

# Early coronary angiography and percutaneous coronary intervention for out of hospital cardiac arrest survivors without ST-segment elevation: a systematic review and meta-analysis

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## Original research

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# Abstract

**Objective:** The meta-analysis aims to identify whether out of hospital cardiac arrest (OHCA) survivors of non ST-segment elevation (NSTEMI) can benefit from early coronary angiography (CAG) and percutaneous coronary intervention (PCI).

**Methods:** The relevant studies from MEDLINE, Cochrane Library, Embase were searched by two independent investigators using a variety of keywords. Stata software (version 12.0, Stata Corp LP, College Station, TX, USA) was used for statistical analysis.

**Results:** A total of 12 studies (9 observational studies, 1 cohort study and 2 randomized control trials) were identified and incorporated into the meta-analysis. For overall analysis, the strategy of early angiography was associated with decreased short-term (hospital discharged) mortality (RR=0.72, 95% CI=0.56-0.93, P=0.000) and long-term (follow up) mortality (RR=0.84, 95% CI=0.71-0.99, P=0.007). However, when analyzed in the subgroup of randomized controlled study, the strategy of early angiography didn't have survival benefit in the randomized controlled study group for short-term mortality (RR=1.12, 95% CI=0.89-1.41, P=0.331) and long-term mortality (RR=1.06, 95% CI=0.85-1.32, P=0.572). Meanwhile, our analysis found that, if early CAG performed, PCI followed by CAG is not associated with hospital discharged mortality (RR=1.14, 95% CI=0.96-1.37, P=0.132) compared with CAG alone. No significant differences between the groups were found in the remaining secondary endpoints.

**Conclusion:** Due to the observational nature of the studies available, we may consider that early CAG and PCI is not be recommended for patients with NSTEMI OHCA.

## Introduction

A report from the American Heart Association (AHA) indicated that out of hospital cardiac arrest (OHCA) is a major health-care concern worldwide[1]. Survival to hospital discharge after Emergency Medical Services (EMS)-treated OHCA was 10.4%, and survival with good functional status was 8.4% based on 73910 cases in 2017[2]. Patients with ST segment elevation myocardial infarction (STEMI) who had OHCA had higher in-hospital mortality (38%) than STEMI patients without OHCA (6%) in a Los Angeles, CA, registry of 4729 STEMI patients from 2011 to 2014[3]. According to the guidelines, Post-resuscitation electrocardiogram ST-elevation sudden cardiac arrest (SCA) is a strong indication for emergency coronary angiography (CAG)[4, 5]. However, the role of early CAG in patients without ST elevation remains unclear. Two reviews conducted in 2016 and 2017 respectively support the use of early CAG in OHCA patients presenting NSTEMI[6, 7]. However, Lemkes et al.[8] published an article indicated that, immediate angiography was not found to be better than delayed angiography with respect to overall survival at 90 days for patients who had been successfully resuscitated after OHCA and had no signs of STEMI[8]. Hence, it is necessary to conduct a systematic review to evaluate the role of early CAG for OHCA survivors without STE. Meanwhile, the role of PCI followed by CAG for OHCA survivors without STE remains

unclear. Thus, we have conducted a meta-analysis of CAG plus PCI versus CAG alone for OHCA survivors without STE.

## **Methods**

### **Search strategy**

We searched the relevant studies from MEDLINE, Cochrane Library, Embase from their inception to March 2019, conference proceedings, and reference lists of relevant articles were also searched. The search strategies in Pubmed, Cochrane Library and Embase were shown in **Supplemental figure 1-3**.

### **Eligibility criteria of original studies**

Inclusion criteria: (1) Participants: we included OHCA survivors without ST-segment elevation, regardless of the gender and ethnicity; (2) Interventions: Immediate CAG with or without PCI; (3) Control: Delayed or no CAG with or without PCI ; (4) Outcomes: Primary outcomes: Hospital discharged mortality and follow-up mortality, Secondary outcomes: Cerebral Performance Category Score of 1 or 2 (CPC 1-2), major bleeding; (5) The study design include randomized controlled trials (RCTs), cohort studies and observational studies.

Exclusion criteria: (1) a study that administered emergency CAG as a control; (2) a study with duplicate publication and/or abstract only.

### **Study selection**

Two reviewers independently identified studies through inclusion criteria by screening the title and abstract of each record and retrieved their full-text if necessary. Any disagreement between the two reviewers was solved with a discussion with a third reviewer. Otherwise, the agreement was accomplished by a consensus.

### **Data extraction and quality assessment**

We designed a pre-defined data extraction form and two reviewers independently extracted the following information from the selected trials: the first author, published year, sample size, mean age, intervention, control and outcomes. Any disagreement between two reviewers was discussed with the third reviewer until a consensus was reached.

Quality assessment was performed by two reviewers. Observational studies were scored in accordance with the Newcastle Ottawa Scale (max score of 9), whereas RCTs were scored as per the Jadad Scale (max score of 5).

### **Data synthesis**

Stata software (version 12.0, Stata Corp LP, College Station, TX, USA) was used for statistical analysis. According to the Cochrane Handbook of Systematic Reviews, we chose risk ratios (RRs) and 95% confidence intervals (CIs) as the appropriate parameters to evaluate the dichotomous outcomes. In terms of continuous outcomes, the mean difference and its 95% CI were used. Between-study heterogeneity was evaluated using an  $I^2$  test (25% or lower is defined as low heterogeneity, 50% as moderate heterogeneity, 75% as high heterogeneity). The fixed-effect model was applied if there was no or low heterogeneity, and pooled RRs were estimated using the Mantel-Haenszel method. Publication bias was assessed if there are more than ten studies in one outcome. All hypotheses were tested at the  $\alpha = 0.05$  level.

## Subgroups analysis

Subgroups will be analyzed based on the different types of studies or the PCI usage.

# Results

## Description of included studies

We identified 369 records based on this search strategy, and 318 potentially eligible records were obtained after removing duplicate publications. After screening the titles

and abstracts, a total of 312 studies were excluded. Six studies with 756 participants were included (**Figure 1**). The characteristics of the included studies are presented in **Table 1**. Risk of bias for the included studies were assessed by the Newcastle Ottawa Scale (for observational studies) or a modified Jadad scale (for RCTs), and the results are presented in **Supplemental table 1-2**.

## Primary outcomes

The primary outcomes included short-term mortality and long-term mortality. For short-term mortality, there were 303/877 (34.5%) deaths in the early CAG group and 552/1110 (49.7%) deaths in the delayed or no CAG group. The early CAG was shown a survival benefit at short-term (RR, 0.72; 95%CI [0.56, 0.93];  $P=0.000$ ). Meanwhile, subgroup analysis was conducted according to the type of study design. Consistently, use of early CAG was shown to decrease mortality after procedure in the observational study group (RR, 0.62, 95%CI [0.54, 0.71];  $P = 0.000$ ); Conversely, there was no difference between the two group in the subgroup of RCTs (RR, 1.12, 95%CI [0.89, 1.41];  $P = 0.331$ ). (**Figure 2**). Importantly, we analyzed the data between

PCI group and non PCI group if early CAG performed. There were 454/1275 (35.6%) in the PCI group and 341/1125 (30.3%) in the non PCI group, there was no difference between PCI group and non PCI group (RR, 1.14, 95%CI [0.96, 1.37];  $P = 0.132$ ). (**Figure 3**).

Similarly, for long-term mortality, there were 310/746 (41.6%) deaths in the early CAG group and 445/943 (47.2%) deaths in the delayed or no CAG group. The early CAG was shown a survival benefit at long-term (RR, 0.84; 95%CI [0.71, 0.99];  $P=0.007$ ). In the subgroup of observational study, there were 204/474 (43%)

deaths in the early CAG group and 352/668 (52.7%) deaths in the delayed or no CAG group. However, in the subgroup of RCTs, there were 106/290 (36.6%) in the early CAG group and 93/275 (33.8%) in the delayed or no CAG group. The subgroup analysis showed that early CAG is associated with lower long-term mortality in the subgroup of observational study (RR, 0.78; 95%CI [0.66, 0.92]; P=0.000) but not in the subgroup of RCTs (RR, 1.06; 95%CI [0.85, 1.32]; P=0.572). (**Figure 4**).

## Secondary outcomes

The secondary outcomes include short- and long-term CPC (1-2) and major bleeding. The results showed that there was no difference between the two groups for all of the secondary outcomes. The detailed data was shown in **Table 2** and **Supplemental figure 4-7**.

## Discussion

Our analysis aims to identify the optimal timing of CAG and whether PCI should be underwent followed by CAG for OHCA survivors without STE. The results showed a survival benefit with early CAG in the setting of NSTEMI OHCA. Conversely, there were no difference between early CAG and delayed CAG when analyzed by subgroup of randomized controlled studies. Meanwhile, our analysis found that PCI followed by CAG didn't affect the mortality and neurological function.

As to the primary endpoints, our analysis did show a hospital discharged survival and long-term survival benefits with early CAG for NSTEMI OHCA when analyzed by the subgroup of observational studies and overall groups. Consistently, two reviews[6, 9] and some observational studies[10-12] support the result of the present analysis. Vadeboncoeur et al.[10] conducted a study including 1230 cases NSTEMI OHCA, the survival to hospital discharge was 78.3% for those without CAG and 81.5% for those who underwent CAG ( $p < 0.0001$ ). A recent meta-analysis[9] of 8 studies reported that the strategy of early CAG was associated with decreased short-term (OR=0.46, 95% CI =0.36-0.56,  $P<0.001$ ) and long-term (OR=0.59, 95%CI=0.44-0.74,  $P<0.001$ ) mortality. Hollenbeck et al.[11] found that patients treated with CAG were more likely to receive mechanical support and were also treated with more aggressive anticoagulation. It has also been suggested that CAG might be associated with timely venous access, invasive hemodynamic monitoring and rapid titration of vasoactive medications. Vadeboncoeur et al.[10] indicated that CAG patients were more likely to be treated with targeted temperature management (TTM), suggesting a higher intensity of care. Although some studies showed no advantage for TTM of 33°C in comparison with TTM of 36°C, they didn't rule out the benefit of TTM[13, 14]. These may explain why early CAG is beneficial for the survival. While, in our opinion, it can't rule out delayed CAG patients have more opportunity to be treated with TTM and other selective strategies.

However, the survival benefit was counteracted with the analysis in subgroup of randomized controlled studies. There are some possible explanations for the absence of benefit of early CAG in the subgroup of randomized controlled studies in the present study. First, this difference could be related to the observational nature, which may have resulted in selection bias that favored treating patients who had a presumed better prognosis with a strategy of early angiography[8]. Second, according to the American

heart association (AHA) guideline, among the 2855 patients who were 30-day survivors of OHCA between 2001 and 2012 in a nationwide registry in Denmark, 10.5% had brain damage or were admitted to a nursing home, and 9.7% died during the 1-year follow-up period[15]. Thus, immediate initiation of targeted temperature management was recommended. Lemkes et al.[8] reported that patients assigned to the immediate angiography group reached their target temperature later than patients in the delayed angiography group. Additionally, Lemkes et al. demonstrated that an acute thrombotic occlusion was found in 3.4% of patients in the immediate angiography group and in 7.6% of patients in the delayed angiography group. This may explain the lack of benefit of early coronary intervention.

Whether patients of OHCA NSTEMI can benefit from PCI remains controversial. Some studies demonstrated that there were no survival benefit for patients with successful PCI compared to no PCI[11, 16]. Wester et al.[16] found that in NSTEMI-SCA patients with significant stenosis ( $\geq 90\%$ ), PCI performed group with an increased unadjusted 30-day mortality (40.9% vs. 32.7%;  $p= 0.011$ ) compared to no PCI group. Meanwhile, Hollenbeck et al.[11] indicated that there was no difference between PCI and no PCI. The above study showed that those who received PCI had 60.0% survived to hospital discharge compared to 68.3% ( $p=0.386$ ) of patients who did not receive PCI. Conversely, Dumas et al.[17] reported that the hospital survival rate was significantly higher in patients in whom a successful PCI was obtained than in patients with no or failed PCI (51% versus 31%;  $P=0.001$ ). Of interest, the present analysis showed that PCI is associated with higher mortality at hospital discharge. Since PCI is associated with improved outcomes in patients with acute thrombotic coronary occlusion[18, 19], but not in patients with stable coronary artery disease[20].

There were several limitations in this review. First, we included observational studies which would result in selective bias. Second, since the result of subgroup (RCTs) analysis is not consistent with the overall analysis in terms of survival benefit, we cannot make a definite conclusion that early CAG is beneficial for the survival. Thus, more rigorous-designed RCTs are needed to verify this conclusion.

## Conclusions

Though the total analysis showed a survival benefit with early CAG in the setting of NSTEMI OHCA. Conversely, there were no difference between early CAG and delayed CAG when analyzed in the subgroup of randomized controlled study. Importantly, our analysis found that, if early CAG performed, PCI followed by CAG is not associated with short-term mortality compared with CAG alone. Due to the observational nature of the studies available, we may consider that early CAG and PCI is not be recommended for patients with NSTEMI OHCA.

## Abbreviations

Out of hospital cardiac arrest OHCA

Non ST-segment elevation NSTEMI

Coronary angiography CAG

Percutaneous coronary intervention PCI

Randomized controlled trials RCTs

Emergency Medical Services EMS

ST segment elevation myocardial infarction STEMI

Sudden cardiac arrest SCA

Cerebral Performance Category Score CPC

Risk ratios RRs

Confidence intervals CIs

Targeted temperature management TTM

American heart association AHA

## **Declarations**

PROSPERO registration number: CRD42019129680

### **Ethical Approval and Consent to participate**

Not applicable.

### **Conflicts of interest statement**

None.

### **Consent for publication**

Not applicable.

### **Availability of supporting data**

Not applicable.

### **Authors' contributions**

Po Huang carried out the analysis and drafted the manuscript. Yuhong Guo and Bo Li carried out the analysis. Qingquan Liu and Xiaolei Fang conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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## Tables And Description Of Supplementary Files

Due to technical limitations, full-text HTML conversion of the tables could not be completed. However, the tables can be accessed as Supplementary Files.

Table 1: the characteristics of the included studies.

Table 2: the summary of meta-analysis.

Supplemental figure 1: the search strategies in Pubmed.

Supplemental figure 2: the search strategies in Cochrane Library.

Supplemental figure 3: the search strategies in Embase.

Supplemental figure 4: the forest figure of short-term CPC1-2 for early CAG versus delayed CAG.

Supplemental figure 5: the forest figure of short-term CPC1-2 for PCI versus no PCI after CAG.

Supplemental figure 6: the forest figure of long-term CPC1-2 for early CAG versus delayed CAG.

Supplemental figure 7: the forest figure of major bleeding for early CAG versus delayed CAG.

Supplemental table 1: Risk of bias for the included studies were assessed by the Newcastle Ottawa Scale (for observational studies) .

Supplemental table 2: Risk of bias for the included studies were assessed by a modified Jadad scale (for RCTs).

## Figures

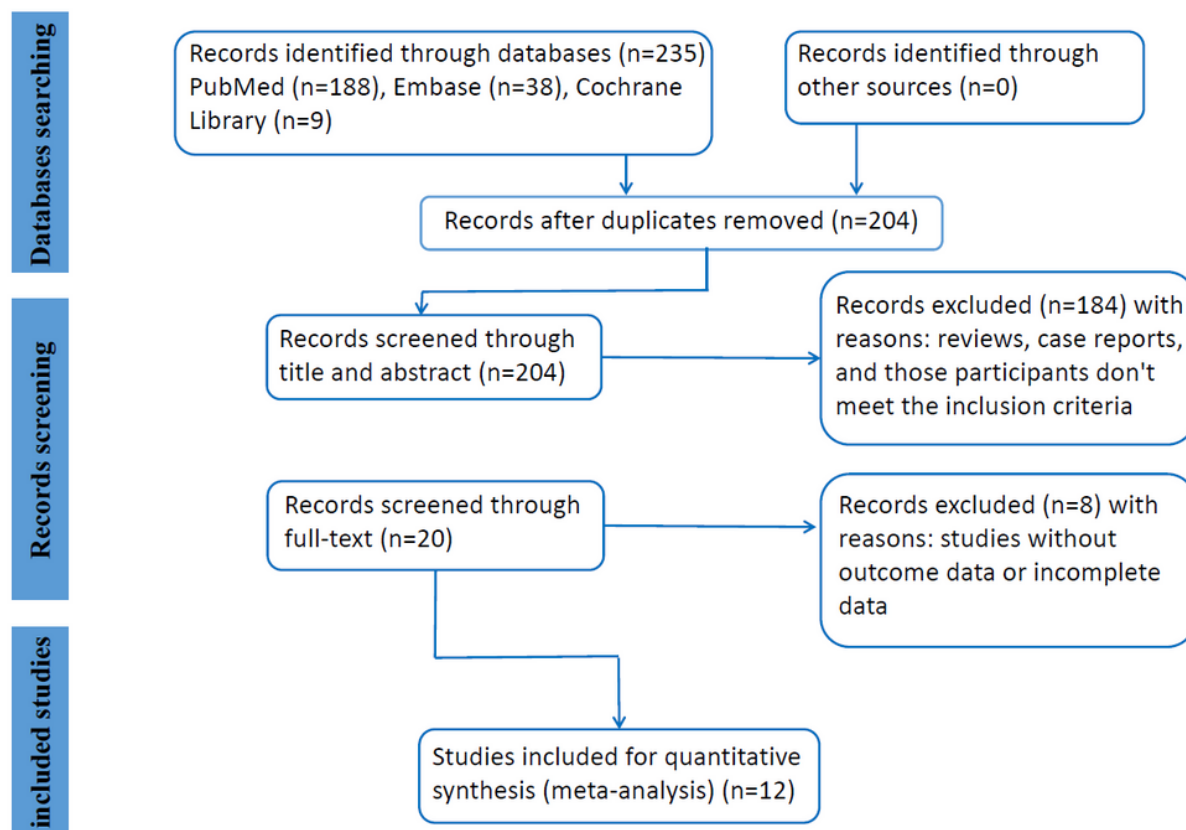
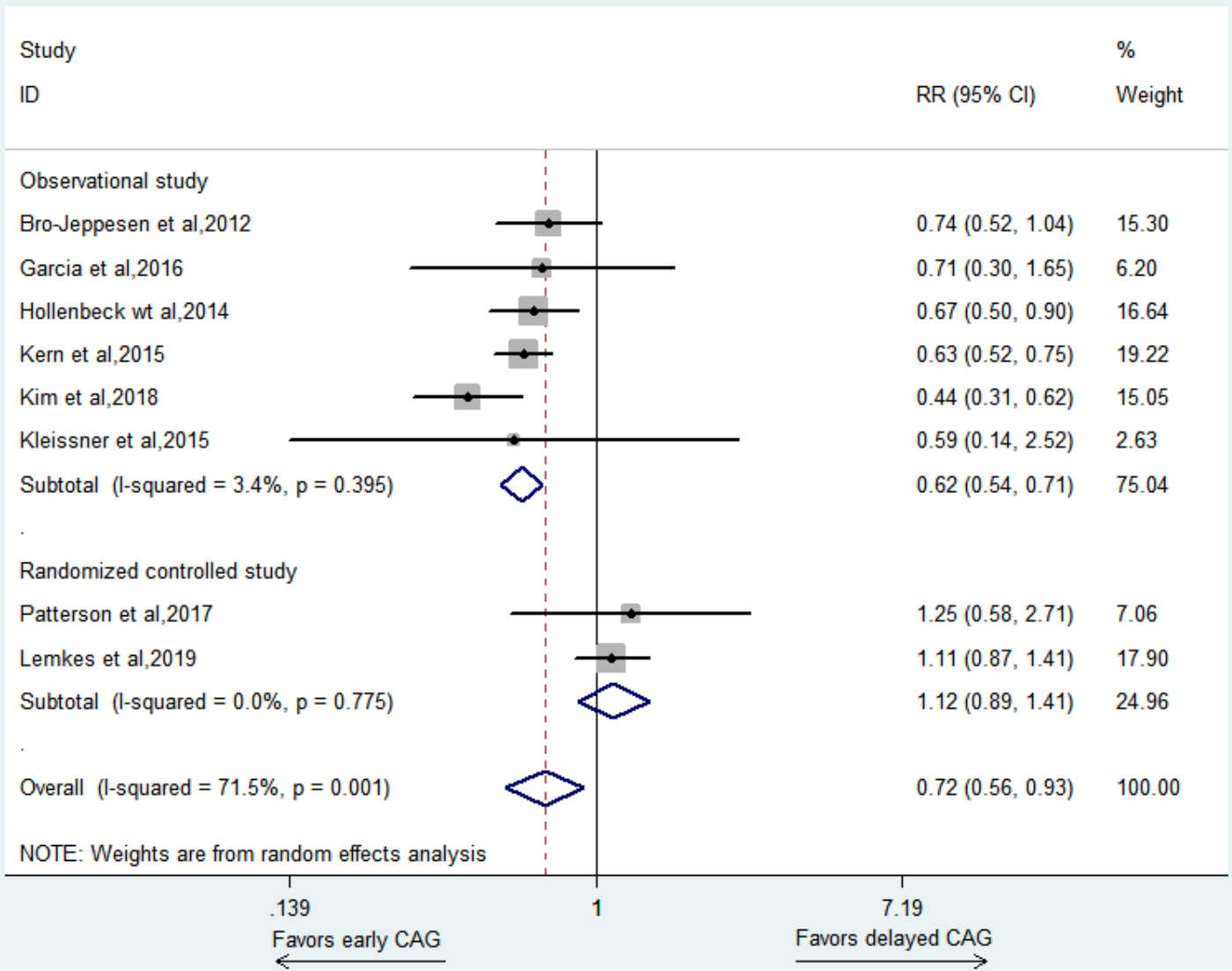


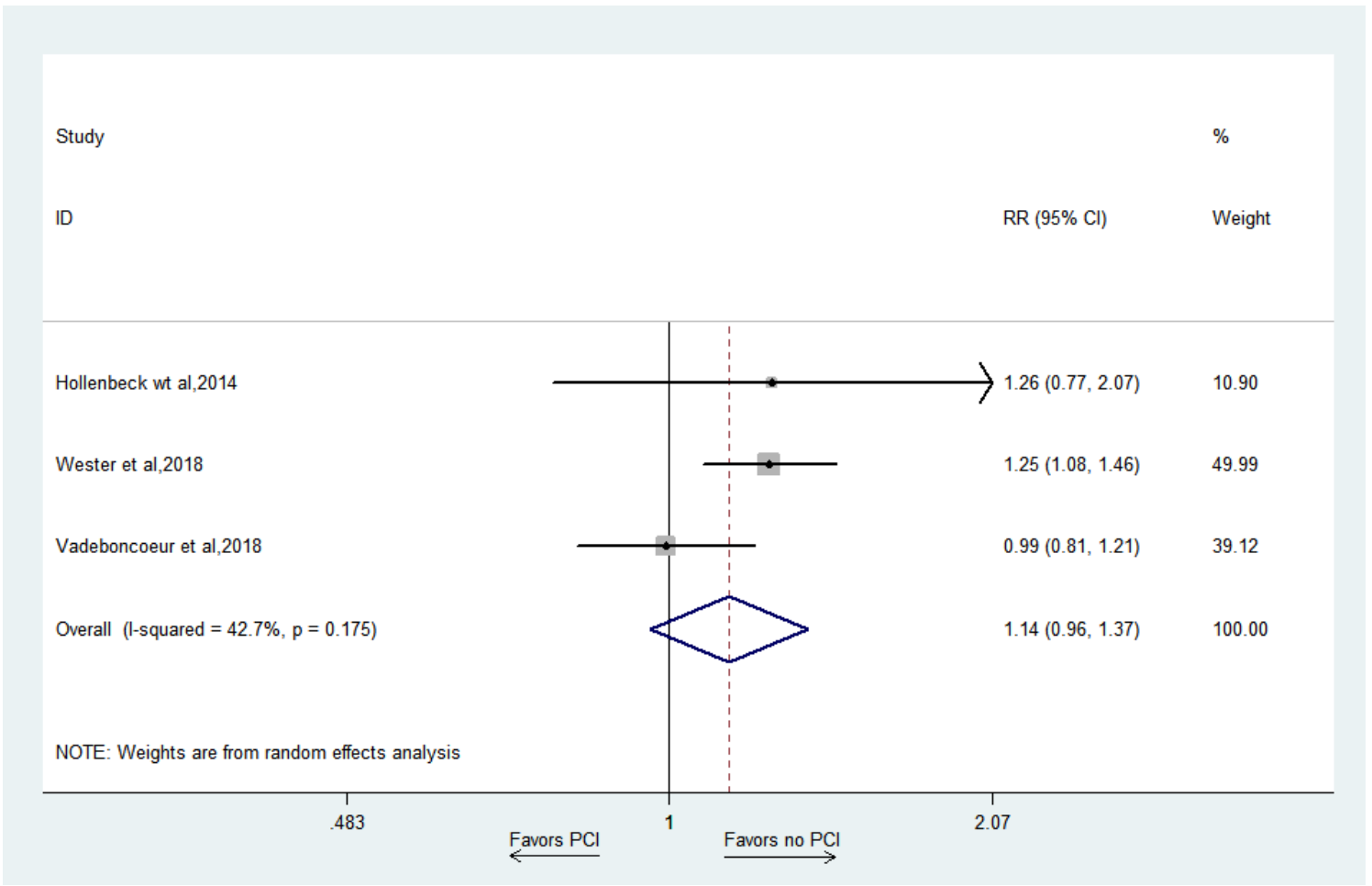
Figure 1

The flow chart of literature screening



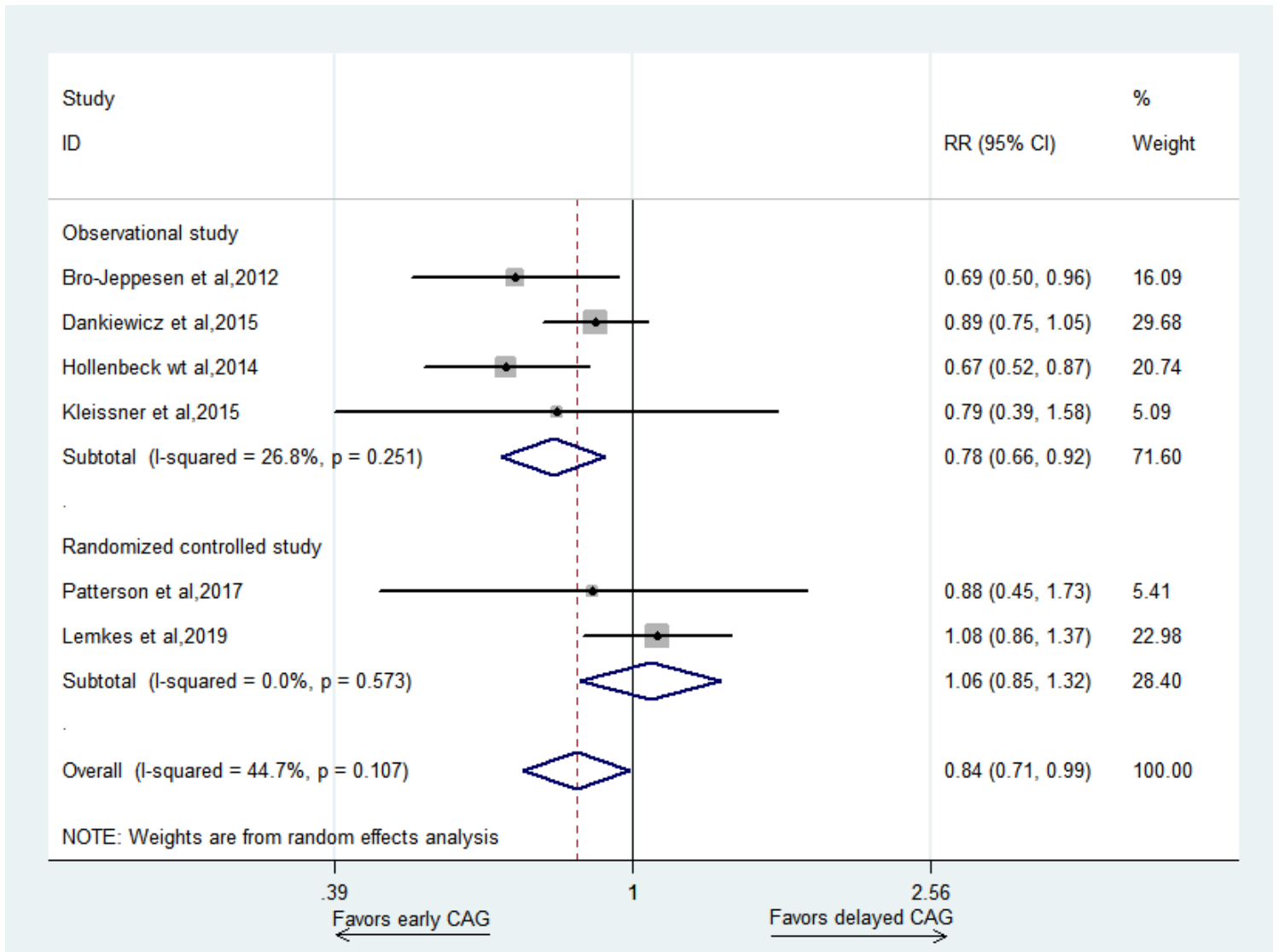
**Figure 2**

The forest plot of short-term mortality between early CAG and delayed CAG



**Figure 3**

The forest plot of short-term mortality between PCI and non PCI



**Figure 4**

The forest plot of long-term mortality between early CAG and delayed CAG

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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