

Prognostic factors associated with left ventricular non-compaction

A PRISMA-compliant meta-analysis

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Abstract

Background: Left ventricular non-compaction (LVNC) is a rare disease with a poor prognosis. Efforts to improve prognosis are limited by the quality and scope of the available evidence on prognostic factors.

Methods: Pubmed, Embase, China National Knowledge Infrastructure, Cochrane Library, Wanfang, and Baidu Scholar were searched and all relevant studies that examined factors related to LVNC prognosis, published before January 2021, were retrieved. Study quality evaluation and data extraction were independently completed by two authors. Statistical analyses were performed using STATA 15.0 software.

Results: A total of 20 cohort studies were included in this study, with a total of 1910 patients. The results of the meta-analysis are as follows: New York Heart Function Association (NYHA) class III/IV (hazard ratio [HR] = 3.93, 95% confidence interval [CI]: 1.66–9.29), (NT-proBNP) increased (HR = 1.98, 95% CI: 1.10–3.58), left ventricular ejection fraction (LVEF) decreased (HR = 1.04, 95% CI: 1.03–1.06), left ventricular end-diastolic diameter (LVEDD) increased (HR = 1.03, 95% CI: 1.01–1.06) was an independent poor prognostic factor, and body mass index (HR = 0.80, 95% CI: 0.64–0.98) was an independent protective factor. Creatinine (CR) level (HR = 1.09, 95% CI: 0.95–1.25) and late gadolinium-enhanced (LGE) imaging (HR = 3.1, 95% CI: 0.85–11.31) has no statistical significance in the prognosis of LVNC.

Conclusion: In LVNC patients, NYHA class III/IV, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, decreased LVEF, and increased LVEDD may lead to poor prognosis, and increased body mass index may improve the prognosis of LVNC. Further clinical research with large sample sizes and long-term follow-ups should be conducted.

PROSPERO Registration Number: 42020152706

Abbreviations: CI = confidence interval, CR = creatinine, HR = hazard ratio, LAD = left atrial diameter, LGE = late gadolinium-enhanced, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVNC = left ventricular non-compaction, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Function Association.

Keywords: left ventricular non-compaction, meta-analysis, prognosis

1. Introduction

Non-compaction of the ventricular myocardium is a relatively rare disease of the heart that commonly co-occurs with congenital ventricular dysplasia. It is characterized by thickened muscle trabeculae and deep recesses communicating between the trabeculae. It is more commonly observed in the left ventricle and is often referred to as left ventricular non-compaction (LVNC).^[1,2]

To date, the epidemiological data on this disease are lacking and further comprehensive studies are needed. Moreover, there are few large-scale studies of LVNC. International studies using echocardiographic diagnosis have reported that the prevalence of LVNC ranges from 0.014% to 0.032%.^[3] It is currently believed that the disease can be diagnosed at any age, and most studies have shown that the incidence of LVNC is higher in men than women. The incidence of LVNC in children aged 0 to 10 years is estimated to be around 0.12/100,000 per year.^[4]

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The datasets generated during and/or analyzed during the current study are publicly available.

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Clinical studies have shown that patients with LVNC have a poor prognosis and a high risk of ventricular tachycardia and sudden death, with an average annual mortality rate of 5% to 12%.^[5]

In recent years, prognostic studies of LVNC from China and other countries around the world have suggested that higher left ventricular diastolic diameter, severe heart failure, atrial fibrillation,^[6,7] and lower ejection fraction^[8] are associated with poor prognosis. Because of the rarity of this disease, most published studies are based on samples that are too small to obtain clear and reliable results. To date, there are no published meta-analyses on the predictors of LVNC prognosis. Thus, to obtain a more reliable result, the current study examined all published literature on prognostic factors for LVNC. A meta-analysis was performed and factors affecting LVNC prognosis were evaluated. The aim was to provide a high-quality and reliable analysis of the current literature to guide a clinical understanding of LVNC prognosis.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.^[9] Because the study did not analyze private patient data, ethical approval was not required. This study was registered on the PROSPERO register, registration number CRD42020152706.

2.1. Literature screening

Pubmed, Embase, China National Knowledge Infrastructure, Cochrane Library, Wanfang, and other databases were searched to collect all relevant literature on LVNC prognosis published before January 2021. The reference lists of retrieved studies were also manually reviewed and relevant studies were retrieved in order to ensure that all relevant literature was included in this study. The database search terms were as follows: LVNC or Non-compaction Cardiomyopathy or LVNC Cardiomyopathy, outcomes or cardiac events or heart failure events, follow-up, prognostic or prognosis. The identified studies were then screened independently by two researchers (Z-GY and Z-JL). First, the titles and abstracts of retrieved studies were screened. After excluding studies that did not meet the inclusion criteria, each study was cross-checked by 2 independent researchers to ensure it met the inclusion criteria. When there was disagreement and a consensus could not be reached, the third researcher (LW) was asked to make the final decision.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: domestic or foreign published study; all patients clinically diagnosed with myocardial densification; study examined prognostic factors related to myocardial densification; the study provided complete raw data or K-M survival curves to obtain hazard ratios (HRs); clear follow-up time; cohort study; clear end-point.

The exclusion criteria were as follows: duplicate publications; studies reporting prognostic factors with HRs <3.

2.3. Data extraction and study quality evaluation

Two investigators independently extracted the data; LW resolved any differences in opinion. The quality of the included studies was evaluated by 2 researchers according to the Newcastle-Ottawa Quality Assessment Scale (NOS) criteria.^[10] When the researchers' scores were not consistent, the third researcher (LW) provided judgement. The maximum score of the NOS scale is 9 points; 0 to 4 points indicates a low-quality study while 5 to 9 points indicates a high-quality study.

2.4. Statistical analyses

We used the HR and 95% confidence intervals (95% CI) to assess the survival benefit of LVNC. Unless the data were able to be directly extracted from the article, Engauge Digitizer version 4.1 (available from <http://sourceforge.net/>) was used to read the Kaplan–Meier curves to obtain the HRs.^[11] STATA 15.0 was used to analyze the data extracted from the included studies. The Q test and I^2 were used to test for heterogeneity among the included studies.^[12] When $P > .1$ and $I^2 < 50\%$, the literature was considered homogeneous. When $P < .1$ and $I^2 \geq 50\%$, the literature was considered heterogeneous. When heterogeneity existed among the included studies, a random-effects model was used for data analysis. When the heterogeneity was large, the cause of the heterogeneity was investigated through sensitivity analyses. When there was no heterogeneity, a fixed-effects model was used for analysis. Subgroup analyses were performed to determine whether New York Heart Function Association classification 3 or 4 grade (NYHA III-IV) and creatinine (CR) were independent predictors of LVNC. Finally, the combined HR value and its 95% CI were calculated. Publication bias was tested using Egger test.^[13]

3. Results

3.1. Study selection, characteristics, and quality evaluation

As of January 2021, a total of 20 articles^[6,7,8,14–30] met the study's inclusion criteria. For a detailed description of the study selection process, see the flowchart (Fig. 1). The total number of patients in the included studies was 1910, with the individual sample sizes ranging from 34 to 339. The following data were collected from each of the included studies: the name of the first author of the paper, country, year of publication, end-point, number of patients, number of male/female and followed-up (Table 1). The NOS scores of the included studies ranged from 6 to 8, indicating that the quality of each study was relatively high (Table 2).

3.2. The influence of general characteristics on the prognosis of LVNC

3.2.1. Analysis of age factors. Including 8 studies.^[6,15,16,18,19,20,26,28] Univariate factor analysis has heterogeneity between studies ($P < .001$, $I^2 = 87.6\%$) and multivariate factor analysis has heterogeneity between studies ($P = .004$, $I^2 = 77.2\%$), all of which are required A random effects model was used. As shown in Figure 2, the univariate analysis group indicated that age was a risk factor for poor prognosis of LVNC (HR = 1.02, 95% CI: 1–1.04), and the multivariate group analysis showed age (HR = 1.03, 95% CI: 0.99–1.07) It is not an independent factor influencing the poor prognosis of LVNC, and it cannot be explained that age has an influence on the prognosis of LVNC.

3.2.2. Analysis of gender factors. Including 10 studies.^[6,15–20,26,28] Whether it is analyzing the influence of male composition (HR = 1.2, 95% CI: 0.87–1.67) on the prognosis of LVNC, or the influence of female composition (HR = 1.14, 95% CI: 0.73–1.77) on the prognosis of LVNC, there is no difference between the studies. Heterogeneity ($I^2 = 0\%$), random effects model can be used. As shown in Figure 3, there is no correlation between gender and the prognosis of LVNC, so it cannot be explained that age has an effect on the prognosis of LVNC.

3.2.3. Analysis of body mass index (BMI) factors. Including 3 studies.^[16,17,28] There is no heterogeneity between univariate factor analysis and multivariate factor analysis ($I^2 = 0\%$), and random effects model can be used. As shown in Figure 4, the univariate group BMI was a protective factor for poor prognosis

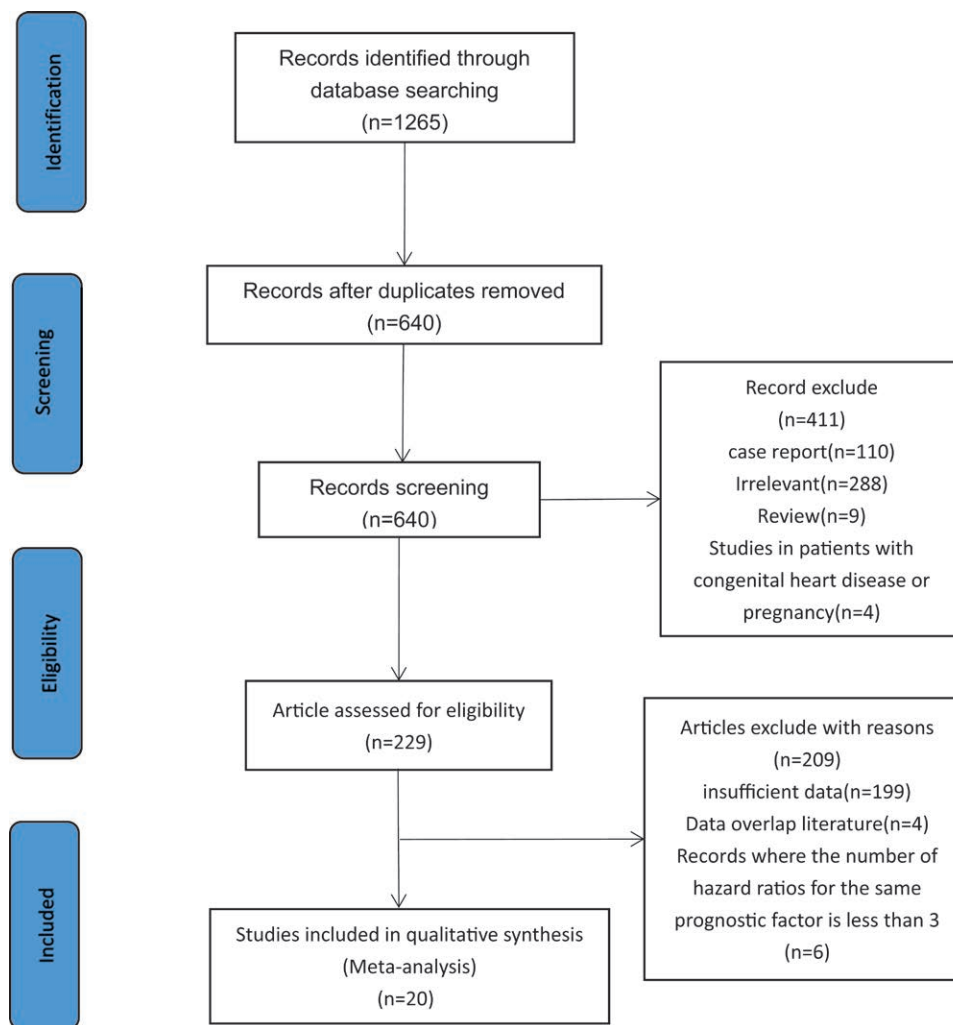


Figure 1. PRISMA flow chart of literature selection. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

of LVNC (HR = 0.82, 95% CI: 0.75–0.90), and the multivariate group analysis showed BMI (HR = 0.8, 95% CI: 0.64–0.98) is an independent protective factor for prognosis, and an increase in BMI can reduce the occurrence of adverse events.

3.3. The impact of accompanying diseases on the prognosis of LVNC

3.3.1. Analysis of LVNC with coronary heart disease. Includes 4 studies.^[16,17,26,28] There is no heterogeneity between studies ($P = .443$, $I^2 = 0\%$). As shown in Figure 5, a random effects model is used. The results showed that there was no correlation between coronary heart disease and poor prognosis of LVNC (HR = 1.01, 95% CI: 0.64–1.62).

3.3.2. Analysis of LVNC with hypertension. Including 3 studies.^[16,17,26] There is heterogeneity among the studies ($P = .079$, $I^2 = 60.7\%$). As shown in Figure 6, a random effects model is used. Hypertension is not a risk factor for poor prognosis of LVNC (HR = 1.05, 95% CI: 0.46–2.39).

3.3.3. Analysis of LVNC with diabetes mellitus. Includes 4 studies.^[16,17,26,28] There is heterogeneity among the studies ($P = .074$, $I^2 = 56.7\%$). As shown in Figure 7, a random effects model was used. Diabetes mellitus is not a risk factor for poor prognosis of LVNC (HR = 1.59, 95% CI: 0.69–3.04).

3.3.4. Analysis of LVNC with atrial fibrillation. Including 8 studies.^[6,8,16,17,18,20,26,28] There is no heterogeneity between studies ($P = .332$, $I^2 = 12.5\%$). As shown in Figure 8, a random effects model can be used. Atrial fibrillation is a risk factor for poor prognosis of LVNC (HR = 1.71, 95% CI: 1.22–2.41), which is statistically significant.

3.3.5. Analysis of NYHA class III/IV in LVNC patients. Five studies were included in the NYHA class III/IV analysis.^[14,16,19,21,28] There was high heterogeneity among the studies ($I^2 = 73.5\%$). A random-effects model was used, as shown in Figure 9. NYHA III-IV (HR = 3.93, 95% CI: 1.66–9.29) was a statistically significant independent risk factor for poor prognosis.

3.4. The influence of laboratory biochemical indexes on the prognosis of LVNC

3.4.1. Analysis of CR level. Four studies were included in this analysis.^[15,16,23,25] The HRs were obtained from the univariate analyses and the multivariate analysis was divided into 2 groups and then combined. For the univariate analysis, high heterogeneity was observed between the studies ($I^2 = 84.9\%$) using a random-effects model, CR (HR = 1.12, 95% CI: 1.02–1.23) was not a statistically significant predictor of LVNC. Similarly, for the multivariate analysis, heterogeneity was observed between the studies ($I^2 = 69.7\%$). Using a random-effects model, CR (HR

Table 1
Main characteristics of the studies.

References	Year of publication	Country of patients	Number of patients	Number of male/female	Median age (yr)	Follow-up (yr)	LVEF (%)	LVEDD/LVESV (mm)	Endpoint
T. He ^[14]	2012	China	36	24/12	47 + 22	2.5 + 0.83	36 + 13	66 + 15	Death, heart transplantation
C. Yan ^[15]	2018	China	61	41/20	40.9 + 19.8	5.71 + 3.9	29.12 + 12.4	61.9 + 12.4	All-cause death
X.J. Gao ^[16]	2011	China	112	89/23	45.82 + 18	1.69 + 1.2	34.34 + 10.95	66.87 + 10.73	Death, heart transplantation, readmission
Gulijakela ^[17]	2016	China	36	22/14	54 + 18.3	0.08–3.83	40.43 + 11.06	59.6 + 8.8	Cardiac death, readmission
T. Tian ^[18]	2013	China	106	83/23	46 + 17	2.9 + 2.1	39 + 14	64 + 10	Death, heart transplantation
Lofiego ^[19]	2006	Italy	65	–	–	0.5–16	31 + 11	67 + 11	Death, heart transplantation
Greutmann ^[6]	2012	Switzerland	115	40/75	–	0.1–19.4	41 + 18	34 + 7	Death, heart transplantation
Stampfli ^[25]	2017	Switzerland	153	91/62	43 + 19.4	18.5 (longest)	–	–	Death, heart transplantation
Gilbert ^[20]	2010	France	105	69/36	45 + 17	2.33 + 1.47	46 + 18	63 + 11	Death, heart transplantation
Jamka ^[21]	2013	Poland	129	81/48	–	4.8 (longest)	–	–	Death, heart transplantation
Q. Ma ^[22]	2014	China	101	67/34	29 + 25	2.6 + 1.4	–	–	Death, heart transplantation
L. Chen ^[23]	2014	China	41	18/23	–	0.8 + 1.5	–	41.7 + 12.9	Death, heart transplantation
X.H. Ning ^[24]	2012	China	64	–	–	2.67 + 2	42 + 14	61 + 11	Death, heart transplantation
Vaibhav ^[26]	2021	America	339	182/157	47.4 (IQR 34–61)	6.3 (median)	45 (IQR 30–58)	55 (IQR 50–62)	All-cause death
S. Stampfli ^[7]	2018	Switzerland	126	–	47.3 (median)	7.4 (median)	42 (median)	–	Death, heart transplantation
Mehmet ^[28]	2016	Turkey	88	57/31	38.6 + 16.7	3.53 (median)	32 + 12.5	59.3 + 9.1	Cardiac death
Femia ^[29]	2020	Sydney	98	55/43	–	6.5 (IQR 5.5–7.5)	62.9 + 6.9 (Preserved) 38.1 + 8.5 (Impaired)	–	Cardiac death, cardiac transplantation, sustained ventricular tachycardia/ventricular fibrillation, ischemic stroke
Macaione ^[30]	2017	Italy	83	54/29	46.3 + 18.9	3.7 + 2.3	–	–	Adverse cardiovascular events
Amzulescu ^[27]	2015	Belgium	162	102/60	55 + 15	3.4 (IQR 1.5–6.3)	24.6 + 8.4	68 + 9	Cardiac death, heart transplantation, LV assist device implantations
Stöllberger ^[8]	2009	Australia	102	72/30	53 + 16	3.8 (IQR 0.02–8.8)	–	–	All-cause death

LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction.

Table 2
The Newcastle-Ottawa Quality Assessment Scale of included study.

Name	Selection			Comparability			Outcome		Score
	Representative of the average in the community	The same community as the exposed cohort	Ascertainment of exposure	Outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up enough for outcomes to occur	Adequacy of follow-up of cohorts	
T. He ^[14]	*	*	*	*	*	*	*	*	8
X.J. Gao ^[16]	*	*	*	*	–	*	*	*	7
Lofiego ^[19]	*	*	*	*	*	*	*	*	8
Greutmann ^[6]	*	*	*	*	–	*	*	*	7
Stampfli ^[25]	*	*	*	*	*	*	*	*	8
Gilbert ^[20]	*	*	*	*	*	*	*	*	8
Jamka ^[21]	*	*	*	*	–	*	*	*	7
Q. Ma ^[22]	–	–	*	*	*	*	*	*	6
T. Tian ^[18]	*	*	*	*	*	*	*	*	8
Gulijakela ^[17]	*	*	*	*	*	*	*	*	8
L. Chen ^[23]	–	–	*	*	*	*	*	*	6
X.H. Ning ^[24]	–	–	*	*	*	*	*	*	6
C. Yan ^[15]	*	*	*	*	–	*	*	*	7
Vaibhav ^[26]	*	*	*	*	*	*	*	*	8
S. Stampfli ^[7]	*	*	*	*	–	*	*	*	7
Mehmet ^[28]	*	*	*	*	*	*	*	*	8
Femia ^[29]	*	*	*	*	*	*	*	*	8
Macaione ^[30]	*	*	*	*	*	*	*	*	8
Amzulescu ^[27]	*	*	*	*	*	*	*	*	8
Stöllberger ^[8]	–	–	*	*	*	*	*	*	6

Note: “*” means 1 point; “–” means 0 point.

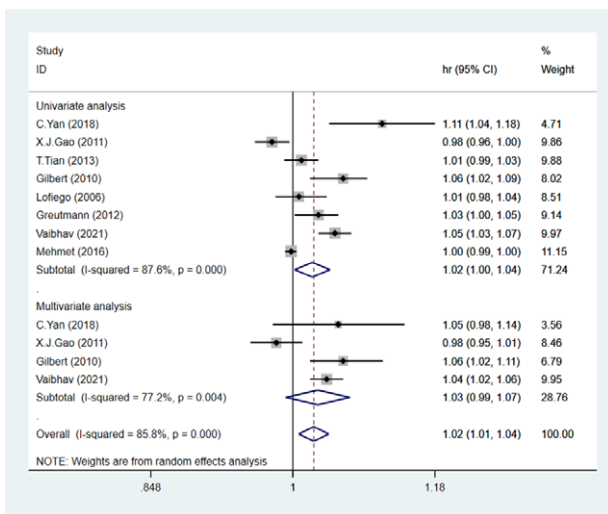


Figure 2. Meta-analysis of age.

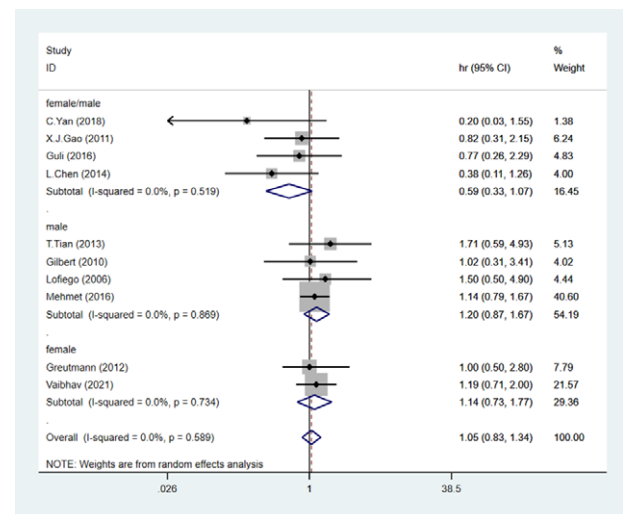


Figure 3. Meta-analysis of gender.

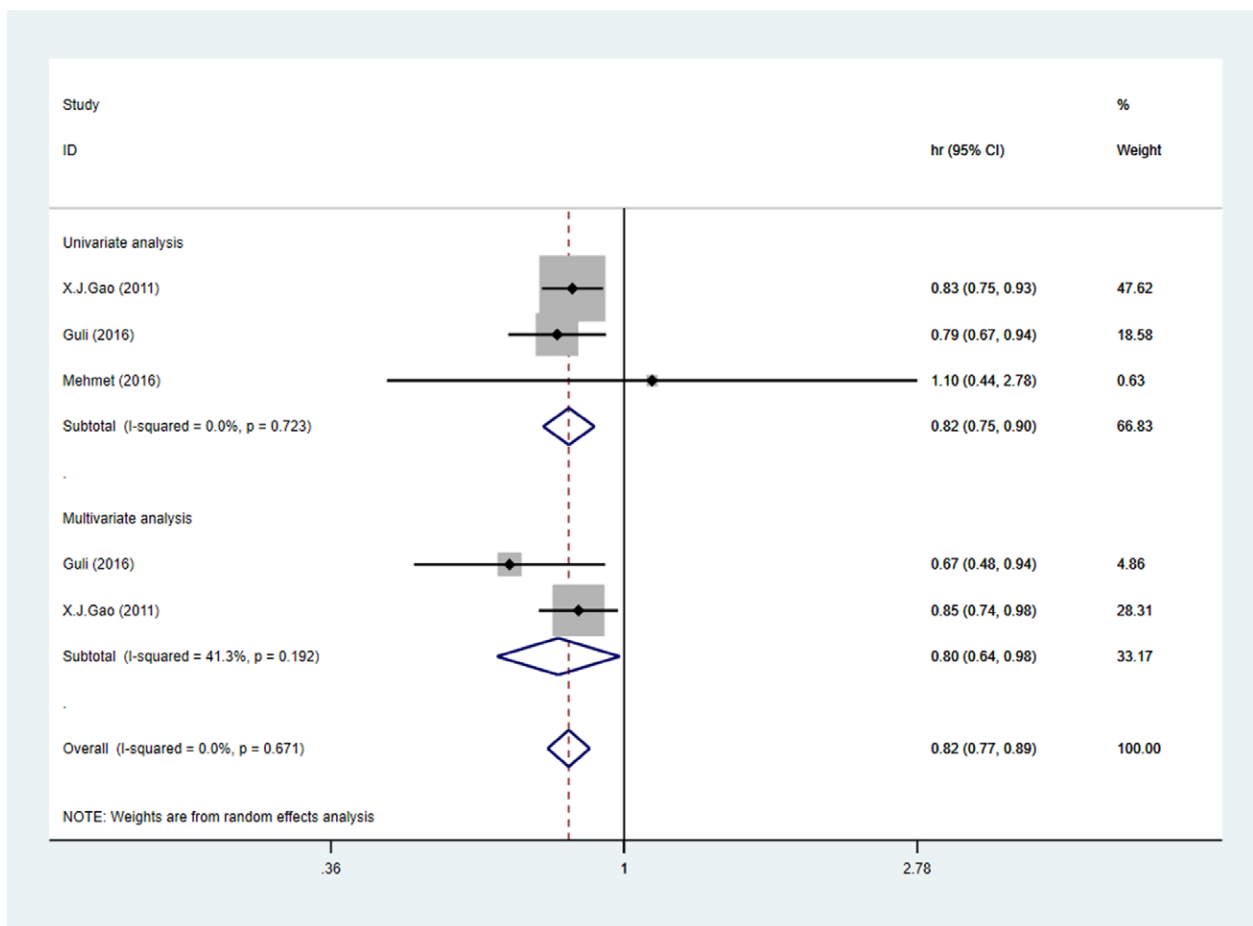


Figure 4. Meta-analysis of BMI. BMI = body mass index.

= 1.09, 95% CI: 0.95–1.25) was not a statistically significant independent risk factor for LVNC prognosis (Fig. 10).

3.4.2. Analysis of N-terminal pro-brain natriuretic peptide. Four studies were included in this analysis^[7,15,16,17]; univariate factor analysis has heterogeneity between studies

($P < .001$, $I^2 = 92.5%$) and multivariate factor analysis does not have heterogeneity between studies ($P = .281$, $I^2 = 21.2%$), all use A random effects model. As shown in Figure 11, the univariate analysis group N-terminal pro-brain natriuretic peptide (NT-proBNP) was a risk factor for poor prognosis of LVNC (HR = 2.51, 95% CI: 1.09–5.81), and the multivariate group analysis showed NT-proBNP (HR = 1.98, 95% CI: 1.10–3.58)

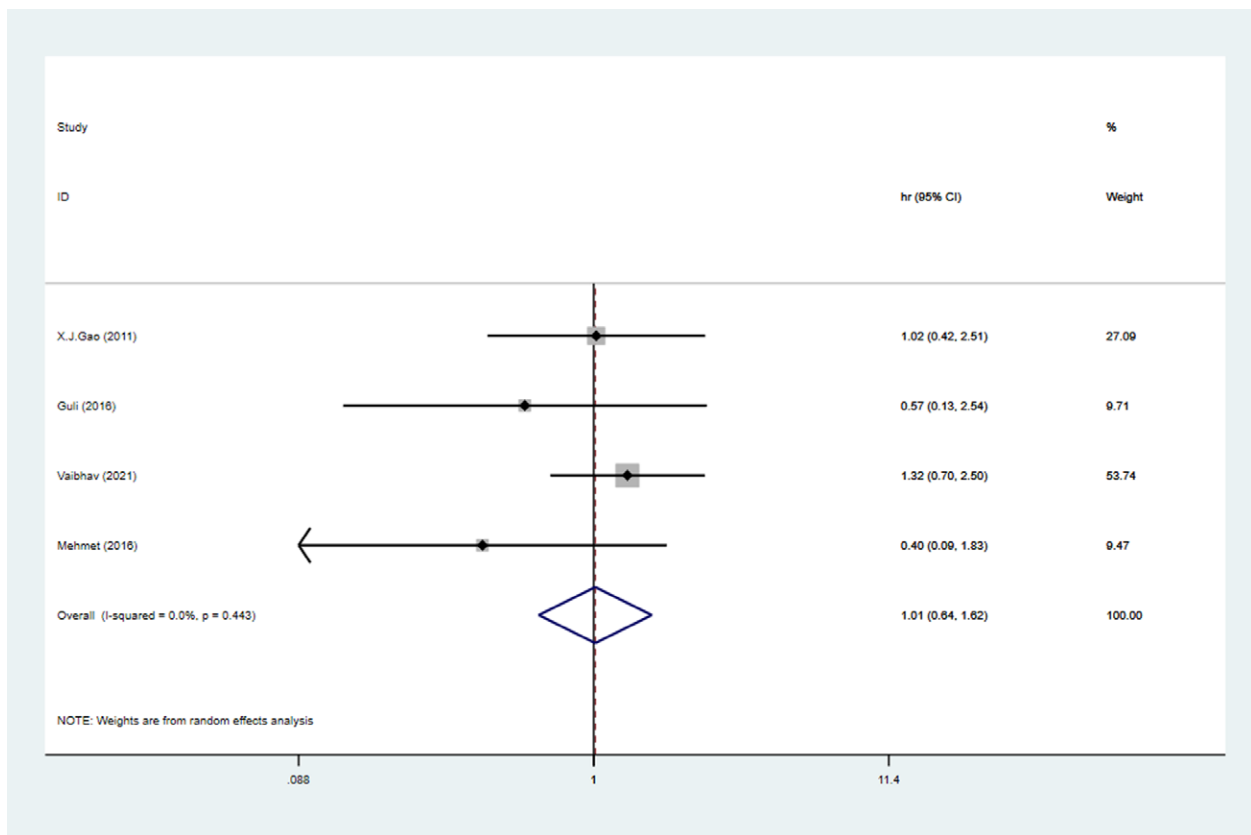


Figure 5. Meta-analysis of coronary heart disease.

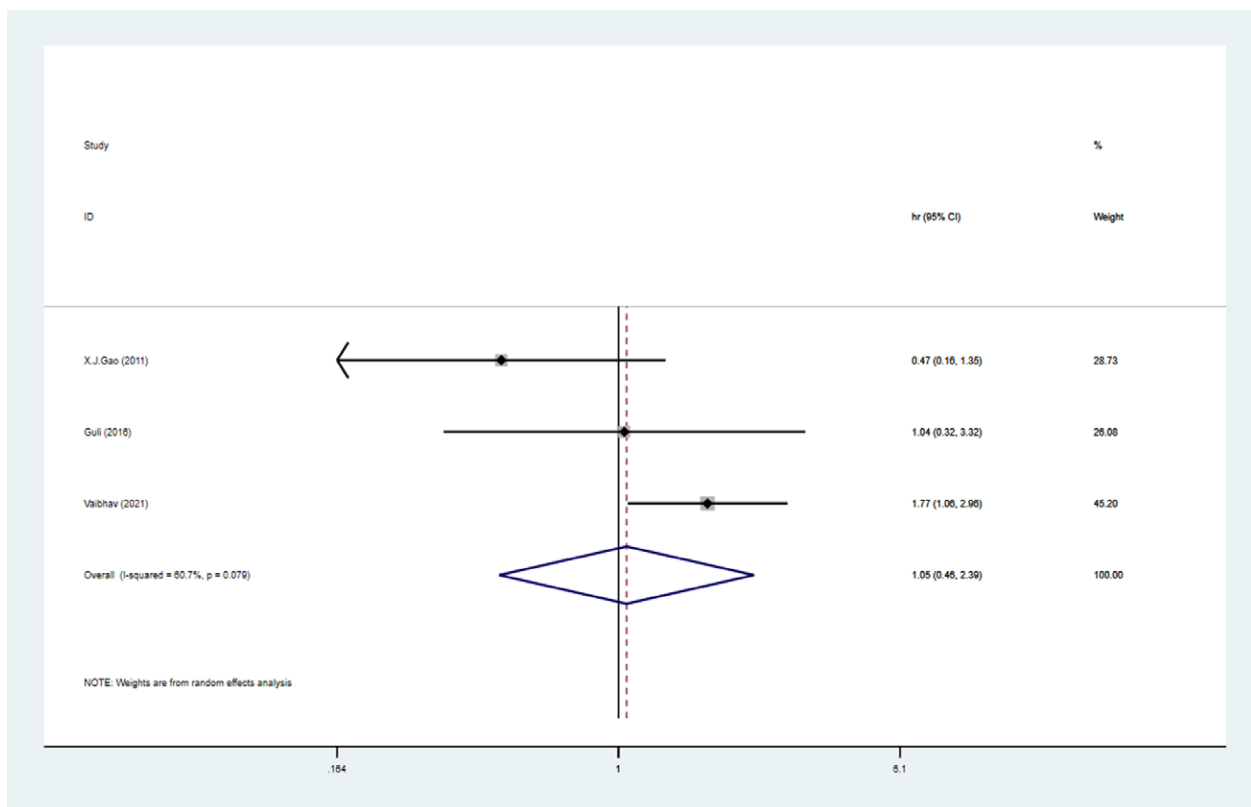


Figure 6. Meta-analysis of hypertension.

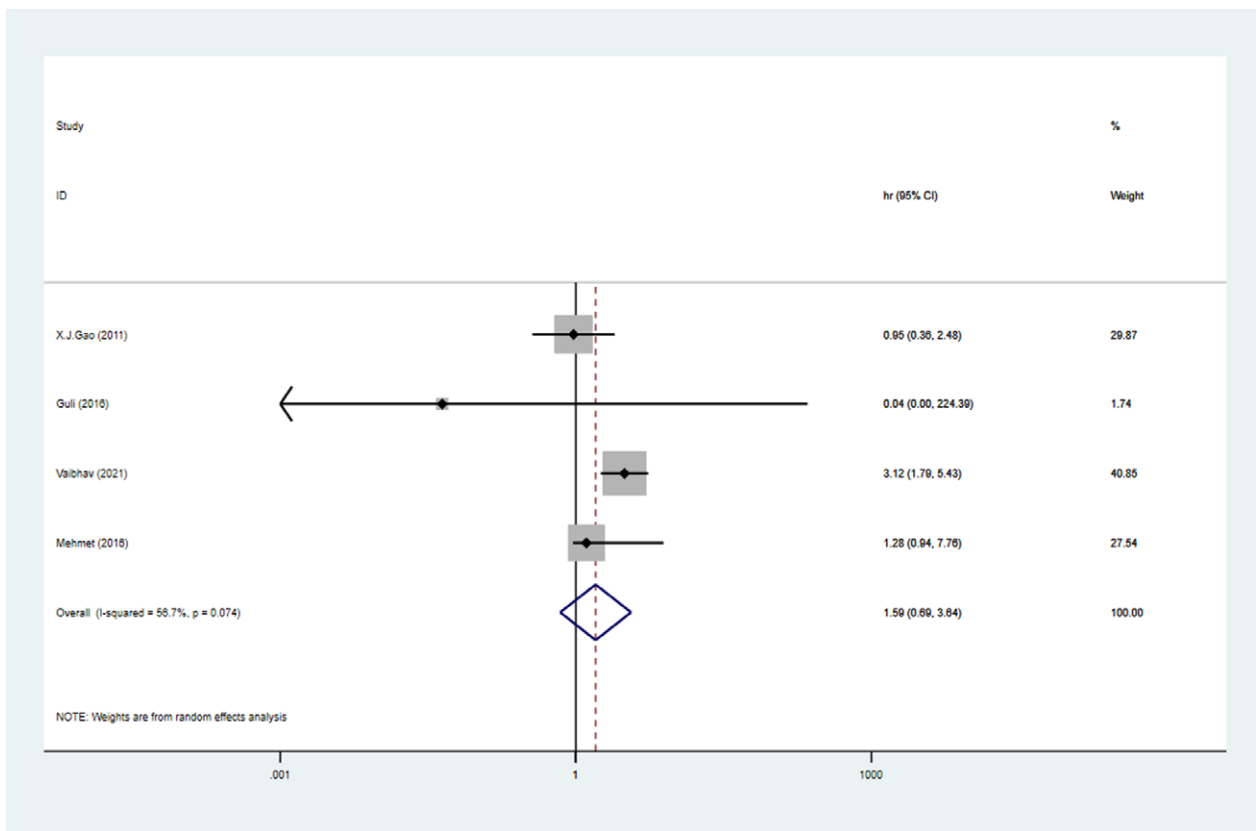


Figure 7. Meta-analysis of diabetes.

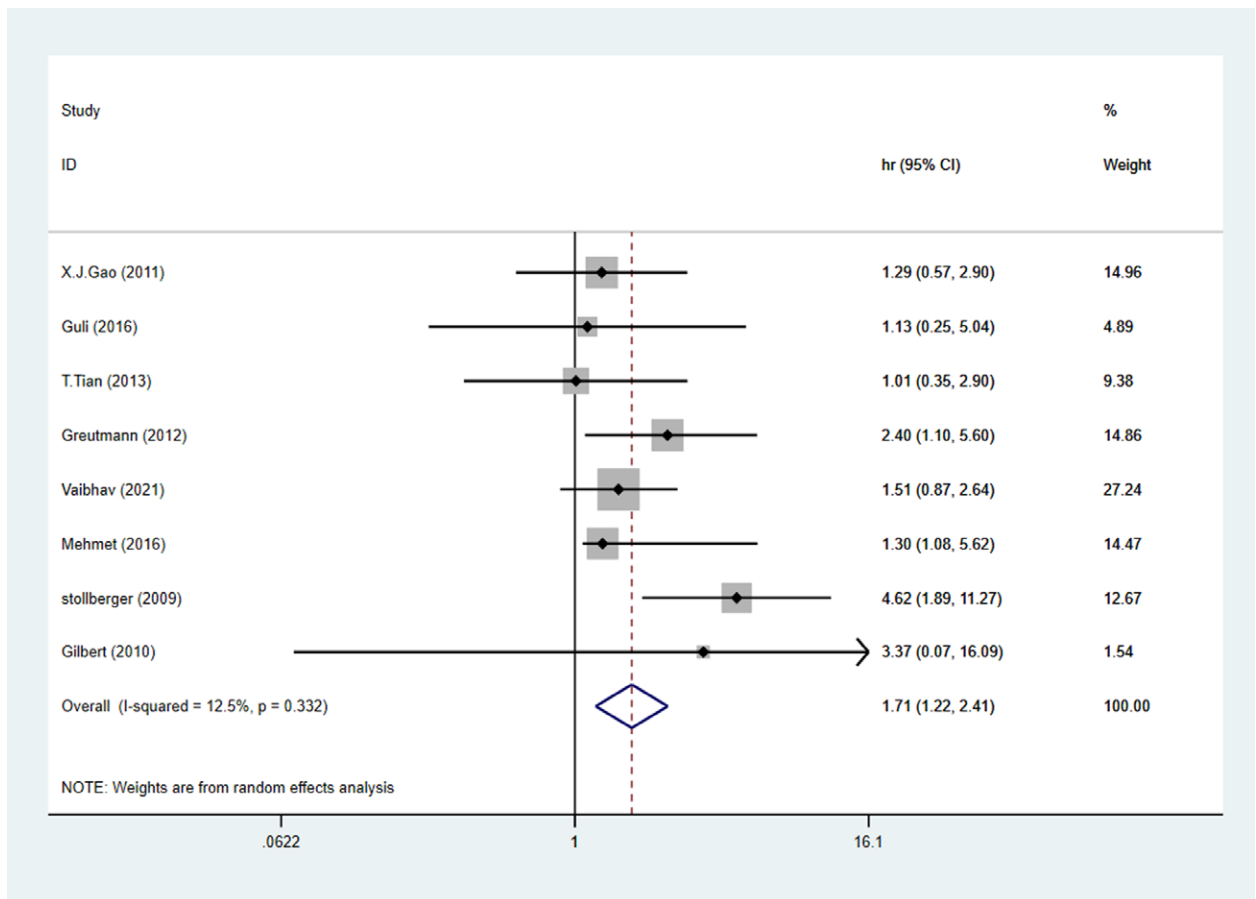


Figure 8. Meta-analysis of atrial fibrillation.

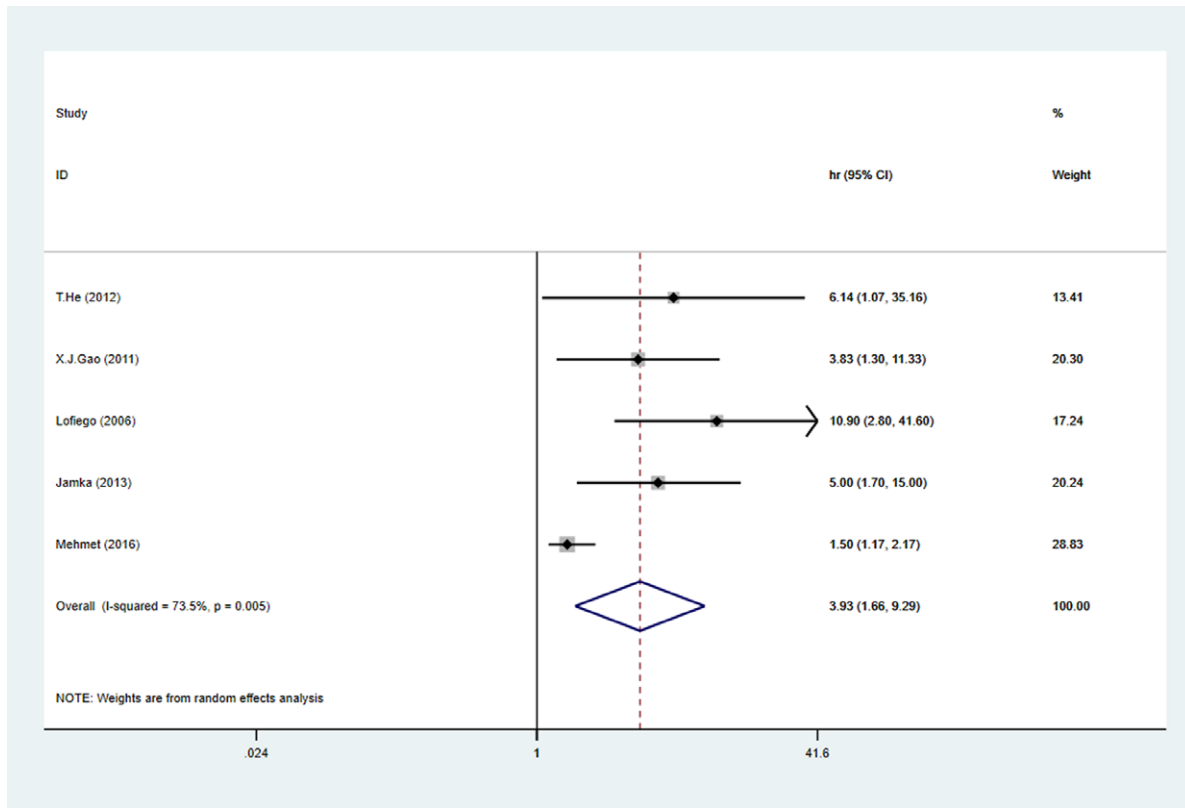


Figure 9. Meta-analysis of NYHA. NYHA = New York Heart Function Association.

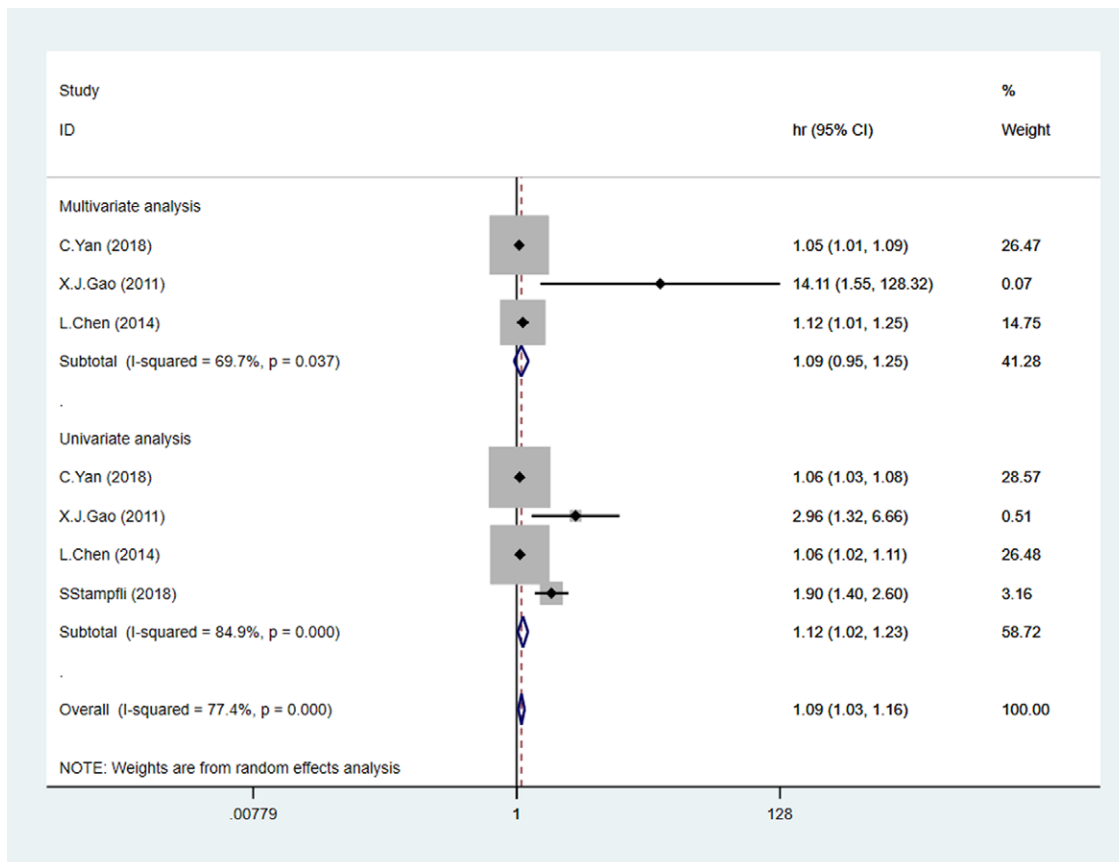


Figure 10. Meta-analysis of creatinine (CR).

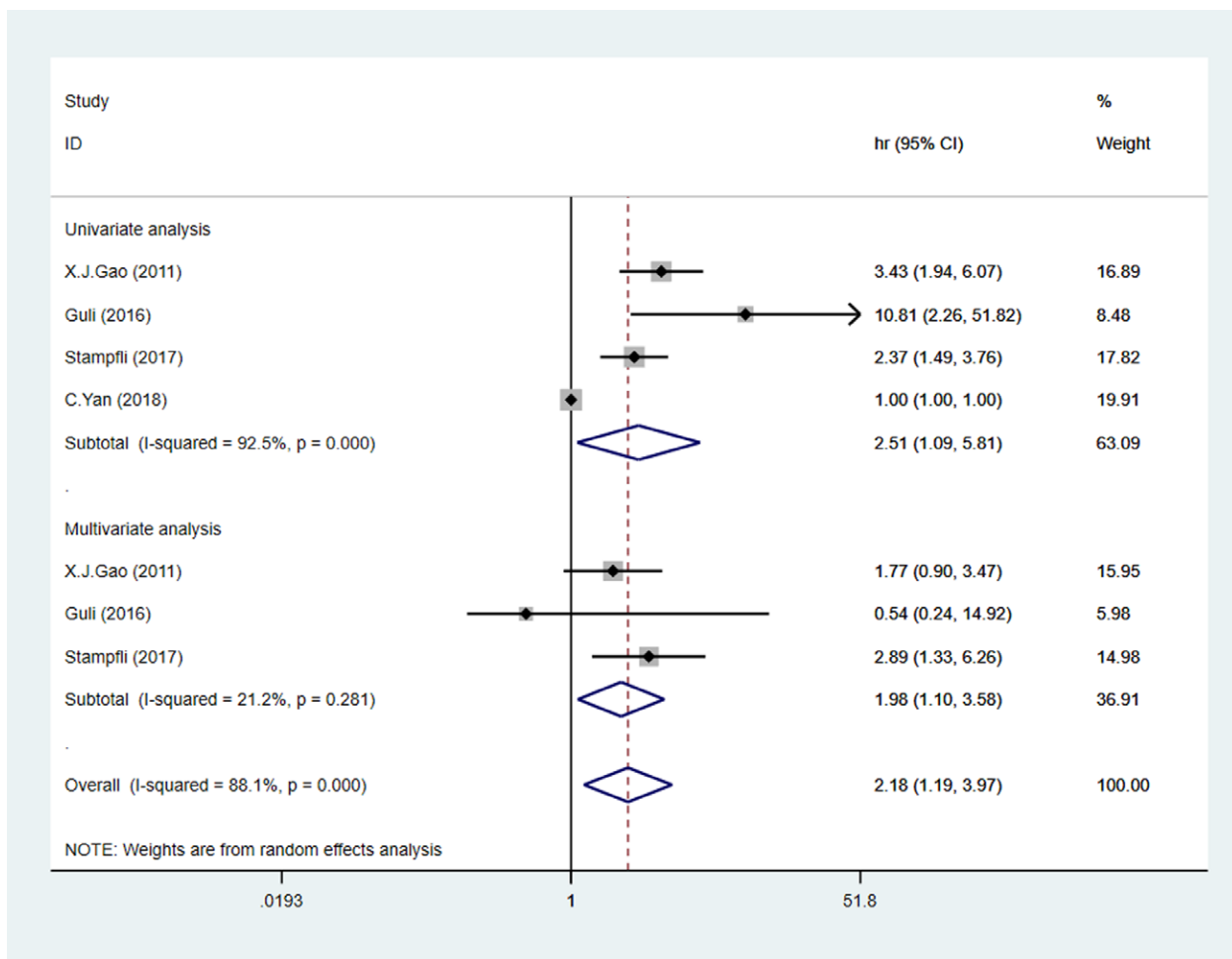


Figure 11. Meta-analysis of NT-proBNP. NT-proBNP = N-terminal pro-brain natriuretic peptide.

is an independent influencing factor of poor prognosis, with statistical significance.

3.5. The influence of echocardiography and cardiac MRI related indexes on the prognosis of LVNC

3.5.1. Analysis of left ventricular ejection fraction. Twelve studies were included in this analysis^[6,7,15–20,24,26,27,28]; there is no heterogeneity between studies, whether as a protective factor or a risk factor ($I^2 = 0\%$). As shown in Figure 12, the increase in left ventricular ejection fraction (LVEF) (HR = 0.95, 95% CI: 0.93–0.96) was statistically significant as a protective factor. LVEF reduction (HR = 3.28, 95% CI: 2.30–4.67) is statistically significant as a risk factor, and as an independent prognostic factor of LVNC (HR = 1.04, 95% CI: 1.03–1.06) is also statistically significant.

3.5.2. Analysis of LVEDD. Eight studies were included in this analysis^[15–18,20,24,26,28]; univariate factor analysis, there is slight heterogeneity between the studies ($P = .032, I^2 = 54.4\%$) multivariate factors Analyze that there is no heterogeneity between the studies ($P = .419, I^2 = 0\%$), and random effects models are used. As shown in Figure 13, the left ventricular end-diastolic diameter (LVEDD) (HR = 1.05, 95% CI: 1.03–1.08) in the univariate analysis group was a risk factor for poor prognosis of LVNC with statistical significance. Multivariate group analysis showed that the LVEDD (HR = 1.05, 95%

CI: 1.03–1.07) is an independent influencing factor of poor prognosis, with statistical significance.

3.5.3. Analysis of left atrial diameter (LAD). Eight studies were included in this analysis.^[15–20,23,28] univariate factor analysis has heterogeneity between studies ($P = .044, I^2 = 51.6\%$), multivariate factor analysis is different There was heterogeneity between the studies ($P = .001, I^2 = 85.9\%$), and random effects models were used. As shown in Figure 14, the LAD in the univariate analysis group was a risk factor for poor prognosis of LVNC (HR = 1.06, 95% CI: 1.02–1.11), which was statistically significant. Multivariate group analysis showed that the LAD (HR = 1.19, 95% CI: 0.96–1.47) is not an independent factor influencing the poor prognosis of LVNC.

3.5.4. Analysis of delayed gadolinium-enhanced imaging. Including 3 studies,^[27,29,30] high heterogeneity between studies ($P < .001, I^2 = 90.3\%$), using random effects model, as shown in Figure 15, late gadolinium-enhanced (LGE) (HR = 3.1, 95% CI: 0.85–11.31) is not an independent prognostic risk factor for LVNC.

3.6. Sensitivity analysis

The results were computed by omitting each study in turn. Meta-analytic random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95% CIs. The scope of one study was significantly different from

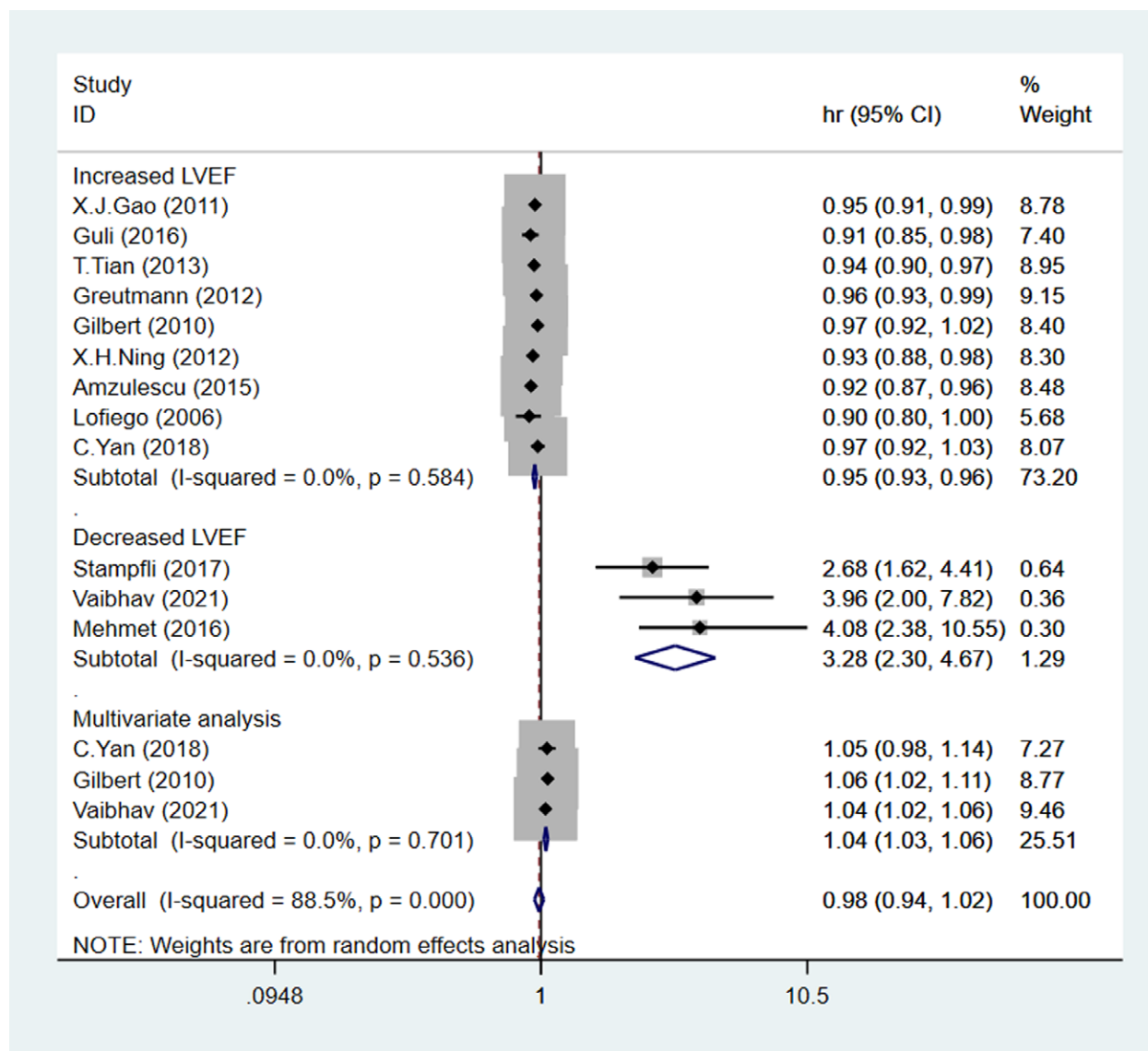


Figure 12. Meta-analysis of LVEF. LVEF = left ventricular ejection fraction.

the other 3 studies, which may have led to the heterogeneity.^[31] Sensitivity analysis showed that the results of NYHA class III/IV, LAD, age factors were stable, and the CR factor changed greatly. As shown in the figure below (Figs. 16–19), for each study, the circle represents the total HR after excluding the study. The horizontal line crossing the circle represents the 95% CI. The short vertical lines at the end of the horizontal line represent the lower and upper limits of 95% CI, respectively.

3.7. Publication bias

In this study, Egger test was used to assess publication bias ($P > .1$ indicates that there is no publication bias). The results showed that there was only publication bias in the analysis of the correlation between NYHA class III/IV ($P = .005$), coronary heart disease ($P = .015$) and diabetes ($P = .048$) and the prognosis of LVNC. In meta-analysis, when the number of included studies is <10 , it is difficult to find the cause of asymmetry, and there is no need to discuss publication bias.^[32] The number of studies included in the above analysis with publication bias is relatively small, so the “cut-and-fill method” cannot be used to assess publication bias.

4. Discussion

Existing research suggests that predictive factors related to poor LVNC prognosis include age of diagnostic, increased left and right atrial and left ventricular diameter, NYHA grade III or above, and NT-proBNP, among others. However, the scope of the literature and the findings are limited and varied and, to date, there are no published meta-analyses on the prognostic factors for LVNC. Therefore, this study used the meta-analytic method to further explore the published evidence on the role of the above factors in LVNC prognosis.

The results of this study show that the age and gender of patients that are clinically concerned, combined with coronary heart disease, hypertension, diabetes, delayed gadolinium-enhanced imaging, and renal function damage are likely to be irrelevant to the prognosis of LVNC, and further study is needed.

An important finding of this study is that CR was not a statistically significant independent risk factor for LVNC prognosis. This is inconsistent with the results of previous studies. Thus, further studies are required to verify this finding and the role of CR in LVNC prognosis. Cardiac insufficiency is the primary clinical manifestation of LVNC. Long-term cardiac insufficiency leads to decreased renal function. CR is an index used

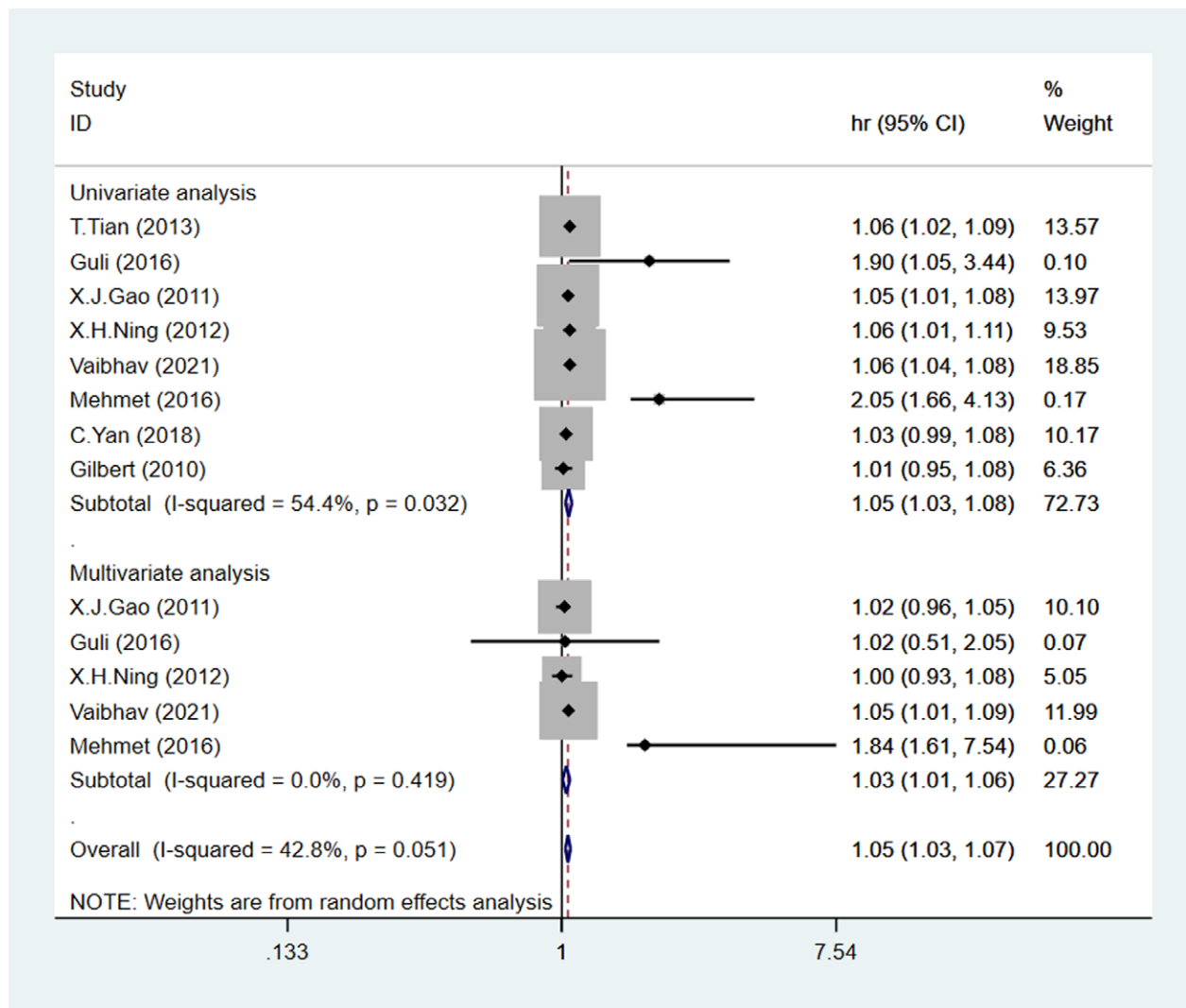


Figure 13. Meta-analysis of LVEDD. LVEDD = left ventricular end-diastolic diameter.

to evaluate renal function. Increased CR levels reflect impaired renal function, which can further exacerbate cardiac dysfunction. Therefore, CR may indicate a poor prognosis to a certain extent, but its prognostic function appears to be limited. The results of this meta-analysis indicate that NYHA class III/IV is an independent risk factor for LVNC prognosis. This finding is consistent with previous research results. Currently, there is no special treatment for LVNC, with treatment primarily directed at cardiac symptoms. Regardless of disease, any patient with heart function classified as NYHA class III/IV usually has a poor prognosis and is at increased risk of death or heart transplantation; this also applies to LVNC patients. Preventing and delaying heart hypofunction is the key to treating LVNC and improving prognosis. Given the above, we argue that this factor need not be studied in too much depth in future research of LVNC prognostic factors; instead, research should focus on other factors that may provide further improvements to a patient's prognosis.

LVEF and NT-proBNP reflect the current state of cardiac function to a certain extent. The results of this study indicate that LVEF and NT-proBNP are independent prognostic factors. A previous prospective study found a correlation between NT-proBNP levels and prognosis in LVNC patients.^[33] A more recent study^[34] reported that patients with a higher level of NT-proBNP may have a shorter survival time than patients

with a lower level of NT-proBNP, indicating that this factor is a marker of poor prognosis. The results of Nay Aung et al^[35] showed that in the absence of moderate to severe left ventricular systolic dysfunction, the number of cardiovascular deaths was significantly reduced, and the reduction of LVEF was an important determinant of the adverse outcome of LVNC patients.

An increase in LVEDD can lead to systolic dysfunction. This study shows that an increase in LVEDD is an independent predictor of the prognosis of LVNC. Oechslin and Jenni^[36] showed that adult patients who died had significantly larger LVEDD than surviving patients. In the general population, the LVEDD is related to the prognosis of dilated cardiomyopathy. LVDD > 55 mm is a predictor of heart failure mortality in patients with pseudohypertrophic muscular dystrophy.^[37]

So far, there are few studies on the prognosis of LVNC by LGE, but LGE detection and its clinical importance have been extensively studied. There is a large amount of scientific evidence about the role of LGE as a predictor of future cardiac events in NCM patients.^[38] This study suggests that LGE is not an influencing factor for the prognosis of LVNC. Because there are fewer included studies and the heterogeneity between studies (e.g., different standards are used in the diagnosis of LVNC between studies), the conclusions are less reliable. Importantly, a meta-analysis^[39] showed that the prognosis of LVNC patients without LGE is better than those with LGE, and

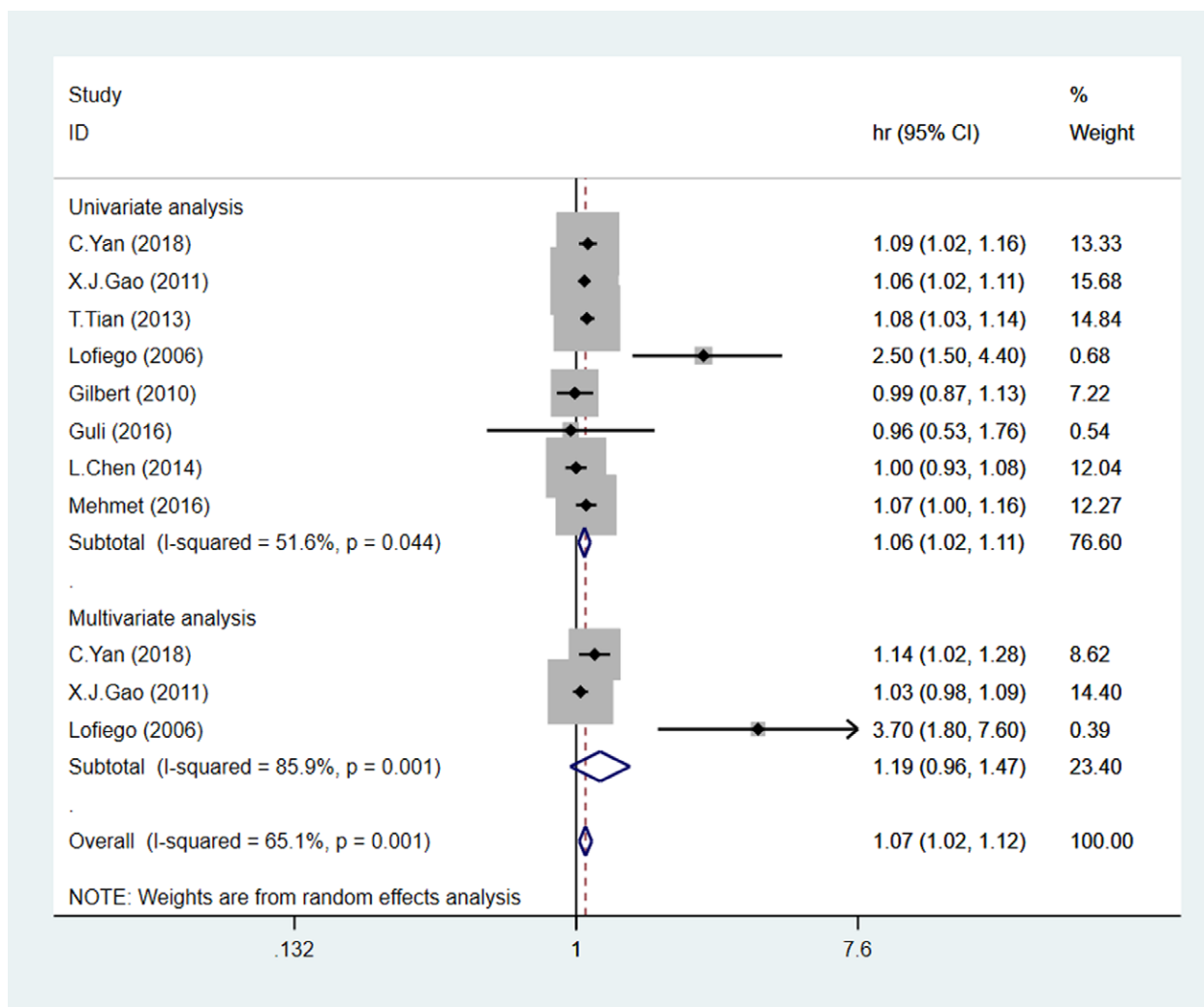


Figure 14. Meta-analysis of left atrial diameter (LAD).

it is recommended to further define the existence and prognostic significance of the disease. LGE must be considered to better risk stratification. Therefore, further research is needed for its influence on the prognosis of LVNC.

In addition to the prognostic factors identified in the current studies, other factors related to poor LVNC have been reported in published studies, including persistent arrhythmia,^[6,19] several genes,^[40] and neuromuscular diseases.^[41,42] However, due to the small number of related studies, these factors could not be evaluated in the current meta-analysis. Waning et al^[43] showed that nearly one-third of NCM patients have mutations in cardiomyopathy genes. The prognosis of LVNC depends on whether it is accompanied by neuromuscular disease, which can be explained by the reduced survival of patients with neuromuscular disease. In fact, when neuromuscular diseases are the underlying disease, heart disease will be more serious, and it will also lead to disorders of the cardiac conduction system and myocardial cells.^[44]

It should be noted that there are some unavoidable limitations of this meta-analysis study, including: heterogeneity: due to the limited number of studies included, we could not complete further analysis of the source of the heterogeneity; publication bias: the reason for publication bias cannot be further understood; choice of research population: LVNC is a rare disease and there are few studies of large samples; thus, this study was unable to access large samples of patients; echocardiography for LVNC diagnosis may be affected by the operator's

experience, the ultrasound machines used, and many other factors, and this may result in inaccurate diagnoses; follow-up of the sample: the length of follow-up in a study is an important factor affecting prognosis research. LVNC has a unique clinical course. If the follow-up time is not long enough, researchers may not observe any adverse cardiovascular events in the patients during the study period. Future studies should perform a long-term systematic follow-up of patients to obtain a comprehensive understanding of the longitudinal risk factors for poor LVNC prognosis.

In summary, study showed that among LVNC patients, NYHA class III/IV, elevated NT-proBNP levels, decreased LVEF, and increased LVEDD may lead to poor prognosis, and increased BMI may improve the prognosis of LVNC.

Author contributions

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Writing – original draft: Ze-Guang Yang.

Writing – review & editing: Ze-Guang Yang, Li Wang.

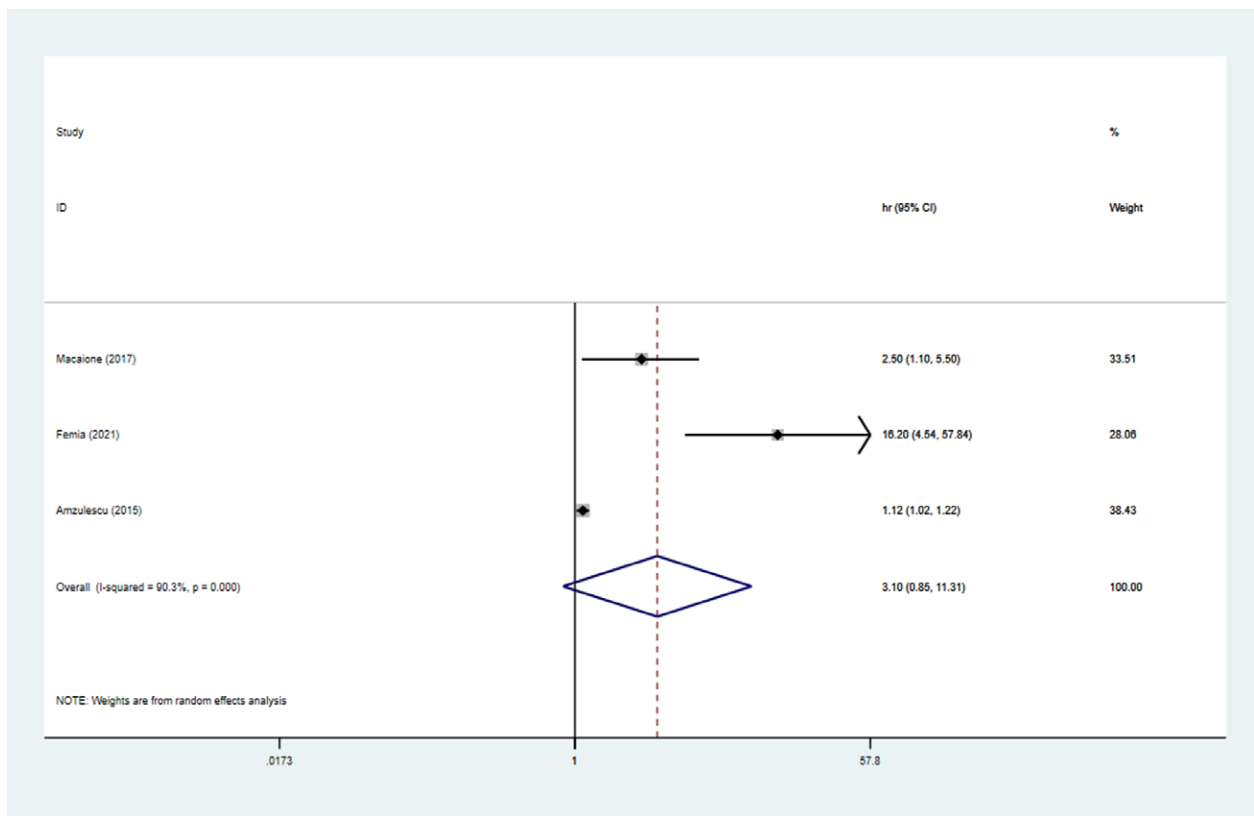


Figure 15. Meta-analysis of late gadolinium-enhanced (LGE).

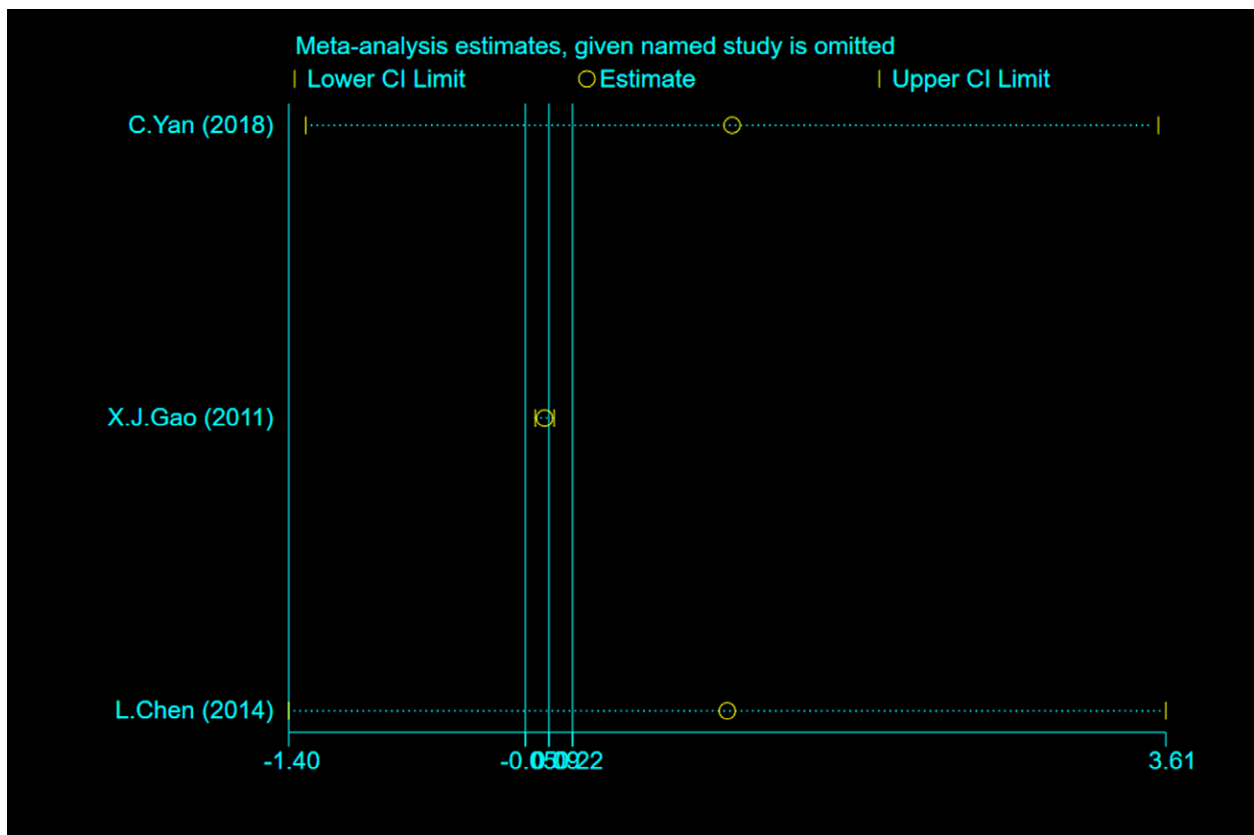


Figure 16. Sensitivity analysis of creatinine (CR).

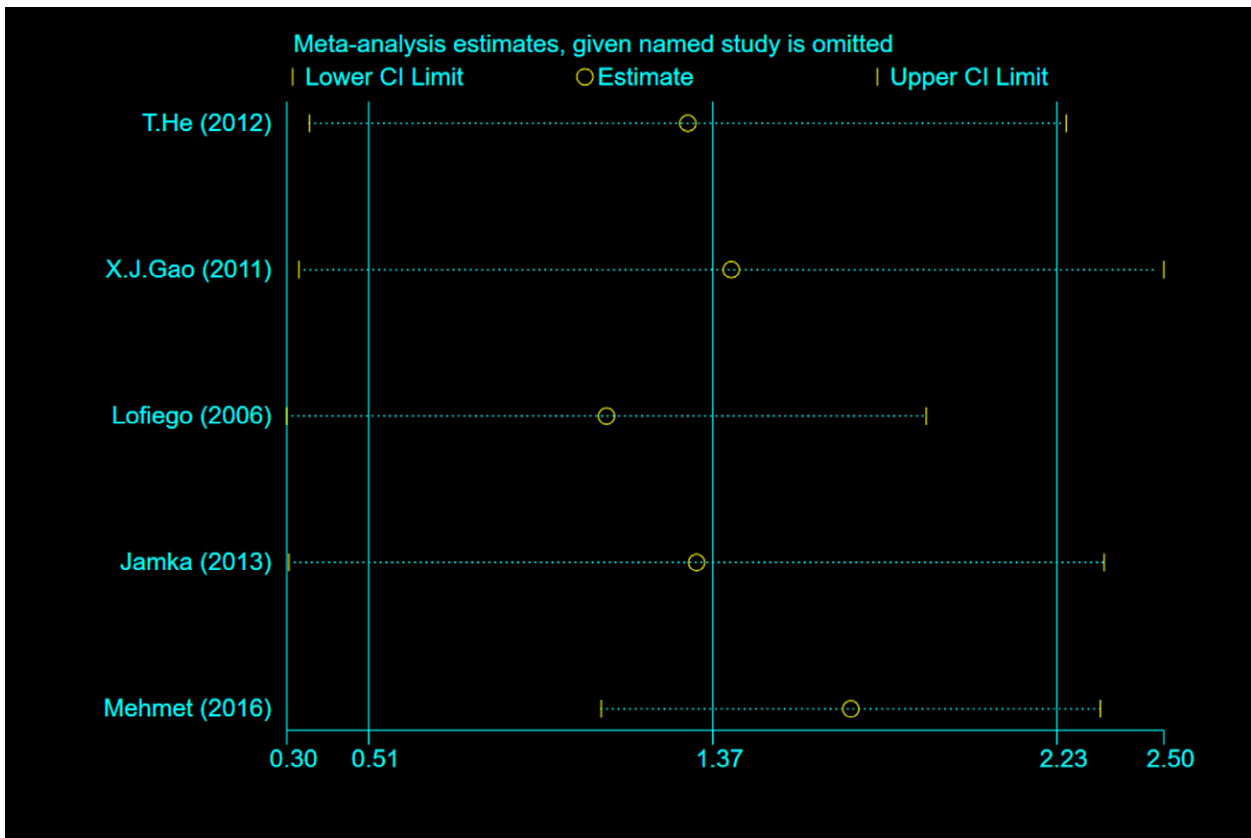


Figure 17. Sensitivity analysis of NYHA III-IV. NYHA = New York Heart Function Association.

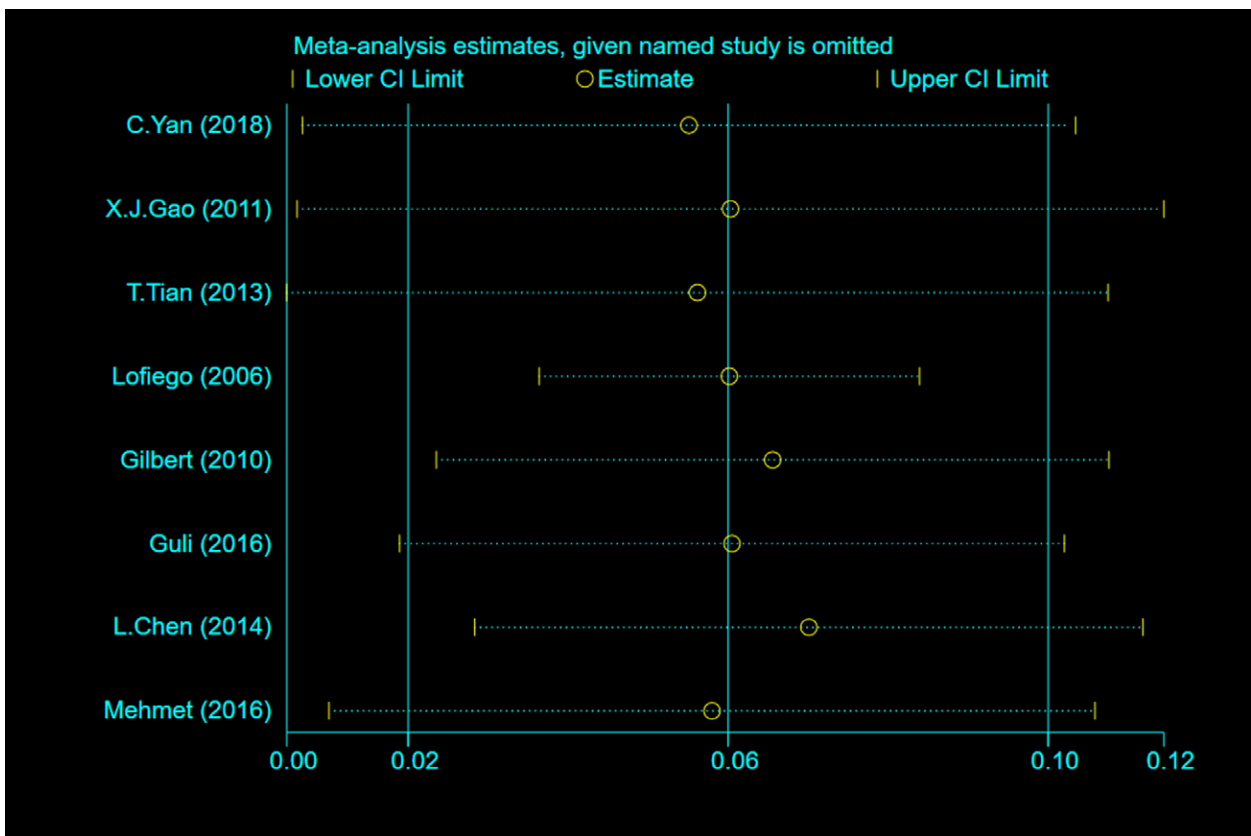


Figure 18. Sensitivity analysis of left atrial diameter (LAD).

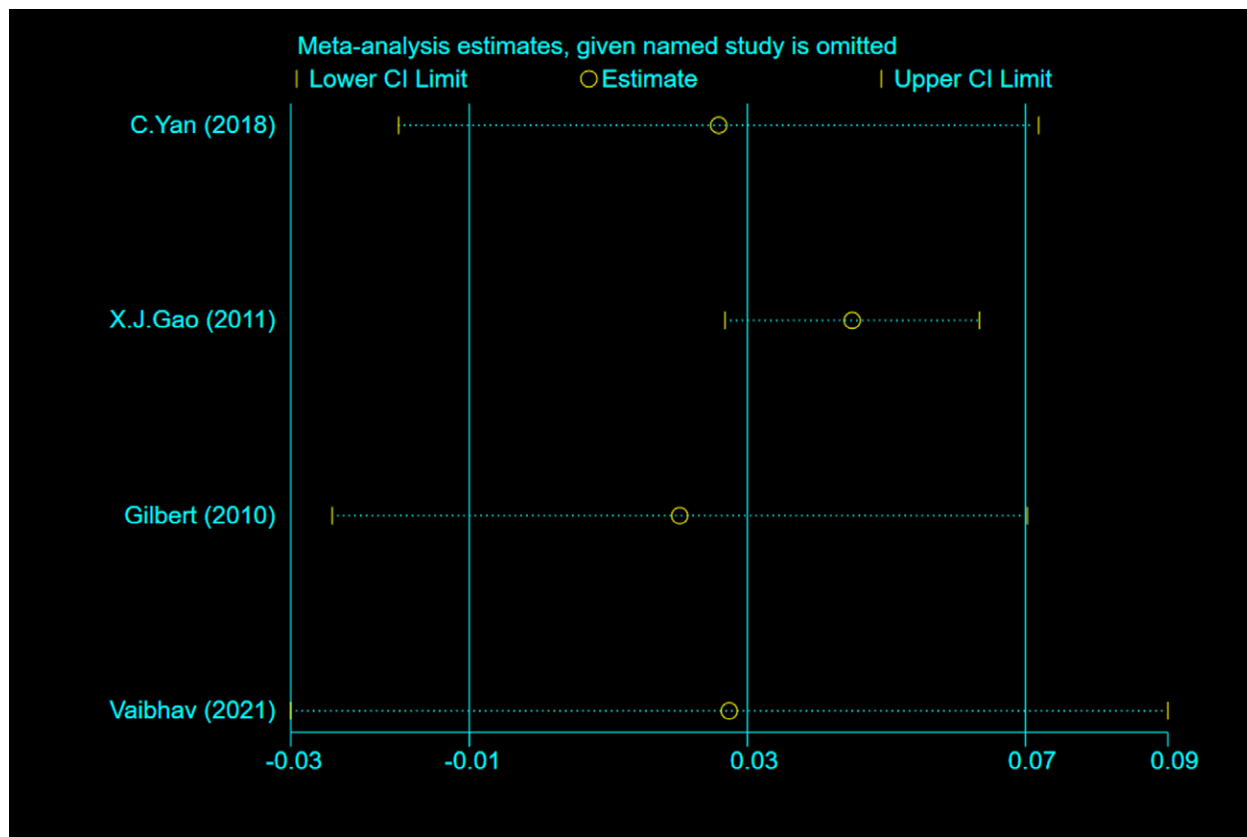


Figure 19. Sensitivity analysis of age.

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