Prognostic significance of left ventricular non-compaction:

A systematic review and meta-analysis of observational studies

Brief title: Meta-analysis of prognosis in LVNC

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Manuscript word count: 4381

ABSTRACT

Background: Although left ventricular non-compaction (LVNC) has been associated with an increased risk of adverse cardiovascular events, the accurate incidence of cardiovascular morbidity and mortality is unknown. We therefore aimed to assess the incidence rate of LVNC-related cardiovascular events.

Methods: We systematically searched observational studies reporting the adverse outcomes related to LVNC. The primary end-point was cardiovascular mortality.

Results: We identified 28 eligible studies enrolling 2501 LVNC patients (mean age: 46 years, male/female ratio: 1.7). After a median follow-up of 2.9 years, the pooled event rate for cardiovascular mortality was 1.92 (95% CI: 1.54 – 2.30) per 100 person-years. LVNC patients had a similar risk of cardiovascular mortality compared to a DCM control group (odds ratio: 1.10, 95% CI: 0.18 – 6.67). The incidence rates of all-cause mortality, stroke and systemic emboli, heart failure admission, cardiac transplantation, ventricular arrhythmias and cardiac device implantation were 2.16, 1.54, 3.53, 1.24, 2.17, and 2.66, respectively, per 100 person-years. Meta-regression and subgroup analyses revealed that left ventricular ejection fraction (LVEF), not the extent of left ventricular trabeculation, had an important influence on the variability of incidence rates. The risks of thromboembolism and ventricular arrhythmias in LVNC patients were similar to dilated cardiomyopathy (DCM) patients. However, LVNC patients had a higher incidence of heart failure hospitalization than DCM patients.

Conclusions: Patients with LVNC carry a similar cardiovascular risk when compared with DCM patients. LVEF, a conventional indicator of heart failure severity, not the extent of trabeculation, appears to be an important determinant of adverse outcomes in LVNC patients.

PORSPERO registration ID: CRD42018096313

Abbreviations

CMR, cardiovascular magnetic resonance

DCM, Dilated cardiomyopathy

HCM, Hypertrophic cardiomyopathy

ICD, Implantable cardioverter defibrillator

LVEDD, Left ventricular end-diastolic diameter

LVEF, Left ventricular ejection fraction

LVNC, Left ventricular non-compaction

LVNC:C, Left-ventricular non-compaction to compaction ratio

NYHA, New York Heart Association classification

QUIPS, Quality In Prognosis Studies

Keywords

Left ventricular non-compaction; Excessive trabeculation; Prognosis

CLINICAL PERSEPCTIVE

In this large meta-analysis of adult patients with left ventricular non-compaction (LVNC) identified by currently accepted imaging criteria, the incidences of objective cardiovascular outcomes appear comparable to those observed in dilated cardiomyopathy. The frequency of adverse outcomes is mostly driven by left ventricular systolic impairment rather than the burden of trabeculation. The diversity of current imaging diagnostic criteria for LVNC creates significant challenges for accurate phenotyping. Further prospective clinical registries with access to individual-level data are required to standardize the LVNC diagnostic criteria, co-morbidities and outcome measures to fully evaluate the prognostic markers of this poorly understood condition.

INTRODUCTION

Left ventricular non-compaction (LVNC) cardiomyopathy is characterized by prominent left ventricular (LV) trabeculations, deep intertrabecular recesses communicating with the ventricular cavity, and a thin and compacted epicardial layer. While LVNC is considered a genetic cardiomyopathy by The American Heart Association [1], the European Society of Cardiology categorizes it as an unclassified cardiomyopathy [2]. Multiple etiologies of the LVNC phenotype have been proposed: it may be familial (inherited) or non-familial (sporadic and proven absent in relatives), and may occur as an isolated disease or in association with genetic diseases and congenital defects [3]. Non-familial and sporadic forms have been described in highly-trained athletes [4], sickle cell anemia [5] and pregnancy [6]. The genetic basis of familial LVNC is still controversial. Most familial cases of LVNC are associated with mutations

in the same genes associated with other types of inherited cardiomyopathies (Figure 1A) [7].

The diagnosis of LVNC has conventionally been made by imaging the left ventricle and demonstrating the presence of specific criteria based mostly upon the relative thickness of the compacted myocardial wall and the mesh of trabeculated ("non-compacted") layer of cardiac muscle using either echocardiography or cardiovascular magnetic resonance (CMR) imaging (**Figure 1B**). All current methodologies used to establish a diagnosis have strengths and weaknesses in how they are derived, their ease of use, the time to acquire the relevant images and their diagnostic accuracy, but there is no evidence to suggest that any particular criteria or imaging modality is superior. However, as image quality and awareness of diagnostic criteria have improved, the LVNC phenotype has emerged as an increasingly-recognized finding with the inherent risk of over-diagnosis noted as a significant concern [8].

The clinical outcomes of LVNC vary widely in the reported literature which perhaps reflects the underlying diversity of study cohorts. In view of the continued uncertainty, we conducted a systematic review of observational cohort studies to explore the clinical outcomes of patients considered to be affected by LVNC.

METHODS

The data, analytic methods and study materials can be obtained from the corresponding author for purposes of reproducing the results or replicating the results. Since this is a meta-analysis of aggregate data from the published literature, no informed consent was

required. Likewise, since we have not recruited new patients, an institutional review board's approval was not necessary.

We aimed to explore the adverse outcomes of patients with LVNC through a systematic review of the literature including prospective longitudinal and retrospective observational studies. The complete study protocol was registered on PROSPERO – an international database of prospectively registered systematic reviews – and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018096313.

We recognized the challenges associated with meta-analyses of observational studies due to variable study designs and inherent biases. Therefore, we conducted this systematic review following the recommendations by the Meta-analysis of Observational Studies in Epidemiology group [9] and the PRISMA guidelines [10].

Search strategy

We searched PubMed and Embase databases, the Cochrane Database of Systematic Reviews, the PROSPERO database (www.crd.york.ac.uk/prospero), and the Clinical Trials Registry (www.clinicaltrials.gov), as well as abstracts from major cardiological societies for potentially relevant articles using a combination of keywords related to trabeculation or LVNC and the cardiovascular outcomes for the period from 1st January 1966 to 3rd July 2019 without any language restriction. Details of the search terms are provided in Supplemental material online.

Selection criteria

Inclusion criteria were: (i) patients over 18 years old; (ii) a diagnosis of LVNC by echocardiographic or CMR criteria; (iii) crude and/or adjusted event rates of all-cause mortality, cardiovascular (CV) mortality, ventricular arrhythmias, sudden cardiac death, heart failure hospitalization, myocardial infarction, stroke, systemic embolic events, new cardiac implantable electronic device and heart transplantation. Definitions of excessive trabeculation according to cardiac imaging were defined by Petersen [11], Chin [12], Jenni [13], Jacquier [14], Grothoff [15], Stacey [16], Stöllberger [17] or Captur [18] criteria. We excluded case reports, non-outcome studies and reviews.

Data extraction

Two authors (F.R., S.D.) performed the screening of titles and abstracts, reviewed the full-text articles, and determined their eligibility. Divergences were solved by consensus and/or involving the third author (N.A.). We also hand-searched the reference list of all eligible articles for additional relevant studies.

We collated study-level covariates and events reported in original publications, using a standardized data extraction form. We translated relevant non-English articles into English. We contacted the authors of studies where clarification of data was required. In studies with overlapping cohorts, we used the data from the most recent study and/or the study with the largest sample size.

Quality assessment

We assessed the individual study-level quality by the Quality In Prognosis Studies (QUIPS) tool [19] which evaluates 32 key considerations across six bias domains: (i) Study Participation, (ii) Study Attrition, (iii) Prognostic Factor Measurement, (iv) Outcome Measurement, (v) Study Confounding, and (vi) Statistical Analysis and Reporting. An overall quality grade (high quality, intermediate quality, low quality) was assigned to each study after considering all six bias domains. Two authors (M.K. and A.A.) independently rated the quality items and disagreements were resolved by another author (N.A.).

Outcomes

The primary end-point was the incidence of CV mortality. Secondary end-points included incidences of all-cause mortality, stroke and systemic embolic events, heart failure requiring hospitalization, cardiac transplantation, ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation) and cardiac device implantation defined as insertion of implantable cardioverter defibrillator (ICD) or cardiac synchronization therapy with ICD.

Statistical analysis

Dichotomous variables were reported as percentages, with continuous variables reported as mean±standard deviation (SD) or median (interquartile range [IQR]), based on data distribution. For each included study, we calculated an event rate with its 95% confidence interval (CI) for every predefined outcome. Event rates were computed as the ratio between the number of events and the person-time in years at risk, in order to account for the heterogeneity of follow-up duration across different studies. We

performed Freeman-Tukey transformation [20] of the number of events for variance stabilization. We added 0.5 to the count in studies with zero event to achieve numerical stability. For studies reporting the event rates in both LVNC subjects and non-LVNC controls, we calculated odds ratio (OR) and 95% CI for each outcome.

We used random-effects models to estimate the summary pooled event rates or odd ratios of pre-specified outcomes using the DerSimonian and Laird method. We graphically presented the results in forest plots, with point estimates of the effect size and 95% CI for each study and the combined estimate. The area of squares and diamonds in the forest plots are proportional to each study weight.

We assessed funnel plot asymmetry which could result from publication bias. We additionally used the Egger's regression asymmetry test for end-points with asymmetric funnel plots. We also performed the non-parametric 'trim-and-fill' procedure which adjusts for funnel plot asymmetry by computing hypothetical missing studies. We formally assessed statistical heterogeneity by a chi-squared test, and quantified it using the inconsistency index (I^2) statistic, which ranges from 0 to 100% and is defined as the percentage of observed between-trial variability that is due to heterogeneity rather than chance. A lack of homogeneity was considered to be significant with an $I^2 \geq 50\%$. We anticipated a high degree of heterogeneity across individual studies due to the multiplicity of LVNC diagnostic criteria and the variability of inclusion and exclusion criteria used by individual studies. Accordingly, we used random-effects models to account for the between-study variabilities in the effect estimates. To explore the possible reasons of heterogeneity, we performed the following secondary analyses: (i)

univariate meta-regression assessing the mediating effect of age, sex (percentage of men), New York Heart Association (NYHA) classification, left ventricular end-diastolic diameter (LVEDD), and left-ventricular non-compaction to compaction ratio (LV NC:C) (for thromboembolic endpoint, we additionally investigated the mediating effects of the percentage of prevalent atrial fibrillation); (ii) subgroup analyses according to person-time at risk in years (sample size multiplied by mean follow-up years), presence of moderate-to-severe left ventricular systolic dysfunction (LVEF < 45%) at the time of recruitment, and overall quality of included studies. We also sought to compare the event rates of the LVNC patients in our study with a recently published meta-analysis of non-ischemic dilated cardiomyopathy (DCM) patients [21], which reported the incidences of cardiovascular mortality, heart failure hospitalization and ventricular arrhythmias. We extracted the sample size, absolute number of events and follow-up duration of individual studies from this DCM meta-analysis to calculate the incidence rate per 100 person-years. The difference in effect estimates between the disease groups and subgroups were assessed with Z-test. We evaluated the impact of a single study on the overall pooled estimate in meta-analysis by removing one study at a time and recomputing the pooled result – this procedure is known as 'leave-one-out' analysis. Additional details on the statistical tests were outlined in Supplemental material online.

A two-sided p-value < 0.05 was considered statistically significant. We performed all analyses and constructed graphs using the 'metafor' package [22] in R version (3.5.0) [23].

RESULTS

Our search strategy yielded 2879 studies, of which 94 full texts were relevant for evaluation (**Figure 2**). Exclusion of non-relevant studies, review articles and studies with duplicated cohorts resulted in 28 publications related to outcomes in LVNC. Searches of the Clinical Trials Registry identified one ongoing study titled "Prognosis of Isolated Left Ventricular Non-compaction in Adults" in France.

The final list (28 studies) consisted of 13 prospective and 15 retrospective observational studies. The studies were published between 1997 and 2019. A total of 2501 patients were included (mean±SD age: 46±7 years, male/female ratio: 1.7) with an overall median follow-up of 2.8 (IQR: 2.3 – 4.1) years. Although the diagnosis of LVNC was based mainly on quantification of excessive trabeculation, the majority of included studies (18 out of 28) comprised cohorts with significantly impaired LV systolic function (mean LVEF < 45%). The main characteristics of included studies are presented in **Table 1** [24–51]. Among 28 studies, the distribution of overall study quality was 18%, 50% and 32% for high, intermediate and low quality, respectively (**Figure 3**).

Primary outcome

Out of 28 included studies, 22 studies provided data on CV mortality in a total of 1822 patients who were followed up for a median (IQR) duration of 2.9 (2.4 – 4.4) years. The pooled incidence rate of CV death was 1.92 (95% CI: 1.54 – 2.30) per 100 person-years (**Figure 4** [25–31,33–38,40–44,47–50]). The funnel plot for the primary outcome appeared asymmetric due to the absence studies in the lower left corner, raising the possibility of publication bias (Egger's regression asymmetry test p = 0.048). Addition of

hypothetical "missing" studies (N = 6) by the trim-and-fill method reduced the pooled CV mortality rate to 1.64 (95% CI: 1.29 – 1.98) per 100 person-years (**Figure 5**).

We observed a substantial between-study heterogeneity (I^2 = 89.6%, p < 0.0001). Therefore, we explored the clinical and statistical sources of heterogeneity by meta-regression and subgroup analyses. The meta-regression analyses investigating the mediating effects of age, proportion of men, proportion of patients with NYHA > 2, LVEDD and LV NC:C did not identify any significant association. In subgroup analyses, studies enrolling patients with moderate-to-severe LV impairment (LVEF < 45%) appeared to have a higher incidence of cardiovascular mortality, compared to studies including patients with mildly impaired or normal LV systolic function (LVEF ≥ 45%) (2.21, 95% CI: 1.82 – 2.61 CV deaths per 100 person-years, I^2 = 76.5% vs 1.19, 95% CI: 0.26–2.13 CV deaths per 100 person-years, I^2 = 93.2%, p for subgroup difference = 0.048). There was no significant difference in event rates when stratified by person-time at risk (an amalgamation of sample size and follow-up duration) of more than 3 years and high/intermediate vs low quality studies (**Figure 6**).

The overall estimate of CV mortality did not change significantly in the leave-one-out sensitivity analysis indicating that no single study had an overwhelming impact on the combined meta-analysis estimate (**Supplemental Figure 1**).

Secondary outcomes

All-cause mortality

Twenty-four studies documented the incidence of all-cause mortality in 2122 patients over a median (IQR) follow-up of 2.6 (2.1 – 4.0) years. The pooled incidence rate of all-cause mortality was 2.16 (95% CI: 1.90 – 2.42) per 100 person-years (**Supplemental Figure 2**). The funnel plot and Egger's regression asymmetry test suggest possible publication bias (Egger's test p = 0.006). After addition of six hypothetical studies in the trim-and-fill sensitivity analysis, the pooled incidence rate decreased to 1.88 (95% CI: 1.60 – 2.16) per 100 person-years.

There was a substantial statistical heterogeneity among studies (I^2 = 78.1%, p < 0.0001). In meta-regression analyses, the proportion of male sex and the percentage of individuals with NYHA > 2 were positively associated with all-cause mortality. In subgroups stratified by LVEF, studies including patients with moderate-to-severe LV impairment (LVEF < 45%) appeared to have a higher incidence of all-cause deaths (p for subgroup difference = 0.011). The leave-one-out analysis was consistent with the overall result.

Stroke and systemic emboli

The event rates of stroke and systemic emboli was reported in 15 studies accounting for 1332 patients with a median (IQR) follow-up of 2.7 (2.4 – 3.8) years. The pooled incidence rate was 1.54 (95% CI: 1.22 – 1.86) per 100 person-years (**Supplemental Figure 3)**. We did not observe asymmetry in the funnel plot. Similar to the primary outcome, we identified a substantial heterogeneity among studies (I^2 = 73.4%, p < 0.0001). Meta-regression analyses did not reveal any mediating influence of age, sex, NYHA classification, LVEDD or prevalent AF. Stratification by the study quality, LVEF or person-time at risk did not show significant differences in the events rates

between subgroups. The leave-one-out sensitivity analysis showed no evidence of bias introduced by any one study.

Heart failure hospitalization

Twelve studies (1028 patients, median [IQR] follow-up: 2.5 [2.1 – 2.9] years) reported the incidence of heart failure hospitalization. The pooled event rate of heart failure hospitalization was 3.53 (95% CI: 2.95 – 4.11) per 100 person-years (**Supplemental Figure 4**). The funnel plot did not appear asymmetric. There was a considerable between-study heterogeneity (I^2 = 87.7%, p<0.0001). Meta-regression analyses identified a positive association between the proportion of symptomatic heart failure (NYHA > 2) at baseline and the incidence of heart failure admission at follow-up (regression coefficient = 0.04 per 1% increase in proportion of cohort with NYHA > 2, p = 0.049). In subgroup analyses, studies with an aggregate person-time at risk > 300 years appeared to have a lower incidence rate (2.77, 95% CI: 1.89 – 3.66, I^2 = 92.5% vs 3.97, 95% CI: 3.34 – 4.60 per 100 person-years, I^2 = 71.6%, p for subgroup difference = 0.031). The leave-one-out analysis was consistent with the overall pooled estimate.

Heart Transplantation

Data on cardiac transplantation rate was available in 14 studies (1576 patients, median [IQR] follow-up: 2.8 [2.4 – 4.9] years). The overall pooled event rate of heart transplantation was 1.24 (95% CI: 0.98 – 1.50) per 100 person-years (**Supplemental Figure 5**). The funnel plot showed sparsely distributed studies with evidence of asymmetry (Egger's p < 0.0001). After addition of one hypothetical study in the trim-and-fill sensitivity analysis, the pooled incidence rate decreased minimally to 1.22 (95%

CI: 0.96 – 1.48) per 100 person-years. The statistical heterogeneity of studies reporting heart transplantation outcome was substantial (I^2 = 71.6%, p < 0.0001). Meta-regression analyses did not reveal any mediating effect of the selected covariates. We again found a lower incidence of heart transplantation in the subgroup with an aggregate person-time at risk > 300 years (1.04, 95% CI: 0.81 – 1.26, I^2 = 60.3% vs 1.79, 95% CI: 1.31 – 2.27 per 100 person-years, I^2 = 35.1%, p for subgroup difference = 0.005). No undue influence from any single study was detected in the leave-one-out analysis.

Ventricular arrhythmias

Nineteen studies with a total sample size of 1445 (median [IQR] follow-up of 2.8 [2.4 – 3.8] years) documented the incidence of ventricular arrhythmias. The calculated pooled event rate was 2.17 (95% CI: 1.78 – 2.56) per 100 person-years (**Supplemental Figure 6**). There was no convincing evidence of publication bias in the funnel plot (Egger's p = 0.05). We identified a substantial heterogeneity among studies (I^2 = 84.4%, p < 0.0001). Meta-regression analyses did not find any significant association with covariates but the subgroup with moderate-severe LV impairment (LVEF < 45%) appeared to have a higher incidence of ventricular arrhythmias (2.30, 95% CI: 1.72 – 2.88, I^2 = 88.4% vs 1.60, 95% CI: 1.23 – 1.97 per 100 person-years, I^2 = 0%, p for subgroup difference = 0.047). The leave-one-out analysis did not show any significant deviation from the overall pooled result.

Cardiac device implantation

The incidence of cardiac device implantation was recorded in 15 studies (1278 patients, median [IQR] follow-up of 2.9 [2.0 – 3.8] years). The pooled incidence rate was 2.66

(95% CI: 1.93 – 3.39) per 100 person-years (**Supplemental Figure 7**). The funnel plot appeared sparse but symmetric. A considerable between-study heterogeneity was present (I^2 = 95.3%, p < 0.0001). The meta-regression analyses identified a negative association between the proportion of male sex and the incidence of cardiac device implantation (regression coefficient = -0.06 per 1% increase in male sex proportion, p = 0.04). Stratified analyses did not find any significant subgroup difference although the inconsistency index (I^2) appeared much lower in some subgroups. We did not find any indication of bias in the leave-one-out analysis.

Comparison with DCM

Two studies out of 22 reported the incidence of CV death in a comparable group of DCM patients. Overall, the LVNC patients did not have significantly higher CV mortality than the DCM group (pooled OR: 1.10, 95% CI: 0.18 – 6.67) (**Figure 7** [43,44]). The pooled event rate of CV death in a previously published meta-analysis of DCM patients [21] (19 studies enrolling 2466 individuals) was comparable to the pooled event rate observed in our study (DCM: 1.92, 95% CI: 1.44 – 2.39 CV deaths per 100 person-years vs. LVNC: 1.92, 95% CI: 1.54 – 2.30 CV deaths per 100 person-years) (**Figure 6, panel D**). Two studies out of 24 provided all-cause mortality data in a DCM control group. In comparison with the DCM group, patients with LVNC did not have significantly higher mortality (pooled OR: 0.67, 95% CI: 0.28 – 1.59). When compared with an external previously published DCM meta-analysis [21], the heart failure hospitalization rate in our study was significantly higher (3.53 vs 2.37 per 100 person-years, p = 0.003). There was no significant difference in the incidence rate of ventricular arrhythmias between our study and the previous DCM meta-analysis [21] (2.17 for LVNC vs 2.14 for DCM per 100 person-years, p = 0.93).

DISCUSSION

In this meta-analysis investigating the prognosis of a large population of adult LVNC patients classified according to contemporary imaging criteria, we identified the following key findings: (i) the overall incidence rates of cardiovascular mortality, all-cause mortality, stroke and systemic emboli, heart failure admission, cardiac transplantation, ventricular arrhythmias and cardiac device implantation were 1.92, 2.16, 1.54, 3.53, 1.24, 2.17, and 2.66, respectively, per 100 person-years, at an intermediate-term follow-up (ii) the incidence of cardiovascular or all-cause mortality in LVNC patients were similar to DCM controls, (iii) the high level of statistical heterogeneity was partly explained by the variability in clinical characteristics (LVEF in particular) and study characteristics such as sample size/study duration, (iv) the incidence rate of ventricular arrhythmias was comparable to DCM patients but heart failure admission rate was higher in LVNC patients.

By investigating the prognosis of real-world patients with excessive trabeculations meeting the imaging diagnostic criteria for LVNC, we aimed to provide much needed information on the natural course of this controversial disease entity. The findings from our study can be regarded as a foundation for further discussion regarding the medical implications of an increasingly-recognized imaging finding, and also highlights important heterogeneity among available published studies.

The incidence rates of cardiovascular and all-cause mortality – arguably, two more reliable and objective outcomes – estimated to be 1.92 and 2.14 per 100 person-years,

respectively, in our meta-analysis, are 25- and 5-fold higher than the event rates in a general population (0.08 and 0.41 per 100 person-years for cardiovascular and all-cause mortality, respectively, in 45-54 years age group in a North American population) [52]. Therefore, a diagnosis of LVNC by current clinical and imaging criteria appears to portend a heightened mortality risk despite a significant diversity of patient population in the individual studies. Nonetheless, when compared to non-ischemic DCM patients, LVNC patients carry a very similar risk of death from cardiovascular causes. We also observed elevated incidences of cardiovascular morbidities in LVNC patients with two most frequent complications being heart failure hospitalization and cardiac device implantation. The heart failure-related hospital admission rate in our meta-analysis was higher than the pooled incidence observed in a comparable DCM meta-analysis (3.52 vs 2.37 per 100 person-years). This finding should be interpreted with caution in view of variability in definition of heart failure decompensation and lack of data on the rigour of heart failure treatment.

There is a notion of an increased risk of systemic thromboembolism attributable to the sluggish blood flow in the deep inter-trabecular recesses in LVNC patients. However, no solid evidence is available to support this hypothesis. Indeed, in our study, the incidence rate of stroke and systemic emboli was 1.54 per 100 person-years which is either lower than or comparable to the event rates reported in: (i) V-HeFT trials in patients with systolic heart failure (2.1 – 2.7 per 100 person-years), (ii) patients with ischemic cardiomyopathy (1.5 per 100 person-years) in SAVE trial [53], and (iii) DCM patients (3.5 per 100 person-years) [54,55].

It is important to consider the incidence rates reported in this meta-analysis in the context of cohort characteristics where 18 out of 28 included studies recruited individuals with significant LV systolic impairment. Subgroup analysis stratified by LVEF demonstrated a significant reduction in the number of CV deaths in the absence of moderate to severe LV systolic dysfunction. Therefore, the risk of achieving the endpoint may in part be contingent upon the development of LV dysfunction. Although the risk to individuals with excessive trabeculations in an unselected and otherwise healthy population is beyond the scope of this study, a previous population study of approximately 3000 asymptomatic individuals did not find any association between the degree of trabeculation and the decline in LV function or incident CV events over a course of nearly 10 years [56].

As anticipated, we observed a high degree of statistical heterogeneity among included studies which can be partially explained by the differences in cohort characteristics and study quality. In our quality assessment by QUIPS criteria, the two most commonly affected bias domains were study participation (i.e. selection bias) and treatment of confounders, reflecting the challenges associated with the observational studies reporting a relatively rare condition. The subsequent meta-regression and subgroup analyses revealed that severity of LV impairment measured by LVEF had an important influence on the variability of incidence rates reported in individual studies. Equivalently, smaller studies with short follow-up duration tended to report higher incidence rates of secondary outcomes. The indicator of between-study variability (I^2 index) was noticeably lower in the subgroup analysis which further supports the importance of well-defined inclusion and diagnostic criteria.

All imaging diagnostic criteria for LVNC consider presence of excessive trabeculation as a cardinal signature of disease. There is a degree of confusion and uncertainty in assigning the disease status due to not-so-infrequent finding of increased trabeculation in otherwise healthy individuals and those with primary DCM or hypertrophic cardiomyopathy. Recent evidence suggests that the extent of trabeculation in asymptomatic low-risk population, LVNC and DCM patients does not determine prognosis [24,25,56]. In this respect, the lack of mediating influence by the LV NC:C on clinical outcomes in our study is concordant with the existing evidence in literature. A recently published meta-analysis of four CMR studies enrolling LVNC patients reported that in the absence of late gadolinium enhancement and LV systolic dysfunction, no hard cardiac event was observed [57]. Therefore, our study, together with mounting evidence from existing literature, underscores the important prognostic role of focal myocardial injury and functional impairment, rather than the morphological appearance of LVNC. Indeed, it is notable that the conventional diagnostic criteria for LVNC have relied principally on ratio measurement and have not included other structural, functional, clinical or familial parameters.

In this study, we systematically reviewed and performed the meta-analysis of the incidence of important cardiovascular outcomes in a large population of real-world LVNC patients. We attempted to synthesize the results in a robust manner giving due consideration to address potential biases where possible. However, we acknowledge several limitations associated with our study. First, the pooled analysis relied on observational, mostly single centre, cohort studies with variable methodological quality as highlighted in the bias assessment, inclusion criteria and definitions of LVNC. Second, our study only focused on the adult population mostly free from congenital

heart disease, thus, the insights obtained from this work cannot be extended to pediatric LVNC or patients with coexisting congenital heart disease. Third, comparison of the rates of incident CV events between LVNC and hypertrophic cardiomyopathy was not performed and should be investigated in a future study. Fourth, meta-regression analyses were limited to the studies without missing covariate information, hence, may be underpowered. Fifth, only a few studies reported the incidence rates in a comparable DCM cohort. Thus, the precision of pooled odds ratio and the level of evidence are weaker. Finally, the incidence rates of adverse events observed in this study only hold true for an intermediate follow-up duration and the long-term consequences of LVNC remain to be elucidated.

An expert group consensus approach to harmonize the diagnostic criteria, risk factors and endpoints is urgently needed to develop a more standardized assessment of LVNC. Future studies including prospective registries should address long term prognosis and could also investigate additional prognostic information provided by fractal analysis, T1 mapping and genotype over current LV NC:C ratio, systolic function and tissue characterization by LGE.

CONCLUSIONS

Patients with LVNC have similar risks of cardiovascular mortality, all-cause mortality, thromboembolic complications and ventricular arrhythmias in comparison with DCM patients. The finding of increased incidence of heart failure hospitalization in isolation should be interpreted with caution and investigated in future well-designed studies.

Traditional indicators of cardiac disease severity such as low LVEF, not the burden of trabeculation, appear to be associated with worse outcomes.

FUNDING

NA is supported by a Wellcome Trust Research Training Fellowship (203553/Z/Z). SEP and NA acknowledge the support through the Barts Biomedical Research Centre which is funded by the National Institute for Health Research.

ACKNOWLEDGMENTS

This work was part of the portfolio of translational research of the NIHR Biomedical Research Centre at Barts and The London School of Medicine and Dentistry.

DISCLOSURES

SEP provides consultancy to Circle Cardiovascular Imaging Inc, Calgary, Canada. Other authors have no conflicts of interest to declare.

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FIGURE TITLES AND LEGENDS

Figure 1. (A) Venn diagram of the number of genes associated with inherited cardiomyopathy; (B) CMR images demonstrating a classic LVNC with a two-layer appearance of thin compact myocardium and excessive trabeculation (top left), isolated LVNC with normal chamber size and function (top right), mixed DCM and LVNC with biventricular involvement (bottom left) and HCM with features of LVNC (bottom right).

(DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; LVNC, left-ventricular non-compaction; HCM, hypertrophic cardiomyopathy; CMR, cardiovascular magnetic resonance)

Figure 2. Flow diagram demonstrating the process of study selection

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Figure 6. Subgroup analyses for cardiovascular mortality: (A) Incidence of cardiovascular mortality in subgroups stratified by person-years > 300, (B) Incidence of cardiovascular mortality in subgroups stratified by LVEF < 45%, (C) Incidence of cardiovascular mortality in subgroups stratified by high vs low-moderate risk of bias, (D) Incidence of cardiovascular mortality in LVNC meta-analysis vs external DCM meta-analysis. The vertical dotted line indicates the pooled average incidence rate. (LVEF, left ventricular ejection fraction; LVNC, left ventricular non-compaction; DCM, dilated cardiomyopathy)

Figure 7. Forest plot of cardiovascular mortality in LVNC patients compared to DCM controls. The vertical dotted line represents the pooled odds ratio. (LVNC, left-ventricular non-compaction; DCM, dilated cardiomyopathy)

TABLES

Table 1. Characteristics of included studies

Author	Year	Cohort characteristics	Control group	N	Age (years)	Male gender (n)	LVNC imaging diagnostic criteria	LVEF (%)	LV end-diastolic dimension *	Follow-up duration (months)	Endpoints
Amzulescu[24]	2015	Prospective single-centre study of non-ischemic DCM patients with co-existing LVNC	None	59	52 ± 13	34	Petersen	24.1 ± 8.3	69 ± 9 mm	40.8	Thromboembolic event
Andreini[25]	2016	Prospective multi-centre study of LVNC patients	None	113	44 ± 17	70	Jenni + Petersen	42.8 ± 16.2	79.7 ± 26.3 ml/m^2	48 ± 24	CV mortality, thromboembolic event, ventricular arrhythmia, heart failure
Aras[26]	2006	Retrospective single-centre study of LVNC patients	None	67	41 ± 18	44	Jenni	43.5± 14.4	58 ± 10 mm	30 ± 12	All-cause mortality, CV mortality, thromboembolic event, ventricular arrhythmia, heart failure
Asfalou[27]	2016	Retrospective single-centre	None	23	47 ± 13	15	Jenni	27 ± 8	67.7 ± 6.6 mm	24	All-cause mortality, CV mortality, thromboembolic

		study of LVNC patients									event, ventricular arrhythmia, ICD implantation, heart failure
Caliskan[28]	2011	Prospective single-centre study of LVNC patients	None	77	40 ± 14	37	Jenni	NR	60.4 ± 9.6 mm	33 ± 24	All-cause mortality, CV mortality, ventricular arrhythmia, cardiac transplantation, heart failure
Cetin[29]	2016	Retrospective single-centre study of LVNC patients	None	88	39 ± 18	57	Jenni	32.0 ± 12.5	59.3 ± 9.1 mm	42.4	All-cause mortality, CV mortality, ventricular arrhythmia, ICD implantation
Correia[30]	2011	Retrospective single-centre study of LVNC patients	None	20	53 ± 20	13	Jenni	45 ± 19	58 ± 11 mm	12 ± 6	All-cause mortality, CV mortality, cardiac transplantation, ICD implantation
Enriquez[31]	2011	Retrospective single-centre study of LVNC patients	None	15	52 ± 17	6	Jenni	27 ± 10	66 ± 11 mm	19	Ventricular arrhythmia, ICD implantation
Gaye[32]	2017	Retrospective multi-centre study of LVNC patients	None	35	47 ± 18	NR	Jenni	32.5 ± 13.8	66.4 ± 9.6 mm	17.2 ± 14.5	All-cause mortality, ventricular arrhythmia, heart failure
Greutmann[33]	2012	Retrospective single-centre	None	132	41 ± 17	46	Jenni	41 ± 18	34 ± 7 mm/m^2	32.4	CV mortality, thromboembolic event, ventricular

		study of LVNC patients									arrhythmia, cardiac transplantation, heart failure
Habib[34]	2011	Prospective multi-centre study of LVNC patients	None	105	45 ± 17	69	Jenni	46 ± 18	63 ± 11 mm	30 ± 18	All-cause mortality, CV mortality, thromboembolic event, ventricular arrhythmia, ICD implantation, cardiac transplantation, heart failure
Ivanov[35]	2017	Prospective single-centre study of LVNC patients	Patients not fulfilling Petersen criteria and with no evidence of congenital heart disease or valve disease	276 (LVNC) / 424 (non-LVNC with compara-ble age and LVEF)	57	147	Petersen	49 ± 17	77 ± 29 ml/m^2	82	All-cause mortality, CV mortality
Kawasaki[36]	2005	Retrospective single-centre study LVNC patients	Age- and sex-matched with individu	10 (LVNC) / 80 (non-LVNC:	50 ± 13	8	Jenni	NR	NR	26 ± 14	All-cause mortality, CV mortality

			als with myocardial infarction, hypertrophic cardiomyopathy and no CV disease	40 MI and 40 HCM)†							
Li[37]	2018	Prospective single-centre study of Chinese LVNC patients	None	83	45	58	Jenni + Petersen	37	62	54	All-cause mortality, CV mortality, cardiac transplantation
Lofiego[38]	2007	Prospective multi-centre study of LVNC patients	None	65	45 ± 16	NR	Jenni	31 ± 11	67 ± 11 mm	46 ± 44	All-cause mortality, CV mortality, thromboembolic event, ventricular arrhythmia, ICD implantation, cardiac transplantation, heart failure
Mazurkiewicz[39]	2017	Prospective single centre study of DCM patients with co-existing LVNC	DCM patients not fulfilling LVNC criteria	127 (LVNC) / 149 (DCM)	33 ± 9	78	Grothoff	27.7 ± 7.5	172.9 ± 29.8 ml/m^2	28.8	All-cause mortality, cardiac transplantation, thromboembolic event

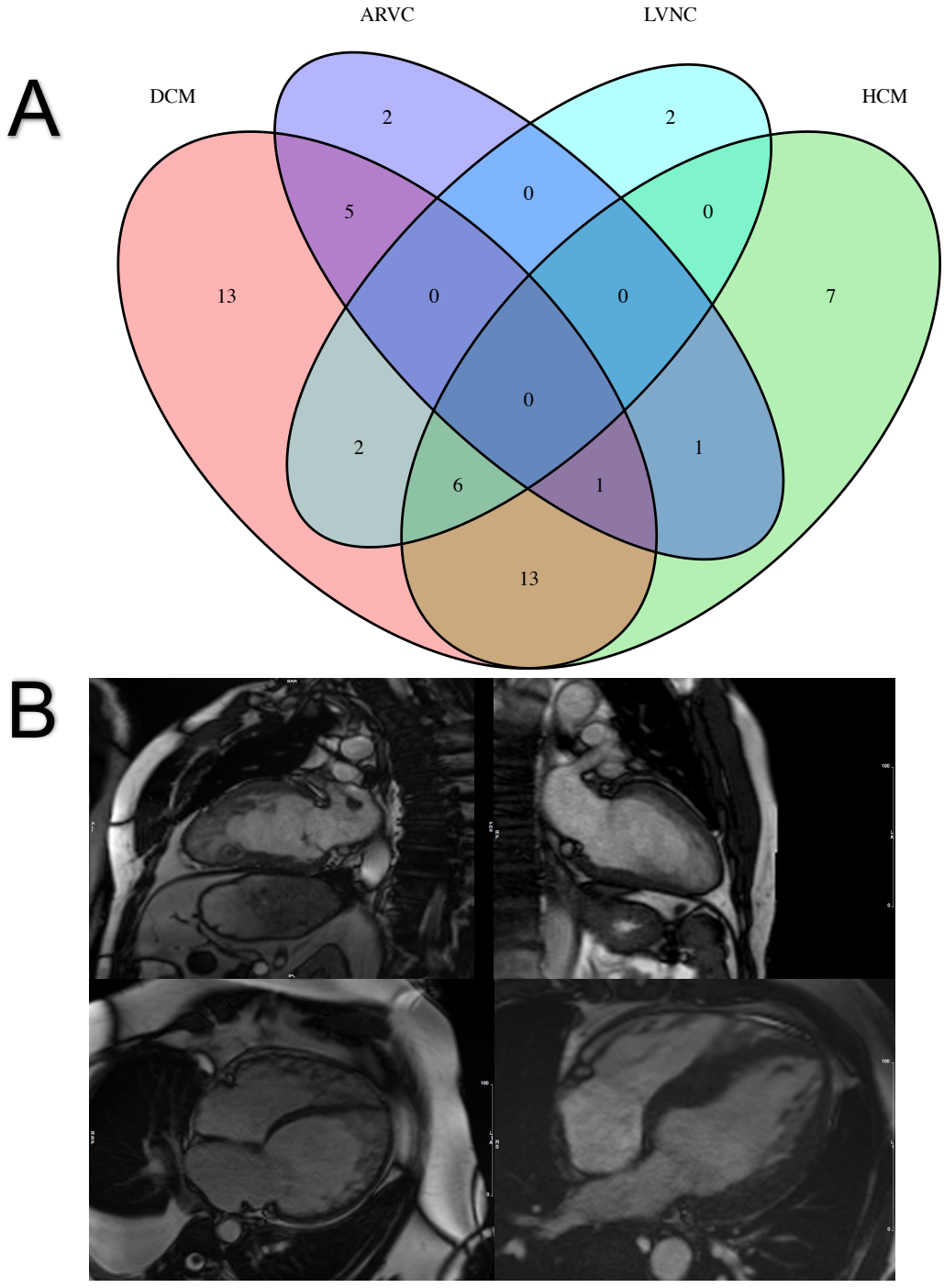
Murphy[40]	2005	Prospective study of unrelated LVNC patients	None	45	37 ± 17	28	Chin+Jenni	NR	58 ± 11 mm	46	All-cause mortality, CV mortality, ventricular arrhythmia, ICD implantation
Peters[41]	2014	Prospective single-centre study of idiopathic LVNC patients	None	55	42 ± 12	21	Jenni	29.6 ± 11.8	59.1 ± 9.8 mm	16.7 ± 5.9	All-cause mortality, CV mortality, thromboembolic event, heart failure, ICD implantation
Ritters[42]	1997	Retrospective single-centre study of LVNC patients	None	17	42 ± 17	14	Jenni	NR	NR	30 ± 28	All-cause mortality, CV mortality, thromboembolic event, cardiac transplantation, heart failure, ventricular arrhythmia
Salazar-Mendiguchía [43]	2019	Retrospective multi-centre study of LVNC patients	Sympto-matic DCM patients	75	50 ± 15	51	Jenni	32	63.8	60	CV mortality, thromboembolic event, cardiac transplantation, ventricular arrhythmia, ICD implantation
Sedaghat-Hamedani[44]	2017	Prospective multi-centre registry of symptomatic LVNC patients	Age-matched non-ischemic DCM patients	68 (LVNC) / 247 (DCM)	41 ± 14	48	Jenni+ Stöllberger+ Petersen	38 ± 15.3	62 ± 12.3 mm	61	All-cause mortality, CV mortality, thromboembolic event, cardiac transplantation, ventricular

											arrhythmia, ICD implantation
Stampfli[45]	2017	Retrospective multi-centre study of LVNC patients	None	153	43 ± 19	91	Jenni	45	NR	72	All-cause mortality, cardiac transplantation
Stanton[46]	2009	Retrospective single-centre study of LVNC patients	Age-, sex- and LVEF-matched DCM patients	30 (LVNC) / 27 (DCM)	39 ± 20	18	Jenni	41	NR	30 ± 14	All-cause mortality, ventricular arrhythmia, ICD implantation
Steffel[47]	2011	Retrospective single-centre study of LVNC patients	None	74	43 ± 16	53	Jenni	40 ± 19	32.7 ± 10 mm/m^2	57.9 ± 41.5	All-cause mortality, CV mortality, ventricular arrhythmia
Stollberger[48]	2018	Prospective single-centre study of LVNC patients; Prevalence of neuromuscular disease associated with LVNC was also assessed.	None	273	53 ± 17	193	Stöllberger	NR	60 ± 13	88.8 ± 68.4	All-cause mortality, CV mortality, ICD implantation, cardiac transplantation
Tian[49]	2014	Retrospective single-centre study of LVNC patients	None	106	46 ± 17	83	Jenni	39 ± 14	61 ± 10 mm	35 ± 25	All-cause mortality, CV mortality, thromboembolic event, ventricular arrhythmia, ICD implantation, cardiac

											transplantation, heart failure
Tian[50]	2017	Prospective single-centre study of older LVNC patients (age ≥ 60 years)	None	35	65 ± 5	28	Petersen	30 ± 11	67 ± 8 mm	35 ± 28	All-cause mortality, CV mortality, heart failure, ventricular arrhythmia, ICD implantation
Waning[51]	2018	Retrospective multi-centre study of LVNC patients	None	275	45	148	Jenni+ Petersen	NR	NR	60	All-cause mortality, thromboembolic event, cardiac transplantation, ventricular arrhythmia, heart failure, ICD implantation

LVNC, left ventricular non-compaction; MI, myocardial infarction; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; NR, not reported

* Unadjusted or indexed left ventricular end-diastolic diameter or volume; † The original study by Kawasaki et al. also reported the event rates in 40 healthy volunteers but these individuals were not included in the control group for this study.



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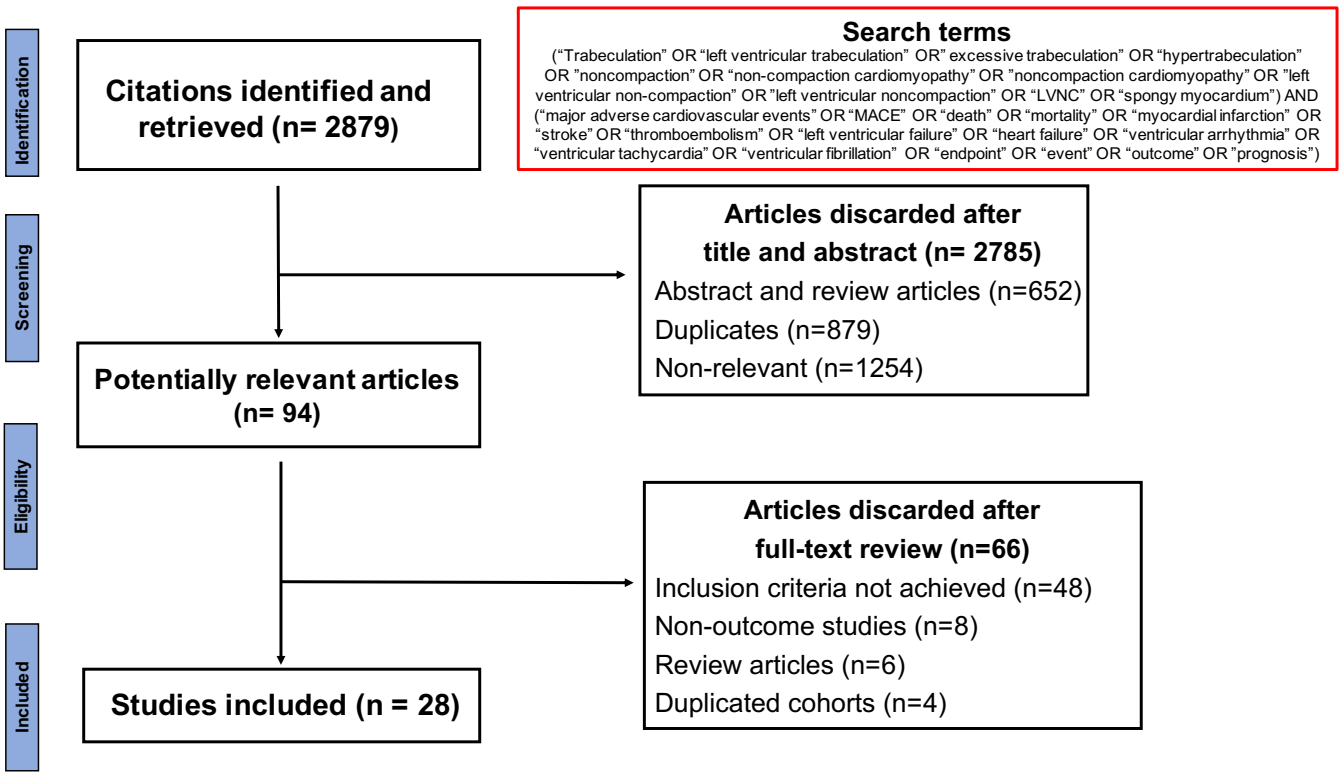

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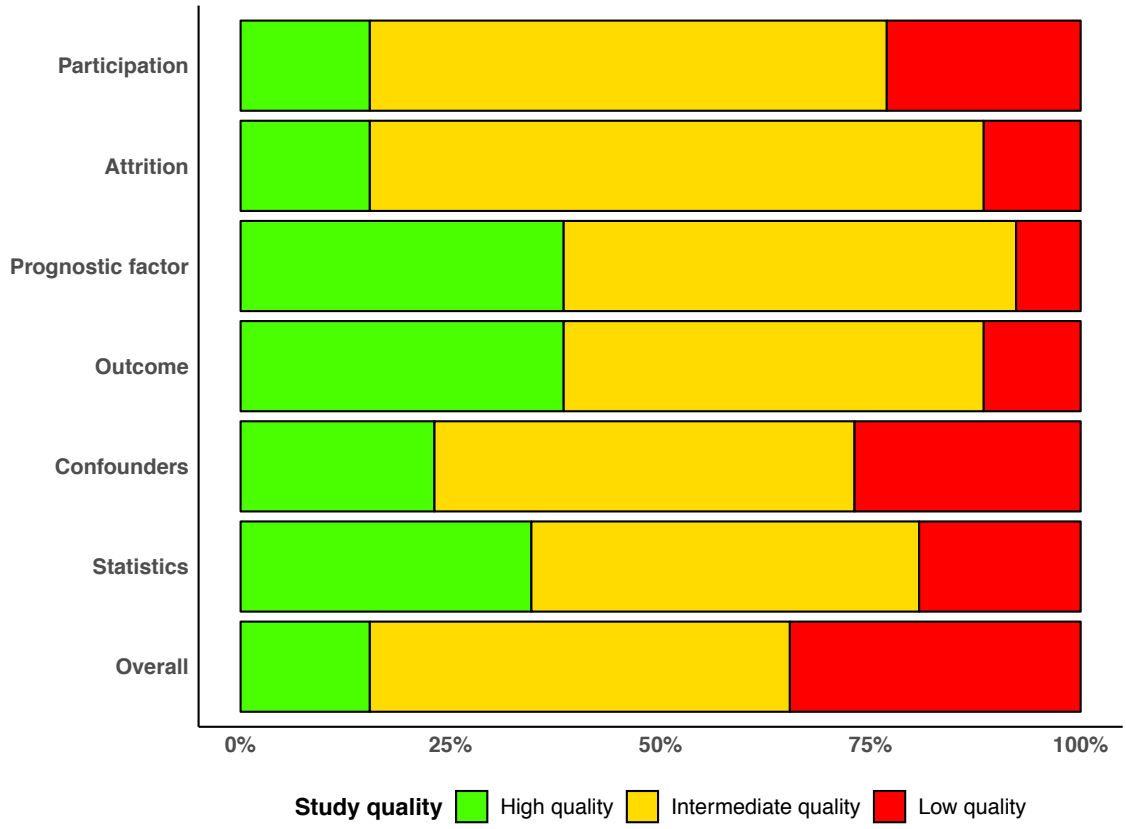

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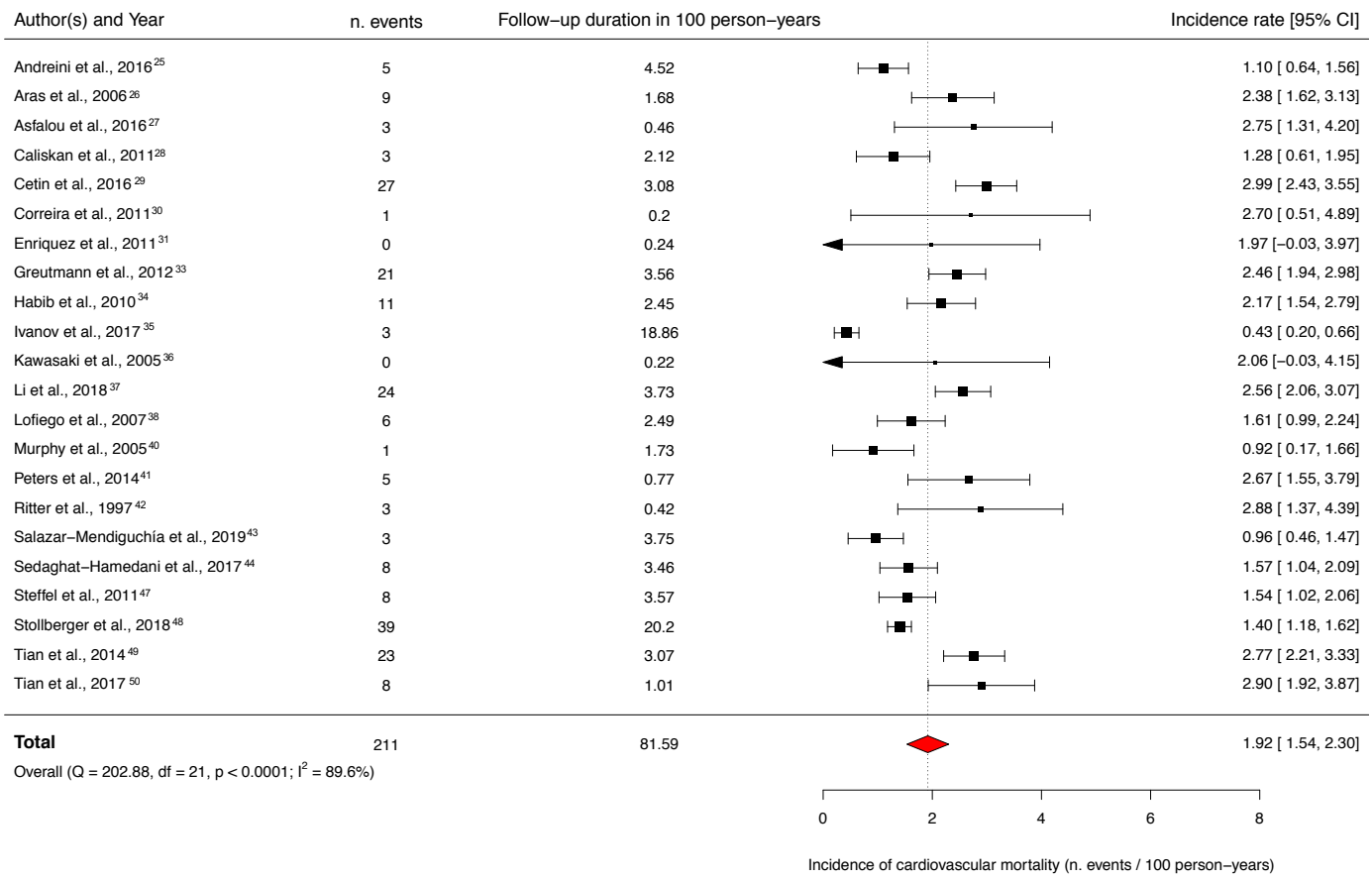

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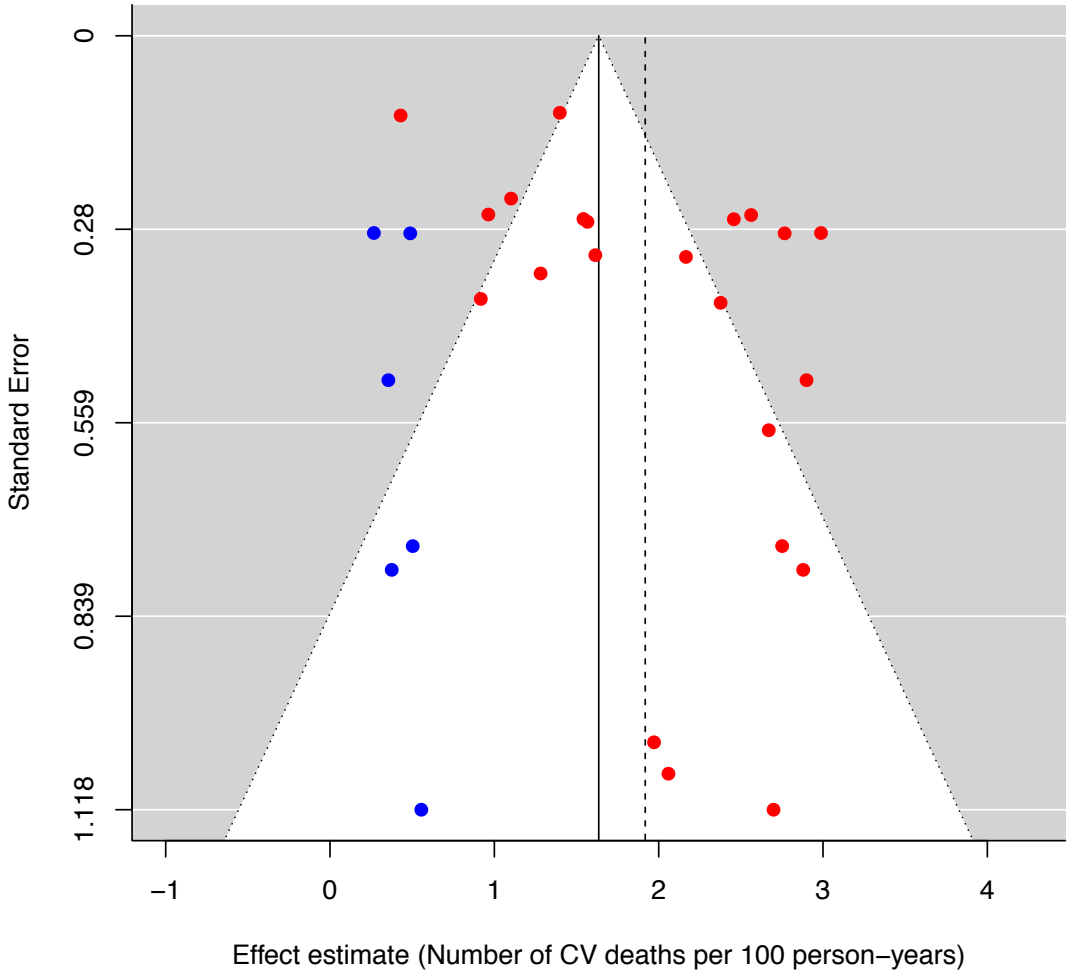

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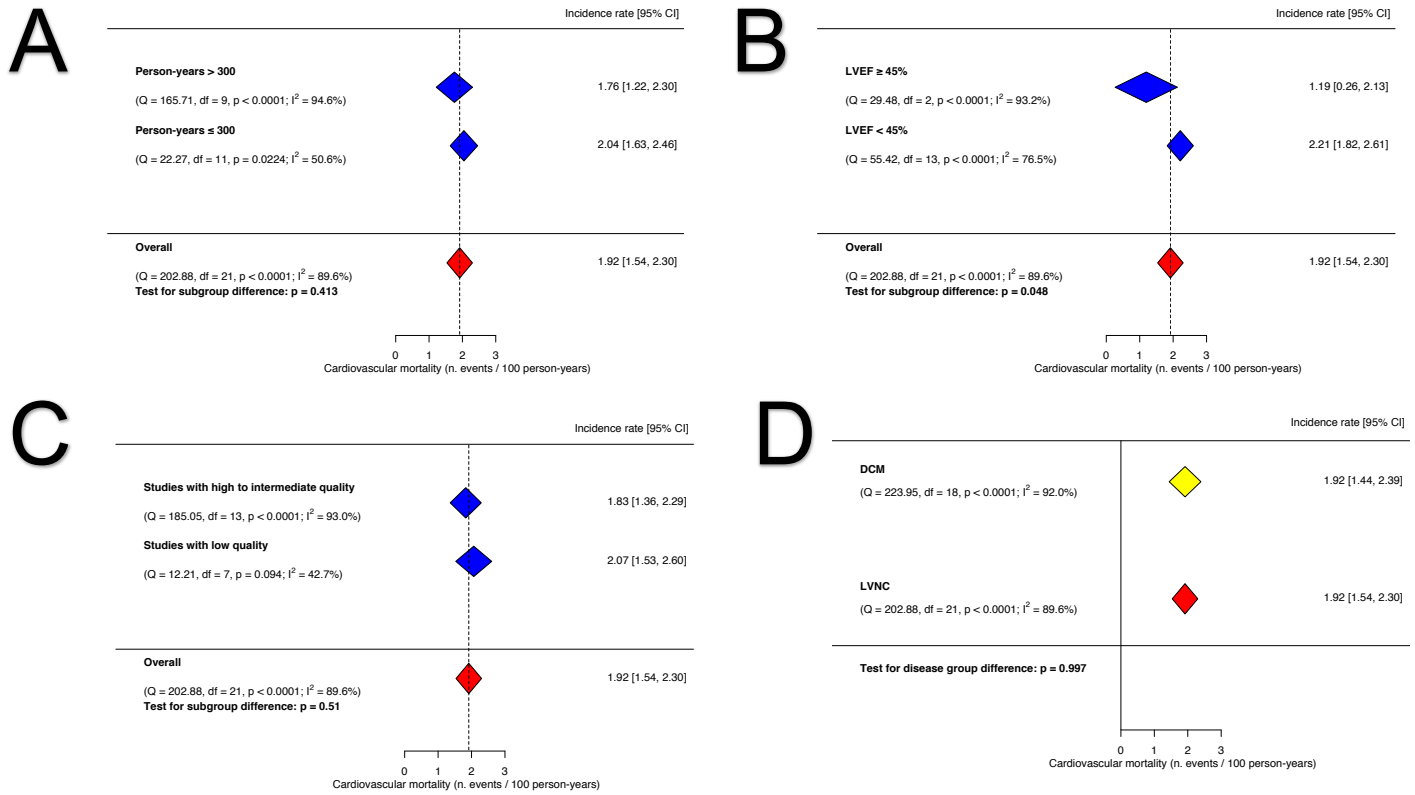

Figure 6. Subgroup analyses for cardiovascular mortality: (A) Incidence of cardiovascular mortality in subgroups stratified by person-years > 300, (B) Incidence of cardiovascular mortality in subgroups stratified by LVEF < 45%, (C) Incidence of cardiovascular mortality in subgroups stratified by high vs low-moderate risk of bias, (D) Incidence of cardiovascular mortality in LVNC meta-analysis vs external DCM meta-analysis. The vertical dotted line indicates the pooled average incidence rate. (LVEF, left ventricular ejection fraction; LVNC, left ventricular non-compaction; DCM, dilated cardiomyopathy)

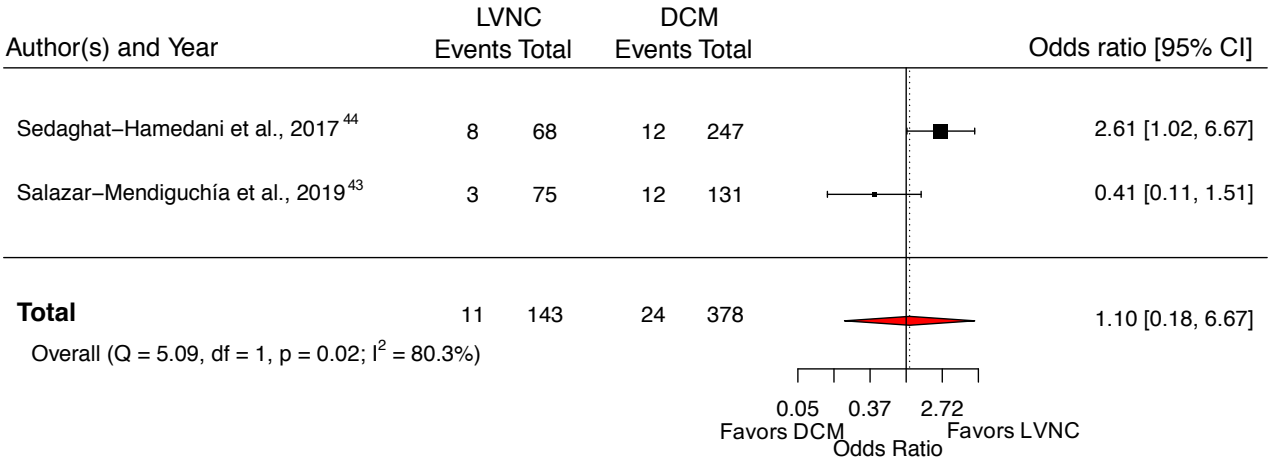

Figure 7. Forest plot of cardiovascular mortality in LVNC patients compared to DCM controls. The vertical dotted line represents the pooled odds ratio.

(LVNC, left-ventricular non-compaction; DCM, dilated cardiomyopathy)