Relationship between serum growth differentiation factor 15, fibroblast growth factor-23 and risk of atrial fibrillation: a systematic review and meta-analysis

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Abstract

Background and Objective: Growth differentiation factor-15 (GDF-15) and fibroblast growth factor-23 (FGF-23) were considered as predictors of the incidence of cardiovascular diseases. The present meta-analysis aimed to elucidate the associations of GDF-15 and FGF-23 with the risk of atrial fibrillation (AF).

Methods: An electronic search was conducted in Cochrane Library, PubMed, and Embase databases from inception until February 27, 2021. The study protocol was registered in PROSPERO database (CRD42020182226).

Results: In total, 15 studies that enrolled 36,017 participants were included. Both serum FGF-23 and GDF-15 was elevated in patients with AF. Analysis of categorical variables showed a higher serum FGF-23 level was associated with increased risk of AF (relative risk (RR)=1.28, 95% confidence interval (CI): 1.05-1.56), but not GDF-15 (RR=0.91, 95% CI: 0.20-4.04). In dose-response analysis, a linear positive association was noted between serum FGF-23 level and the risk of AF ($P_{nonlinear}$ = 0.9507), with a RR elevation by 7% for every 20 pg/ml increase in the serum FGF-23 level (95% CI: 1.02–1.13). No remarkable linkage was found between serum GDF-15 level and the risk of AF, and the overall RR for the association between a 100 ng/L increment in GDF-15 level and AF was 1.01 (95% CI: 0.998–1.02).

Conclusion: Our study showed a positive linear correlation of serum FGF-23 level with the risk of AF. However, no significant association was found between GDF-15 and risk of AF. Further studies are warranted to clarify whether serum FGF-23 level may be significant to predict the risk of AF.

1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia in clinical practice, and is associated with high morbidity and mortality [1, 2]. Although several important cardiovascular and non-cardiovascular risk factors such as hypertension, age and diabetes were identified, the prediction of AF occurrence has remained a main clinical challenge. In recent years, several biomarkers have shown a promising predictive performance for cardiovascular diseases (e.g., AF). Among them, growth/differentiation factor-15 (GDF-15) and fibroblast growth factor-23 (FGF-23) have been comprehensively investigated [3].

FGF-23 is a bone-derived hormone that plays an important role in regulating the metabolism of phosphate and 1,25-dihydroxyvitamin D [4]. In addition, it inhibits the renal synthesis of calcitriol and the secretion of parathyroid hormone from the parathyroid glands [4]. Besides, higher FGF23 levels are linked with an increased risk of cardiovascular mortality [3, 5]. GDF-15 is a growth factor that belongs to the transforming growth factor-β family. The expression of GDF15 rapidly increases in response to oxidative stress, myocardial stretch, volume overload, and myocardial inflammation [6]. The expression levels of GDF-15 and FGF-23 have been shown to be associated with the prognosis of severe cardiovascular diseases, such as heart failure and AF [7, 8]. Moreover, these markers may be closely correlated with an increased risk of AF in the general population [7, 9-12]. Conversely, several cohorts have reported a null association[13]. Therefore, we aim to assess the relationship between baseline GDF-15/FGF-23 levels and the development of AF and the potential dose-dependent effects.

2. Methods

This study was conducted following the guidelines of the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) **(Supplemental Table S1).** Additionally, this study was registered with PROSPERO (International prospective register of systematic reviews. http: www.york.ac.uk/inst/crd)-registration number- CRD42020182226.

2.1 Literature search

We searched the PubMed database, Embase database, and Cochrane database using the following keywords up to February 27, 2021, with no language restriction. The search terms according to PICOS were as follows:

Exposure:

For GDF-15: ‘growth differentiation factor 15’ OR ‘macrophage inhibitory cytokine 1’ OR ‘prostate differentiation factor’ OR ‘GDF-15’.

For FGF-23: ‘fibroblast growth factor-23’ OR ‘FGF-23 protein’ OR ‘fibroblast growth factor 23’ OR ‘FGF-23 protein’ OR ‘phosphatonin’ OR ‘tumor-derived hypophophatemia inducing factor’.

Outcomes:

For AF: ‘atrial fibrillation’ OR ‘atrial flutter’ OR ‘atrial arrhythmia’ OR ‘atrial tachycardia’.

The detailed description of the search strategy was described in **Supplemental Table S2**.

2.2 Study selection

Endnote X9 (Thomson Reuters, New York, NY) database is used to manager all citations. The abstract that is relevant to the Association between GDF-15 and FGF-23 was reviewed for full-text.

The inclusion criteria were: (1) The article reported serum GDF-15/FGF-23 levels in the atrial fibrillation and non-atrial fibrillation populations; (2) Studies designed as observational studies (cohort, nest-control, or case-control) reported the association between baseline serum GDF-15/FGF-23 level and risk of AF, with adjusted odds ratios (OR), relative risk (RR) or hazard ratio (HR), and the corresponding 95% confidence interval (CI), or providing data to calculate these

estimate effects. The exclusion criteria were: (1) articles with incomplete data provided, such as letter, comment, and review; (2) the cross-sectional studies were excluded due to the high risk for bias; (3) articles involved specific genetic polymorphisms; (4) AF were expressed at tissue or cell level, such as degree of structural remodeling.

If same population were used in multiple studies, we included the most informative article.

2.3 Data extraction and quality assessment

According to the above inclusion criteria, the researchers (Z.Q-T and X-L) independently evaluated the eligibility of the literature. The basic characteristics of each study were extracted, including the first author, year of publication, age, gender, complications, sample size, adjusted estimated effect, 95% confidence interval of each category, and adjustments. We use the Newcastle-Ottawa Scale (NOS) for quality assessment to evaluate the quality of the articles with scores range from 0 to 9. A higher grade (≥7) indicates a moderate-high quality; otherwise, regarded as a low-quality[14, 15].

2.4 Statistical analysis and bias risk assessment

The researchers converted the effect measure into its natural logarithm (RR), and calculated the standard error (selog [RR]) according to the corresponding 95% CI. Random-effects models were used considering the potential heterogeneity across studies. GDF-15 and FGF-23 levels were converted into a uniform unit in all included studies (pg/ml for FGF-23, ng/ml for GDF-15). To compare the GDF-15 level of between AF and control group, GDF-15 or FGF-23 level expressed as quartiles and medians are converted to mean and standard deviation [16, 17]. We calculated the standardized mean difference (SMD) in GDF-15/FGF-23 between those with AF and those without AF. The SMD represents the difference between the weighted mean and SD of the GDF-15/FGF-23 of individuals with AF and that of the controls. For the linear exposure-effect analysis, to estimate study-specific slopes and 95% CIs, the method described by *Greenland and Longnecker* [18] was used. The robust error meta-regression method developed by *Xu and Doi*[19, 20] was applied for the non-linear dose-response analysis. It needs to know the levels of GDF-15 and FGF-23 and their estimate effect with variance estimates for at least two quantitative exposure categories. If the median or average level was not provided in the article, we used the average of the lower and upper limits of each category to estimate the midpoint. If the terminal category was open, we assumed that the length of the open interval was the same as that of the adjacent interval[21, 22]. We applied I^2 statistics to estimate the heterogeneity between studies. Low heterogeneity, moderate heterogeneity, and high heterogeneity was defined as I^2 <50%, 50%-75%, > 75%, respectively[23]. Review Manager (RevMan) version 5.4.1 (The Cochrane Collaboration 2014; Nordic Cochrane Center Copenhagen, Denmark) and STATA (Version 16.0, Stata Corp LP, College Station, Texas, USA) software were used for statistical analysis. $P < 0.05$ with two-tails was considered statistically significant. In addition, to study possible factors influencing results, subgroup analysis stratified by study design and adjustments (sex, NT-pro BNP and CRP).

3. Results

3.1 Study selection

A total of 389 publications were initially retrieved (PubMed=78; the Cochrane Library=48; and Embase=263). After removing 50 duplicates and 188 irrelevant citations, the full-text of the remaining 151 articles were reviewed, and 15 studies (9 for GDF-15 and 6 for FGF-23) were finally included. The flowchart of the study selection is shown in **Figure 1.** Excluded studies with detailed reasons (n=31) are summarized in **Supplementary Table S3**.

3.2 Study characteristics and quality of the eligible studies

Table 1 shows the characteristics of the eligible studies. For GDF-15, 9 studies with 1,721 cases/10,602 individuals were included. In general, the eligible studies were published from 2011 to 2020, and their sample size ranged from 100 to 3,217 participants. Four studies reported the association between serum GDF-15 level and the risk of AF in the general population [7-9, 24], 2 studies concentrated on patients who received coronary artery bypass graft [25, 26], and 2 studies reported this association in patients with recurrent AF after catheter ablation [27, 28]. The majority of the eligible studies were performed in Europe [7, 10, 24-27] (n=6), two studies were undertaken in China [8, 28], and only one study was conducted in the United States [9].

Six studies enrolling 3,138 cases and 25,415 participants reported the association between serum FGF-23 level and the risk of AF from 2014 to 2020 [3, 5, 11, 29-31]. Four studies reported an association between FGF-23 and AF in the general population [3, 11, 29, 30], one study was based on patients with CKD [5], and one study reported an association between FGF-23 and postoperative atrial fibrillation [31]. Among them, 3 studies were performed in the United States[3, 5, 11], and others were conducted in Asian (n=1) [29] or European countries (n=2) [30, 31].

Ascertainment of AF in most studies was mainly conducted through electrocardiography or medical records; the study of Shao's study did not specify the measurement of AF diagnosis [8].

These studies achieved Newcastle-Ottawa Scale (NOS) scores greater than 6 points, and their estimated quality was acceptable (**Supplementary Table S4**).

3.3 GDF-15

3.3.1 Comparison of serum GDF-15 level between patients with and without AF

A total of 7 studies with 1200 cases/4332 individuals were included [7, 8, 24-28]. Compared with the patients with AF, serum GDF-15 level was elevated in patients with AF (standardized mean difference (SMD): 0.25, 95% CI: 0.07-0.42; I2=75%), with a significant heterogeneity (**Figure 2A**).

3.3.2 Association between GDF-15 and risk of AF

In the categorical analysis, two cohorts (313 cases and 3153 individuals) were included [9, 26]. The results showed that a high level of GDF-15 was not significantly associated with an increased risk of AF (RR=0.91, 95% CI: 0.20-4.04; I2=87%), and a significant heterogeneity was detected (**Figure 2B**).

In the dose-effect analysis, 5 cohorts from four publications[9, 10, 24, 28], covering 819 cases and 8281 individuals were included. The overall RR for assessing the association between a 100 ng/L increment in GDF-15 level and AF risk was 1.01 (95% CI: 0.998-1.02; I2=35%), with no evidence of heterogeneity (**Figure 2B**). The nonlinear analysis was not performed due to limited data. In the pre-defined subgroup analyses stratified by study design, adjusted for gender, NT-pro BNP and CRP, the results were still not significant. No significant subgroup differences were found among these groups (P>0.05) (**Supplementary Figures 1A-D**).

3.4 FGF-23

3.4.1 Comparison of FGF-23 level between patients with and without AF

Four studies [29, 31-33] that enrolled 994 cases and 5318 individuals were included to explore the difference in FGF-23 level between AF and non-AF patients. Patients with AF exhibited an elevated serum FGF-23 level (SMD: 0.55, 95% CI: 0.13-0.98; I2=94%), with substantial evidence of heterogeneity (**Figure 3A**).

3.4.2 Association between FGF-23 level and risk of AF

In the categorical analysis, three studies with 2752 cases and 23973 participants were included[3, 11, 33]. The pooled RR for the correlation of serum FGF-23 level with AF risk was 1.28 (95% CI: 1.05-1.56, I2=34%), with no evidence of heterogeneity (**Figure 3B**). According to pre-defined subgroup analyses, the results were stable and no subgroup differences were detected among these groups (P>0.05) (**Supplementary Figure 1E-G**).

Three cohorts in two studies covering 2092 AF cases and 20,097 participants were included in the dose-response analysis [3, 11]. There was a linear correlation between serum FGF-23 level and the risk of AF ($P_{non\text{-}linear}$ =0.9507), with a FGF-23 cutoff value of 62 pg/ml for significantly increased risk of AF (**Figure 4**). The overall RR for the association between a 20 pg/ml increase in serum FGF-23 level with AF risk was 1.07 (95% CI: 1.02-1.13; I2=0%), with no evidence of heterogeneity (**Figure 3B**). All included studies were adjusted for gender and NT-pro BNP in the exposure- response analysis; thus, the dose-response analysis in subgroups stratified by gender and NT-pro BNP were not performed.

4. Discussion

4.1 Major findings

The present study showed that serum FGF-23 level was linearly correlated with the risk of AF, with a RR increase by 7% for every 20 pg/ml elevation in FGF-23 level. However, although AF patients had a higher serum GDF-15 level, a positive correlation of serum GDF-15 level with the risk of AF was not established, either in the categorical or continuous variables analyses.

4.2 Comparison with previous studies

4.2.1 GDF-15

The relationship between serum GDF-15 level and the risk of AF remains inconclusive [34, 35]. Importantly, although we found a noticeable increase in serum GDF-15 level in patients with AF compared with those without AF, no positive correlation between GDF-15 and AF risk was found. This result was confirmed in the sensitivity and subgroup analyses. These results were not surprising. Consistently, in a community-based Swedish study, a neutral association was reported between serum GDF-15 level and the risk of AF (hazard ratio (HR): 1.141, P=0.12) [36]. Notably, the GDF-15 level that can predict adverse outcomes (e.g., major bleeding) of patients with AF, rather than markers for AF incidence among the general population, has been reported. Moreover, the prognostic value of GDF-15 for other outcomes of AF patients, such as recurrence of AF after catheter ablation, was also reported in several studies [28, 37, 38]. However, owing to the limited sample size, the association between serum GDF-15 level and the risk of AF should be further evaluated.

4.2.2 FGF-23

As for FGF-23, previous studies regarding the association between serum FGF-23 level and the risk of AF yielded inconsistent results [3, 11, 33]. A cross-sectional study of Japanese cardiac patients first reported a U-shaped relationship between serum FGF23 level and the prevalence of AF [39]. However, the ARIC study demonstrated an approximately linear correlation of serum FGF-23 level with the incidence of AF [40]. A meta-analysis indicated a positive correlation of serum FGF-23 level with the risk of AF, but only categorical variables were analyzed and the potential dose-dependent effects were not evaluated [41]. The present study, for the first time, showed a positive linear correlation of serum FGF2-3 level with the risk of AF, and a 20 pg/ml elevation in serum FGF-23 level increased the risk of AF by 7%. Notably, the relationship between serum FGF23 level and AF incidence might be markedly influenced by kidney function. Alson et al. found a linear association in the overall population in the ARIC cohort. However, a U-shaped relationship was found for a subgroup of eGFR> 60 mL/min per 1.73 $m^{2,}$, and an inverse U-shaped relationship was suggested for a subgroup of eGFR <60 mL/min per 1.73 m^2 [40]. FGF-23 is a well-known important mediator in the pathology of chronic kidney disease (CKD) [42], and these discrepancies can be justified. In the present meta-analysis, all included studies were adjusted for CKD, suggesting a CKD-independent effect assessment of the association between serum FGF-23 level and the risk of AF. Consistently, another prospective cohort study showed that, for the enrolled 3,876 patients with mild-to-severe CKD, a 1-U increase in serum FGF23 level increased the risk of AF by 47%[33]. The potential reasons for the discrepancies among these studies might be attributed to significant differences in the relevant risk factor profiles or the incidence of AF. Moreover, as an early biomarker for CKD, Klotho deficiency contributes to soft-tissue calcification in CKD, and Klotho was considered as a co-receptor for FGF23 function [43]. Besides, α-Klotho deficiency in CKD patients may exacerbate α-Klotho–independent cardiac toxicity of FGF23, thereby promoting the incidence of AF [44]. However, a limited number of studies have detected the serum α-Klotho level; therefore,

further studies are warranted to assess the role of α-Klotho in elucidating the association between serum FGF-23 level and the risk of AF, especially in patients with CKD.

4.3 Potential mechanisms

Several potential mechanisms can explain the association between serum FGF-23 level and the risk of AF. FGF-23 plays a pivotal role in the regulation of mineral homeostasis, and can promote myocardial remodeling and myocardial hypertrophy, causing endothelial dysfunction [3, 45]. In case of high serum levels of FGF-23, the levels of calcium, phosphorus, and vitamin D in the body cannot be properly regulated. FGF-23 upregulation may also activate the renin-angiotensin-aldosterone system (RAAS), which plays a role in atrium remodeling and influences the hemodynamics of the kidneys [46], thereby indirectly affecting the cardiac function [47]. Furthermore, studies have demonstrated that FGF-23 significantly activates the protein kinase C (PKC) signaling pathway, resulting in abnormal sodium channel conductance, affecting cardiac function and disrupting heart rate [48, 49]. In addition, FGF-23 can also activate the TGF-β signaling pathway, leading to the activation of fibroblasts [50].

4.4 Implications and further research

NT-proBNP and CRP play important roles in the occurrence and development of AF [13]. The association of serum FGF-23 level with the risk of AF was not noticeable in the subgroups without adjustment for NT-proBNP and CRP level in the categorical analysis, but only one study was included. Besides, in the dose-dependent effect analysis, all studies were adjusted for NT-proBNP/CRP and positive results could be achieved. The above-mentioned results suggested that FGF-23 could increase the risk of AF independent of NT-proBNP and CRP, while additional studies were needed to confirm our results.

To date, several risk models have been established for predicting the incidence of AF in the general population [34-37]. Recent studies have shed light on the roles of biomarkers in improving the predictive abilities of AF risk scores. Our study showed the predictive value of serum FGF-23 level for AF. Further studies are needed to examine the predictive performance by adding FGF-23 to the existing AF prediction scores.

Also, although our study did not yield a positive correlation between GDF-15 and AF risk, GDF-15 has been applied as a biomarker for predicting the risk of cardiovascular disease [51, 52], and prognosis of AF [53]. According to several large cohort studies, the biomarker-based ABC (age, biomarker and clinical history) scoring incorporating GDF-15 has demonstrated good predicting ability for embolization and bleeding events in AF patients [54-56]. Hijazi et al. showed that the ABC bleeding score performed better than the HAS-BLED and ORBIT scores [57], which suggests they might have a promising clinical application in the future.

4.5 Study limitations

This was the first study that assessed the dose-dependent associations of FGF-23 and GDF-15 with the risk of AF. Nevertheless, several limitations of this study should be pointed out. Firstly, only a relatively small number of articles was included in this meta-analysis, and some articles used unconventional units of GDF-15 level and they were excluded [36]. Secondly, a moderate or a high degree of heterogeneity was found in this meta-analysis. The heterogeneity might be partly due to differences in participants' characteristics, study design, and methods of analysis. Heterogeneity become smaller after removing Chen's study [29], which suggests the heterogeneity derives from region. Besides, race- or gender-dependent subgroup analyses were not performed because we did not have sufficient patient-level data. Thirdly, we processed midpoint imputation for the dose-dependent association assessment, which might cause bias in the results. Fourth, although serum FGF-23 level was elevated in patients with CKD, due to data restrictions, subgroup analyses stratified by CKD were not conducted. Further studies are needed to elucidate the association of serum FGF23 level with the risk of AF in patients with or without CKD. Finally, because of the inherent flaws of observational studies, causality could not be proved forcefully.

5. Conclusions

In summary, our study showed a positive linear correlation of serum FGF-23 level with the risk of AF. No significant association between serum GDF-15 level and the risk of AF was found. Further studies are needed to verify whether FGF-23 may be of great significance in predicting the risk of AF.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Competing interests

The authors declare no competing financial interests.

Authors' contributions

Guarantor of the article: X-L, P-Y

Authors' contributions: X-L contributed to the study concept and design and revised the draft. Z.Q-T and S.S-H performed the search strategy and contributed to database research, acquisition of data, and statistical analyses. All the authors participated in data analysis, reviewed, and approved the final manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Basic characteristics of the articles included in the meta-analysis of GDF 15, FGF-23 and risk of atrial fibrillation

Author, years	Country	Study design/Mean follow-up time	Study populations	Cases/Sample size	Mean age/Male	Baseline comorbidities (%)	AF diagnosis	Outcome report
GDF-15								
Bening, 2019	Germany	Prospective cohort/NA	NA Postoperative atrial fibrillation	38/229	68.45/83.41%	NA	ECG	Difference
Bouchot, 2015	France	Prospective cohort/1 year	University Hospital of Dijon Postoperative atrial fibrillation	34/100	64.02/92.00%	Hypertension: 64.0 Diabetes: 36.0	ECG	Difference Risk of AF
Lamprea-Montealegre, 2019	USA	Prospective cohort/1 year	Chronic Renal Insufficiency Cohort study CKD patients	279/3053	NA/NA	CVD history: 28.0 HF history: 6.0 Diabetes: 48.0	ECG	Risk of AF
Rienstra,2014	Netherlands	Retrospective cohort/10 years	Community-based Framingham Heart Study	242/3217	59.00/46.00%	Diabetes: 11.0 HF: 1.0 Myocardial infarction: 4.0	ECG	Risk of AF
Santema, 2019	Netherlands	Prospective cohort/NA	Six centers in Scotland	733/1758	72.50/72.53%	Diabetes history: 34.5; Stroke history: 10.4; Hypertension history: 68.9	ECG	Difference
Shao, 2014	China	Prospective cohort/NA	Second Hospital of Tianjin Medical University	67/134	66.60/43.38%	Hypertension: 65.7 Diabetes: 13.4	NA	Difference Risk of AF
Smit,2011	Netherlands	Prospective cohort/1 year	University Medical Center Groningen AF recurrence	30/100	65.00/74.00%	Hypertension: 67.0 HF history: 20.0 Coronary artery disease: 18.0 Diabetes: 14.0	ECG	Difference
Svennberg, 2016	Sweden	Prospective cohort/13 years	The Uppsala Longitudinal Study of Adult Men	113/883	71.00/100.00%	Diabetes: 10.3	ECG	Difference
		Prospective cohort/10 years	The Prospective Investigation	148/978	70.00/49.00%	Diabets: 11.7		

			of the Vasculature in Uppsala Seniors					
Wei,2020	China	Prospective cohort/14 months	Peking University Third Hospital Postoperative atrial fibrillation	37/150	64.00/56.76%	Hypertension 62.7 Diabetes: 23.3 Coronary artery diseas: 12.7 Chronic HF: 6.7	ECG	Difference Risk of AF
FGF-23								
Alonso2014	USA	Retrospective cohort/17 years	Atherosclerosis Risk in Communities study	1572/12349	NA/NA	Diabetes: 14.3	ECG	Risk of AF
Chen2020	China	Prospective cohort/NA	Dongguan Songshan Lake Central Hospital	240/390	60.01/68.21%	NA	ECG	Difference
Maan, 2016	Greece	Retrospective cohor/10.6 years	Multi-Ethnic Study of Atherosclerosis study	77/983	59.68/43.03%	Diabetes: 11.2	ECG	Difference Risk of AF
Mathew 2014	USA	Retrospective cohor/7.7 yearst	Multi-Ethnic Study of Atherosclerosis	291/6398	NA/46.73%	Diabetes: 12.3 Hypertension: 36.4	ECG and physician claims data	Risk of AF
		Retrospective cohort/8 years	Cardiovascular Health Study	229/1350	NA/28.67%	Diabetes: 10.6 Hypertension: 46.0		
Mehta2016	USA	Prospective cohort/7.6 years	Chronic Renal Insufficiency Cohort CKD patients	660/3876	57.66/55.21%	Hypertension: 86.1 Diabetes: 48.5 HF: 9.7 CVD: 13.5	ECG	Difference Risk of AF

Mizia-Stec 2018	Poland	Case-control study/NA	NA Postoperative atrial fibrillation	69/NA	56.59/66.70%	Coronary artery disease: 20.3 Hypertension: 59.4 Diabetes: 17.4	ECG	Difference

Abbreviations:

NA: not applicable; SR: sinus rhythm; ECG: electrocardiograms; NT-proBNP: N-terminal pro-B-type natriuretic peptide; IL-6: interleukin 6; eGFR, estimated glomerular filtration rate; EF: ejection fractions; LV: left-ventricular; BB: beta-blockers; ACE-I: angiotensin-converting enzyme inhibitors; ECG: electrocardiogram; AF: Atrial fibrillation; NT-proBNP: N-Terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate; LAD: left atrial diameter; LAAV: left atrial appendage flow velocity; CPVI: circumferential pulmonary vein isolation; CRP: C-reactive protein; BNP: B-type natriuretic peptide; FGF-23: fibroblast growth factor-23; GDF-15: Growth differentiation factor-15; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HF: heart failure; CVD: cardiovascular disease; CKD: chronic kidney disease. Difference: comparison of serum GDF-15 or FGF-23 level between patients with and without AF.

Figures

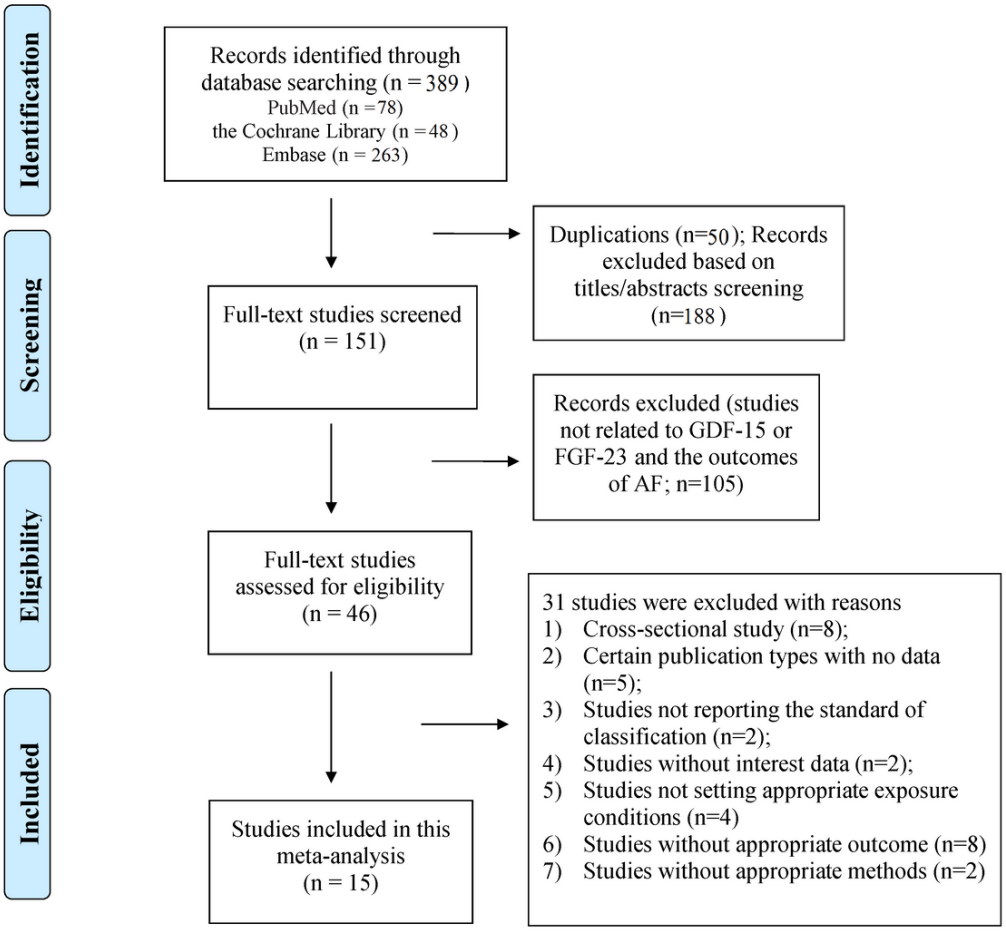

Figure 1

Flowchart of the study selection.

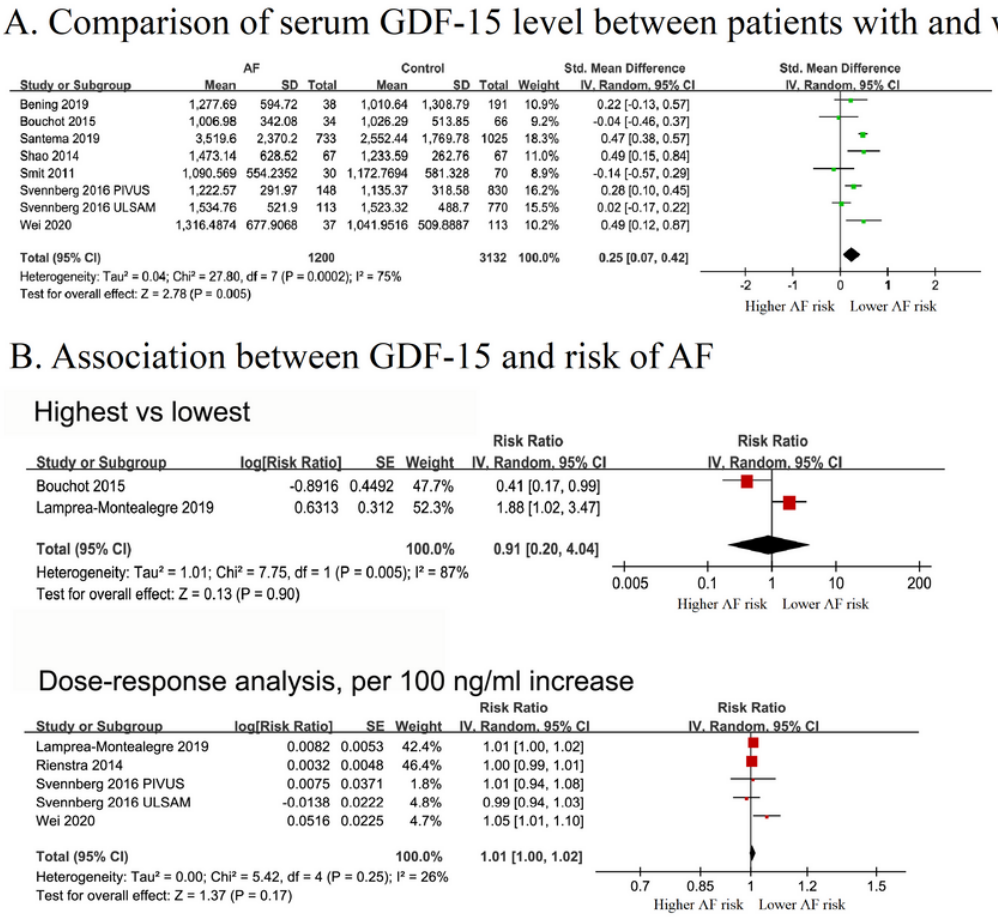

Figure 2

Forest plot showing the differences in serum growth differentiation factor 15 in control without AF and patients with AF **(A)** and the association between serum growth differentiation factor 15 and atrial fibrillation **(B)**, **upper panel**: categorical analysis between growth differentiation factor 15 level and the risk of AF; **lower panel**: dose-response association between growth differentiation factor 15 and the risk of atrial fibrillation, per a 100 ng/ml increase.

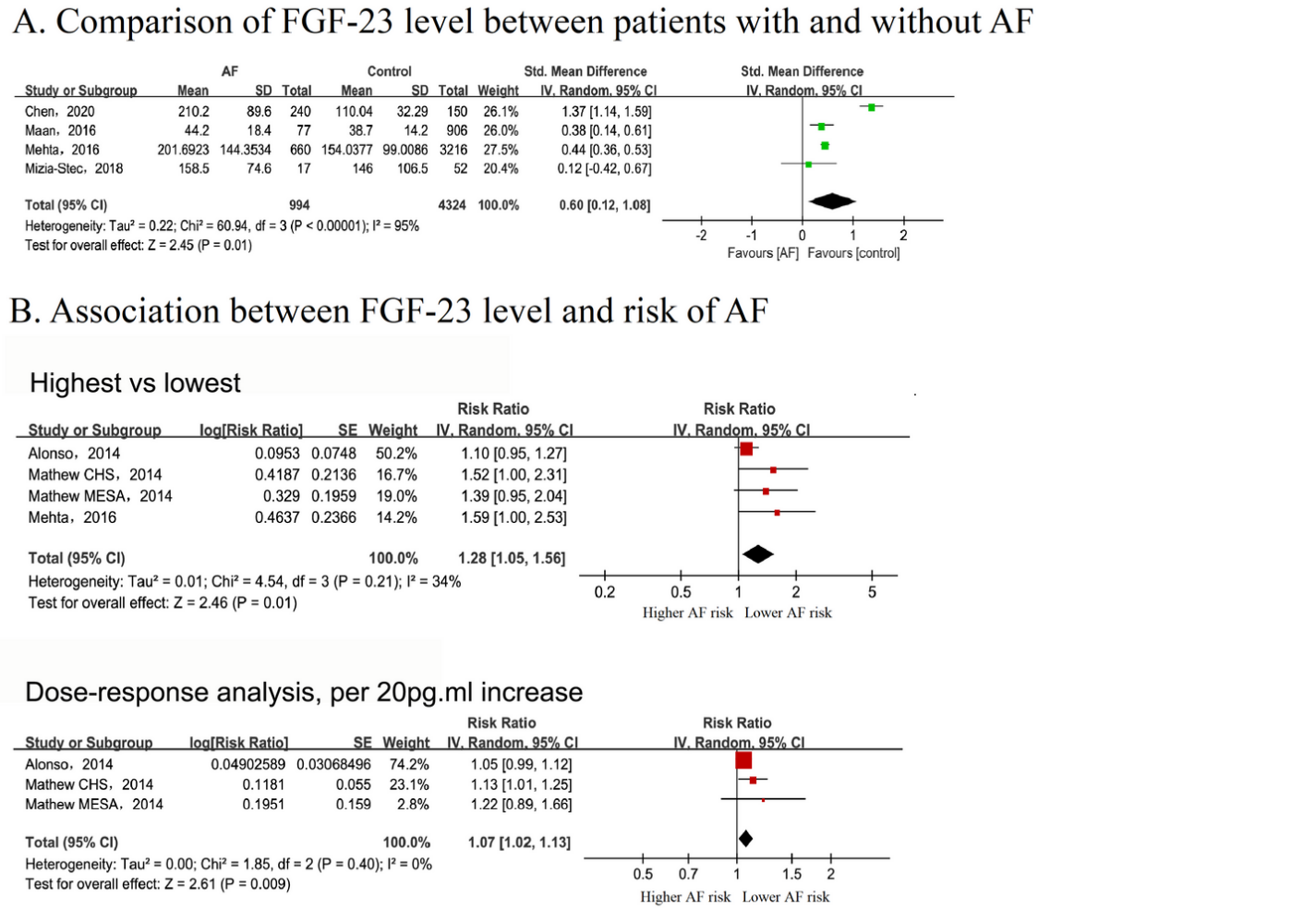

Figure 3

Forest plot showing the differences in serum fibroblast growth factor-23 level in control without AF and patients with AF **(A)** and the association between serum fibroblast growth factor-23 level and the risk of AF **(B)**, **upper panel**: categorical analysis between fibroblast growth factor-23 level and the risk of AF; **lower panel**: dose-response association between fibroblast growth factor-23 level and the risk of AF, per 20 pg/ml increase.

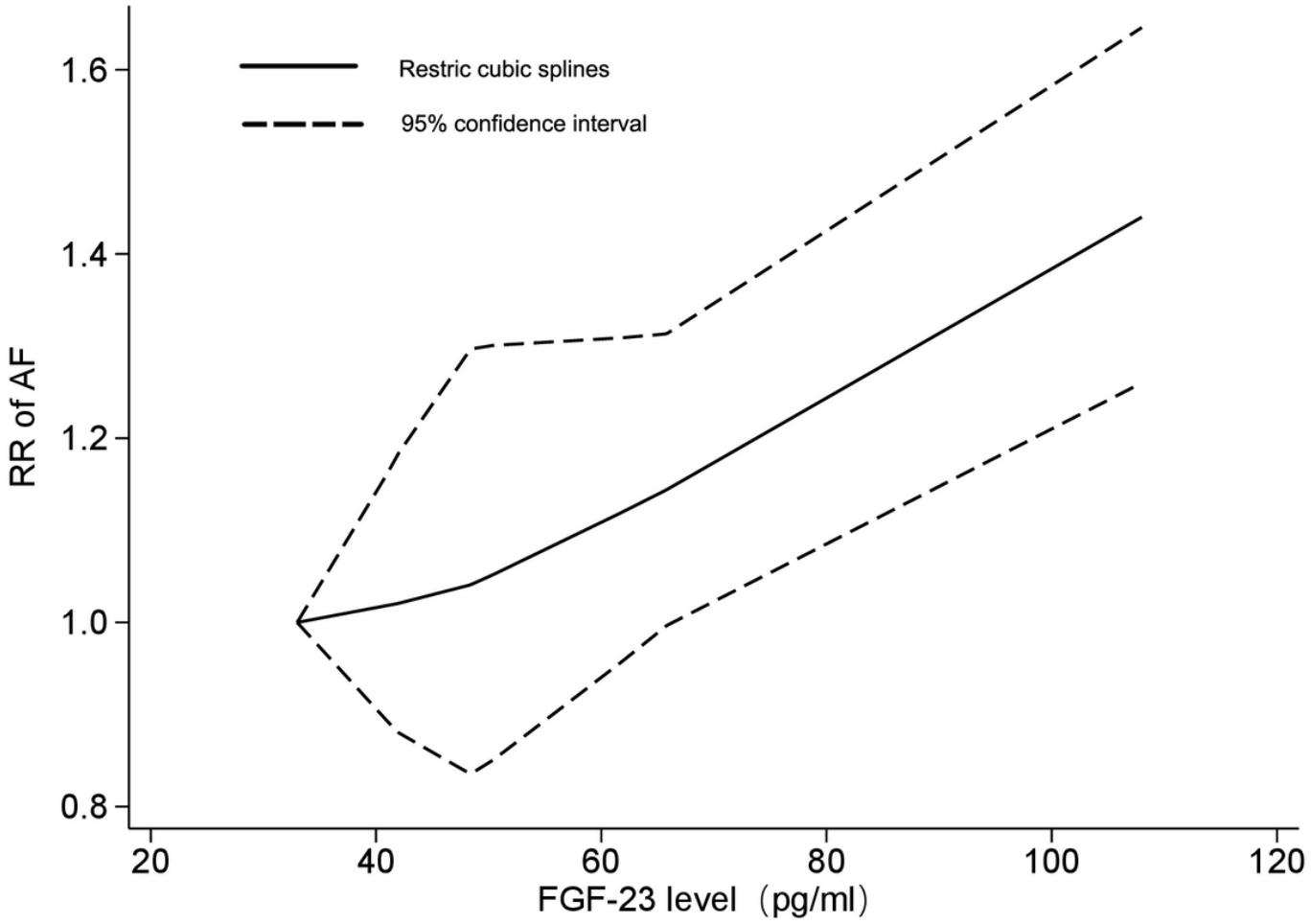

Figure 4

The dose-response association between the fibroblast growth factor-23 level and the risk of AF.

A non-linear exposure-effect analysis, the solid and dashed lines represent the estimated relative risk and the 95% confidence interval, respectively.

Supplementary Files

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