforming growth factor-β (TGF-β), vascular endothelial growth factor, and mitogen-activated protein kinases [65, 66]. In animal models, *TTN*tv has also resulted in a shift in cardiac metabolism away from the use of long-chain fatty acids to glycolysis, which is an established, short-term adaptive response of the heart to stressors [67, 68] and which can active mTORC1-dependent cascades [69]. The principal foundation of the pathophysiological series initiated by truncating *TTN* variants is nonsense-mediated decay of the protein-truncating variant mRNA. Alternatively, a abnormal protein can be produced by alternative splicing events or partial read-through of the ribosomes with the resulting product staying inactive (loss of function) or even being deleterious, for instance by forming aggregates or inhibiting the function of the wild-type protein [70]. In case of LVNC cardiomyopathy, Sedaghat-Hamedani et al. identified 12 *TTN*tv in 68 index patients. These were mainly located in the A-band, which is a region that harbors most pathogenic Titin variations described in DCM. mRNA-sequencing from myocardial biopsies from 3 Stop-gain variant carriers of this cohort suggested nonsense-mediated RNA-decay (NMD) to be the most likely pathomechanism leading to loss-of-function of the mutated Titin-allele and most likely a gene dosage effect. Furthermore, they identified in a family with genetic LVNC cardiomyopathy a novel variant p.R634L in the RS domain of the *TTN* splice-factor "*RNA Binding Motif Protein 20*" (*RBM20*), which led to TTN mis-splicing, resulting in giant *TTN* isoforms (G-N2BA), which showed differences to mis-splicing observed in RBM20-caused DCM [11].

Till now, there are only a limited number of appropriate disease models for LVNC to investigate above mentioned disease hypotheses. MIB1 loss-of-function, for instance, or Tafazzin knock-down in mice largely resembles the human LVNC cardiomyopathy phenotype, regarding morphology, arrhythmia and decreased survival rates [34, 71, 72]. By this approach and using iPS-systems, NOTCH and TGF-β signalling could be identified as a central pathway in developing non-compaction phenotype [34, 73]. Whereas many studies suggested that the predominant pathomechanism of LVNC is lack of compaction of the trabecular layer, recent experimental work hypothesized that the compacted layer results from intrinsic proliferation [74, 75]. Hence, it is currently difficult to fully embark on models of LVNC, which underlines the importance of robust data derived from patient studies.

Limitations

This meta-analysis was based on published results and aggregated data from the respective cohorts. There is a substantial chance of selection bias, since there is a high chance that preferentially patients with comorbid conditions or clinically apparent symptoms were screened with echocardiography and diagnosed with LVNC. The diagnosis of LVNC in individual studies was made using different imaging-based classification systems, e.g., echocardiography-based (e.g., Chin, Jenni or Stöllberger criteria) or MRI-based criteria (e.g., Petersen criteria) [76]. The algorithms were developed in well-characterized cases of diseased patients, but neglected the findings in larger populations of asymptomatic individuals [9]. Some of these diagnostic criteria have also been adapted during the years.

Conclusion

Our data summarize the clinical presentation of non-compaction in a considerably large dataset. The presented data indicate that the morphological trait of non-compaction alone is not sufficient to predict worse prognosis. Hence,

we recommend that if non-compaction is observed in cardiac imaging, careful clinical investigation and taking an (familial) anamnesis should follow. If there are signs, symptoms or history of cardiomyopathy in the family, a multimodal diagnostic workflow with clinical examination, ECG, cardiac imaging, cardiac biomarkers and family/genetic screening should be conducted to distinguish between benign morphological trait and manifest cardiomyopathy. Also, systematically follow-up of these individuals is recommended by the authors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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