# Prognostic Significance of Right Bundle Branch Block for Patients with Acute Myocardial Infarction: A Systematic Review and Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background:        The aim of the current meta-analysis was to assess the effect of right bundle branch block (RBBB) on mortality outcome in patients with acute myocardial infarction (AMI).

Material/Methods:  Embase, PubMed, and Cochrane databases were searched through January 2015 using the keywords "RBBB", "mortality", "AMI", "Coronary Heart Disease", and "cardiovascular". An odds ratio (OR) of RBBB on mortality endpoints was calculated using random-effects models.

Results:           RBBB was associated with significantly increased overall mortality in patients with AMI. The OR of RBBB for deaths was 1.56 [95% confidence interval (CI), 1.44 to 1.68, p<0.001]. Moreover, RBBB showed a considerable effect on both in-hospital mortality (OR: 1.94, 95% CI: 1.60 to 2.37, p=0.002) and long-term mortality (OR: 1.49, 95% CI: 1.37 to 1.62, p<0.001).

Conclusions:       RBBB is associated with an increased risk of all-cause mortality and indicates a poorer prognosis in patients with AMI.

MeSH Keywords:     Bundle-Branch Block • Meta-Analysis • Mortality • Myocardial Infarction • Prognosis

Abbreviations:     RBBB – right bundle branch block; CHD – coronary heart disease; AMI – acute myocardial infarction; ECG – electrocardiogram; CI – confidence interval; OR – odds ratio; LBBB – left bundle branch block; STEMI – ST-elevated myocardial infarction; NSTEMI – non-ST-elevated myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; NYHA – New York Heart Association; CK – creatine kinase; CK-MB – creatine kinase-MB; cTnI – cardiac troponin I; eGFR – estimated GFR; LVEF – left ventricular ejection fraction; WMI – wall motion index; AV – atrioventricular

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## Background

As a defect in the cardiac conduction system, right bundle branch block (RBBB) is determined when electrocardiogram (ECG) shows a notched R wave typically displayed as an M-shaped rsr' complex, secondary ST-T change in lead V1, slurred S wave in lead I, and V6 with right axis deviation. QRS duration exceeding 120 ms indicates complete RBBB. The RBBB itself is more vulnerable to damage due to its anatomic nature as a superficial branch with limited blood perfusion compared with the left bundle branch block (LBBB). Epidemiologically, the prevalence of RBBB increases in the elderly population. Much more common than LBBB, the presence of RBBB in a young and healthy person usually does not indicate a pathological condition with clinical relevance. RBBB is basically considered a benign ECG finding without accompanying disease. However, in other cases, RBBB may be associated with underlying pulmonary and heart disease, such as cor pulmonale, pulmonary embolus, ischemic heart disease, rheumatic heart disease, myocarditis, degeneration of cardiac conduction system, and congenital heart disease.

Acute myocardial infarction (AMI) occurs when sudden blockade of the coronary artery stops blood perfusion to the myocardium. Most AMIs are caused by coronary artery disease, in which the rupture of an unstable atherosclerotic plaque plays an importance role. Since the pre-thrombolytic era, observational studies have been conducted to investigate the association of RBBB and the prognosis in AMI, but the results remains uncertain. Some studies showed RBBB was associated with larger infarct size, heart failure, ventricular arrhythmias, death, and poorer outcomes [1–6], while others did not find a significant prognostic value of RBBB in AMI [7–12]. To the best of our knowledge, no meta-analysis has been performed to study the effect of RBBB on the prognosis of AMI. Therefore, we conducted this systematic review and meta-analysis to evaluate the association of RBBB and risk of mortality in patients with AMI.

## Material and Methods

### Search strategy

Two authors (Li Xiang and Anyuan Zhong) independently searched the PubMed, Embase, and Cochrane databases to identify relevant studies published up to January 13, 2015, using the key words "RBBB", "mortality", "AMI", "Coronary Heart Disease (CHD)", and "cardiovascular". A manual search of the reference of retrieved studies for additional relevant publications was also performed.

### Inclusion criteria

Studies were included if they met the following criteria: (1) used a well-defined cohort design or case-control design; (2) clearly stated RBBB as a major exposure in patients with AMI; (3) and presented odds ratios (OR) for mortality with a 95% confidence interval (CI) or reported sufficient data to calculate these parameters.

### Data extraction

Data extraction was performed independently by 2 investigators (Li Xiang and Anyuan Zhong). The following information and data were extracted: names of the first authors, publication year, study design, sample size, study population, duration of follow-up, endpoints, country, OR with 95% CI, and adjusting factors. The endpoints included in-hospital death, long-term mortality, and all-cause mortality. Disagreements between reviewers were solved by discussion with a third author (Tao You) and consensus.

### Statistical analysis

Dichotomous data were analyzed using an OR with 95% CI. Heterogeneity among studies was assessed using Cochrane's Q test and $I^2$ test. A DerSimonian Laird's random-effects model was applied to pool the ORs when considerable heterogeneity was indicated by $I^2>25\%$ or $P<0.10$; otherwise, the fixed-effects model was used to attain the summary estimates. Sensitivity analysis was performed to determine the influence of each study on the overall results by excluding studies sequentially. Funnel plots and the Egger's test were adopted to evaluate the potential publication bias [13]. Statistical analyses were performed using Stata software version 11 (StataCorp LP, College Station, Texas), and a 2-sided p value ≤0.05 was considered statistically significant.

## Results

### Search results and study characteristics

The workflow of identifying eligible studies is shown in Figure 1 [4,14–21]. There were 4266 studies identified through database searches, including 505 from PubMed, 3644 from Embase, and 117 from Cochrane. After reviewing titles, excluding the duplicates or irrelevant studies and reviewing abstracts, 32 full-text articles entered the detailed review. Subsequent full-text review helped to exclude 20 studies that did not report patients with CHD, 1 study on patients with chronic coronary artery disease, and another study investigating patients with angina pectoris. Finally, we included 10 published studies with full text in this meta-analysis. The characteristics of each
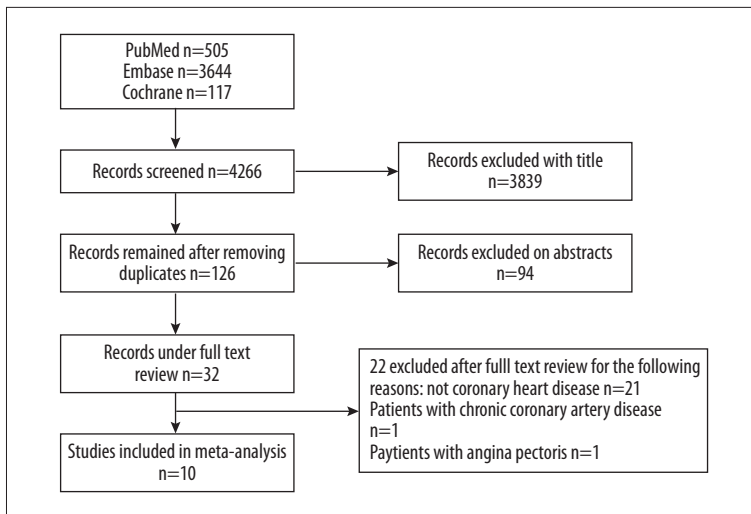
**Figure 1.** Flow diagram of eligible studies included in the meta-analysis.

study are displayed in Table 1. There were a total of 63 103 patients from 10 studies with ST-elevated myocardial infarction (STEMI) and non-ST-elevated myocardial infarction (NSTEMI).

### RBBB and the risk of total mortality

We conducted a random-effects meta-analysis and found that the presence of RBBB in patients with AMI was associated with a significantly increased risk for total mortality (OR 1.56; 95% CI: 1.44 to 1.68). In accordance, $I^2$ was 73% (P<0.001) (Figure 2), indicating considerable heterogeneity across included studies.

### Subgroup analysis

We performed subgroup analysis subject to the time of mortality. Both the in-hospital mortality (OR 1.94, 95% CI=1.60 to 2.37, p=0.002) and the long-term mortality (OR 1.49; 95% CI=1.37 to 1.62, P<0.001) were shown to be significantly increased in association with RBBB (Figure 2). This heterogeneity could not be resolved by the aforementioned subgroup analysis.

### Sensitivity analysis

The results of a sensitivity analysis showed that exclusion of each study individually did not yield substantial impact on the summary OR, which maintained consistency during repetitive evaluation with a random effects model, indicating favorable stability of the current results from meta-analysis (Figure 3).

### Publication bias

A funnel plot for the 10 eligible studies showed that balanced diffusion was shown in Figure 1, suggesting no considerable publication bias across included studies. Egger's regression was used for confirmation and yielded a similar result (Figure 4).

## Discussion

Traditionally, RBBB was considered an isolated ECG finding with minor clinical relevance. However, growing evidence from a variety of clinical observations focusing on both cardiac and non-cardiac disease has revealed the potential risk of this once so-called benign ECG pattern. The prognostic value of RBBB is thought to be related to underling disease. Of note, a number of investigations looking into ischemic heart disease showed that RBBB due to AMI might be associated with the severity of disease and act as a predictor for adverse outcome. In this case, extensive infarction impairing the bundle branch may act as the underlying mechanism. Interestingly, some large-scale registries involving the general population also showed that RBBB was associated with long-term mortality even in those who did not have a previous history of cardiovascular disease.

The clinical characteristics and prognosis of AMI patients accompanied by branch bundle block (BBB), including LBBB and RBBB, have attracted growing interest from physicians since the 1970s [22,23]. In 1999, the ACC/AHA Guideline for the management of patients with ST-Elevation myocardial infarction suggested that the symptom of chest pain accompanied by LBBB should be managed like ST-segment elevation. Despite development of evolving medical treatments in the past few years, patients who have AMI associated with LBBB have been found to have worse short- and long-term outcomes [24–26]. In 2012, both ESC and ACC/AHA guidelines for patients with ST-elevation myocardial infarction listed new-onset LBBB as an indication for emergency revascularization. LBBB has been determined to be an independent predictor of poor prognosis in AMI, while the prognostic value of RBBB in AMI has not yet been proved. In the past few years, there have been only a few relevant observations, which did not yield a consistent result. The impact of RBBB on mortality risk was reported in a number of cohort and retrospective studies. Antonio et al.

**Table 1.** Baseline characteristics of included studies.

| Study | Subjects | No. | Duration | Adjusting Factors | Country | Mortality |
|---|---|---|---|---|---|---|
| Brilakis, 2001 [4] | Community-based with AMI | 894 | 5 (years) | In-hospital: age, heart rate, Killip class, use of angiotensin-converting enzyme inhibitors, within 24 hours; long-term: age, heart rate, Killip class, history of AMI. | USA | Long-term, in-hospital |
| Vivas, 2010 [14] | With STEMI undergoing primary PCI | 913 | 19 (months) | Age, diabetes mellitus, previous AMI/PCI, Killip class, LVEF, peak CK/troponin, anterior AMI, proximal occlusion | Spain. | In-hospital |
| Guerrero, 2005 [15] | AMI underwent emergency catheterization | 3053 | 1 (year) | Ejection fraction, multivessel disease, thrombolysis in MI flow | USA | Long-term, in-hospital |
| Kleemann, 2008 [16] | NSTEMI/STEMI | 6403/ 20233 | 1/1.3 (years) | Age, sex, diabetes, renal failure, cardiogenic shock, HR of N100/min, ejection | Germany | Long-term, in-hospital |
| | | | | Fraction (EF) of <40%, reperfusion, statin, and β-blocker therapy | | |
| Ricou, 1991 [17] | Patients who had inferior Q-wave MI | 1634 | 1 (year) | Age, left ventricular failure and history of MI | USA | In-hospital |
| Juárez-Herrera, 2010 [18] | Patients with STEMI | 4555 | 35 days | Age, sex, diabetes, hypertension, hyperlipidemia, current smoker, previous AMI, AMI location, killip class | Mexican | In-hospital |
| Christian, 2011 [19] | Patients with MI | 6676 | 15 (years) | Age, HF, arterial hypertension, diabetes, gender, WMI, thrombolysis, COPD, angina, and eGFR | Denmark | In-hospital |
| Moreno, 2001 [2] | Consecutive patients diagnosed with AM1 | 1239 | 1 (year) | Age, gender, previous chronic HF, previous MI, diabetes, anterior location, Killip class, HR and SBP at admission, thrombolytic treatment, CK | Spain | In-hospital |
| Kurisu, 2007 [20] | Patients with a first anterior AMI | 430 | 30 days | Age, gender, hypertension, prodromal angina, time to angiography ≤6 h, spontaneous reperfusion, multivessel disease | Japan | In-hospital |
| Wong, 2006 [21] | Patients during the early phase of AMI | 17073 | 30 days | Recruitment region, age, gender, previous AMI, previous coronary or vascular disease, diabetes mellitus, and smoking, the time to randomization, SBP, pulse rate, and Killip class | New Zealand | In-hospital |

AMI – acute myocardial infarction; STEMI – ST-elevated myocardial infarction; PCI – percutaneous coronary intervention; CK – creatine kinase; LVEF – left ventricular ejection fraction; NSTEMI – non ST-elevated myocardial infarction; eGFR – estimated GFR; WMI – wall motion index; COPD – chronic obstructive pulmonary disease; HF – heart failure; HR – heart rate; SBP – systolic blood pressure.

found that the development of RBBB was an independent predictor for increased mortality in patients with AMI [2]. Emmanouil et al. indicated that patients with RBBB at the onset of AMI had lower left ventricular function, whereas both in-hospital and long-term mortality appeared higher than in those cases without a conduction block [4]. Mayra et al. reported that in the presence of RBBB, patients with AMI developed more co-morbidities and had a higher mortality risk [15].

In addition, Thomas et al. revealed that RBBB in patients with STEMI rather than NSTEMI was associated with increased in-hospital and long-term mortality [16]. According to the study by Sameer et al. looking into patients with angina, higher long-term cardiovascular mortality was seen in patients with RBBB compared to those without bundle branch block [27]. Francois et al. showed that both in-hospital and 1-year mortalities were significantly increased in patients with RBBB, despite basic
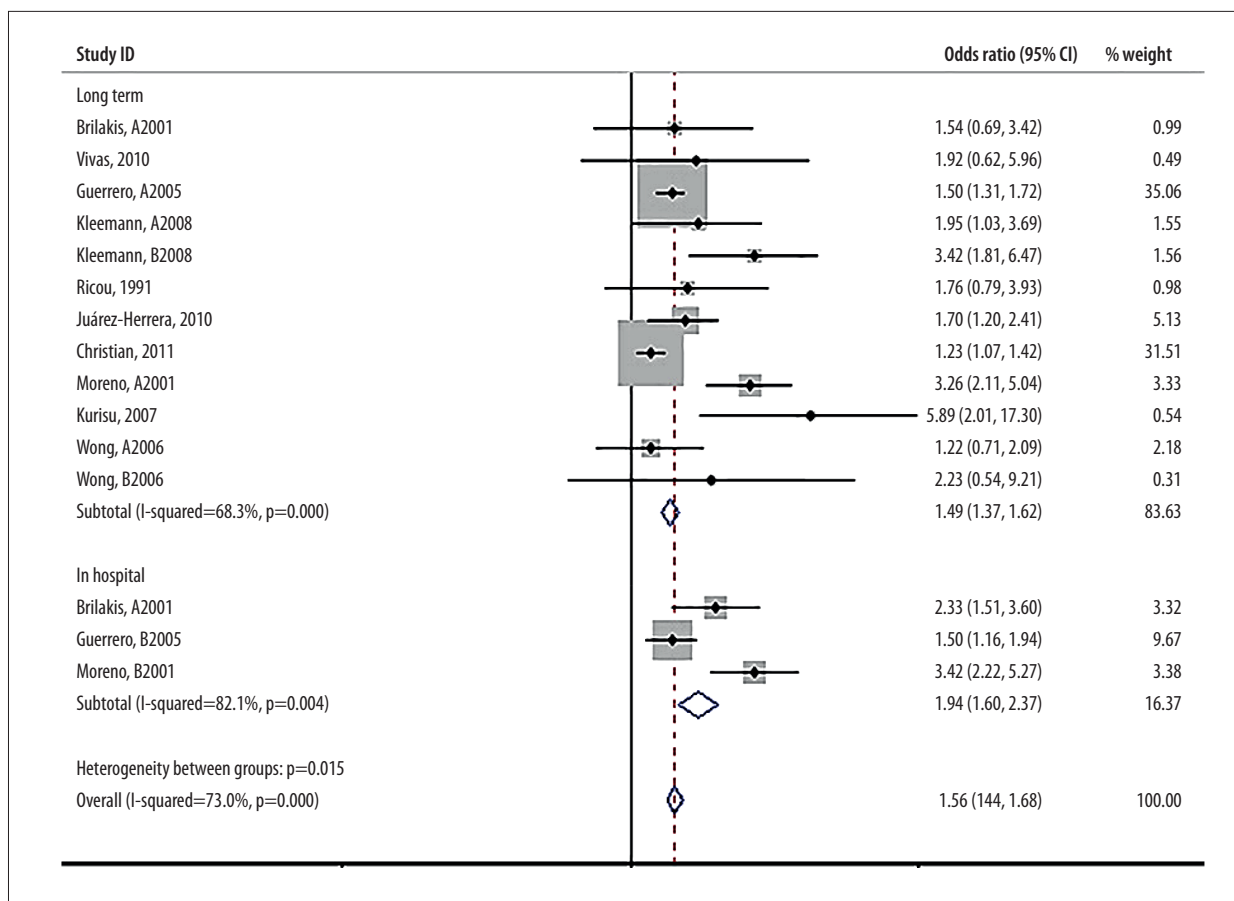
**Figure 2.** Forest plot showing mortality risk in AMI patients with RBBB.
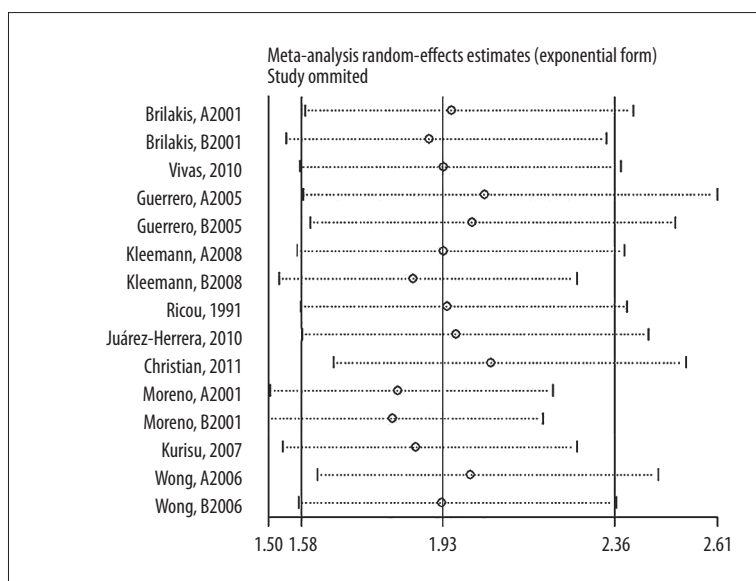


**Figure 3.** Sensitivity analysis of the meta-analysis of mortality risk of RBBB in AMI.

cardiac conditions, such as heart failure or myocardial infarction [17]. Christian et al. studied patients with compromised LV ejection fraction from the TRACE trial and found that RBBB was a predictor of mortality risk [19].

According to previous studies, compared with patients without bundle branch block, patients with RBBB showed the following features: there are more patients with advanced age and male sex [2,4,14–17,19,20] and more patients with a past medical history
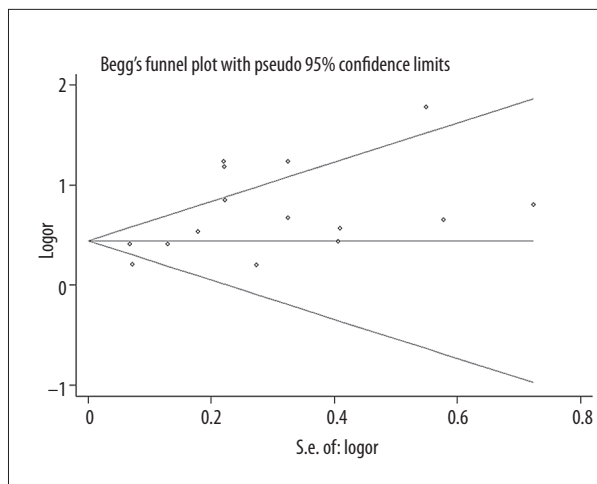
**Figure 4.** Funnel plots with pseudo 95% confidence limits for studies reporting mortality risk of RBBB in AMI.

of diabetes mellitus or hypertension [2,14–16,19]. However, Satoshi et al. reported that there was no significant difference in the comorbidity of diabetes mellitus or hypertension between those with and without RBBB. Conversely, Antonio et al. even found the opposite result, indicating there were more comorbidities in patients without bundle branch block compared with those with RBBB. David et al. showed that RBBB in patients with anterior wall myocardial infarction was also correlated with lesions of the left anterior descending artery [14,18,20,21]; multiple studies have also demonstrated higher in-hospital and long-term mortality in patients of AMI with RBBB [2,4,14–21], and the rate of death was even similar to LBBB [4]. There are conflicting results: Francois Ricou indicated that the occurrence of RBBB in patients of AMI was an independent predictor of long-term morality [17,18], but did not present the same value for in-hospital mortality [16,17]; persistent RBBB was considered to be a stronger predictor for death in transient RBBB [20].

The prognostic value of RBBB on mortality outcome may be explained by its effect on a series of confounding factors in AMI. Spectacularly, a number of studies revealed that RBBB is sometimes associated with a history of AMI [4,14,17,19]; regardless of reperfusion therapy using percutaneous coronary intervention (PCI) [14] or coronary artery bypass graft (CABG) [15]. Patients with RBBB showed more obvious clinical manifestations such as angina [19,20], tachycardia [2,4,16], higher Killip [2,4,14] and New York Heart Association (NYHA) class [19]. In the case of laboratory tests, the peak levels of myocardial necrotic markers including Creatine kinase (CK), Creatine kinase-MB (CK-MB), and Cardiac troponin I (cTnI) were significantly elevated in patients with RBBB [2,14,15,21] according to David et al. Additionally, RBBB was reported by Christian et al. as a predictor for elevated estimated GFR (eGFR) [19]. Structurally, a series of studies demonstrated that the left ventricular ejection fraction (LVEF) was lower in patients with AMI in the presence of RBBB

compared with those without RBBB [2,4,14,19]. Thomas et al. further classified and confirmed the same results in the STEMI group but not in the NSTEMI group. Christian et al. showed that patients with AMI accompanied by RBBB had higher wall motion index (WMI) [19]. In both STEMI and NSTEMI patients, RBBB was associated with higher comorbidity of heart failure, high degree atrioventricular (AV) block, and major bleeding as well as cardiogenic shock [2,14,16]. In this meta-analysis, considerable heterogeneity existed among studies, even in a sub-group analysis according to different country or origin, follow-up duration and study type. This indicates that other confounding factors may contribute to the overall heterogeneity. Nevertheless, the result of the meta-analysis was still considered stable after correction for publication bias and sensitivity.

Brilakis et al. defined newly diagnosed RBBB as those present on admission but not recorded on previous ECG within the preceding year, while pre-existing RBBB as those present in any previous ECG. They showed that the newly diagnosed RBBB was associated with significantly higher in-hospital mortality compared with pre-existing RBBB (33.5% *vs.* 5.3%) [4], which is consistent with the result reported by Hod et al. (39% *vs.* 8.8%) [22]. Wong CK et al. reported that the 30-days mortality in patients with newly diagnosed and pre-existing RBBB was 33% and 11.6%, respectively. [21]. The pre-existing RBBB can be seen appears in patients with cardiomyopathy, valvular disease, pulmonary disease, as well as in healthy population., Generally, no clinical intervention is considered in those with RBBB but no symptoms. However, newly diagnosed RBBB associated with AMI often suggests left anterior descending branch lesion, proximal occlusion of coronary artery and larger infarct size. It is also associated with complications including heart failure, arrhythmias and increased mortality rate.

The current meta-analysis shed substantial light on the current knowledge of RBBB in AMI, different from previous studies, which mainly discussed LBBB. The sample size of this study included over 60,000 patients, with the longest follow-up time of nearly 15 years. Both in-hospital and long-term mortality were considered in this study, as well as total mortality.

Our study revealed that the presence of RBBB in AMI increased mortality rate both in hospital, long term, and in total, and the long-term mortality rate is the most high; all of them has statistical significance. Thus, early identification of RBBB associated with AMI can help the clinician to develop targeted treatment programs and further improve the long-term prognosis of patients.

A previous meta-analysis showed that RBBB in heart failure is related to a higher mortality rate compare to normal conduction. Until now, different results from studies have looked into the role of RBBB in AMI. This meta-analysis pooled cohort studies on the prognostic power of RBBB for mortality outcomes

in patients with AMI, suggesting that RBBB is related to significantly increased deaths. To our knowledge, this is the first meta-analysis on RBBB and mortality risk in coronary atherosclerotic disease. However, the underlying mechanism remains to be elucidated, and further large-scale observational studies can help confirm the prognostic value of RBBB.

### Limitations

There were several limitations in our study. First, our selection criteria for studies, which were restricted to those published in English, might produce language bias. Second, the study could not adjust for every confounding factor; thus, we were unable to prove the presence of RBBB as an independent predictor of mortality. Third, among the 10 included studies, there are only two studies which compared newly

diagnosed and pre-existing RBBB. Furthermore, we have not found any further publications after a renewal literature search for RBBB in AMI. In that case, there may be insufficient data for subgroup analysis comparing different types of RBBB in the current study.

### Conclusions

In summary, our study is the first meta-analysis demonstrating that the presence of RBBB in patients with AMI is associated with an increased risk for mortality, which makes it a potential marker of prognosis in coronary atherosclerotic disease. Findings from the current study may reinforce the knowledge of practical predictive methods for AMI.

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