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Association of Metabolic Syndrome with Adverse Outcomes in Patients with Stable Coronary Artery Disease: A Meta-Analysis

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ABSTRACT

A consensus has not been reached on the association of metabolic syndrome (MetS) with adverse outcomes in patients with stable coronary artery disease (CAD). The purpose of this systematic review and meta-analysis was to summarize the prognostic implication of MetS in patients with stable CAD. We comprehensively searched articles indexing in PubMed and Embase databases until August 14, 2022. Original studies investigating the association of MetS with adverse outcomes in patients with stable CAD were included. Seven studies including 32 736 patients with stable CAD were identified. Depending on the definition of MetS, the reported prevalence of MetS ranged from 23.4 % to 63 %. Meta-analysis showed that patients with MetS conferred an increased risk of all-cause mortality [risk ratio (RR) 1.22; 95 % confidence intervals (CI) 1.15–1.19], cardiovascular mortality (RR 1.49; 95 % CI 1.16–1.92), and MACEs defined by death, myocardial infarction, revascularization, cardiac arrest, or angina admission (RR 1.47; 95 % CI 1.20–1.79), respectively. Leave-one-out sensitivity analysis indicated the robustness of the value of MetS in prediction of all-cause mortality. MetS may be an independently predictor of adverse outcomes in patients with stable CAD. However, future studies are required to consolidate the current evidence due to the small number of studies included.

Introduction

Stable coronary artery disease (CAD) is a common type of ischemic heart disease. This condition refers to the patients stabilized after acute coronary syndrome (ACS), or documented plaque by catheterization or angiography [1]. Clinically, asymptomatic, or controlled angina patients are considered stable [2]. Despite the advance in evidence-based therapies and vascular technique, patients with stable CAD are still suffered from premature mortality and recurrent cardiovascular events [3–5]. Therefore, improving risk stratification remains a challenge in stable CAD patients.

Metabolic syndrome (MetS) refers to a condition of physiological and metabolic abnormalities including hyperglycemia, abdominal obesity, hypertension, dyslipidemia, and insulin resistance. A recently published meta-analysis concluded that MetS was associated with higher risk of long-term all-cause death in patients with acute coronary syndrome [6]. However, this well-designed meta-analysis only focused on the acute phase CAD patients. The reported prevalence of MetS was 47.3 % in patients with stable CAD [7], indicating MetS is also a common condition in the stable phase. A consensus has not been reached on the association between MetS and survival outcomes in patients with stable CAD [8–12]. These conflicting results may be linked to the different definitions of MetS or follow-up duration.

Given these controversial findings, we performed the present systematic review and meta-analysis to clarify the prognostic implication of MetS in patients with stable CAD, in terms of major ad-

verse cardiovascular events (MACEs), cardiovascular or all-cause mortality.

Materials and Methods

Literature search

We report this study according to the checklists of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [13]. Two independent authors comprehensively searched articles indexing in PubMed and Embase databases until August 14, 2022, using the combined items: ("metabolic syndrome") AND ("coronary artery disease" OR "coronary heart disease" OR "ischemic heart disease") AND ("stable" OR "stabilized" OR "chronic") AND ("follow-up" OR "follow up"). No language restriction was imputed. The detailed search strategy is summarized in **Supplemental Text S1**. References of pertinent articles were also manually searched for identification of additional studies.

Study selection

Two authors independently scanned the titles and/or abstracts and then retrieved the potentially eligible articles for full-text eligibility assessment. Inclusion criteria included: 1) participants: patients with a diagnosis of stable CAD; 2) predictor: MetS; 3) comparison: patients with MetS vs. those without; 4) outcomes of interest: major adverse cardiovascular events (MACEs, including cardiac arrest, myocardial infarction, angina admission, revascularization, cardiovascular death or, all-cause mortality); 5) type of study: post hoc analysis of randomized controlled trials or cohort studies; and 6) reported multivariable adjusted risk summary of above-mentioned outcomes for patients with MetS vs. those without. Exclusion criteria included: 1) patients with acute stage of CAD; 2) reported unadjusted risk estimate; and 3) lack of value of MetS in predicting outcomes of interest.

Data extraction and quality assessment

Two independent authors recorded the following information from the included studies: first author' name, publication year, country of region, number of patients, gender distributions, baseline age of the patients, definition of MetS, prevalence of MetS, definition of MACEs, follow-up duration, risk estimate adjusted for the maximal covariates, adjustment for covariates. Methodological quality of these included studies was evaluated by two independent authors using a 9-point Newcastle-Ottawa Scale (NOS) for cohort [14]. Studies with 4 to 6 points were deemed to have moderate quality and those with 7 to 9 points were graded as high quality. Disagreements on the data extraction and quality assessment were settled by discussion.

Data analysis

The association of MetS with adverse outcomes was summarized by pooling the adjusted risk ratio (RR) with 95 % confidence interval (CI) reported from the individual study. The degree of heterogeneity was checked via the I^2 statistic ($I^2 \geq 50$ % indicating statistically significant) and/or Cochrane Q-test ($p < 0.10$ indicating statistically significant). A random effect model was selected for meta-analysis when there was significant heterogeneity; otherwise, a fixed-effect model was selected for meta-analysis. Both the Begg's test [15] and the Egger's test [16] were used to explore the likelihood of publication bias. To investigate the robustness of the pooling result, we run a leave-one-out sensitivity analysis. Moreover, subgroup analyses were performed according to study design, sample sizes, and duration of follow-up. All data were analyzed using Stata 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Search results and study characteristics

Of 469 records identified in the electronic database search, a total of 7 studies [8–12, 17, 18] satisfied the inclusion criteria. The detailed studies selection process is summarized in ▶ **Fig. 1**. ▶ **Table 1** shows the main features of the included studies. The demographic characteristic and comorbidities of the included studies summarized in **Supplemental Table S1**. These eligible studies were published from 2006 to 2018. Three studies [8, 9, 11] were post hoc analysis of clinical trials and others were cohort designs A total of 32 736 patients with stable CAD were identified, with sample size ranging between 589 and 15 524. The length of follow-up varied from 2.0 years to 20 years. One study [10] used the modified WHO criteria to define the MetS and others selected the National Cholesterol Education Program's Adults Treatment Panel III (NCEP-ATP III) criteria. The reported prevalence of MetS ranged from 23.4 % to 63 %. The quality score of the included studies was at least 7 (**Supplemental Table S2**), indicating high methodological quality.

All-cause mortality

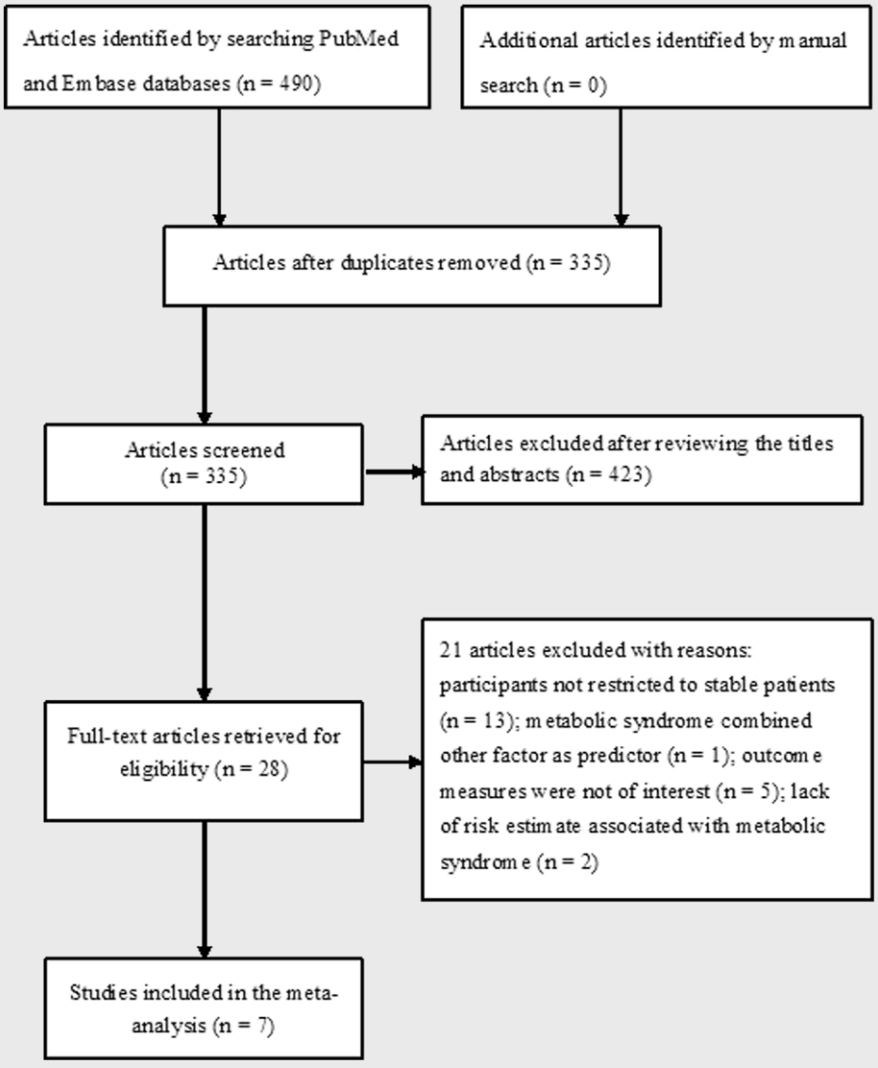
Data on all-cause mortality were reported in 6 studies [8–12, 17]. A fixed-effect model meta-analysis (▶ **Fig. 2**) indicated that patients with MetS conferred an increased risk of all-cause mortality (RR 1.22; 95 % CI 1.15–1.19) compared with those without MetS, without significant heterogeneity ($I^2 = 12.6$ %; $p = 0.335$). Leave-one out sensitivity analysis showed the pooled RR of all-cause mortality ranged from 1.21 to 1.25 and low 95 % CI ranged from 1.09 to 1.15 (All p-values < 0.05). When we removal of one study [17] with the largest sample size, the pooled of all-cause mortality was 1.25 (95 % CI 1.09–1.45). ▶ **Table 2** summarizes the results of subgroup analysis and the value of MetS in predicting all-cause mortality was not obviously affected by study design, sample size, or length of follow-up.

Cardiovascular mortality

Two studies [9, 18] reported the data on cardiovascular mortality. A fixed-effect meta-analysis indicated that patients with MetS had an increased risk of cardiovascular mortality (RR 1.49; 95 % CI 1.16–1.92; ▶ **Fig. 3**) compared with those without MetS, without significant heterogeneity ($I^2 = 0.0$ %; $p = 0.364$).

Major adverse cardiovascular events

Two studies [8, 9] reported the data on MACEs. ▶ **Fig. 3** shows significant heterogeneity between these two studies ($I^2 = 70.8$ %, $p = 0.064$; ▶ **Fig. 4**). A random effect model meta-analysis showed



▶ **Fig. 1** Flow chart showing selection process of the study.

that patients with MetS conferred an increased risk of MACEs (RR 1.47; 95 % CI 1.20–1.79) compared with those without MetS,

Publication bias

The Begg's test and Egger's test were not run to investigate publication bias because less than recommended arbitrary number of 10 studies in each analyzed outcome. These statistical tests are potentially unreliable under such circumstance [19].

Discussion

The current systematic review and meta-analysis consolidated the evidence that MetS was associated with higher risk of MACEs, cardiovascular or all-cause mortality in patients with stable CAD. Patients with stable CAD having MetS conferred a 22 %,49 %, and 47 % higher risk of all-cause mortality, cardiovascular mortality, and MACEs, respectively. Presence of MetS may provide important prognostic information in patients with stable CAD.

An early meta-analysis has concluded that MetS was associated with higher risk of all-cause mortality patients with CAD undergoing revascularization [20]. A recent meta-analysis demonstrated that the presence of MetS was associated with 2.35-fold and 25 % higher risk of in-hospital and long-term all-cause mortality, respectively [6]. By contrast, the current meta-analysis focused on the stable CAD patients. Besides all-cause mortality outcome, the values of MetS in predicting cardiovascular mortality and MACEs were also evaluated.

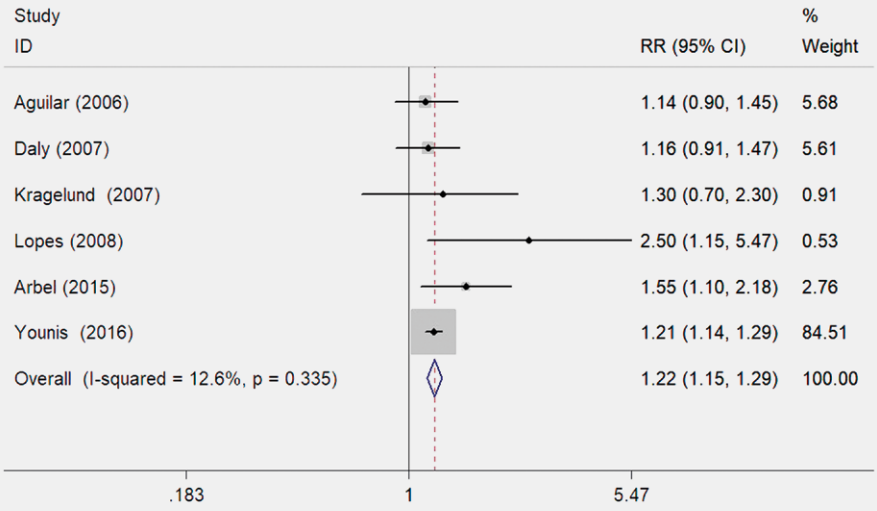
One [10] of the included study has investigated the gender-specific effect of MetS on all-cause mortality in patients with stable CAD. In the multivariable Cox regression analysis, MetS only provided prognostic information in women (Relative risk 2.2; 95 % CI: 1.1–4.3) but not in men (Relative risk 1.0; 95 % CI 0.5–1.9). However, more studies should address the gender-specific effect of MetS on adverse outcomes in patients with stable CAD.

This meta-analysis has important implications for clinical practice. Depending on the assessment tool used for MetS, the report-

▶ **Table 1** Main characteristic of the included studies.

Author/year [Ref]	Region	Design	Sample size	Definition of MetS	Prevalence of MetS (%)	Definition of MACEs	Outcomes HR/RR (95% CI)	Follow-up	Adjustment for covariates
Aguilar 2006 [8]	Multi- nations	Post hoc	3319	NCEP-ATP III	53.3	Death, recurrent MI, revascularization, or angina admission	Total death 1.14 (0.90–1.45) MACEs 1.33 (1.15–1.53)	3.1 years	Age, sex, high-sensitivity CRP
Daly 2007 [9]	Europe	Post hoc	8937	NCEP-ATP III	23.4	Cardiovascular death, MI, or cardiac arrest	Total death 1.16 (0.91–1.47) CV death 1.39 (1.03–1.86) MACEs 1.63 (1.39–1.92)	4.2 years	Age, sex, TC, smoking status, DM
Kragelund 2007 [10]	Denmark	Cohort	1041	Modified WHO	30	–	Total death 1.3 (0.7–2.3)	9.2 years	Age, sex, family history, previous MI, hypercholesterolemia, smoking, creatinine clearance, LVEF, TC, severity of CAD, insulin resistance, fasting glucose, hypertension, TG, HDL, BMI, DM
Lopes 2008 [11]	Brazil	Post hoc	589	NCEP-ATP III	52.3	–	Total death 2.5 (1.15–5.47)	2.0 years	Age, sex, smoking status, ethnicity, TC, number of diseases, treatment allocation
Arbel 2015 [12]	Israel	Cohort	1634	NCEP-ATP III	27.7	–	Total death 1.55 (1.10–2.18)	4.4 years	Multivariate Cox proportional hazard analysis
Younis 2016 [17]	Israel	Cohort	15524	NCEP-ATP III	48	–	Total death 1.21 (1.14–1.29)	20 years	Age, sex, smoking, creatinine, DM, hypertension, heart failure, previous MI, or stroke, medication
Mayer Jr 2018 [18]	Czech Republic	Cohort	1692	NCEP-ATP III	63	–	CV death 1.82 (1.10–3.00)	5.0 years	Multivariate Cox proportional hazard analysis

HR: Hazard ratio; RR: Risk ratio; CI: Confidence intervals; P: Prospective; R: Retrospective; NP: Not provided; MetS: Metabolic syndrome; MI: Myocardial infarction; BMI: Body mass index; DM: Diabetes mellitus; HF: Heart failure; PCI: Percutaneous coronary intervention; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; WBC: White blood cell; ACEI: Angiotensin-converting enzyme inhibitors; NCEP-ATP III: National Cholesterol Education Program's Adults Treatment Panel III.



▶ **Fig. 2** Forest plots showing pooled RR with 95 % CI of all-cause mortality for patients with versus without metabolic syndrome.

▶ **Table 2** Subgroup analysis on all-cause mortality.

Subgroup	No. of studies	Pooled RR	95 % CI	Heterogeneity between studies
Publication year				
Before 2015	4	1.20	1.02–1.41	p = 0.292; I^2 = 12.5 %
Since 2015	2	1.22	1.15–1.30	p = 0.163; I^2 = 48.7 %
Sample size				
≥ 2000	3	1.20	1.13–1.27	p = 0.853; I^2 = 0.0 %
< 2000	3	1.58	1.20–2.09	p = 0.416; I^2 = 0.0 %
Study design				
Cohort	3	1.22	1.15–1.30	p = 0.369; I^2 = 0.0 %
Post hoc analysis	3	1.19	1.01–1.40	p = 0.161; I^2 = 45.2 %
Follow-up duration				
≥ 5 years	2	1.21	1.14–1.29	p = 0.814; I^2 = 0.0 %
< 5 years	4	1.25	1.08–1.45	p = 0.139; I^2 = 45.5 %

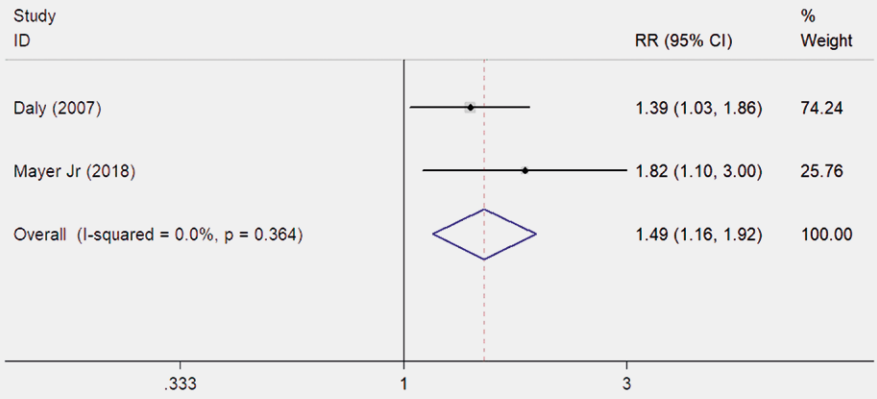
RR: Risk ratio; CI: Confidence interval; MetS: Metabolic syndrome.

ed prevalence of MetS ranged from 23.4 % to 63 % in the stable CAD patients. Given the higher prevalence of MetS and its negative effect on the prognosis, metabolic status should be monitored closely in patients with stable CAD. Active management of individual components of MetS may improve secondary prevention for these high-risk subgroup patients.

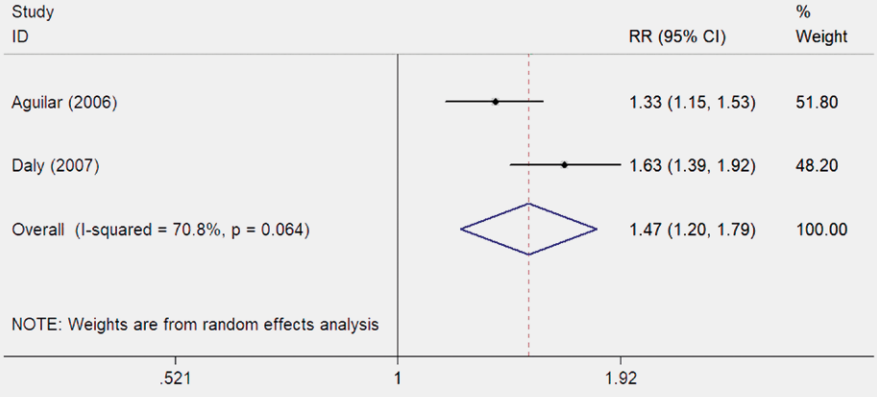
This systematic review and meta-analysis have several limitations. First, most of the included studies defined the MetS by the NCEP-ATP III criteria, which prevented us to compare the prognostic impact with other criteria. Second, different degree of confounding factors was adjusted in the included studies. Lack of adjusting residual confounders may lead to overestimate the risk summary. Moreover, therapeutic options may also affect the prognostic utility of MetS. Third, results of subgroup analysis are potentially unreliable due to the small number of studies included. Fourth, significant heterogeneity existed in pooling MACEs outcome. Different definition of MACEs, length of follow-up, or adjusting covariates may be correlated with the significant heterogeneity. Fifth, this systematic review and meta-analysis was not prospectively registered in PROSPERO database. Finally, apart from diabetes, individual components of MetS had varying associations with all-cause mortality [9, 11]. However, we could not determine whether the excessive risk was driven by the specific component of MetS due to insufficient of such data.

Conclusions

MetS may be an independent predictor of adverse outcomes in patients with stable CAD. However, additional studies are required to consolidate the current evidence due to the small number of stud-



▶ **Fig. 3** Forest plots showing pooled RR with 95 % CI of cardiovascular mortality for patients with versus without metabolic syndrome.



▶ **Fig. 4** Forest plots showing pooled RR with 95 % CI of major adverse cardiovascular events for patients with versus without metabolic syndrome.

ies included. Whether intervention on MetS could improve the prognosis of stable CAD patients should be further investigated in future studies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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