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Review article

Pentraxin-3 in coronary artery disease: A meta-analysis

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ABSTRACT

Aims: Studies on the prognostic significance of circulating pentraxin-3 level in patients with coronary artery disease (CAD) have yielded conflicting results. The aim of this meta-analysis was to evaluate the prognostic value of circulating pentraxin-3 level in CAD patients.

Materials/methods: We made a systematic literature search in Pubmed, Embae, CNKI, Wanfang, and VIP database from their inception to January 10, 2019 for prospective cohort studies that investigated the association between pentraxin-3 level and adverse outcomes in patients with CAD. The outcome measures were all-cause mortality, cardiac death, and cardiac events (cardiac death, nonfatal myocardial infarction, heart failure or coronary revascularization). Multivariable-adjusted risk ratio (RR) with 95% confidence intervals (CI) was pooled for the highest versus the lowest pentraxin-3 group to summarize the predictive value.

Results: Nine studies were included, enrolling 5,174 CAD patients. Overall, CAD patients with the highest pentraxin-3 level had an increased risk of all-cause mortality (RR 1.81; 95% CI 1.43–2.28), cardiac death (RR 1.77; 95% CI 1.38–2.26), and cardiac events (RR 1.61; 95% CI 1.16–2.25). However, elevated pentraxin-3 level appeared to not significantly increase the risk of cardiac events (RR 1.63; 95% CI 0.71–3.72) in stable CAD subgroup.

Conclusions: In CAD patients, elevated circulating pentraxin-3 level is possibly an independent predictor of all-cause mortality, cardiac death, and cardiac events. However, interpretation of these findings should be with caution due to the small number of studies analyzed.

1. Introduction

Coronary artery disease (CAD) is the most common of the cardiovascular diseases. The spectrum of CAD usually includes stable angina, unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI). Unstable angina, STEMI, and NSTEMI are collectively termed as acute coronary syndrome (ACS). Despite substantial improvements in medical care, CAD remains a leading cause of higher risk of hospitalization and death worldwide [1]. Therefore, risk stratification of morbidity and mortality is necessary CAD patients, particularly in those with ACS.

Vascular inflammation plays an important role in the development and progression of atherosclerosis [2]. Inflammation was linked to adverse cardiovascular events in patients with CAD [3]. Pentraxin-3, a multimeric acute-phase protein, is mainly synthesized by various cells in response to inflammatory stimulus [4,5]. Particularly, the expression of pentraxin-3 is increased in human atherosclerotic plaques [6]. Several studies [7–12] but not all [13] have shown that increased pentraxin-3 level was associated with an increased risk of all-cause mortality or cardiac death in both clinically stable CAD and ACS. However, studies [9,11,12,14–19] regarding the usefulness of pentraxin-3 level for predicting cardiac events have yielded conflicting results. Nevertheless, the magnitude of the predictive value of pentraxin-3 varied considerably among the available studies [5].

Currently, the predictive significance of pentraxin-3 for adverse outcomes in CAD patients has not been systematically evaluated. We therefore performed this meta-analysis to systematically assess the predictive value of elevated pentraxin-3 level in CAD patients, in terms of all-cause mortality, cardiac death, and cardiac events.

2. Materials and methods

2.1. Search strategy

The current meta-analysis followed the checklist of the Meta-Analysis of Observational Studies in Epidemiology [20]. We performed a systematic literature search in Pubmed, Embae, CNKI, Wanfang, and VIP database for studies published up to January 10, 2019 without language restriction. The following search terms and keywords were used with combination: “pentraxin-3” AND “coronary artery disease”

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OR “coronary heart disease” OR “myocardial infarction” OR “acute coronary syndrome” OR “unstable angina. In addition, bibliographies from relevant articles were manually searched for any possible missing studies.

2.2. Study selection

Articles satisfying the following inclusion criteria were selected: (1) case-control, prospective or retrospective cohort as study design; (2)CAD patients as study population; (3) baseline pentraxin-3 elevation as exposure; (4) all-cause mortality, cardiac death, and cardiac events (recurrent myocardial infarction, unstable angina pectoris, target vessel revascularization, cardiac death or heart failure) as outcome measures; and (5) provided multivariate-adjusted hazard ratio (HR), risk ratio (RR) or odds ratio (OR) with their 95% confidence intervals (CI) on the above mentioned adverse outcomes for the highest versus the lowest pentraxin-3 level. For multiple publications adopting the same population, only results from the most recent article were considered. The following studies were excluded: (1) heart failure not directly preceded by a CAD diagnosis; (2) patients after heart surgery; (3) reported unadjusted risk estimate or pentraxin-3 analyzed as a continuous variable; and (4) conference abstract, reviews or letter to editor as study design.

2.3. Data extraction and quality assessment

Two authors independently scanned the titles or abstracts, and retrieved full-text eligible articles. From each selected article, the extracted information consisted of: surname of the first author, year of publication, country of study population, study design, type of patients, number of patients, mean age of patients at baseline, proportion of female gender, definition of cardiac event, cut-off point for pentraxin-3 elevation, number of each event, follow-up time, fully adjusted risk estimate, adjustment for confounders, and study quality score. Quality assessment was done using a nine-star Newcastle–Ottawa Scale (NOS) [21], which evaluate the selection of study groups, comparability of groups, and ascertainment of outcomes. Studies that received a total of 7 or above stars are judged to be of high quality. Any disagreements were resolved by discussion with a third reviewer and reached an agreement.

2.4. Data synthesis and analysis

The multivariate-adjusted RR and 95% CI for all-cause mortality, cardiac death, and cardiac events were pooled by comparing the highest with the lowest pentraxin-3 level group. Heterogeneity across studies was examined by the I^2 statistic and Cochrane Q test. A random effect model was selected according to the I^2 statistic > 50% or *P*-value of Cochrane Q test < 0.1. Otherwise, we applied a fixed-effect model. Subgroup analyses were conducted by the type of CAD (stable CAD or ACS). Sensitivity analysis was performed by a leave-one-out study approach in order to observe the reliability of the pooling risk summary. A funnel plot and the Egger’s linear regression test [22] was scheduled to examine the publication bias when the outcomes included at least 5 studies. Statistical analyses were conducted in STATA 12.0 (StataCorp, TX, USA).

3. Results

3.1. Search results and study characteristics

A flow chart detailing the study selection process is presented in Fig. 1. After removing duplicated records, a total of 1083 articles were identified from the electronic database search and reference lists checking. Of which, 44 full text articles were retrieved for detailed assessment and 9 studies (10 articles) [7–12,14–16,19] were included in the meta-analysis.

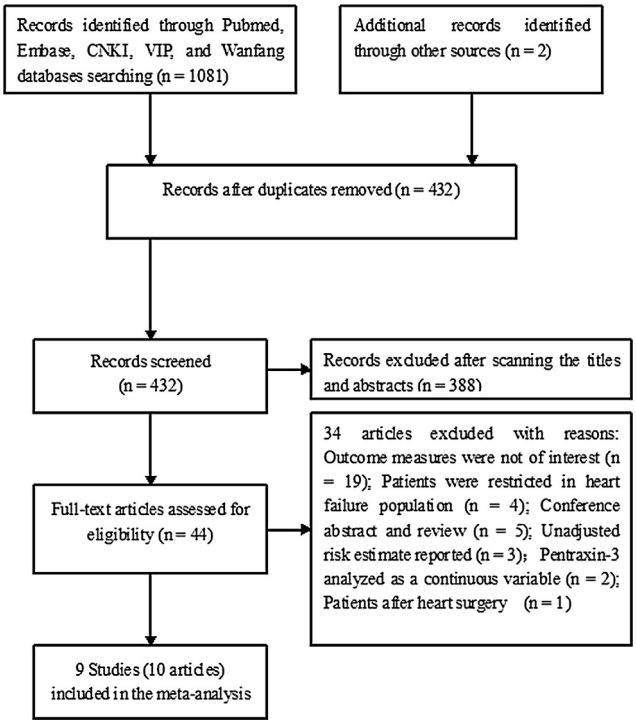

Fig. 1. Flow chart showing the study selection process.

The main characteristics of the selected studies are summarized in Table 1. A total number of 5,174 CAD patients were included, with sample sizes varying from 84 to 982. The proportion of women ranged from 12.9% to 38.7%. Six studies [7,9–12,16] enrolled ACS patients and three studies [8,14,15] enrolled patients with stable CAD. The mean age of patients ranged from 55.5 to 69.5 years old. Mean follow-up duration ranged from 1.0 month to 7.0 years. Total NOS score of individual studies ranged from 6 to 8 stars. Supplemental Table S1 detailed the results of methodological quality assessment.

3.2. Impact of pentraxin-3 on all-cause mortality

Four studies [7,8,10,11] reported the all-cause mortality as an outcome. As shown in Fig. 2, CAD patients with the highest pentraxin-3 level had an increased risk of all-cause mortality (RR 1.81; 95% CI 1.43–2.28) in a fixed-effect model. There was no heterogeneity across studies (I^2 = 0.1%; P = 0.391). A leave-out one study sensitivity analysis did not significantly alter the pooled risk summary (data not shown). Stratified analysis according to the type of CAD showed similar prognostic value of pentraxin-3 level in ACS (RR 1.82; 95% CI 1.28–2.58) and stable CAD (RR 1.80; 95% CI 1.32–2.46) subgroup.

3.3. Impact of pentraxin-3 on cardiac death

Two studies [9,12] reported the association between pentraxin-3 and cardiac death in acute myocardial infarction (AMI) patients. As shown in Fig. 3, AMI patients with the highest pentraxin-3 level had an increased risk of cardiac death (RR 1.77; 95% CI 1.38–2.26) in a fixed-effect model. There was no significant heterogeneity between studies (I^2 = 30.1%; P = 0.232).

3.4. Impact of pentraxin-3 on cardiac events

Five studies [9,14–16,19] reported cardiac events as an outcome. As shown in Fig. 4, CAD patients with the highest pentraxin-3 level had an increased risk of cardiac events (RR 1.61; 95% CI 1.16–2.25) in a random effect model. There was significant heterogeneity across studies

Table 1
Main characteristic of the included studies.

Author/ year	Region	Study design	Patients	Sample size (% women)	Age (years)	Definition of cardiac events	Pentraxin-3 cutoff value (ng/mL)	No. event HR/OR (95% CI)	Follow-up (months)	Variables in adjustment model
Latini 2004 [7]	Italy	Prospective cohort	AMI	724 (30.9)	31.9% > 70	—	Tertiles 3 vs. 1 (> 10.73 vs. ≤ 5.49)	Total death (54) 3.55 (1.43–8.83);	3.0	Age, sex, smoking, hypertension, DM, Killip class, heart rate, SBP, anterior MI site, and creatine kinase
Dubin 2012 [8]	USA	Prospective cohort	Stable CAD	986 (18.6)	66.7 ± 11.0	—	Tertiles 3 vs. 1 (≥0.81 vs. ≤ 0.47)	Total death (344) 1.70 (1.20–2.40)	37	Age, sex, race, hypertension, DM, smoking, CRP, and eGFR
Guo 2014 [9]	China	Retrospective cohort	NSTEMI	525 (37.5)	57.7 ± 9.3	Recurrent MI, unstable angina pectoris, TVR	High vs low (≥3.0 vs. < 3.0)	Cardiac events (36) 1.36 (1.09–1.68); Cardiac death (20) 1.59 (1.18–2.15)	1.0	Age, gender, BMI, DM, SBP, DBP, LVEF, hypertension, hyperlipidemia, smoker, heart rate, hs-CRP, cTnT, and NT-proBNP
Miyazak 2014 [14]	USA	Prospective case-control	Stable CAD (MI survivors)	749 (12.9)	60 ± 10	Recurrent MI or coronary death	Quartiles 4 vs.1; (≥5.05 vs. < 2.6)	Cardiac events (413) 1.08 (0.68–1.72)	60	Age, sex, smoking, LVEF, DM, CRP, SBP, DBP, glucose, HDL, eGFR, triglycerides, and medication
Liu 2014 [15]	China	Prospective cohort	Stable CAD	596 (21.6)	65.9 ± 8.1	Cardiac death, nonfatal MI, TVR	High vs low; (> 4.38 vs. < 4.38)	Cardiac events (82) 2.51 (1.47–4.31)	36	Age, LVEF, DM, multiple stents, CCSA class, cTnI, and hs-CRP
Akgul 2015 [10]	Turkey	Prospective cohort	STEMI	499 (20.4)	55.5 ± 12.3	—	High vs low; (≥3.2 vs. < 3.2)	Total death (52) 2.3 (1.2–4.9)	24	Age, gender, DM, hypertension, Killip class, unsuccessful procedure, LVEF, anemia, creatinine, and peak troponin
Mjelva 2016 [11]	Norway	Prospective cohort	Suspected ACS	871 (38.7)	69.5 ± 14.4	Cardiac death and recurrent non-fatal cardiac disease	Quartiles 4 vs.1; (> 9.5 vs. < 3.5)	Total death (332) 1.62 (1.11–2.37); Cardiac events (36)# 1.39 (0.83–2.33)	84 (24 for cardiac events)	Age, sex, smoking, hypertension, eGFR, DM, hypercholesterolemia, congestive HF, NYHA, CAD, cTnT, BNP, and hs-CRP
Altay 2017 [12]	Turkey	Prospective cohort	AMI	140 (27.1)	59.7 ± 12.3	—	Tertiles 3 vs. 1 (≥4.27 vs. ≤ 1.63)	Cardiac death (9) 2.18 (1.43–3.32)	60	Multi-variate adjustment
Qiu 2017 [16]	China	Prospective cohort	STEMI	84 (25.0)	55.8 ± 13.3	Nonfatal MI or HF, cardiac death	Tertiles 3 vs. 1 (≥6.90 vs. < 2.53)	Cardiac events (26) 3.64(1.34–7.59)	3.0	Age, gender, cTnI, and NT-proBNP

Abbreviations: HR, hazard ratio; OR, odds ratio; CI, confidence intervals; MI, myocardial infarction; AMI, acute MI; ACS, acute coronary syndrome; STEMI, ST segment elevated myocardial infarction; NSTEMI, non-STEMI; MACE, major adverse cardiovascular events; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, c-reactive protein; hs-CRP, high sensitivity CRP; WC, waist circumference; cTn, cardiac troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; TVR, target vessel revascularization; CAD, coronary artery disease; HF, heart failure; CCSA, Canadian Cardiovascular Society Angina; NOS, Newcastle-Ottawa Scale. # Data from Brügger-Andersen's study [19] with 24 months' follow-up.

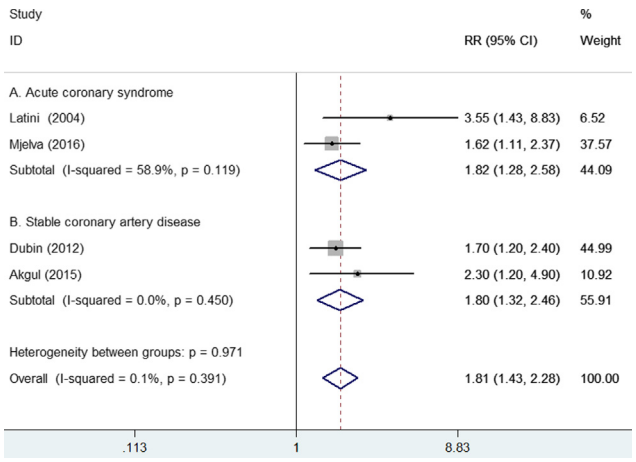

Fig. 2. Forest plots showing risk ratio and 95% confidence intervals of all-cause of mortality for the highest versus lowest pentraxin-3 level.

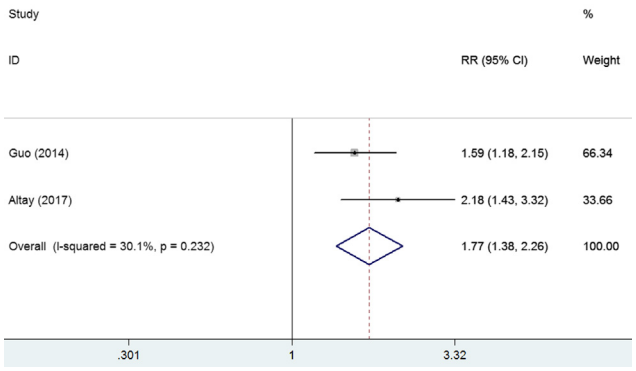

Fig. 3. Forest plots showing risk ratio and 95% confidence intervals of cardiac death for the highest versus lowest pentraxin-3 level.

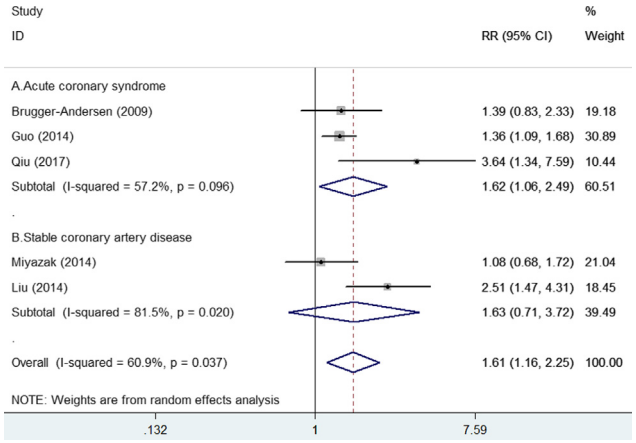

Fig. 4. Forest plots showing risk ratio and 95% confidence intervals of cardiac events for the highest versus lowest pentraxin-3 level.

(I^2 = 60.9%; P = 0.037). A leave-out one study sensitivity analysis did not significantly change the pooled risk summary (data not shown). No evidence of publication bias was observed by the symmetrical funnel plot (Fig. 5) and Egger's linear regression test (P = 0.283). Subgroup analysis indicated the elevated pentraxin-3 level was associated with an increased cardiac events in ACS patients (RR 1.62; 95%CI 1.06–2.49) but not in stable CAD patients subgroup (RR 1.63; 95%CI 0.71–3.72).

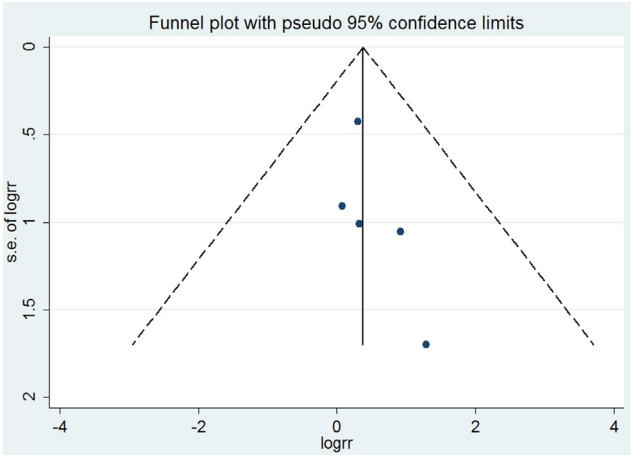

Fig. 5. Funnel plot of cardiac events.

4. Discussion

This meta-analysis shows that elevated circulating pentraxin-3 level is independently associated with increased risk of all-cause mortality, cardiac death, and cardiac events in CAD patients. CAD patients with the highest pentraxin-3 level had an 81% and 77% higher risk of all-cause mortality and cardiac death, respectively. Moreover, ACS patients with the highest pentraxin-3 level had a 62% higher risk of cardiac events. These findings suggest that pentraxin-3 seems a promising prognostic marker among CAD patients.

There was not a substantial difference between ACS and stable CAD findings for predicting all-cause mortality. Despite the pooled risk estimate of cardiac event was similar in ACS and stable CAD patients, the prognoctic value in stable CAD was not statistically significant. However, these findings should be interpretated with caution due to the small number of studies included in the subgroup analysis.

Early risk stratification is essential in patients with CAD for better medical care, particularly in those with ACS. Inflammatory biomarkers are usually used for risk stratification among CAD patients [23]. Pentraxin-3 may be identified as an early marker of local inflammation in the vasculature [24]. According to the primary structure of the subunit, pentraxin family is divided into short pentraxins and long pentraxins [25]. C-reactive protein (CRP) belongs to the short pentraxin family. Clinically, CRP had yielded incremental prognostic value in the risk stratification of both stable CAD [26] and ACS [27] patients. Pentraxin-3 is the prototype of the long pentraxin family [28]. Similar to CRP, our meta-analysis indicated that pentraxin-3 elevation significantly increased risk of all-cause mortality and cardiac death. Nevertheless, high pentraxin-3 level might represent a surrogate marker of CAD complexity and severity in clinically stable patients [29]. Also, pentraxin-3 level increased after the onset of symptoms, peaking 7 h in STEMI patients, which is substantially earlier than CRP [30], and therefore it may be a better prognostic marker of than CRP among these acute patients [11,18].

There were several studies that did not satisfy our inclusion criteria. The main reasons for exclusion were that they assessed the prognostic value of pentraxin-3 by continuous variable analysis or uninteresting outcome measures reported. In patients hospitalized for unstable angina/NSTEMI, each 10-fold increment pentraxin-3 significantly increased 3.86-fold risk of cardiac events (cardiac death and re-hospitalization for ACS or worsening heart failure) [18]. By contrast, each unit ln-transformed level of pentraxin-3 increase did not emerge as an independent predictor of 1-year mortality (OR 1.2; 95% CI 0.6–2.3) in non-ST-elevation ACS patients [13].Moreover, increased level of pentraxin-3 was also an independent predictor of 1-year combined endpoint of left ventricle dysfunction or mortality (OR 3.70; 95% CI

1.33–10.28) among patients with STEMI [17]. In patients after cardiac surgery, elevated pentraxin-3 was independently associated with 1-year major adverse cardiovascular events (OR 1.13; 95% CI 1.05–1.22)[31].

This meta-analysis had several potential limitations. First, potential misclassification of patients may have occurred because pentraxin-3 level was only measured at baseline rather than dynamic determination during the follow-up period. Second, cutoff values of elevated pentraxin-3 level varied across the included studies, which prevent us to establish an optimal threshold of pentraxin-3 elevation. Third, we did not investigate the prognostic value of continuous pentraxin-3 level due to the limited number of these studies. Fourth, result of publication bias based on the Egger's test may be unreliable because of small number of studies analyzed [32]. Finally, despite adjustments for multiple covariates across studies, residual risk factors and medications might have confounded the results. Lack of adjusting important confounding may have led to slightly overestimate the pooled risk summary.

5. Conclusions

This meta-analysis indicates that elevated circulating pentraxin-3 level is possibly an independent predictor of all-cause mortality, cardiac death as well as cardiac events in patients with CAD. Determination of pentraxin-3 has potential to improve risk stratification of CAD patients. However, interpretation of the present findings should be with caution due to the small number of studies analyzed.

Conflict of interest

There are no conflicts of interest for any of the authors.

Authors' contributions

Xue Li contributed to study design, interpretation, and final approval. Yi Chu and Jiwei Teng contributed to literature search, study selection, and data extraction. Yi Chu deafted the manuscript. Pin Feng and Hui Liu contributed to statistical analysis. Fangfang Wang revised and edited the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.03.017.

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