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The prognostic utility and diagnostic efficacy of intracoronary electrocardiogram recorded during percutaneous coronary intervention—a Meta-Analysis

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Abstract

Objective

Intracoronary electrocardiogram (IC-ECG) recording has been shown to be sensitive and reliable for detecting myocardial viability and local myocardial ischemia in some studies. But IC-ECG is neither widely used during percutaneous coronary intervention (PCI) nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic utility and diagnostic efficacy of IC-ECG recorded during PCI.

Methods

Relevant studies were identified by searches of MEDLINE until June 19th, 2021. Observational studies and diagnostic studies which reported the prognostic utility and diagnostic efficacy of IC-ECG were included. Data were extracted independently by two authors and summary estimates were obtained using a random effects model.

Results

Of the 12 included studies, 7 studies reported the clinical outcomes (821 patients) and 6 studies reported the diagnostic efficacy (485 patients) of IC-ECG. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) of ST-segment elevation recorded by IC-ECG were 4.65 (1.69-12.77), 5.08 (1.10-23.44), 4.53 (0.79-25.90) and 1.83 (0.93-3.62) for major adverse cardiac events, myocardial infarction, cardiac death, and revascularization, respectively. The weighted mean difference (WMD) was 6.49 (95%CIs 3.84-9.14) for ejection fraction when ST-segment resolution was recorded, and 0.86 (95%CIs -8.55-10.26) when ST-segment elevation was recorded. The pooled

sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with 95%CIs of ST-segment elevation were 0.83 (0.74-0.89), 0.87 (0.79-0.93), 6.57 (4.01-10.76), 0.20 (0.13-0.29), and 33.37 (19.36-57.52) respectively.

Conclusions

These findings provide quantitative data supporting that IC-ECG had good diagnostic efficacy for local myocardial injury, and could predict clinical outcomes.

Key words: intracoronary electrocardiogram, prognostic utility, diagnostic efficacy, meta-analysis.

Strengths and limitations of this study

Strengths

1. There were large number of patients analyzed.

2. We performed meta-regression and heterogeneities analysis to find out the source of heterogeneities.

Limitations

1. Limited by the published studies, we could only perform meta-analysis of observational studies.

2. We did not perform sensitivity analysis of the timing when the IC-ECG was recorded, limited by the number of studies.

Key questions

What is already known about this subject? Invasive diagnostic tools are recommended for guiding PCI by the guidelines, but these tools are not always available. In some cases, the catheters or pressure wires, may not pass through the lesions or may be damaged. The cost are also important additional considerations. IC-ECG might be an alternative choice, but need to be assessed its prognostic utility and diagnostic efficacy.

What does this study add? This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic utility and diagnostic efficacy of IC-ECG recorded during PCI. And we found that IC-ECG had good diagnostic efficacy for local myocardial injury, and could predict clinical outcomes.

How might this impact on clinical practice? Our results indicated that IC-ECG had potential value for guiding PCI. Further researches should consider the correlation between the timing when the IC-ECG was recorded and clinical outcomes.

Introduction

Percutaneous coronary intervention (PCI) is a well-established therapeutic strategy for patients with coronary artery disease (CAD). Except for coronary angiography (CAG), several invasive diagnostic tools, such as fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) are recommended for guiding PCI by the guidelines[1]. But these tools are not always available. In some cases, catheters or pressure wires, may not pass through the lesions or may be damaged when crossing the stents or calcified lesions[2-5]. Moreover, for some patients, the cost of these tools are important additional considerations.

Intracoronary electrocardiogram (IC-ECG) recording, with a guidewire functioning as a unipolar electrode, might be an alternative tool for guiding PCI. In some studies, the ST-segment elevation or resolution recorded by IC-ECG during or after PCI procedures have been shown to be sensitive and reliable for detecting myocardial viability, local myocardial ischemia, or microvascular obstruction[5-16]. But IC-ECG is neither widely used during PCI nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic utility and diagnostic efficacy of IC-ECG recorded during PCI.

Methods

The meta-analysis was conducted according to the checklist of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[17] and the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE)[18]. We performed a systematic search of relevant studies published through June 19th,

2021, in the MEDLINE database.

Search strategy

Accessing MEDLINE database, we performed a literature search for studies published until June 19th, 2021 using the following search terms and key words: ((intracoronary) AND (electrocardiogram OR ECG OR EKG)) AND (st segment). We manually checked the reference list of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) Published in the English language; (2) Had an observational study design; (3) Enrolled patients with CAD who were undergoing PCI; (4) Reported the clinical outcomes during follow-ups, such as major adverse cardiac events (MACEs), cardiac death, myocardial infarction, ejection fraction (EF), and repeat revascularization. (5) Reported the diagnostic efficacy of IC-ECG. (6) Presented estimates of odds ratios (ORs) with 95% confidence intervals (CIs) or reported data necessary to calculate these. Animal, autopsy, duplicated, and phantom studies were excluded. Moreover, studies would be excluded if IC-ECG was not one of the study objects.

Data extraction

From each retrieved article, two authors independently extracted the following data: name of the first author, year of publication, location where the study was performed, study design, number of cases, follow-up period, proportion of men, mean or median age, inclusion criteria, exclusion criteria, reference standard, ORs or event

rates, EF during following-up, and the diagnostic efficacy of IC-ECG. The true-positive, true-negative, false-positive, and false-negative values were also estimated, using the data we extracted from the studies.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

We directly extracted ORs from each study, or indirectly estimated ORs by calculating event rates. And then we pooled ORs using a random-effects meta-analysis method. For EF, we pooled unstandardized mean difference using a random-effects meta-analysis method. Summary sensitivities, specificities, diagnostic odds ratios, positive and negative likelihood ratios with their 95% CIs of IC-ECG were obtained using random effect models with DerSimonian Laird methods[19]. Summary receiver-operating-characteristic (SROC) curves were constructed and the areas under the SROC curves (AUC) was performed to assess the diagnostic accuracy of IC-ECG.

To perform quality assessment, two authors independently assessed the prognostic studies' qualities by using the Downs-Black criteria[20] and the diagnostic studies' qualities by using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) tool[21]. The Downs-Black criteria devised an instrument consisting of 27 questions that evaluate reporting, external validity, internal validity (bias and confounding), and statistical power. All questions received scores 0 or 1, with the exception of question 5, which ranged from 0 to 2, depending on whether the

statistical power of the survey was explicitly stated in the article as being at least 80%. Thus, the maximum score achievable by an article was 27 points. The QUADAS tool contained 14 questions which could be used for assessing the quality of diagnostic studies. Disagreements were resolved by consensus.

Statistical heterogeneities between studies were evaluated with the I^2 statistic[22], which estimates the percentage of total variation across studies due to true between-study differences rather than chance, with I^2 values of 25, 50, and 75% representing low, medium, and high heterogeneities, respectively. We explored sources of heterogeneities through Galbraith plot[23] and meta-regression analysis. The Begg asymmetry tests[24] for clinical outcomes and Deeks' asymmetry test[25] for the diagnostic studies were performed to assess the publication bias. P values that were less than 0.05 were considered statistically significant. All statistical analyses were carried out with STATA, version 16.0 (Stata Corp, College Station, Texas).

Results

Literature search

The details of search steps are shown in Figure 1. We identified and screen 480 articles from our preliminary search. After screening abstracts, 440 articles were excluded because the study objects were not IC-ECG. 16 articles were excluded because they were not clinical trials. Bigler's study compared deep learning with manually obtained IC-ECG results[26], and was excluded. 23 articles were identified for full review. Among these articles, 2 duplicated studies were excluded. 9 articles were excluded because they did not report ORs, diagnostic accuracy, or data

necessary to calculate these. Finally, there were 12 studies included in our meta-analysis. 7 studies reported the clinical outcomes and 6 studies reported the diagnostic efficacy of IC-ECG.

Study characteristics

The characteristics of included studies are shown in Table 1 and Supplement table 1. There were 6 cohort studies, 1 case-control study and 5 diagnostic studies in our meta-analysis. There were 1198 cases included in our meta-analysis totally. Among these cases, 821 cases and 485 cases were included in the meta-analysis for clinical outcomes and diagnostic efficacy of IC-ECG respectively. The proportion of men was 68.8%. The inclusion criteria of the included articles was CAD patients, including stable or unstable angina pectoris, and myocardial infarction. The clinical outcomes reported in these studies were mainly MACEs, cardiac death, myocardial infarction, repeat revascularization, and EF. The reference standards reported in the diagnostic studies were varied, including FFR[5, 13], echocardiogram[14], surface ECG[12], and troponin[15, 16].

The correlation between clinical outcomes and ST-segment elevation recorded by IC-ECG

Pooled OR for MACE is shown in Figure 2a. The inclusion criteria of these studies were patients with angina and stable conditions. MACEs were defined as cardiac death, myocardial infarction, revascularization, and hospitalization for heart failure in Ikenaga's study[10]. In Uetani's study[11] and Balian's study[12], MACEs were defined as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG

after PCI procedures was significantly associated with higher risk of MACE (OR 4.65, 95%CIs 1.69-12.77). There were mild heterogeneities among studies (I^2=30.1%, p=0.239). And there was no publication bias (the result was shown in Supplement figure 1a, p=0.602).

Pooled ORs for cardiac death, myocardial infarction, and revascularization are shown in Figure 2b-2d. The inclusion criteria of these studies were patients with angina or non ST-segment elevation myocardial infarction (NSTEMI). In the meta-analysis for cardiac death, Ikenaga's study[10] was excluded because there were no events. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of myocardial infarction (OR 5.08, 95%CIs 1.10-23.44), but not cardiac death (OR 4.53, 95%CIs 0.79-25.90) nor revascularization (OR 1.83, 95%CIs 0.93-3.62). There were no heterogeneities among studies (cardiac death, I^2=0%, p=0.494; myocardial infarction, I^2=0%, p=0.567; revascularization, I^2=0%, p=0.642). And there were no publication bias (cardiac death, p=0.317; myocardial infarction, p=0.317; revascularization, p=0.602, and the results were shown in Supplement figure 1b-1d).

The correlation between EF and different results recorded by IC-ECG during follow-up

The correlation between EF and different results recorded by IC-ECG are shown in Figure 3. We divided the included studies into 2 subgroups according to the different evaluation methods reported by the studies. One was ST-segment resolution, and the other one was ST-segment elevation. In the subgroup of ST-segment

resolution, inclusion criteria were patients with ST-segment elevation myocardial infarction (STEMI). The pooled weighted mean difference (WMD) was 6.49, with 95%CIs 3.84-9.14. There were no heterogeneities (I^2=0%, p=0.525). And there was no publication bias (the result was shown in Supplement figure 2a, p=0.317). The inclusion criteria of ST-segment elevation subgroup were patients with NSTEMI (Hishikari, et al[7]) or anterior myocardial infarction (Yajima, et al[9]). The pooled WMD was 0.86, with 95%CIs -8.55-10.26. There were heterogeneities (I^2=86.3%, p<0.01), but no publication bias (the result was shown in Supplement figure 2b, p=0.317).

Diagnostic efficacy of ST-segment elevation recorded by IC-ECG

The pooled diagnostic efficacy is shown in Table 2 and the forest pots are shown in Supplement figure 3. The SROC curve is shown in Figure 4a. All the included studies compared ST-segment elevation recorded by IC-ECG to reference standards. Among these 6 diagnostic studies, 5 studies[5, 12, 13, 15, 16] studied the diagnostic efficacy for myocardial injury or ischemia. The other one studied the diagnostic efficacy for myocardial viability[14]. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.83 (95%CIs 0.74-0.89), 0.87 (95% 0.79-0.93), 6.57 (95%CIs 4.01-10.76), 0.20 (95%CIs 0.13-0.29), and 33.37 (95%CIs 19.36-57.52) respectively. The AUC of SROC was 0.92 (95%CIs 0.89-0.94). There were heterogeneities (I^2=67%, p=0.024), but no publication bias (p=0.97, the result was shown in Supplement figure 4).

Meta-regression and heterogeneities analysis of the diagnostic studies

The Galbraith (radial) plot[23] for diagnostic studies is shown in Figure 4b. Abaci's study [14] was located outside the 95% boundaries in the Galbraith plot, indicating that this study was the source of heterogeneities. We also performed meta-regression and the results are shown in Supplement table 2. Significant heterogeneities were found when year of publication was 2003, location was Turkey, and reference standard was echocardiogram. These results all indicated that Abaci's study was the main source of heterogeneities. After omitting Abaci's study, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.78 (95%CIs 0.72-0.84), 0.89 (95% 0.82-0.94), 7.4 (95%CIs 4.40-12.30), 0.24 (95%CIs 0.19-0.32), and 30 (95%CIs 16-56) respectively. The AUC of SROC was 0.86 (95%CIs 0.82-0.88), and I^2=0%. The results of diagnosis were also the source of heterogeneities. There were 3 studies[5, 12, 15] studied the diagnostic efficacy for myocardial injury. The pooled sensitivity and specificity of these 3 studies were 0.76(0.70-0.83) and 0.92(0.87-0.96), respectively.

Quality assessment

Results of quality assessment adapted from Downs-Black criteria were shown in Supplement table 3. Studies could reach the maximum of 27 points, but no study reached this limit. Only 3 studies[6, 7, 11] reported the confounders. 2 studies[6, 12] did not report the adverse events. Most of the studies reported the characteristics of patients lost to follow-up, except 2 studies[9, 11]. We could hardly evaluate the external validity of all the studies, because none of them described the proportion of the source population from which the patients are derived. No studies tried to blind

study subjects to the intervention they received, while 4 studies[6-8, 10] blinded reviewers to the results of measurements between different groups. No studies had randomized design. Only 2 studies [7, 11] performed adjustment for confounders in the analysis of main outcomes, and 3 studies [7, 8, 12] reported the numbers of patients lost to follow-up.

Results of quality assessment adapted from QUADAS tool were shown in Supplement table 4. All the studies clearly described the methods. No studies described whether they blinded reviewers to the results of IC-ECGs, while 3 studies [12-14] blinded reviewers to the results of reference standards. Only 2 studies[12, 14] reported the intermediate results, and 2 studies[5, 12] explained the withdrawals.

Discussion

Our results from the meta-analysis of observational studies indicated that ST-segment elevation recorded by IC-ECG after PCI procedures for stable angina patients linked to worse MACE outcomes. For angina or NSTEMI patients, ST-segment elevation was significantly associated with higher risk of myocardial infarction during follow-up, but not cardiac death nor revascularization. ST-segment resolution recorded by IC-ECG after PCI procedures for STEMI patients was significantly associated with increased EF during follow-up. But ST-segment elevation during PCI procedures did not significantly link to increased or decreased EF. After meta-regression analysis, ST-segment elevation recorded by IC-ECG showed good diagnostic efficacy for myocardial injury or ischemia.

ST-segment shift pattern recorded by ECG during acute myocardial infarction was

reported 100 years ago [27]. And ST-segment deviation recorded by surface ECG was a part of the universal definition of myocardial infarction[28]. However, surface ECG was not reliable for detecting local myocardial ischemia during PCI procedures in real time. In this case, IC-ECG was more reliable and sensitive for detecting ischemia[29]. Moreover, impaired microvascular perfusion during PCI might lead to periprocedural myocardial infarction, indicating worse outcomes. IC-ECG could detect local ischemia, which was found to be well associated with impaired microvascular perfusion[10]. Although there were several invasive diagnostic tools for guiding PCI, IC-ECG appeared to be potential tools for detecting myocardial ischemia in real time and guiding PCI.

The results from this meta-analysis indicated that ST-segment elevation recorded by IC-ECG after PCI procedure was significantly associated with worse MACE outcomes and higher risk of myocardial infarction in angina or NSTEMI patients, but not significantly associated with cardiac death nor revascularization. Although there were trends that the risks of cardiac death and revascularization were higher when ST-segment elevation was observed, more cases might be needed to prove this hypothesis. ST-segment elevation recorded by IC-ECG might be observed when higher pressure or longer duration balloon inflation was performed, indicating local ischemia. Local myocardial ischemia could be confirmed by testing myocardial biomarkers. Interestingly, IVUS guided stent overexpansion was associated with higher periprocedural creatine kinase-MB isoenzyme level, but lower risk of target lesion revascularization and mortality at 1 year[30]. Therefore, IC-ECG might provide useful information for guiding stent expansion[10]. Moreover, Ikenaga found more plaque

rupture and vulnerable plaque when ST-segment elevation was observed on IC-ECG[10]. IC-ECG could help to distinguish the plaque, and might be a potential tool for guiding PCI.

According to our meta-analysis, EF was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG in STEMI patients. ST-segment resolution on surface ECG which was observed 90 minutes after the initial therapy was found to be significantly associated with smaller infarct size and fewer deaths[31]. But surface ECG could not explore some small infarct zone sometimes[8]. Furthermore, restoration of coronary flow didn't mean normal myocardial perfusion nor better outcomes[32]. IC-ECG could provide real time ST-segment information, and was found to be well associated with microvascular obstruction and infarct size[6]. In our meta-analysis, ST-segment resolution recorded by IC-ECG was significantly associated with higher EF, meaning better recovery of heart function. This finding was similar to previous studies. In the subgroup of ST-segment elevation, there were heterogeneities between 2 studies. In Hishikari's study[7], ST-segment elevation recorded by IC-ECG was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's study[9], the result was different in anterior myocardial infarction patients. The possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI procedure might indicate prolonged local myocardial ischemia and worse outcome, as we described above. The result of Hishikari's study that lower EF was observed in ST-

segment elevation group, was one of these evidence. On the other hand, there might be myocardium stun after acute myocardial infarction[33]. The results of Yajima's study showed that ST-segment elevation recorded by IC-ECG after balloon inflation could predict myocardial viability and better outcomes[9]. These findings showed that IC-ECG might help to optimize PCI procedure by providing real time information, which could predict clinical outcomes.

After heterogeneities analysis and omitting 1 study, the pooled sensitivity was 0.78 (95%CIs 0.72-0.84), and specificity was 0.89 (95% 0.82-0.94) for diagnosing myocardial injury or ischemia. And the AUC of SROC was 0.86 (95%CIs 0.82-0.88). Although the pooled likelihood ratios [7.4 (95%CIs 4.40-12.30) for positive, and 0.24 (95%CIs 0.19-0.32) for negative likelihood ratios] or diagnostic odds ratio [30 (95%CIs 16-56)] were not very satisfactory, the results still indicated that IC-ECG had good diagnostic efficacy. These results indicated that IC-ECG could be used for diagnosing myocardial injury or ischemia. Comparing to surface ECG, IC-ECG had higher diagnostic efficacy. Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be easily performed and produce real time information. Although Abaci's study was omitted after meta-regression analysis, this study still produced important results. Like Yajima's study which was mentioned above, Abaci's study recorded IC-ECG after balloon inflation, not PCI procedures. Both of these 2 studies found a good correlation between ST-segment elevation during PCI procedures and myocardial viability. In short, IC-ECG had potential value for guiding PCI.

The strengths of our study were the large number of patients analyzed. However,

there were limitations to our study. First, limited by the published studies, we could only perform meta-analysis of observational studies. Second, not all the included studies performed blind methods, adjustments for confounders, or reports of patients lost to follow-up. Thus the results of quality assessment were not so satisfactory. Third, there were some heterogeneities of our results. But after heterogeneities analysis, these heterogeneities could be eliminated or explained. Forth, we did not perform sensitivity analysis of the timing when the IC-ECG was recorded, limited by the number of studies. But we found that recording IC-ECG in different phases of PCI procedures might produce different information which might help decision making. Further researches should consider the correlation between the timing when the IC-ECG was recorded and clinical outcomes.

Conclusions

IC-ECG had good diagnostic efficacy for local myocardial injury, and could predict clinical outcomes, which could be easily performed and produce real time information during and after PCI procedures. IC-ECG could be an alternative tool for guiding PCI.

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Contributorship Statement

Design and Planning Pan Yizhi MD, PhD

Data collection Huang Jiankai, MD, PhD; Fan Jun, MD, PhD

Data analysis Li Weiji, MD, PhD; Chen Pingan, MD, PhD; He Jialin, MBBS

Statistics and Conduct Li Weiji, MD, PhD; He Jialin, MBBS

Drafting article and Reporting Li Weiji, MD, PhD; He Jialin, MBBS; Fan Jun, MD, PhD

Guarantor Pan Yizhi MD, PhD

Ethics committee approval

We do not need ethics committee approval for our study because it is meta-analysis and we did not access primary patient/animal data nor interact with any patients/animals. We collected and synthesized data from previous studies published on MEDLINE database.

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Not applicable.

Disclosure

None.

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Figure legends

Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during follow-up, but was not significantly associated with cardiac death nor revascularization. OR, odds ratio; CI, confidence interval; IC-ECG, intracoronary electrocardiogram; MACE, major adverse cardiac event.

Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. WMD, weighted mean difference; CI, confidence interval; IC-ECG, intracoronary electrocardiogram.

Figure 4 The SROC curve of ST-segment elevation recorded by IC-ECG and the Galbraith (radial) plot for the diagnostic studies. The SROC curve and the AUC showed a good diagnostic accuracy for ST-segment elevation recorded by IC-ECG. And the Galbraith plot showed that Abaci's study was the main source of heterogeneities. The plots with numbers represented the studies included in the analysis. ① Balian, et al, 2011; ② Abaci, et al, 2003; ③ FIESTA, 2018; ④ Balian, et al, 2006; ⑤ Wang, et al,

2011; ⑥ Vassilev, et al, 2016. SENS, sensitivity; SPEC, specificity; SROC, summary receiver-operating-characteristic; AUC, areas under the SROC curves; IC-ECG, intracoronary electrocardiogram.

Tables

Studies	Study design	No. of cases	Male (%)	Age (years old)	Follow-up (months)	Reference standards
Ikenaga, et al. 2018, Japan[10]	Cohort study, single center	84	36.8	67.4±9.9	12	N/A
Wong, et al. 2013, Australia[6]	Cohort study, single center	64	82.8	61.0±10.0	3	N/A
Hishikari, et al. 2016, Japan[7]	Cohort study, single center	111	73.9	68.8±12.6	35*	N/A
Uetani, et al. 2009 Japan[11]	Case-control study, single center	339	66.4	69.7±8.6	In hospital	N/A
Balian, et al. 2005, Italy[8]	Cohort study, single center	50	84.0	59.3±11.0	6	N/A

Table 1 The characteristics of included studies.

Yajima, et al. Japan[9]	2001,	Cohort study, single center	65	75.4	61.3±7.0	1	N/A
Balian, et al. Italy[12]	2006,	Cohort study, single center	108	87.3	61.7±10.0	12±5	Surface ECG
Balian, et al. Italy[13]	2011,	Diagnostic study	48	52.0	65.0±9.0	N/A	FFR
Abaci, et al. Turkey[14]	2003,	Diagnostic study	71	84.5	54.0±11.0	N/A	Low-dose dobutamine echocardiography
FIESTA. Bulgaria[5]	2018,	Diagnostic study	37	69.0	65.0±10.0	N/A	FFR
Wang, et al. China[15]	2011,	Diagnostic study	86	67.4	54.5±10.2	N/A	Troponin T
Vassilev, et al. Bulgaria[16]	2016,	Diagnostic study	135	59.2	65.1±10.0	N/A	Troponin I

* The median followed-up period of this study was 35 months (28-40 months).

N/A, not available. ECG, electrocardiogram. FFR, fractional flow reserve.

Table 2 Summary results of meta-analysis of diagnostic studies

Studies and year of publication	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio
Vassilev, et al. 2018	0.78(0.67-0.86)	0.86(0.75-0.94)	5.73(2.97-11.03)	0.26(0.17-0.40)	22.13(8.82-55.52)
Wang, et al. 2011	0.77(0.60-0.90)	0.94(0.84-0.99)	13.11(4.31-39.89)	0.24(0.13-0.45)	54.00(13.21-220.78)
Balian, et al. 2006	0.74(0.60-0.85)	0.95(0.86-0.99)	14.31(4.70-43.59)	0.27(0.17-0.44)	52.18(13.90-195.87)
FIESTA. 2018	0.88(0.64-0.99)	0.75(0.51-0.91)	3.53(1.62-7.69)	0.16(0.04-0.59)	22.50(3.76-134.65)
Abaci, et al. 2003	0.95(0.85-0.99)	0.75(0.48-0.93)	3.78(1.61-8.86)	0.07(0.02-0.23)	52.00(10.26-263.61)

Balian, et al. 2011	0.81(0.61-0.93)	0.86(0.65-0.97)	5.92(2.04-17.24)	0.22(0.10-0.50)	26.60(5.59-126.60)
Summary	0.83(0.74-0.89)	0.87(0.79-0.93)	6.57(4.01-10.76)	0.20(0.13-0.29)	33.37(19.36-57.52)

All the results were reported with 95% confidence intervals.

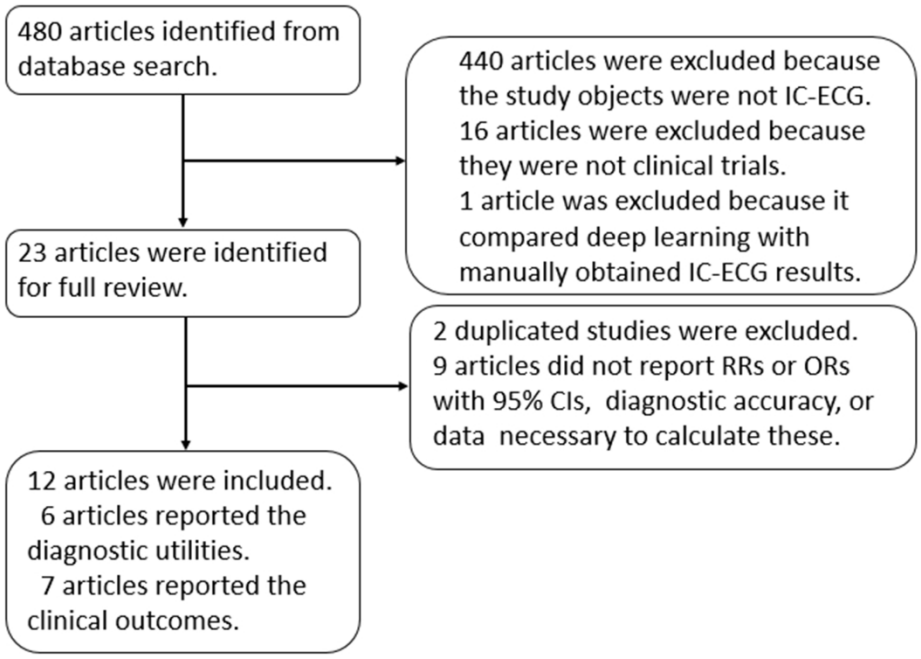

Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

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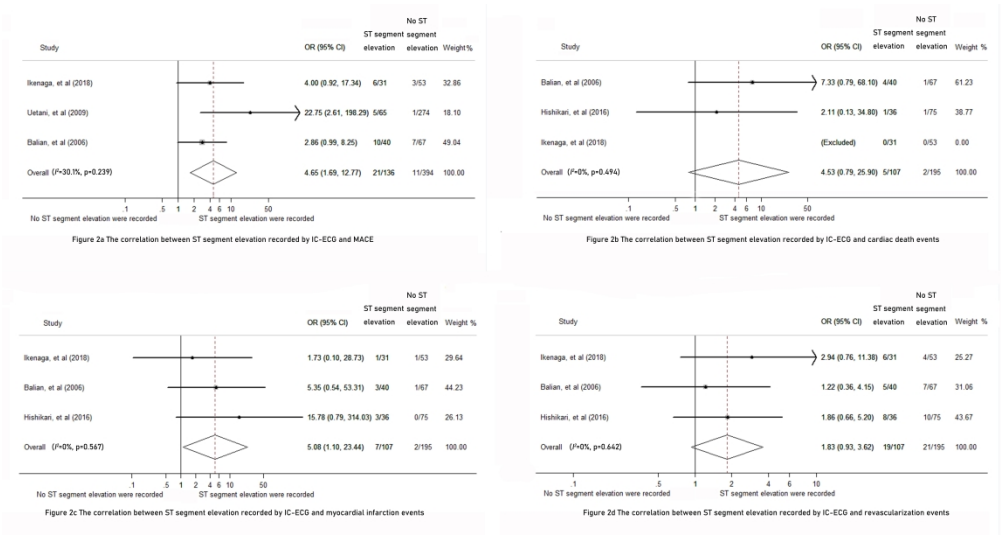

Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during follow-up, but was not significantly associated with cardiac death nor revascularization. OR, odds ratio; CI, confidence interval; IC-ECG, intracoronary electrocardiogram; MACE, major adverse cardiac event.

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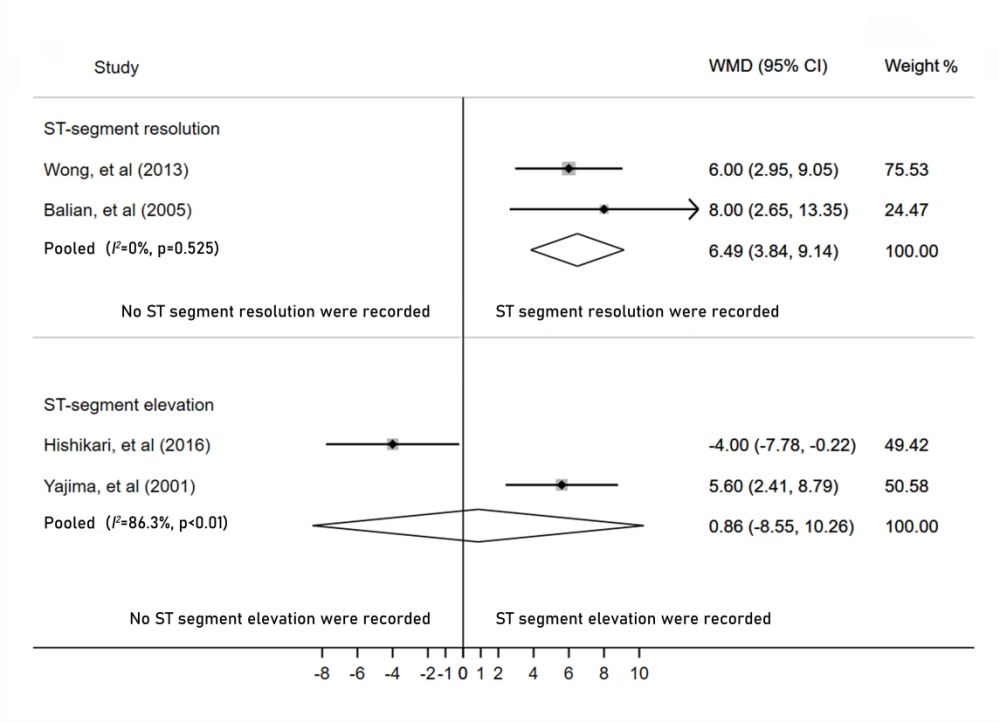

Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. WMD, weighted mean difference; CI, confidence interval; IC-ECG, intracoronary electrocardiogram.

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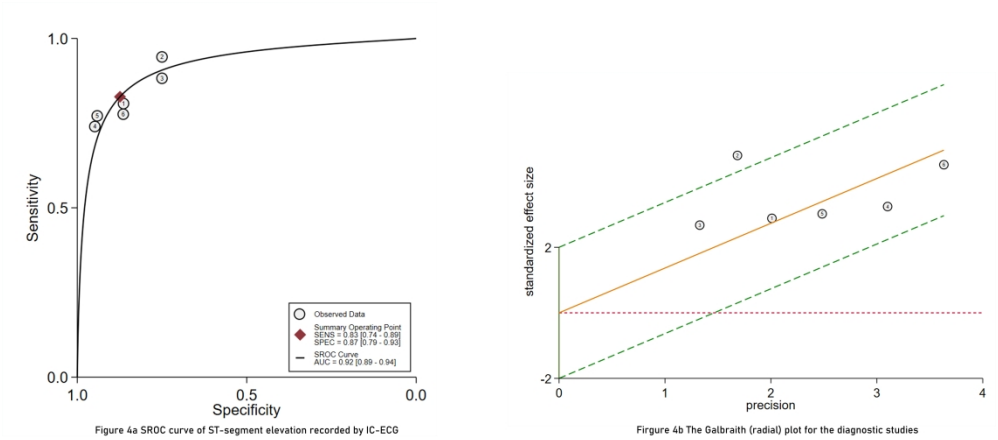

Figure 4 The SROC curve of ST-segment elevation recorded by IC-ECG and the Galbraith (radial) plot for the diagnostic studies. The SROC curve and the AUC showed a good diagnostic accuracy for ST-segment elevation recorded by IC-ECG. And the Galbraith plot showed that Abaci's study was the main source of heterogeneities. The plots with numbers represented the studies included in the analysis. ① Balian, et al, 2011; ② Abaci, et al, 2003; ③ FIESTA, 2018; ④ Balian, et al, 2006; ⑤ Wang, et al, 2011; ⑥ Vassilev, et al, 2016. SENS, sensitivity; SPEC, specificity; SROC, summary receiver-operating-characteristic; AUC, areas under the SROC curves; IC-ECG, intracoronary electrocardiogram.

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SUPPLEMENTAL MATERIAL

Supplement Table 1 Characteristic of included studies.

Studies	Inclusion criteria	Exclusion criteria	Clinical endpoints
Ikenaga, et al. 2018, Japan[10]	Patients with stable angina pectoris who underwent elective PCI for a single, native, de novo coronary lesion and performed FD-OCT and IC-ECG both at baseline and after the procedure in this study.	(i) acute coronary syndrome; (ii) elevated preprocedural cardiac biomarker; (iii) reduced renal function (Estimated glomerular filtration rate <30 mL/min per 1.73m2). Lesion-related exclusion criteria were the vessels within a myocardial territory of previous MI, the left main trunk, ostium lesions, extremely tight lesions or tortuous vessels where we	Major adverse cardiac event (MACE), which was defined as cardiac death, MI, repeat revascularization and/or hospitalization for heart failure.

		expected difficulty in advancing soft-tip guidewire or the FD-OCT catheter, severe calcified lesions needed for debulking device, target vessel reference diameter of ≥4mm expected limitation in FD-OCT evaluation and angiographic evidence of coronary dissection or major side branch (>1mm) occlusion after the procedure.
Wong, et al. 2013, Australia[6]	Patients with acute STEMI who underwent primary-PCI.	patients aged <18 years, previous myocardial infarction in the same territory, The relationship between intracoronary ST-segment resolution and MVO assessed

		contraindications to CMR (e.g., claustrophobia) and contraindication to gadopentetate dimeglumine (e.g., known hypersensitivity to gadopentetate dimeglumine or creatinine clearance ⩽ 60 mL/min/1.73 m2).	by CMR 4 days after primary-pacemaker implantation or PCI.
Hishikari, et al. 2016, Japan[7]	Patients' symptoms of coronary ischemia that were worsening or occurring at rest for more than 10 min within the past 12 hours, unequivocal changes on an	(1) age<21 years, (2) STEMI, (3) history of MI, (4) history of PCI, (5) renal insufficiency with a baseline serum creatinine level >1.8 mg/dL (133 lmol/L),	In hospital: ventricular arrhythmias, congestive heart failure, cardiogenic shock, and cardiac death. Follow-up: Adverse events included fatal

	admission ECG elevated cardiac biomarkers and no contraindication for PCI	(6) multivessel CAD or left main CAD, (7) patients in whom the absence of significant CAD or culprit lesion could not be identified according to the angiogram, and (8) major (>1.5 mm) side branch occlusion after PCI.	arrhythmias, cardiac death, nonfatal MI, revascularization or congestive heart failure requiring hospitalization.
Uetani, et al. 2009 Japan[11]	Consecutive patients who underwent apparently successful elective coronary stent implantations. All had angina, documented myocardial ischemia, or both.	1) emergency coronary angioplasty within 24 h of onset; 2) elevated pre-procedural cardiac biomarker; 3) active congestive heart failure; 4) severe lesion	Post-procedure cardiac biomarkers and in hospital major adverse cardiac event, which was defined as cardiac death and MI.

		characteristics not suitable for soft-tip guidewire; 5) angioplasty with debulking device (directional coronary atherectomy or rotational atherectomy); 6) Thrombolysis In Myocardial Infarction (TIMI) flow grade 1 to 2 of target vessel at the end of procedure; and 7) multivessel stenting in a single procedure.
Balian, et al. 2005, Italy[8]	Absence of cardiogenic shock, adequacy of echocardiographic window, IRA occlusion (TIMI flow	Patients with previous AMI, ventricular conduction disturbances on standard ECG, Left ventricular ejection fraction and infarct zone wall motion score index.

	grade 0-1) or patency (TIMI flow grade 2) with a severe (>90%) stenosis, and a successful primary stenting.	or ventricular pacing were.	
Yajima, et al. 2001, Japan[9]	Patients with a first episode of anterior myocardial infarction underwent emergency coronary angioplasty within 12 hours of onset.	contraindication of coronary angiogram, >50% stenosis in the left main coronary artery, >75% stenosis in another major coronary artery, prior myocardial infarction, cardiogenic shock, cardiomyopathy, and right or left bundle branch block on the ECG.	coronary events, clinical outcomes, left ventriculogram measurements and myocardial viability

Balian, et al. 2006, Italy[12]	Men and women who were at least 18 years old, had normal CK-MB and cardiac troponin I (cTnI) values before the procedure and were in stable condition, without angina in the previous 48 hours. Further criteria for inclusion were that the PCI procedure was successful and an optimal final result was obtained.	Unstable patients, patients with ventricular conduction disturbances on standard ECG or ventricular pacing, and those who had procedural complications were excluded.	Adverse events included death, nonfatal MI, or a new coronary revascularization procedure. Major coronary events included death or nonfatal MI.
Balian, et al. 2011, Italy[13]	Patients undergoing elective coronary angiography with single-vessel intermediate stenosis (40–70% diameter narrowing) on	prior ST segment elevation myocardial infarction, prior coronary revascularization, ostial stenosis, presence of left	N/A

	quantitative assessment were considered for this study.	bundle branch block, non-sinus rhythm or paced rhythm in resting ECG and a contraindication to adenosine infusion. Patients who were taking digitalis or had ST/T wave abnormalities that precluded the interpretation of ischemic ECG were also excluded.	
Abaci, et al. 2003, Turkey[14]	Recent (<1 month) Q-wave MI; angiographically documented regional wall motion abnormality; single, non-occlusive significant stenosis (⩾70% by quantitative	Patients with poor acoustic window, postinfarction angina, active congestive heart failure, bundle branch block, atrial fibrillation, valvular disease,	N/A

	measurements) in the IRA; and scheduled revascularization of the IRA for angiographic and clinical reasons.	significant stenosis in the non-IRA, and collateral filling to the IRA.
FIESTA. 2018, Bulgaria[5]	Patients with stable or unstable angina were included. The inclusion criterion was angiographic bifurcation lesions in a native coronary artery with a diameter ⩾2.5 mm and ⩽4.5 mm and an side branch diameter ⩾2.0 mm.	patients with ST-segment elevation myocardial infarction and those with non-cardiac comorbid conditions with a life expectancy of less than one year. In addition, patients with left main coronary artery stenosis, total occlusion, lesion of interest located at an infarct-related artery, subjects with

		LVEF <30%, subjects with a moderate or severe degree of valvular heart disease or primary cardiomyopathy and patients with bundle branch blocks, and atrial fibrillation/flutter with no identifiable isoelectric line were excluded.	
Wang, et al. 2011, China[15]	Patients were included if they (1) received elective PCI for single vessel; (2) had unstable angina, which did not onset within 48 hours, with normal CK-MB or	Patients were excluded if they (1) had increased CK-MB or troponin T before PCI; (2) had intraventricular block, ventricular escape, and atrial	N/A

	troponin T before PCI; (3) had ideal results during the procedure.	fibrillation found on ECG; (3) had complication occurred during the procedures, including slow flow, no flow, stent thrombosis, acute coronary occlusion, and perforation.	
Vassilev, et al. 2016, Bulgaria[16]	At least 18 years old, with stable or unstable angina, angiographic bifurcation lesions located in a native coronary artery with diameter of ⩾ 2.5 mm and ⩽ 4.5 mm and side branch with diameter of ⩾ 2.0 mm.	patient with ST-segment elevation myocardial infarction and those with non-cardiac co-morbid conditions with life expectancy <1 year. The following patients were also excluded: 1) left main coronary	N/A

artery stenosis, 2) total occlusion before occurrence of SB, 3) lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5) subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6) patients with bundle branch blocks, atrial fibrillation patient with ST-segment elevation myocardial infarction and those

with non-cardiac co-morbid conditions with life expectancy <1 year. The following patients were also excluded: 1) left main coronary artery stenosis, 2) total occlusion before occurrence of SB, 3) lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5) subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6)

	patients with bundle branch blocks, atrial fibrillation/flutter with no identifiable isoelectric line.

PCI, percutaneous coronary intervention. FD-OCT, frequency-domain optical coherence tomography. IC-ECG, intracoronary electrocardiogram. CAD, coronary artery disease. MI, myocardial infarction. STEMI, ST-segment elevation myocardial infarction. MVO, microvascular obstruction. CMR, cardiac magnetic resonance. ECG, electrocardiogram. FFR, fractional flow reserve. IRA, infarct-related artery. TIMI, thrombolysis in myocardial infarction. CK-MB, creatine kinase-myoglobin. LVEF, left ventricular ejection fraction.

Supplement Table 2 Meta regression analysis for the diagnostic studies.

Variables	Category	LRT chi-square	P value	I^2	95%CI of I^2
Year of publication	2003	6.51	0.04	69	(31, 100)
	2006	2.38	0.30	16	(0, 100)
	2011	0.97	0.61	0	(0, 100)

	2016	1.20	0.55	0	(0, 100)
	2018	1.50	0.47	0	(0, 100)
Location	Bulgaria	2.03	0.36	1	(0, 100)
	China	1.61	0.45	0	(0, 100)
	Italy	1.49	0.47	0	(0, 100)
	Turkey	6.51	0.04	69	(31, 100)
Golden standards	ECG	2.38	0.30	16	(0, 100)
	Echocardiogram	6.51	0.04	69	(31, 100)
	FFR	0.98	0.61	0	(0, 100)
	Troponin	1.45	0.48	0	(0, 100)
Result of diagnosis	Myocardial injury	7.53	0.02	73	(41, 100)
	Myocardial ischemia	0.98	0.61	0	(0, 100)
	Myocardial viability	6.51	0.04	69	(31, 100)

LRT, likelihood ratio test. CI, confidence interval. ECG, electrocardiogram. FFR, fractional flow reserve.

Supplement Table 3 Quality assessment adapted from Downs-Black criteria for studies reported clinical outcomes.

Question	Ikenaga, et al. 2018	Wong, et al. 2013	Hishikari, et al. 2016	Uetani, et al. 2009	Balian, et al. 2005	Yajima, et al. 2001	Balian, et al.2006
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	No	Yes	Yes	Yes	No	No	No
6	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Yes	No	Yes	Yes	Yes	Yes	No
9	Yes	Yes	Yes	No	Yes	No	Yes
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes

11	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
12	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	No	No	No	No	No	No	No
15	Yes	Yes	Yes	No	Yes	No	No
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22	Yes	Yes	Yes	Yes	Yes	Yes	Yes

23	No	No	No	No	No	No	No
24	No	No	No	No	No	No	No
25	No	No	Yes	Yes	No	No	No
26	Unable to determine	Unable to determine	Yes	Unable to determine	Yes	No	Yes
Total score	18	18	21	18	19	16	17

Supplement Table 4 Quality assessment adapted from QUADAS tool for diagnostic studies.

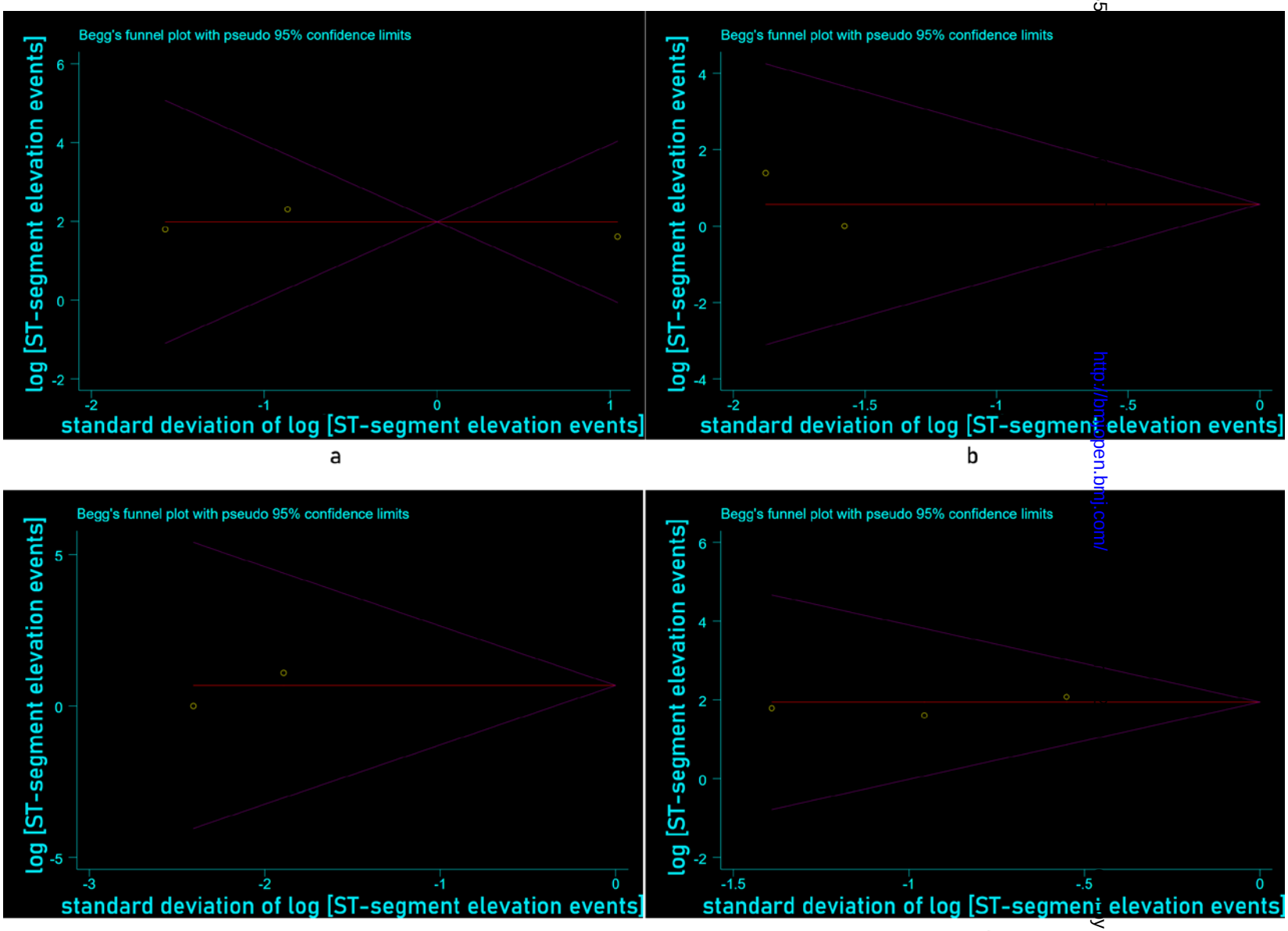
Question	Balian, et al. 2006	Balian, et al. 2011	Abaci, et al. 2003	FIESTA. 2018	Wang, et al. 2011	Vassilev, et al. 2016
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes	Yes	Yes

2. Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes	Yes
6. Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the reference standard independent of the index test (i.e. the index test did not	Yes	Yes	Yes	Yes	Yes	Yes

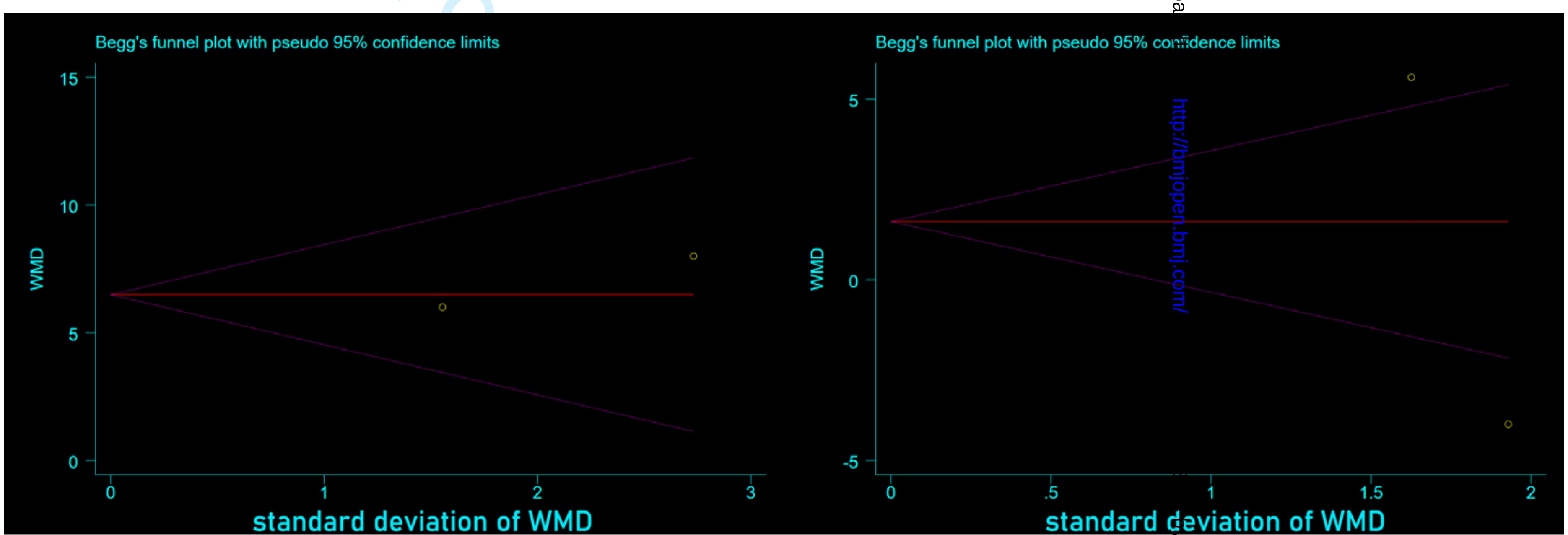
form part of the reference standard)?						
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Unaware	Unaware	Unaware
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Unaware	Unaware	Unaware	Unaware	Unaware	Unaware
12. Were the same clinical data available	Yes	Yes	Yes	Yes	Yes	Yes

when test results were interpreted as would be available when the test is used in practice?						
13. Were uninterpretable/ intermediate test results reported?	Yes	Unaware	Yes	Unaware	Unaware	Unaware
14. Were withdrawals from the study explained?	Yes	Unaware	Unaware	Yes	Unaware	Unaware

Supplemental Figures and Figure Legends



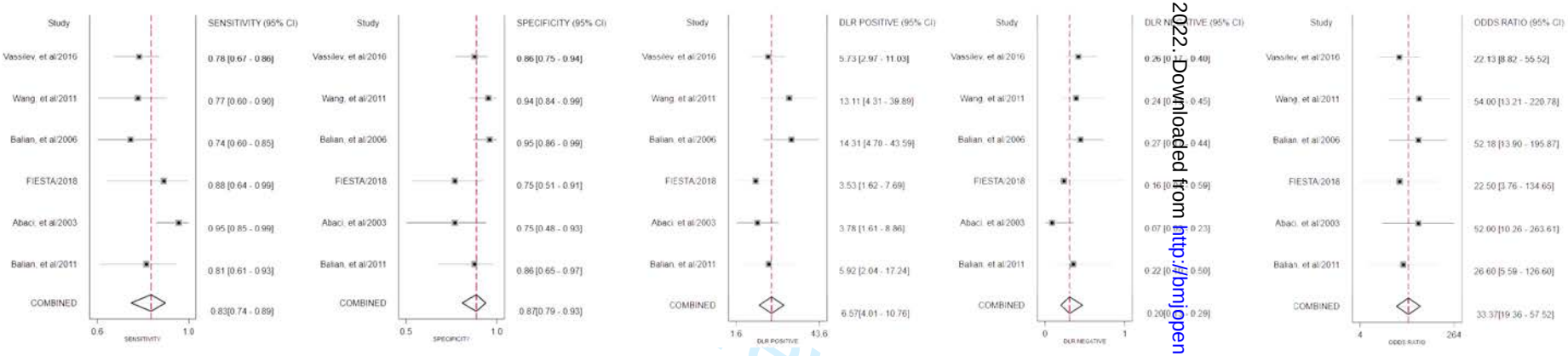
Supplement Figure 1 Publication bias assessment for studies reported clinical outcomes. Using Begg asymmetry test, we found no publication bias in the meta-analysis for the clinical outcomes of (a) major adverse cardiac event, (b) cardiac death, (c) myocardial infarction, and (d) revascularization, with p value= 0.602, 0.317, 0.317, and 0.602, respectively.



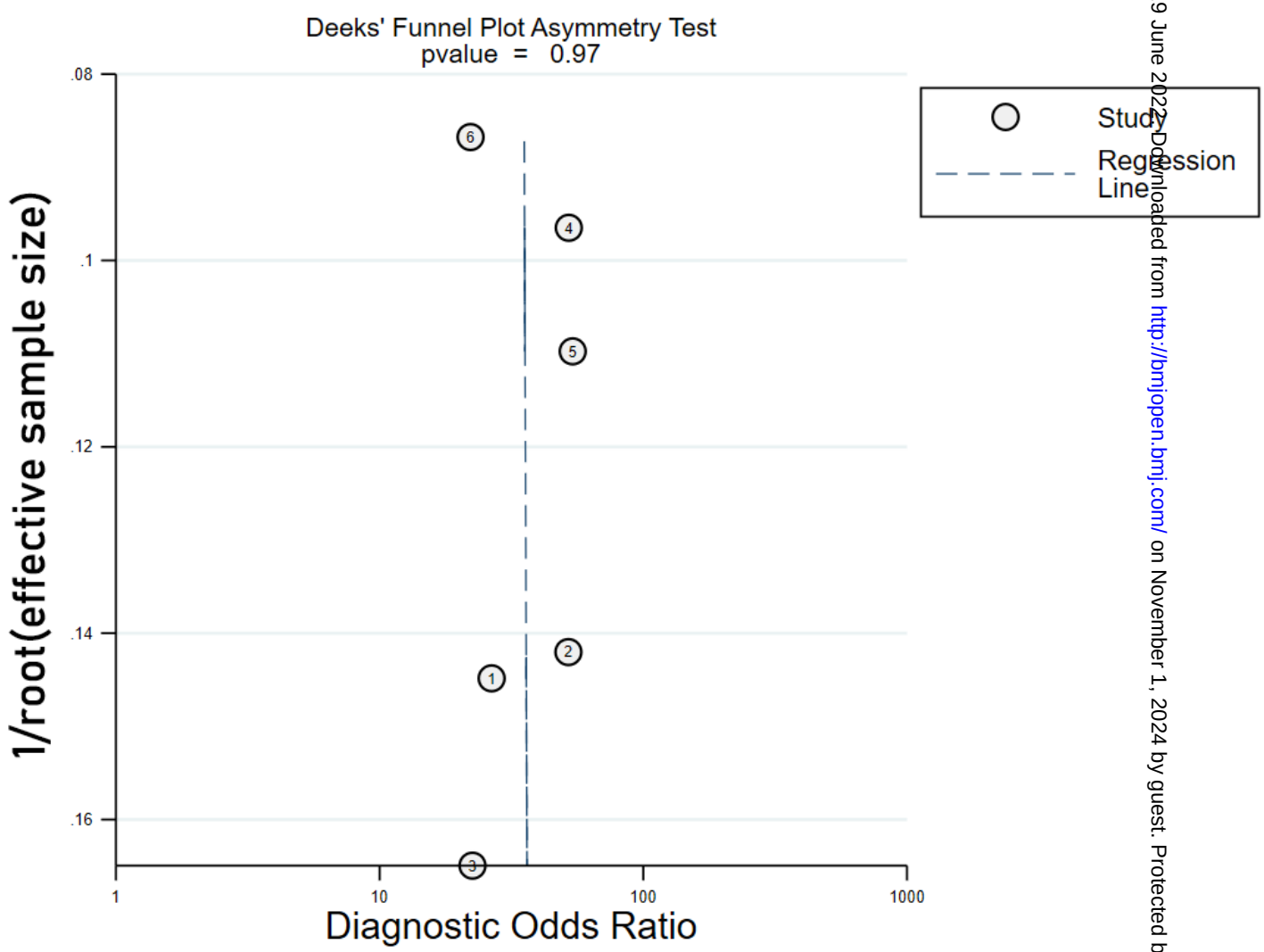
a b

Supplement Figure 2 Publication bias assessment for studies reported ejection fraction. Using Begg asymmetry test, we found no publication bias in the meta-analysis for (a) ST-segment resolution recorded by IC-ECG, and (b) ST-segment elevation. Both p values were 0.317. WMD,

weighted mean difference. IC-ECG, intracoronary electrocardiogram.



Supplement Figure 3 Forest plots of meta-analysis for diagnostic studies. The meta-analysis for diagnostic studies were performed by using random effect models with DerSimonian Laird methods. The pooled sensitivity was 0.83 (95%CIs 0.74-0.89), specificity was 0.87 (95% 0.79-0.93), positive likelihood ratio was 6.57 (95%CIs 4.01-10.76), negative likelihood ratio was 0.20 (95%CIs 0.13-0.29), and diagnostic odds ratio was 33.37 (95%CIs 19.36-57.52). DLR, diagnostic likelihood ratio. CI, confidence interval.



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Supplement Figure 4 Publication bias assessment for diagnostic studies. Using Deeks' asymmetry test, we found no publication bias and p=0.97. The plots with numbers represented the studies included in the analysis. ① Balian, et al, 2011; ② Abadi, et al, 2003; ③ FIESTA, 2018; ④ Balian, et al, 2006; ⑤ Wang, et al, 2011; ⑥ Vassilev, et al, 2016.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	The value of Intracoronary electrocardiogram in guiding percutaneous coronary intervention—a Meta-Analysis	Title Page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3-4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5-6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6
Study characteristics	17	Cite each included study and present its characteristics.	7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-12
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13
	23b	Discuss any limitations of the evidence included in the review.	16-17
	23c	Discuss any limitations of the review processes used.	16-17
	23d	Discuss implications of the results for practice, policy, and future research.	17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	17
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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The prognostic and diagnostic accuracy of intracoronary electrocardiogram recorded during percutaneous coronary intervention—a Meta-Analysis

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Disclaimers

Authors' statement of this article is not an official position of Guangzhou First People's Hospital, Guangzhou Medical University.

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There were no sources of support for this study.

Disclosure

Please refer to the ICMJE disclosure form we submitted.

Abstract

Objective

Intracoronary electrocardiogram (IC-ECG) recording has been shown to be sensitive and reliable for detecting myocardial viability and local myocardial ischemia in some studies. But IC-ECG is neither widely used during percutaneous coronary intervention (PCI) nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic and diagnostic accuracy of IC-ECG recorded during PCI.

Methods

Relevant studies were identified by searches of MEDLINE until June 19th, 2021. Observational and diagnostic studies which reported the prognostic or diagnostic accuracy of IC-ECG were included. Data were extracted independently by two authors. Summary estimates of clinical outcomes were obtained using a random effects model. Summary diagnostic accuracy was obtained by using a Bayesian bivariate random effects model.

Results

Of the 12 included studies, 7 studies reported the clinical outcomes (821 patients) and 6 studies reported the diagnostic accuracy (485 patients) of IC-ECG. The pooled odds ratios with 95% confidence intervals (CIs) of ST-segment elevation recorded by IC-ECG were 4.65 (1.69-12.77), 5.08 (1.10-23.44), 4.53 (0.79-25.90) and 1.83 (0.93-3.62) for major adverse cardiac events, myocardial infarction, cardiac death, and revascularization, respectively. The weighted mean difference were 6.49 (95%CIs

3.84-9.14) for ejection fraction when ST-segment resolution was recorded, and 0.86 (95%CIs -8.55-10.26) when ST-segment elevation was recorded. The pooled sensitivity and specificity of ST-segment elevation were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94) respectively.

Conclusions

These findings provide quantitative data supporting that IC-ECG had promising diagnostic ability for local myocardial injury, and could predict clinical outcomes.

Key words: intracoronary electrocardiogram, prognostic accuracy, diagnostic accuracy, meta-analysis.

Strengths and limitations of this study

Strengths

1. There were relatively large number of patients analyzed.

2. We used Bayesian meta-analysis to reduce the bias when assessing the diagnostic accuracy.

Limitations

1. Limited by the published studies, we could only perform meta-analysis of observational studies.

2. We did not perform sensitivity analysis of the timing when the IC-ECG was recorded, and different types of CADs, limited by the number of studies.

Introduction

Percutaneous coronary intervention (PCI) is a well-established therapeutic strategy for patients with coronary artery disease (CAD). Except for coronary angiography (CAG), several invasive diagnostic tools, such as fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) are recommended for guiding PCI by the guidelines[1]. But these tools are not always available. In some cases, catheters or pressure wires, may not pass through the lesions or may be damaged when crossing the stents or calcified lesions [2-5]. Moreover, for some patients, the costs of these tools are important additional considerations.

Intracoronary electrocardiogram (IC-ECG) recording, with a guidewire functioning as a unipolar electrode, might be an alternative tool for guiding PCI. In some studies, the ST-segment elevation or resolution recorded by IC-ECG during or after PCI procedures have been shown to be sensitive and reliable for detecting myocardial viability, local myocardial ischemia, or microvascular obstruction [5-16]. But IC-ECG is neither widely used during PCI nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic and diagnostic accuracy of IC-ECG recorded during PCI.

Methods

The meta-analysis was conducted according to the checklist of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[17] and the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE)[18]. We performed a systematic search of relevant studies published through June 19th,

2021, in the MEDLINE database.

Search strategy

Accessing MEDLINE database, we performed a literature search for studies published until June 19th, 2021 using the following search terms and key words: ((intracoronary) AND (electrocardiogram OR ECG OR EKG)) AND (st segment). The search strategy is shown in Supplement table 1. We manually checked the reference lists of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) Published in the English language; (2) Had an observational study design; (3) Enrolled patients with CAD who were undergoing PCI; (4) Reported the clinical outcomes during follow-ups, such as major adverse cardiac events (MACEs), cardiac death, myocardial infarction, ejection fraction (EF), and repeat revascularization. (5) Reported the diagnostic accuracy of IC-ECG. (6) Presented estimates of odds ratios (ORs) with 95% confidence intervals (CIs) or reported data necessary to calculate these. Animal, autopsy, duplicated, and phantom studies were excluded. Moreover, studies would be excluded if IC-ECG was not one of the study objects.

Data extraction

From each retrieved article, two authors independently extracted the following data: name of the first author, year of publication, location where the study was performed, study design, number of cases, follow-up period, proportion of men, mean

or median age, inclusion criteria, exclusion criteria, reference standard, ORs or event rates, EF during following-up, and the diagnostic accuracy of IC-ECG. The true-positive, true-negative, false-positive, and false-negative rates were also estimated, using the data we extracted from the studies.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

We directly extracted ORs from each study, or indirectly estimated ORs by calculating event rates. And then we pooled ORs using a random-effects meta-analysis method. For EF, we pooled unstandardized mean difference using a random-effects meta-analysis method. Summary sensitivity and specificity with their 95% credibility intervals of IC-ECG were obtained by using Bayesian bivariate random effects meta-analysis[19-21]. Bayesian summary receiver-operating-characteristic (SROC) curves were constructed and the areas under the Bayesian SROC curves (AUC) were performed to assess the diagnostic accuracy of IC-ECG[20,21].

To perform quality assessment, two authors independently assessed the prognostic studies' qualities by using the Newcastle-Ottawa Scale (NOS)[22] and the diagnostic studies' qualities by using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) tool [23]. The NOS evaluated 3 parameters (selection, comparability, and outcome) divided across 8 items. Each item was scored from 0 to 1 star, except for comparability, which could be adapted to the specific topic of

interest to score up to 2 stars. Thus, the maximum score for each study was 9. Studies with <3 stars were at a high risk of bias and would be excluded. The QUADAS tool contained 14 questions which could be used for assessing the qualities of diagnostic studies. Disagreements were resolved by consensus.

Statistical heterogeneities between prognostic studies were evaluated with the I^2 statistic [24], which estimates the percentage of total variation across studies due to true between-study differences rather than chance, with I^2 values of 25, 50, and 75% representing low, medium, and high heterogeneities, respectively. We performed conflict of evidence analysis for diagnostic studies by extending the random effects distribution, using a scale mixture of normal distributions per random effect[20]. After splitting the studies' weighs, we could find out the heterogeneities if the posterior probabilities of studies were greater than 0.7. The Begg asymmetry tests[25] for studies which reported clinical outcomes were performed to assess the publication bias. P values that were less than 0.05 were considered statistically significant. Statistical analyses were carried out with STATA, version 16.0 (Stata Corp, College Station, Texas), and R statistical software with "bamdit" packages[20].

Results

Literature search

The details of search steps are shown in Figure 1. We identified and screen 480 articles from our preliminary search. After screening abstracts, 440 articles were excluded because the study objects were not IC-ECG. 16 articles were excluded because they were not clinical trials. Bigler's study compared deep learning with

manually obtained IC-ECG results[26], and was excluded. 23 articles were identified for full review. Among these articles, 2 duplicated studies were excluded. 9 articles were excluded because they did not report ORs, diagnostic accuracy, or data necessary to calculate these. Finally, there were 12 studies included in our meta-analysis. 7 studies reported the clinical outcomes and 6 studies reported the diagnostic accuracy of IC-ECG.

Study characteristics

The characteristics of included studies are shown in Table 1 and Supplement table 2. There were 7 cohort studies and 6 diagnostic studies in our meta-analysis. There were 1198 cases included in our meta-analysis totally. Among these cases, 821 cases and 485 cases were included in the meta-analysis for prognostic and diagnostic accuracy of IC-ECG respectively. The proportion of men was 68.8%. The inclusion criteria of the included articles were CAD patients, including stable or unstable angina pectoris, and myocardial infarction. The clinical outcomes reported in these studies were mainly MACEs, cardiac death, myocardial infarction, repeat revascularization, and EF. The reference standards reported in the diagnostic studies were varied, including FFR[5,13], echocardiogram[14], and troponin[12,15,16].

The correlation between clinical outcomes and ST-segment elevation recorded by IC-ECG

Pooled OR for MACE is shown in Figure 2a. The inclusion criteria of these studies were patients with angina and stable conditions. MACEs were defined as cardiac death, myocardial infarction, revascularization, and hospitalization for heart failure in

Ikenaga's study[10]. In Uetani's study[11] and Balian's study[12], MACEs were defined as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE (OR 4.65, 95%CIs 1.69-12.77). There were mild heterogeneities among studies (I^2=30.1%, p=0.239). And there was no publication bias (the result is shown in Supplement figure 1a, p=0.602).

Pooled ORs for cardiac death, myocardial infarction, and revascularization are shown in Figure 2b-2d. The inclusion criteria of these studies were patients with angina or non ST-segment elevation myocardial infarction (NSTEMI). In the meta-analysis for cardiac death, Ikenaga's study[10] was excluded because there were no events. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of myocardial infarction (OR 5.08, 95%CIs 1.10-23.44), but not cardiac death (OR 4.53, 95%CIs 0.79-25.90) nor revascularization (OR 1.83, 95%CIs 0.93-3.62). There were no heterogeneities among studies (cardiac death, I^2=0%, p=0.494; myocardial infarction, I^2=0%, p=0.567; revascularization, I^2=0%, p=0.642). And there were no publication bias (cardiac death, p=0.317; myocardial infarction, p=0.317; revascularization, p=0.602, and the results are shown in Supplement figure 1b-1d).

The correlation between EF and different results recorded by IC-ECG during follow-up

The correlation between EF and different results recorded by IC-ECG are shown in Figure 3. We divided the included studies into 2 subgroups according to the

different evaluation methods reported by the studies. One was ST-segment resolution, and the other one was ST-segment elevation. In the subgroup of ST-segment resolution, inclusion criteria were patients with ST-segment elevation myocardial infarction (STEMI). The pooled weighted mean difference (WMD) was 6.49, with 95%CIs 3.84-9.14. There were no heterogeneities (I2=0%, p=0.525). And there was no publication bias (the result is shown in Supplement figure 2a, p=0.317). The inclusion criteria of ST-segment elevation subgroup were patients with NSTEMI (Hishikari, et al[7]) or anterior myocardial infarction (Yajima, et al [9]) . The pooled WMD was 0.86, with 95%CIs -8.55-10.26. There were heterogeneities (I^2=86.3%, p<0.01), but no publication bias (the result is shown in Supplement figure 2b, p=0.317).

Diagnostic accuracy of ST-segment elevation recorded by IC-ECG

Abaci's study reported the diagnostic accuracy for myocardial viability[14], while the other 5 diagnostic studies reported the diagnostic accuracy for myocardial injury or ischemia. Therefore, we excluded Abaci's study when we performed Bayesian meta-analysis for diagnostic studies. The pooled diagnostic accuracy and the predictive posterior rates are shown in Supplement figure 3. The Bayesian SROC curve and the AUC are shown in Figure 4. The pooled sensitivity and specificity were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94), respectively. And predictive posterior sensitivity and specificity were 0.76 (95% credibility intervals 0.39-0.96) and 0.85 (95% credibility intervals 0.50-0.98), respectively. The AUC of Bayesian SORC was 0.65 (95% credibility intervals 0.56-0.69). After splitting the studies' weighs, there were no heterogeneities and the posterior

probabilities of studies were all smaller than 0.7. The posterior distributions of the component weights are shown in Supplement figure 4.

Quality assessment

Results of quality assessment adapted from NOS are shown in Supplement table 3. All the studies reached over 3 stars, but no study reached the maximum score. Considering all the studies included CAD patients, no study got scored in the fourth item of selection section. Only 3 studies[6,7,11] reported the confounders and were scored 2 stars in the comparability section. Two studies[9,11] reported the in-hospital outcomes and did not report the patients lost to follow-up, therefore, they were not scored in the second and third items of outcome section.

Results of quality assessment adapted from QUADAS tool are shown in Supplement table 4. All the studies clearly described the methods. No studies described whether they blinded reviewers to the results of IC-ECGs, while 3 studies[12-14] blinded reviewers to the results of reference standards. Only 2 studies[12,14] reported the intermediate results, and 2 studies[5,12] explained the withdrawals.

Discussion

Our results from the meta-analysis of observational studies indicated that ST-segment elevation recorded by IC-ECG after PCI procedures for stable angina patients linked to worse MACE outcomes. For angina or NSTEMI patients, ST-segment elevation was significantly associated with higher risk of myocardial infarction during follow-up, but not cardiac death nor revascularization. ST-segment resolution

recorded by IC-ECG after PCI procedures for STEMI patients was significantly associated with increased EF during follow-up. But ST-segment elevation during PCI procedures did not significantly link to increased or decreased EF. After Bayesian meta-analysis, ST-segment elevation recorded by IC-ECG showed promising diagnostic ability for myocardial injury or ischemia.

ST-segment shift pattern recorded by ECG during acute myocardial infarction was reported 100 years ago [27]. And ST-segment deviation recorded by surface ECG was a part of the universal definition of myocardial infarction[28]. However, surface ECG was not reliable for detecting local myocardial ischemia during PCI procedures in real time[29]. In this case, IC-ECG was more reliable and sensitive for detecting local ischemia[30]. For instance, in Vassilev's study, they found that when they pulled back the guidewire, the elevated ST-segment would suddenly normalize if the wire tip exited the border of ischemic territory[16]. Although IC-ECG was more sensitive than surface ECG when assessing left ascending artery and circumflex territory, It should be noted that IC-ECG was less sensitive when assessing right coronary artery territory[31,32]. On the other hand, impaired microvascular perfusion during PCI might lead to periprocedural myocardial infarction, indicating worse outcomes. IC-ECG could detect local ischemia, which was found to be well associated with impaired microvascular perfusion[10]. For instance, in Sato's study, the prolongation of ST-segment elevation time recorded by IC-ECG was associated with higher max-lipid core burden index 4mm detected by near-infrared spectroscopy with IVUS in stable angina patients, which might indicate distal embolization and microvascular disease[33].

The results from this meta-analysis indicated that ST-segment elevation recorded by IC-ECG after PCI procedure was significantly associated with worse MACE outcomes and higher risk of myocardial infarction in angina or NSTEMI patients, but not significantly associated with cardiac death nor revascularization. Although there were trends that the risks of cardiac death and revascularization were higher when ST-segment elevation was observed, more cases might be needed to prove this hypothesis. ST-segment elevation recorded by IC-ECG might be observed when higher pressure or longer duration balloon inflation was performed, indicating local ischemia. Local myocardial ischemia could be confirmed by testing myocardial biomarkers. Vassilev's study found that the maximal ST-segment elevation during inflation significantly correlated with final absolute ST-segment elevation and creatine kinase-MB isoenzyme increase post PCI, but not with troponin[16]. Interestingly, IVUS guided stent overexpansion was associated with higher periprocedural creatine kinase-MB isoenzyme level too, but lower risk of target lesion revascularization and mortality at 1 year[34]. Therefore, IC-ECG might provide useful information for guiding stent expansion[10]. Moreover, Ikenaga and Sato found more plaque rupture, vulnerable plaque or higher lipid core burden when ST-segment elevation was observed, even persisted on IC-ECG[10,33]. IC-ECG could help to distinguish the plaque, optimizing medical therapies or PCI strategies. For instance, we could use vasodilators, loading dose of statin, or embolic protection devices to reduce distal embolization[33]. And, Vassilev's studies found that IC-ECG had good correlation with FFR, which might be used in guiding bifurcation PCI procedures[5,16].

According to our meta-analysis, EF was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG in STEMI patients. ST-segment resolution on surface ECG which was observed 90 minutes after the initial therapy was found to be significantly associated with smaller infarct size and fewer deaths[35]. But surface ECG could not explore some small infarct zone sometimes[8]. Furthermore, restoration of coronary flow didn't mean normal myocardial perfusion nor better outcomes[36]. IC-ECG could provide real time ST-segment information, and was found to be well associated with microvascular obstruction and infarct size[6]. In our meta-analysis, ST-segment resolution recorded by IC-ECG was significantly associated with higher EF, meaning better recovery of heart function. This finding was similar to previous studies. In the subgroup of ST-segment elevation, there were heterogeneities between 2 studies. In Hishikari's study[7], ST-segment elevation recorded by IC-ECG was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's study[9], the result was different in anterior myocardial infarction patients. The possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI procedure might indicate prolonged local myocardial ischemia and worse outcome, as we described above. The result of Hishikari's study that lower EF was observed in ST-segment elevation group, was one of these evidences. On the other hand, there might be myocardium stun after acute myocardial infarction[37]. The results of Yajima's study showed that ST-segment elevation recorded by IC-ECG after balloon inflation

could predict myocardial viability and better outcomes[9]. These findings showed that IC-ECG might help to optimize PCI procedure by providing real time information, which could predict clinical outcomes.

The diagnostic studies included in our study reported 3 reference standards. After excluding Abaci's study, there were still 2 reference standards. And the reference standards (FFR and troponin) for diagnosing myocardial ischemia or injury were not perfect. Also, there were too few studies included in our meta-analysis. Considering these situations, we used Bayesian meta-analysis to assess the pooled diagnostic accuracy of IC-ECG. There were already several papers illustrated this method to reduce the bias which came from the different or imperfect reference standards[20,21,38,39]. The results of our Bayesian meta-analysis showed the promising diagnostic ability of IC-ECG for diagnosing myocardial ischemia or injury. Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be easily performed and produce real time information. Although Abaci's study was excluded when performing the meta-analysis, this study still provided important results. Like Yajima's study which was mentioned above, Abaci's study recorded IC-ECG after balloon inflation, not PCI procedures. Both of these 2 studies found a good correlation between ST-segment elevation and myocardial viability. In short, IC-ECG had potential value for guiding PCI.

The strengths of our study were the relatively large number of patients analyzed. And we used Bayesian meta-analysis to reduce the bias when assessing the diagnostic accuracy. However, there were limitations to our study. First, limited by the published

studies, we could only perform meta-analysis of observational studies. And the wide CIs of ORs were the results of low event rates reported in the studies, especially in the no ST-segment elevation group. Second, not all the included studies performed adjustments for confounders, or reports of patients lost to follow-up. Thus, the results of quality assessment were not so satisfactory. Third, there were varied and imperfect reference standards reported in the diagnostic studies. Therefore, we chose Bayesian meta-analysis to assess the pooled diagnostic accuracy, reducing the bias. Forth, we did not perform sensitivity analysis of the timing when the IC-ECG was recorded, and different types of CADs, limited by the number of studies. But in the meta-analysis of clinical outcomes, there were no heterogeneities or publication bias. These results indicated that different types of CADs had little influence on the ORs. And we found that recording IC-ECG in different phases of PCI procedures might produce different information which might help decision making. Further researches should consider whether the correlation between IC-ECG measures and clinical outcomes depend on the timing of the IC-ECG.

Conclusions

IC-ECG had promising diagnostic ability for local myocardial injury, and could predict clinical outcomes, which could be easily performed and produce real time information during and after PCI procedures. IC-ECG could be an alternative tool for guiding PCI when other invasive tools are not available.

Contributorship Statement

Design and Planning Pan Yizhi MD, PhD

Data collection Huang Jiankai, MD, PhD; Fan Jun, MD, PhD

Data analysis Li Weiji, MD, PhD; Chen Pingan, MD, PhD; He Jialin, MBBS

Statistics and Conduct Li Weiji, MD, PhD; He Jialin, MBBS

Drafting article and Reporting Li Weiji, MD, PhD; He Jialin, MBBS; Fan Jun, MD, PhD

Guarantor Pan Yizhi MD, PhD

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Registration and protocol

Our study was not registered, and we did not prepare a protocol according to the PRISMA-P statement.

Competing interests

The authors have declared that no competing interests exist.

Availability of data, code and other materials

Our study is meta-analysis and all the raw data were extracted from the studies published in MEDLINE database. All data relevant to the study are included in the article and uploaded as supplementary information. The original template data

collection forms, data extracted from included studies, data used for all analyses, and analytic code used in the study are not publicly available.

Ethics committee approval

We do not need ethics committee approval for our study because it is meta-analysis and we did not access primary patient/animal data nor interact with any patients/animals. We collected and synthesized data from previous studies published on MEDLINE database.

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Figure legends

Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during follow-up, but was not significantly associated with cardiac death nor revascularization. OR, odds ratio; CI, confidence interval; IC-ECG, intracoronary electrocardiogram; MACE, major adverse cardiac event.

Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. WMD, weighted mean difference; CI, confidence interval; EF, ejection fraction; IC-ECG, intracoronary electrocardiogram.

Figure 4 The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and the posterior distribution of AUC. Each circle identifies the true positive rate versus the false positive rate of each study. The AUC was 0.65 (95% credibility intervals 0.56-0.69). TPR, true positive rate; FPR, false positive rate; SROC, summary receiver-

operating-characteristic; AUC, areas under the Bayesian SROC curve; IC-ECG, intracoronary electrocardiogram.

Tables

Studies	Study design	No. of cases	Male (%)	Age (years old)	Follow-up (months)	Reference standards
Ikenaga, et al. 2018, Japan[10]	Cohort study, single center	84	36.8	67.4±9.9	12	N/A
Wong, et al. 2013, Australia[6]	Cohort study, single center	64	82.8	61.0±10.0	3	N/A
Hishikari, et al. 2016, Japan[7]	Cohort study, single center	111	73.9	68.8±12.6	35*	N/A
Uetani, et al. 2009 Japan[11]	Cohort study, single center	339	66.4	69.7±8.6	In hospital	N/A
Balian, et al. 2005,	Cohort study, single	50	84.0	59.3±11.0	6	N/A

Table 1 The characteristics of included studies.

Italy[8]		center					
Yajima, et al. Japan[9]	2001,	Cohort study, single center	65	75.4	61.3±7.0	1	N/A
Balian, et al. Italy[12]	2006,	Cohort study and diagnostic study, single center	108	87.3	61.7±10.0	12±5	Troponin I
Balian, et al. Italy[13]	2011,	Diagnostic study	48	52.0	65.0±9.0	N/A	FFR
Abaci, et al. Turkey[14]	2003,	Diagnostic study	71	84.5	54.0±11.0	N/A	Low-dose dobutamine echocardiography
FIESTA. Bulgaria[5]	2018,	Diagnostic study	37	69.0	65.0±10.0	N/A	FFR
Wang, et al.	2011,	Diagnostic study	86	67.4	54.5±10.2	N/A	Troponin T

China[15]						
Vassilev, et al. 2016, Bulgaria[16]	Diagnostic study	135	59.2	65.1±10.0	N/A	Troponin I

* The median followed-up period of this study was 35 months (28-40 months).

N/A, not available. FFR, fractional flow reserve.

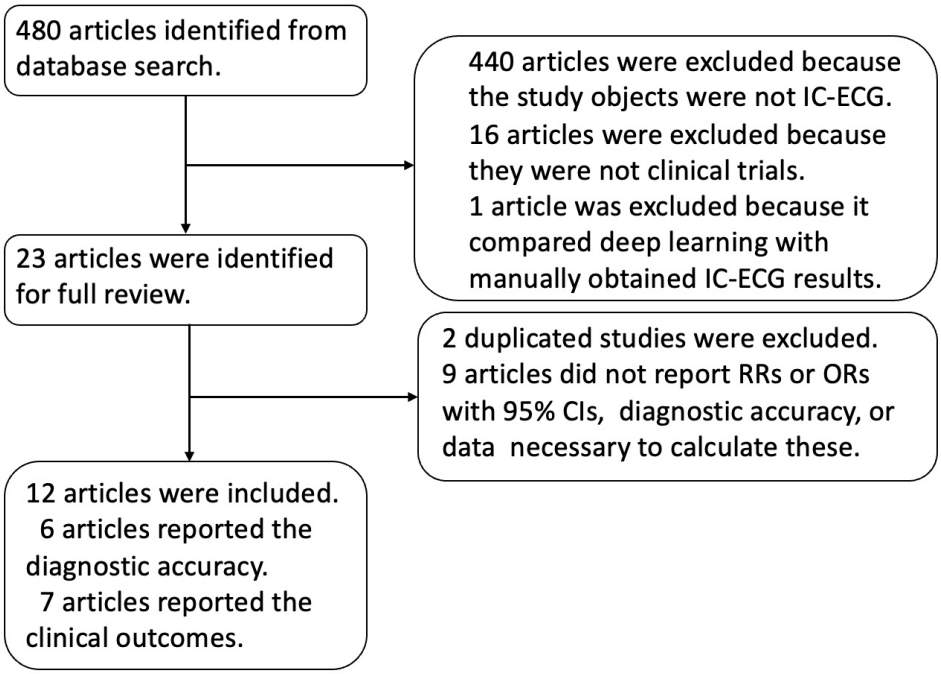

Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

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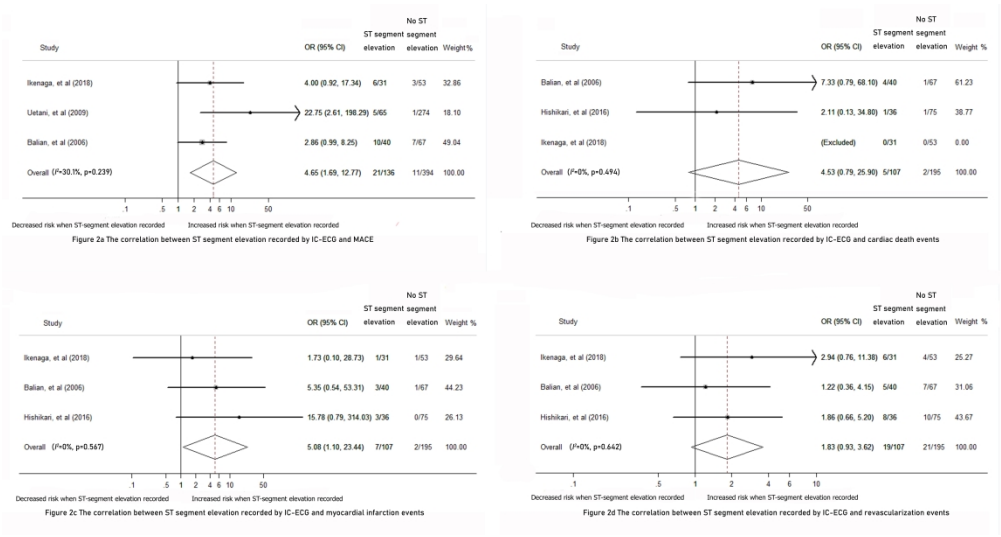

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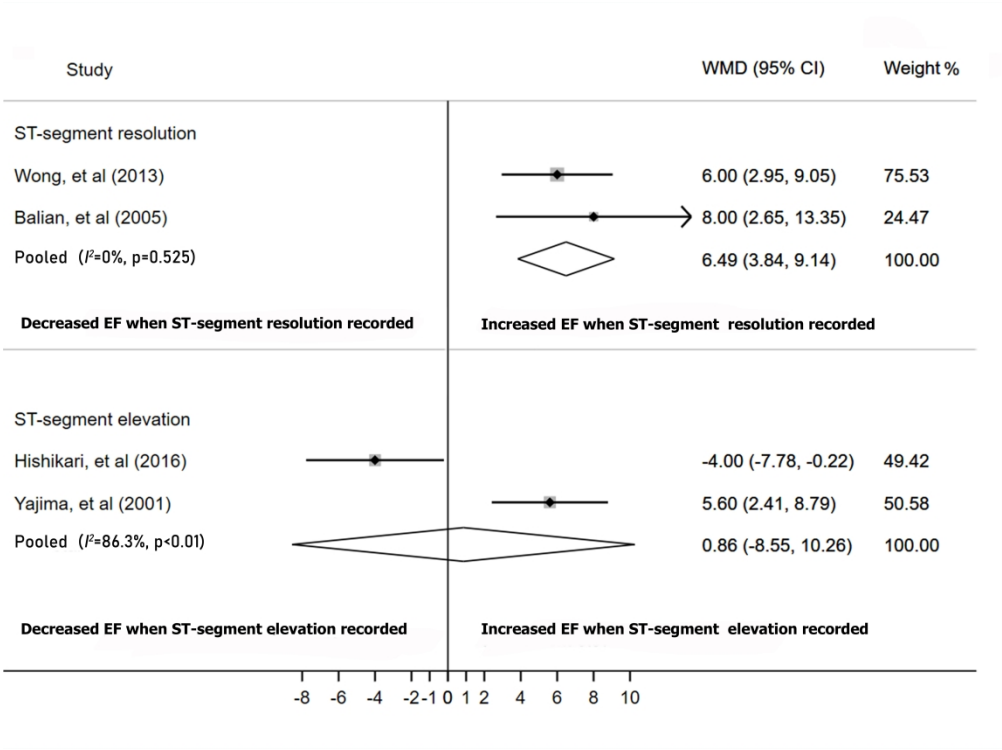
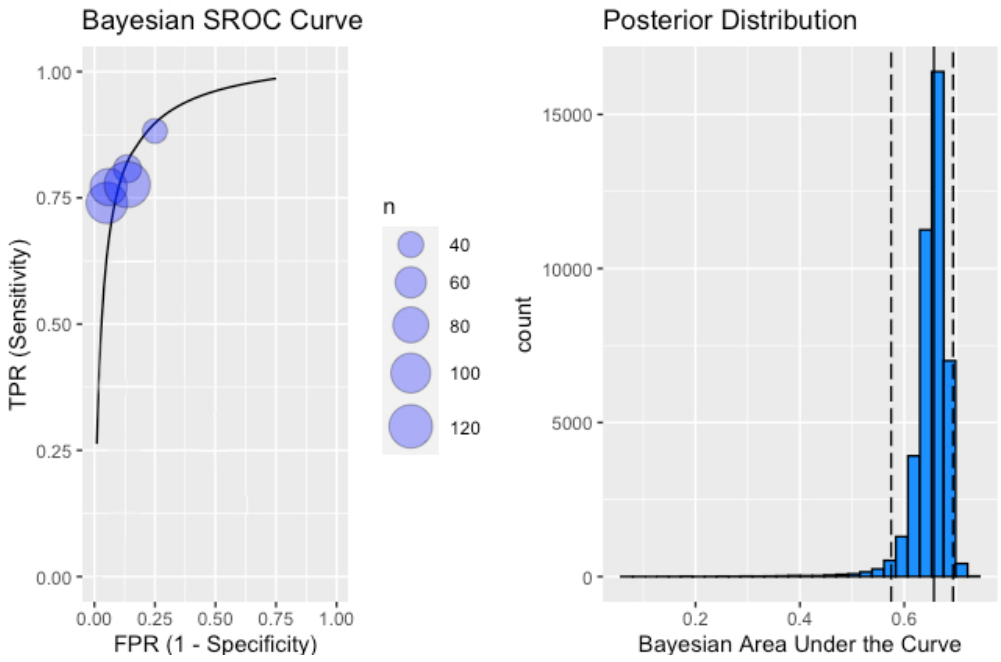


Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. WMD, weighted mean difference; CI, confidence interval; EF, ejection fraction; IC-ECG, intracoronary electrocardiogram.



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SUPPLEMENTAL MATERIAL

Supplement Table 1 Search Strategy June 19th, 2021 (PubMed)

No	Search	Hits
1	((intracoronary) AND (electrocardiogram OR ECG OR EKG)) AND (st segment)	480
2	Search 1; Filters: clinical trials	113

Note: We still screened all the articles' abstracts in case of omission.

Supplement Table 2 Characteristic of included studies.

Studies	Inclusion criteria	Exclusion criteria	Clinical endpoints
Ikenaga, et al. 2018, Japan[10]	Patients with stable angina pectoris who underwent elective PCI for a single, native, de novo coronary lesion and performed FD-OCT and IC-ECG both at baseline and after the procedure in this study.	(i) acute coronary syndrome; (ii) elevated preprocedural cardiac biomarker; (iii) reduced renal function (Estimated glomerular filtration rate <30 mL/min per 1.73m2). Lesion-related exclusion criteria were the vessels within a myocardial territory of previous MI, the left main trunk, ostium lesions, extremely tight lesions or tortuous vessels where we	Major adverse cardiac event (MACE), which was defined as cardiac death, MI, repeat revascularization and/or hospitalization for heart failure.

		expected difficulty in advancing soft-tip guidewire or the FD-OCT catheter, severe calcified lesions needed for debulking device, target vessel reference diameter of ≥4mm expected limitation in FD-OCT evaluation and angiographic evidence of coronary dissection or major side branch (>1mm) occlusion after the procedure.	
Wong, et al. 2013, Australia[6]	Patients with acute STEMI who underwent primary-PCI.	patients aged <18 years, previous myocardial infarction in the same territory,	The relationship between intracoronary ST-segment resolution and MVO assessed

		contraindications to CMR (e.g., claustrophobia) and contraindication to gadopentetate dimeglumine (e.g., known hypersensitivity to gadopentetate dimeglumine or creatinine clearance ⩽ 60 mL/min/1.73 m2).	by CMR 4 days after primary-pacemaker implantation or PCI.
Hishikari, et al. 2016, Japan[7]	Patients' symptoms of coronary ischemia that were worsening or occurring at rest for more than 10 min within the past 12 hours, unequivocal changes on an	(1) age<21 years, (2) STEMI, (3) history of MI, (4) history of PCI, (5) renal insufficiency with a baseline serum creatinine level >1.8 mg/dL (133 lmol/L),	In hospital: ventricular arrhythmias, congestive heart failure, cardiogenic shock, and cardiac death. Follow-up: Adverse events included fatal

	admission ECG elevated cardiac biomarkers and no contraindication for PCI	(6) multivessel CAD or left main CAD, (7) patients in whom the absence of significant CAD or culprit lesion could not be identified according to the angiogram, and (8) major (>1.5 mm) side branch occlusion after PCI.	arrhythmias, cardiac death, nonfatal MI, revascularization or congestive heart failure requiring hospitalization.
Uetani, et al. 2009 Japan[11]	Consecutive patients who underwent apparently successful elective coronary stent implantations. All had angina, documented myocardial ischemia, or both.	1) emergency coronary angioplasty within 24 h of onset; 2) elevated pre-procedural cardiac biomarker; 3) active congestive heart failure; 4) severe lesion	Post-procedure cardiac biomarkers and in hospital major adverse cardiac event, which was defined as cardiac death and MI.

		characteristics not suitable for soft-tip guidewire; 5) angioplasty with debulking device (directional coronary atherectomy or rotational atherectomy); 6) Thrombolysis In Myocardial Infarction (TIMI) flow grade 1 to 2 of target vessel at the end of procedure; and 7) multivessel stenting in a single procedure.	
Balian, et al. 2005, Italy[8]	Absence of cardiogenic shock, adequacy of echocardiographic window, IRA occlusion (TIMI flow	Patients with previous AMI, ventricular conduction disturbances on standard ECG,	Left ventricular ejection fraction and infarct zone wall motion score index.

	grade 0-1) or patency (TIMI flow grade 2) with a severe (>90%) stenosis, and a successful primary stenting.	or ventricular pacing were.	
Yajima, et al. 2001, Japan[9]	Patients with a first episode of anterior myocardial infarction underwent emergency coronary angioplasty within 12 hours of onset.	contraindication of coronary angiogram, >50% stenosis in the left main coronary artery, >75% stenosis in another major coronary artery, prior myocardial infarction, cardiogenic shock, cardiomyopathy, and right or left bundle branch block on the ECG.	coronary events, clinical outcomes, left ventriculogram measurements and myocardial viability

Balian, et al. 2006, Italy[12]	Men and women who were at least 18 years old, had normal CK-MB and cardiac troponin I (cTnI) values before the procedure and were in stable condition, without angina in the previous 48 hours. Further criteria for inclusion were that the PCI procedure was successful and an optimal final result was obtained.	Unstable patients, patients with ventricular conduction disturbances on standard ECG or ventricular pacing, and those who had procedural complications were excluded.	Adverse events included death, nonfatal MI, or a new coronary revascularization procedure. Major coronary events included death or nonfatal MI.
Balian, et al. 2011, Italy[13]	Patients undergoing elective coronary angiography with single-vessel intermediate stenosis (40–70% diameter narrowing) on	prior ST segment elevation myocardial infarction, prior coronary revascularization, ostial stenosis, presence of left	N/A

	quantitative assessment were considered for this study.	bundle branch block, non-sinus rhythm or paced rhythm in resting ECG and a contraindication to adenosine infusion. Patients who were taking digitalis or had ST/T wave abnormalities that precluded the interpretation of ischemic ECG were also excluded.	
Abaci, et al. 2003, Turkey[14]	Recent (<1 month) Q-wave MI; angiographically documented regional wall motion abnormality; single, non-occlusive significant stenosis (⩾70% by quantitative	Patients with poor acoustic window, postinfarction angina, active congestive heart failure, bundle branch block, atrial fibrillation, valvular disease,	N/A

	measurements) in the IRA; and scheduled revascularization of the IRA for angiographic and clinical reasons.	significant stenosis in the non-IRA, and collateral filling to the IRA.
FIESTA. 2018, Bulgaria[5]	Patients with stable or unstable angina were included. The inclusion criterion was angiographic bifurcation lesions in a native coronary artery with a diameter ⩾2.5 mm and ⩽4.5 mm and an side branch diameter ⩾2.0 mm.	patients with ST-segment elevation myocardial infarction and those with non-cardiac comorbid conditions with a life expectancy of less than one year. In addition, patients with left main coronary artery stenosis, total occlusion, lesion of interest located at an infarct-related artery, subjects with

		LVEF <30%, subjects with a moderate or severe degree of valvular heart disease or primary cardiomyopathy and patients with bundle branch blocks, and atrial fibrillation/flutter with no identifiable isoelectric line were excluded.	
Wang, et al. 2011, China[15]	Patients were included if they (1) received elective PCI for single vessel; (2) had unstable angina, which did not onset within 48 hours, with normal CK-MB or	Patients were excluded if they (1) had increased CK-MB or troponin T before PCI; (2) had intraventricular block, ventricular escape, and atrial	N/A

	troponin T before PCI; (3) had ideal results during the procedure.	fibrillation found on ECG; (3) had complication occurred during the procedures, including slow flow, no flow, stent thrombosis, acute coronary occlusion, and perforation.	
Vassilev, et al. 2016, Bulgaria[16]	At least 18 years old, with stable or unstable angina, angiographic bifurcation lesions located in a native coronary artery with diameter of ⩾ 2.5 mm and ⩽ 4.5 mm and side branch with diameter of ⩾ 2.0 mm.	patient with ST-segment elevation myocardial infarction and those with non-cardiac co-morbid conditions with life expectancy <1 year. The following patients were also excluded: 1) left main coronary	N/A

artery stenosis, 2) total occlusion before occurrence of SB, 3) lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5) subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6) patients with bundle branch blocks, atrial fibrillation patient with ST-segment elevation myocardial infarction and those

with non-cardiac co-morbid conditions with life expectancy <1 year. The following patients were also excluded: 1) left main coronary artery stenosis, 2) total occlusion before occurrence of SB, 3) lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5) subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6)

	patients with bundle branch blocks, atrial fibrillation/flutter with no identifiable isoelectric line.

PCI, percutaneous coronary intervention. FD-OCT, frequency-domain optical coherence tomography. IC-ECG, intracoronary electrocardiogram. CAD, coronary artery disease. MI, myocardial infarction. STEMI, ST-segment elevation myocardial infarction. MVO, microvascular obstruction. CMR, cardiac magnetic resonance. ECG, electrocardiogram. FFR, fractional flow reserve. IRA, infarct-related artery. TIMI, thrombolysis in myocardial infarction. CK-MB, creatine kinase-myoglobin. LVEF, left ventricular ejection fraction.

Supplement Table 3 Quality assessment adapted from the Newcastle-Ottawa Scale for studies reported clinical outcomes.

	Selection			Comparability	Outcome			
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score

Ikenaga, et al. 2018[10]	✵		✵	✵			✵	✵	✵	6
Wong, et al. 2013[6]	✵		✵	✵		✵✵	✵	✵	✵	8
Hishikari, et al. 2016[7]	✵		✵	✵		✵✵	✵	✵	✵	8
Uetani, et al. 2009[11]	✵		✵	✵		✵✵	✵			6
Balian, et al. 2005[8]	✵		✵	✵			✵	✵	✵	6
Yajima, et al. 2001[9]	✵		✵	✵			✵			4
Balian, et al.2006[12]	✵		✵	✵			✵	✵	✵	6

Supplement Table 4 Quality assessment adapted from QUADAS tool for diagnostic studies.

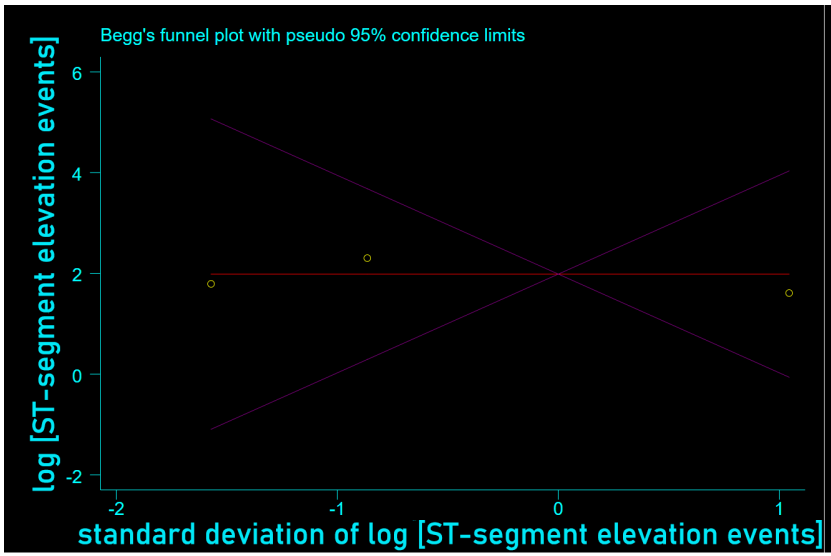
Question	Balian, et al. 2006[12]	Balian, et al. 2011[13]	Abaci, et al. 2003[14]	FIESTA. 2018[5]	Wang, et al. 2011[15]	Vassilev, et al. 2016[16]
1. Was the spectrum of patients	Yes	Yes	Yes	Yes	Yes	Yes

representative of the patients who will receive the test in practice?						
2. Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes	Yes
6. Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes	Yes	Yes

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Unaware	Unaware	Unaware
11. Were the reference standard results interpreted without knowledge of the results	Unaware	Unaware	Unaware	Unaware	Unaware	Unaware

of the index test?						
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes	Yes	Yes	Yes
13. Were uninterpretable/ intermediate test results reported?	Yes	Unaware	Yes	Unaware	Unaware	Unaware
14. Were withdrawals from the study explained?	Yes	Unaware	Unaware	Yes	Unaware	Unaware

Supplemental Figures and Figure Legends



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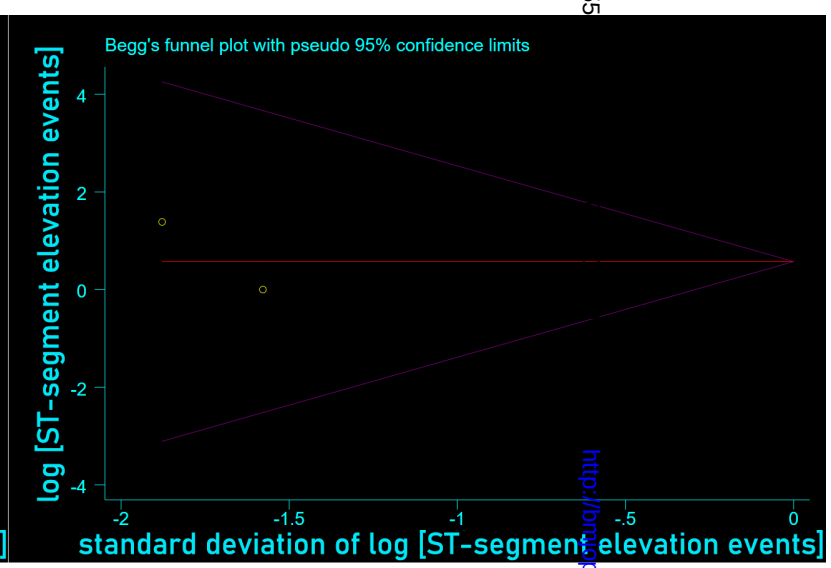

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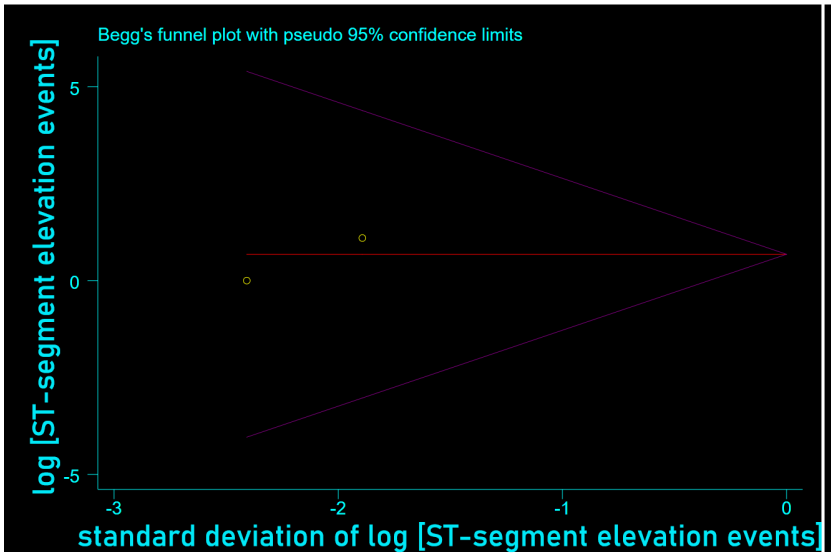

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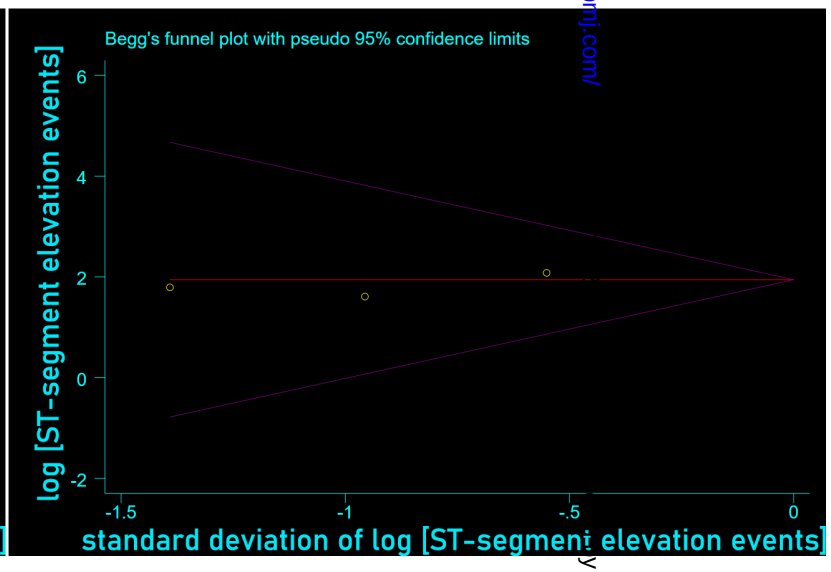
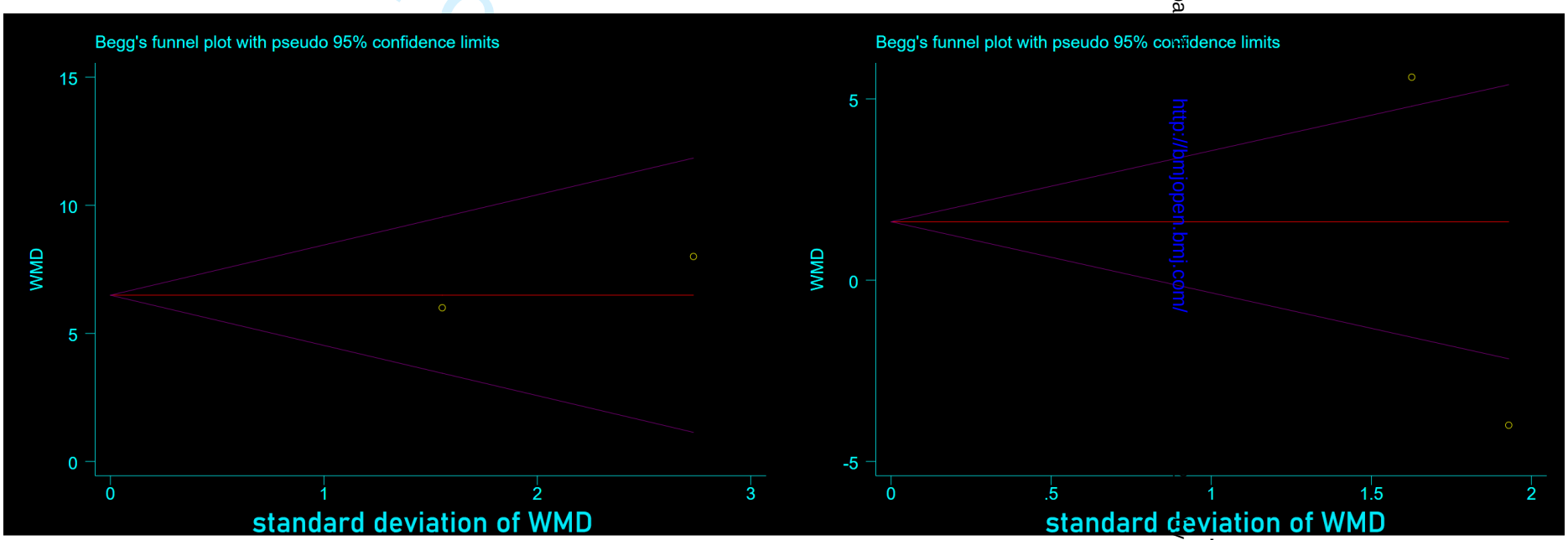


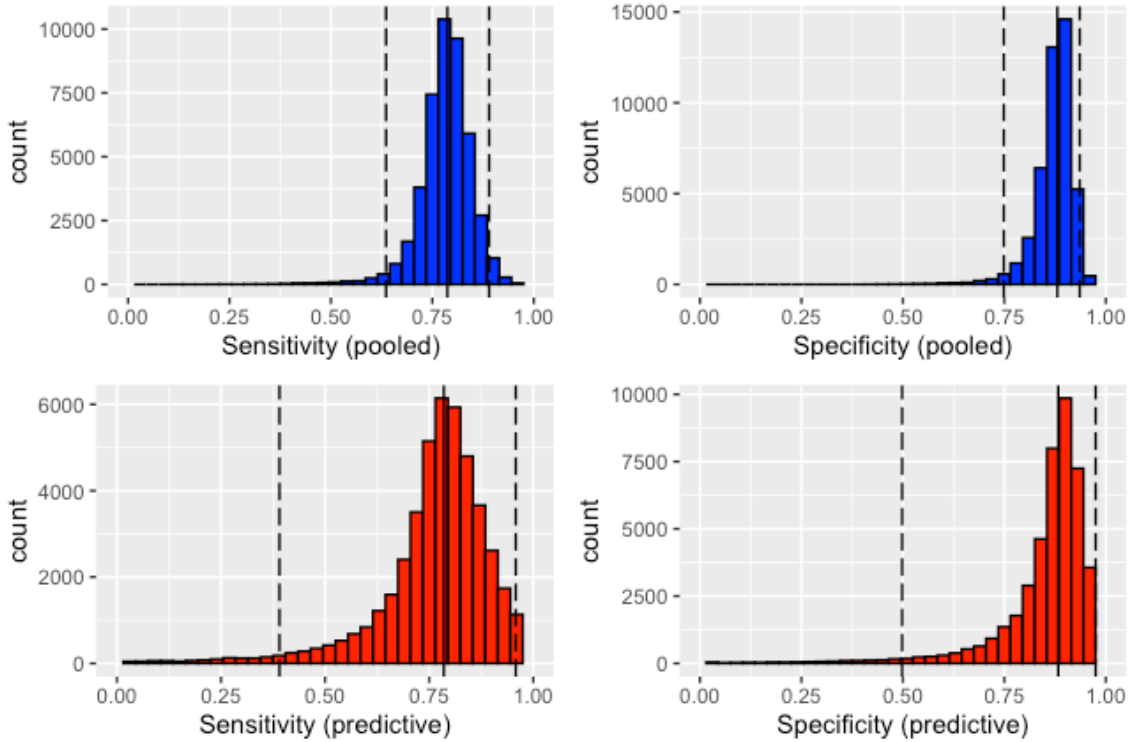
d

Supplement Figure 1 Publication bias assessment for studies reported clinical outcomes. Using Begg asymmetry test, we found no publication bias in the meta-analysis for the clinical outcomes of (a) major adverse cardiac event, (b) cardiac death, (c) myocardial infarction, and (d) revascularization, with p value= 0.602, 0.317, 0.317, and 0.602, respectively.



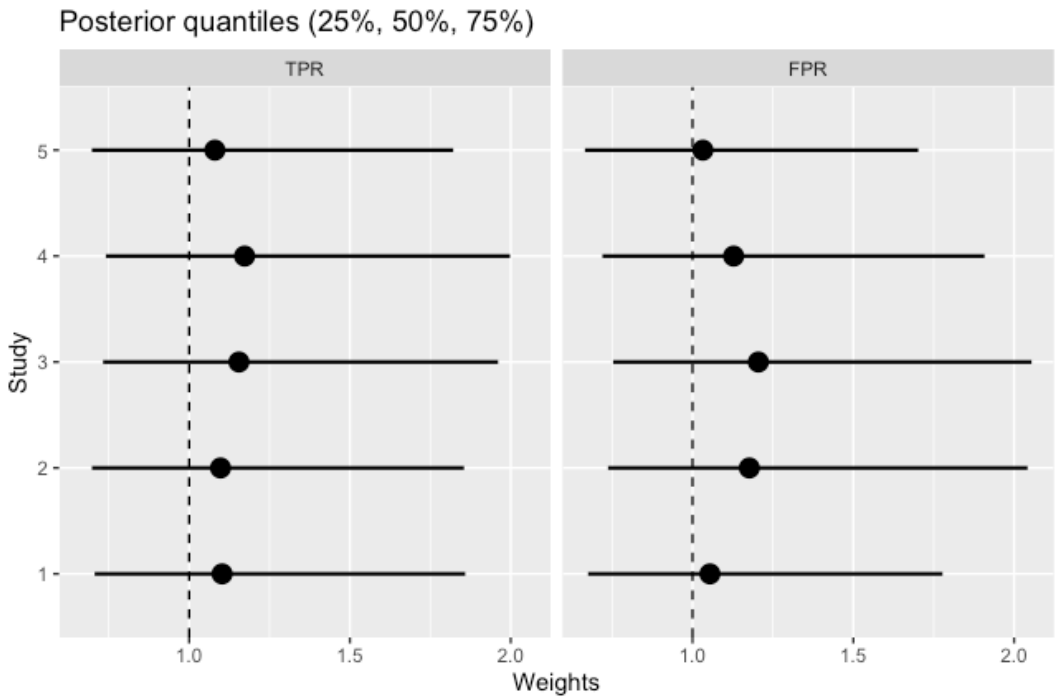
Supplement Figure 2 Publication bias assessment for studies reported ejection fraction. Using Begg asymmetry test, we found no publication bias in the meta-analysis for (a) ST-segment resolution recorded by IC-ECG, and (b) ST-segment elevation. Both p values were 0.317. WMD,

weighted mean difference. IC-ECG, intracoronary electrocardiogram.



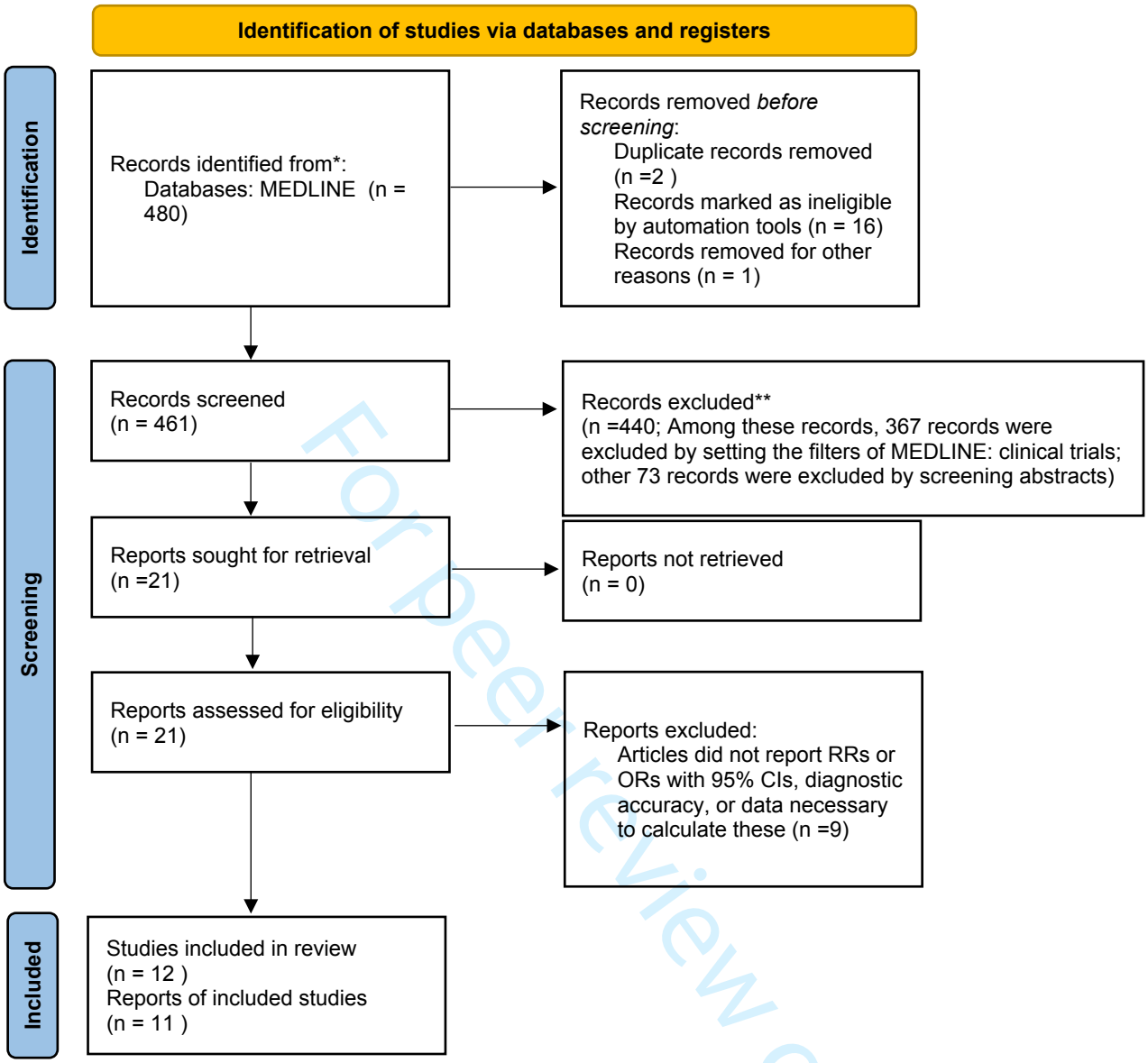
Supplement Figure 3 Posterior distributions for the pooled sensitivity and specificity and their predictive posteriors. The pooled sensitivity and specificity (upper) were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94), respectively. And predictive posterior sensitivity and specificity (lower) were 0.76 (95% credibility intervals 0.39-0.96) and 0.85 (95% credibility intervals 0.50-0.98),

respectively.



Supplement Figure 4 Posterior distributions of the component weights of the diagnostic studies. Study 1: Balian, et al, 2011; Study 2: FIESTA, 2018; Study 3: Balian, et al, 2006; Study 4: Wang, et al, 2011; Study 5: Vassilev, et al, 2016. There was no significant deviation. And the posterior probabilities of studies were all smaller than 0.7. TPR, true positive rate; FPR, false positive rate.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	The prognostic and diagnostic accuracy of intracoronary electrocardiogram recorded during percutaneous coronary intervention—a Meta-Analysis	Title Page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5 and supplement table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7-8 and 10
Study characteristics	17	Cite each included study and present its characteristics.	Page 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8-11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 8-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 8-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 8-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 8-11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 8-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-12
	23b	Discuss any limitations of the evidence included in the review.	Page 15-16
	23c	Discuss any limitations of the review processes used.	Page 15-16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 17
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 17
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 17
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Page 17
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 17

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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The prognostic and diagnostic accuracy of intracoronary electrocardiogram recorded during percutaneous coronary intervention—a Meta-Analysis

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Disclaimers

Authors' statement of this article is not an official position of Guangzhou First People's Hospital, Guangzhou Medical University.

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There were no sources of support for this study.

Disclosure

Please refer to the ICMJE disclosure form we submitted.

Abstract

Objective

Intracoronary electrocardiogram (IC-ECG) recording has been shown to be sensitive and reliable for detecting myocardial viability and local myocardial ischemia in some studies. But IC-ECG is neither widely used during percutaneous coronary intervention (PCI) nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic and diagnostic accuracy of IC-ECG recorded during PCI.

Methods

Relevant studies were identified by searches of MEDLINE until June 19th, 2021. Observational and diagnostic studies which reported the prognostic or diagnostic accuracy of IC-ECG were included. Data were extracted independently by two authors. Summary estimates of clinical outcomes were obtained using a random effects model. Summary diagnostic accuracy was obtained by using a Bayesian bivariate random effects model.

Results

Of the 12 included studies, 7 studies reported the clinical outcomes (821 patients) and 6 studies reported the diagnostic accuracy (485 patients) of IC-ECG. The pooled odds ratios with 95% confidence intervals (CIs) of ST-segment elevation recorded by IC-ECG were 4.65 (1.69-12.77), 5.08 (1.10-23.44), 4.53 (0.79-25.90) and 1.83 (0.93-3.62) for major adverse cardiac events, myocardial infarction, cardiac death, and revascularization, respectively. The weighted mean difference were 6.49 (95%CIs

3.84-9.14) for ejection fraction when ST-segment resolution was recorded, and 0.86 (95%CIs -8.55-10.26) when ST-segment elevation was recorded. The pooled sensitivity and specificity of ST-segment elevation were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94) respectively.

Conclusions

These findings provide quantitative data supporting that IC-ECG had promising diagnostic ability for local myocardial injury, and could predict clinical outcomes.

Key words: intracoronary electrocardiogram, prognostic accuracy, diagnostic accuracy, meta-analysis.

Strengths and limitations of this study

Strengths

1. There were relatively large number of patients analyzed.
2. We used Bayesian meta-analysis to reduce the bias when assessing the diagnostic accuracy.

Limitations

1. Limited by the published studies, we could only perform meta-analysis of observational studies.
2. We did not perform sensitivity analysis for the timing when the IC-ECG was recorded, different types of CADs, different definitions of significant ST-segment changes on IC-ECG or different guide wires used in the studies, limited by the number of studies.

Introduction

Percutaneous coronary intervention (PCI) is a well-established therapeutic strategy for patients with coronary artery disease (CAD). Except for coronary angiography (CAG), several invasive diagnostic tools, such as fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) are recommended for guiding PCI by the guidelines [1]. But these tools are not always available. In some cases, catheters or pressure wires, may not pass through the lesions or may be damaged when crossing the stents or calcified lesions [2-5]. Moreover, for some patients, the costs of these tools are important additional considerations.

Intracoronary electrocardiogram (IC-ECG) recording, with a guidewire functioning as a unipolar electrode, might be an alternative tool for guiding PCI. In some studies, the ST-segment elevation or resolution recorded by IC-ECG during or after PCI procedures have been shown to be sensitive and reliable for detecting myocardial viability, local myocardial ischemia, or microvascular obstruction [5-16]. But IC-ECG is neither widely used during PCI nor recommended in guidelines. This up-to-date meta-analysis of published studies was conducted to evaluate the prognostic and diagnostic accuracy of IC-ECG recorded during PCI.

Methods

The meta-analysis was conducted according to the checklist of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [17] and the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE) [18]. We performed a systematic search of relevant studies published through June 19th,

2021, in the MEDLINE database.

Search strategy

Accessing MEDLINE database, we performed a literature search for studies published until June 19th, 2021 using the following search terms and key words: ((intracoronary) AND (electrocardiogram OR ECG OR EKG)) AND (st segment). The search strategy is shown in Supplement table 1. We manually checked the reference lists of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) Published in the English language; (2) Had an observational study design; (3) Enrolled patients with CAD who were undergoing PCI; (4) Reported the clinical outcomes during follow-ups, such as major adverse cardiac events (MACEs), cardiac death, myocardial infarction, ejection fraction (EF), and repeat revascularization. (5) Reported the diagnostic accuracy of IC-ECG. (6) Presented estimates of odds ratios (ORs) with 95% confidence intervals (CIs) or reported data necessary to calculate these. Animal, autopsy, duplicated, and phantom studies were excluded. Moreover, studies would be excluded if IC-ECG was not one of the study objects.

Data extraction

From each retrieved article, two authors independently extracted the following data: name of the first author, year of publication, location where the study was performed, study design, number of cases, follow-up period, proportion of men, mean

or median age, inclusion criteria, exclusion criteria, reference standard, ORs or event rates, EF during following-up, and the diagnostic accuracy of IC-ECG. The true-positive, true-negative, false-positive, and false-negative rates were also estimated, using the data we extracted from the studies.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

We directly extracted ORs from each study, or indirectly estimated ORs by calculating event rates. And then we pooled ORs using a random-effects meta-analysis method. For EF, we pooled unstandardized mean difference using a random-effects meta-analysis method. Summary sensitivity and specificity with their 95% credibility intervals of IC-ECG were obtained by using Bayesian bivariate random effects meta-analysis [19-21]. Bayesian summary receiver-operating-characteristic (SROC) curves were constructed and the areas under the Bayesian SROC curves (AUC) were performed to assess the diagnostic accuracy of IC-ECG [20,21].

To perform quality assessment, two authors independently assessed the prognostic studies' qualities by using the Newcastle-Ottawa Scale (NOS) [22] and the diagnostic studies' qualities by using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) tool [23]. The NOS evaluated 3 parameters (selection, comparability, and outcome) divided across 8 items. Each item was scored from 0 to 1 star, except for comparability, which could be adapted to the specific topic of

interest to score up to 2 stars. Thus, the maximum score for each study was 9. Studies with <3 stars were at a high risk of bias and would be excluded. The QUADAS tool contained 14 questions which could be used for assessing the qualities of diagnostic studies. Disagreements were resolved by consensus.

Statistical heterogeneities between prognostic studies were evaluated with the I^2 statistic [24], which estimates the percentage of total variation across studies due to true between-study differences rather than chance, with I^2 values of 25, 50, and 75% representing low, medium, and high heterogeneities, respectively. We performed conflict of evidence analysis for diagnostic studies by extending the random effects distribution, using a scale mixture of normal distributions per random effect [20]. P values that were less than 0.05 were considered statistically significant. Statistical analyses were carried out with STATA, version 16.0 (Stata Corp, College Station, Texas), and R statistical software with "bamdit" packages [20].

Results

Literature search

The details of search steps are shown in Figure 1. We identified and screen 480 articles from our preliminary search. After screening abstracts, 440 articles were excluded because the study objects were not IC-ECG. 16 articles were excluded because they were not clinical trials. Bigler's study compared deep learning with manually obtained IC-ECG results [25], and was excluded. 23 articles were identified for full review. Among these articles, 2 duplicated studies were excluded. 9 articles were excluded because they did not report ORs, diagnostic accuracy, or data

necessary to calculate these. Finally, there were 12 studies included in our meta-analysis. 7 studies reported the clinical outcomes and 6 studies reported the diagnostic accuracy of IC-ECG.

Study characteristics

The characteristics of included studies are shown in Table 1 and Supplement table 2. There were 7 cohort studies and 6 diagnostic studies in our meta-analysis. There were 1198 cases included in our meta-analysis totally. Among these cases, 821 cases and 485 cases were included in the meta-analysis for prognostic and diagnostic accuracy of IC-ECG respectively. The proportion of men was 68.8%. The inclusion criteria of the included articles were CAD patients, including stable or unstable angina pectoris, and myocardial infarction. The clinical outcomes reported in these studies were mainly MACEs, cardiac death, myocardial infarction, repeat revascularization, and EF. The difference of the definitions that significant ST-segment changes on IC-ECG in each study was not very great. The reference standards reported in the diagnostic studies were varied, including FFR [5,13], echocardiogram [14], and troponin [12,15,16].

The correlation between clinical outcomes and ST-segment elevation recorded by IC-ECG

Pooled OR for MACE is shown in Figure 2a. The inclusion criteria of these studies were patients with angina and stable conditions. MACEs were defined as cardiac death, myocardial infarction, revascularization, and hospitalization for heart failure in Ikenaga's study [10]. In Uetani's study [11] and Balian's study [12], MACEs were defined

as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE (OR 4.65, 95%CIs 1.69-12.77). There were mild heterogeneities among studies (I^2=30.1%, p=0.239).

Pooled ORs for cardiac death, myocardial infarction, and revascularization are shown in Figure 2b-2d. The inclusion criteria of these studies were patients with angina or non ST-segment elevation myocardial infarction (NSTEMI). In the meta-analysis for cardiac death, Ikenaga's study [10] was excluded because there were no events. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of myocardial infarction (OR 5.08, 95%CIs 1.10-23.44), but not cardiac death (OR 4.53, 95%CIs 0.79-25.90) nor revascularization (OR 1.83, 95%CIs 0.93-3.62). There were no heterogeneities among studies (cardiac death, I^2=0%, p=0.494; myocardial infarction, I^2=0%, p=0.567; revascularization, I^2=0%, p=0.642).

The correlation between EF and different results recorded by IC-ECG during follow-up

The correlation between EF and different results recorded by IC-ECG are shown in Figure 3. We divided the included studies into 2 subgroups according to the different evaluation methods reported by the studies. One was ST-segment resolution, and the other one was ST-segment elevation. In the subgroup of ST-segment resolution, inclusion criteria were patients with ST-segment elevation myocardial infarction (STEMI). The pooled weighted mean difference (WMD) was 6.49, with

95%CIs 3.84-9.14. There were no heterogeneities (I2=0%, p=0.525). The inclusion criteria of ST-segment elevation subgroup were patients with NSTEMI (Hishikari, et al [7]) or anterior myocardial infarction (Yajima, et al [9]) . The pooled WMD was 0.86, with 95%CIs -8.55-10.26. There were heterogeneities (I^2=86.3%, p<0.01).

Diagnostic accuracy of ST-segment elevation recorded by IC-ECG

Abaci's study reported the diagnostic accuracy for myocardial viability [14], while the other 5 diagnostic studies reported the diagnostic accuracy for myocardial injury or ischemia. Therefore, we excluded Abaci's study when we performed Bayesian meta-analysis for diagnostic studies. The inclusion criteria of included studies were angina patients with stable conditions. The pooled diagnostic accuracy and the predictive posterior rates are shown in Supplement figure 1. The Bayesian SROC curve and the AUC are shown in Figure 4. The pooled sensitivity and specificity were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94), respectively. The AUC of Bayesian SORC was 0.65 (95% credibility intervals 0.56-0.69). And there were no heterogeneities. The posterior distributions of the component weights which were used for conflict of evidence analysis are shown in Supplement figure 2.

Quality assessment

Results of quality assessment adapted from NOS are shown in Supplement table 3. All the studies reached over 3 stars, but no study reached the maximum score. Considering all the studies included CAD patients, no study got scored in the fourth item of selection section. Only 3 studies [6,7,11] reported the confounders and were

scored 2 stars in the comparability section. Two studies [9,11] reported the in-hospital outcomes and did not report the patients lost to follow-up, therefore, they were not scored in the second and third items of outcome section.

Results of quality assessment adapted from QUADAS tool are shown in Supplement table 4. All the studies clearly described the methods. No studies described whether they blinded reviewers to the results of IC-ECGs, while 3 studies [12-14] blinded reviewers to the results of reference standards. Only 2 studies [12,14] reported the intermediate results, and 2 studies [5,12] explained the withdrawals.

Discussion

Our results from the meta-analysis of observational studies indicated that ST-segment elevation recorded by IC-ECG after PCI procedures for stable angina patients linked to worse MACE outcomes. For angina or NSTEMI patients, ST-segment elevation was significantly associated with higher risk of myocardial infarction during follow-up, but not cardiac death nor revascularization. ST-segment resolution recorded by IC-ECG after PCI procedures for STEMI patients was significantly associated with increased EF during follow-up. But ST-segment elevation during PCI procedures did not significantly link to increased or decreased EF. After Bayesian meta-analysis, IC-ECG showed promising diagnostic ability for myocardial injury or ischemia.

ST-segment shift pattern recorded by ECG during acute myocardial infarction was reported 100 years ago [26]. And ST-segment deviation recorded by surface ECG was a part of the universal definition of myocardial infarction [27]. However, surface ECG

was not reliable for detecting local myocardial ischemia during PCI procedures in real time [28]. In this case, IC-ECG was more reliable and sensitive for detecting local ischemia [29]. Although IC-ECG was more sensitive than surface ECG when assessing left ascending artery and circumflex territory, It should be noted that IC-ECG was less sensitive when assessing right coronary artery territory [30,31]. On the other hand, impaired microvascular perfusion during PCI might lead to periprocedural myocardial infarction, indicating worse outcomes. IC-ECG could detect local ischemia, which was found to be well associated with impaired microvascular perfusion [10]. For instance, in Sato's study, the prolongation of ST-segment elevation time recorded by IC-ECG was associated with higher max-lipid core burden index 4mm detected by near-infrared spectroscopy with IVUS in stable angina patients, which might indicate distal embolization and microvascular disease [32].

The results from this meta-analysis indicated that ST-segment elevation recorded by IC-ECG after PCI procedure was significantly associated with worse MACE outcomes and higher risk of myocardial infarction in angina or NSTEMI patients, but not significantly associated with cardiac death nor revascularization. Although there were trends that the risks of cardiac death and revascularization were higher when ST-segment elevation was observed, more cases might be needed to prove this hypothesis. ST-segment elevation recorded by IC-ECG might be observed when higher pressure or longer duration balloon inflation was performed, indicating local ischemia. Local myocardial ischemia could be confirmed by testing myocardial biomarkers. Vassilev's study found that the maximal ST-segment elevation during inflation

significantly correlated with final absolute ST-segment elevation and creatine kinase-MB isoenzyme increase post PCI, but not with troponin [16]. Interestingly, IVUS guided stent overexpansion was associated with higher periprocedural creatine kinase-MB isoenzyme level too, but lower risk of target lesion revascularization and mortality at 1 year [33]. Therefore, IC-ECG might provide useful information for guiding stent expansion [10]. Moreover, Ikenaga and Sato found more plaque rupture, vulnerable plaque or higher lipid core burden when ST-segment elevation was observed, even persisted on IC-ECG [10,32]. IC-ECG could help to distinguish the plaque, optimizing medical therapies or PCI strategies. For instance, we could use vasodilators, loading dose of statin, or embolic protection devices to reduce distal embolization [32]. And, Vassilev's studies found that IC-ECG had good correlation with FFR, which might be used in guiding bifurcation PCI procedures [5,16].

According to our meta-analysis, EF was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG in STEMI patients. ST-segment resolution on surface ECG which was observed 90 minutes after the initial therapy was found to be significantly associated with smaller infarct size and fewer deaths [34]. But surface ECG could not explore some small infarct zone sometimes [8]. Furthermore, restoration of coronary flow didn't mean normal myocardial perfusion nor better outcomes [35]. IC-ECG could provide real time ST-segment information, and was found to be well associated with microvascular obstruction and infarct size [6]. In our meta-analysis, ST-segment resolution recorded by IC-ECG was significantly associated with higher EF, meaning better recovery of heart function. This finding was similar to

previous studies. In the subgroup of ST-segment elevation, there were heterogeneities between 2 studies. In Hishikari's study [7], ST-segment elevation recorded by IC-ECG was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's study [9], the result was different in anterior myocardial infarction patients. The possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI procedure might indicate prolonged local myocardial ischemia and worse outcome, as we described above. The result of Hishikari's study that lower EF was observed in ST-segment elevation group, was one of these evidences. On the other hand, there might be myocardium stun after acute myocardial infarction [36]. The results of Yajima's study showed that ST-segment elevation recorded by IC-ECG after balloon inflation could predict myocardial viability and better outcomes [9]. These findings showed that IC-ECG might help to optimize PCI procedure by providing real time information, which could predict clinical outcomes.

The diagnostic studies included in our study reported 3 reference standards. After excluding Abaci's study, there were still 2 reference standards. And the reference standards (FFR and troponin) for diagnosing myocardial ischemia or injury were not perfect. Also, there were too few studies included in our meta-analysis. Considering these situations, we used Bayesian meta-analysis to assess the pooled diagnostic accuracy of IC-ECG. There were already several papers illustrated this method to reduce the bias which came from the different or imperfect reference

standards [20,21,37,38]. The results of our Bayesian meta-analysis showed the promising diagnostic ability of IC-ECG for diagnosing myocardial ischemia or injury. Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be easily performed and produce real time information. But some details might affect the diagnostic accuracy when performing IC-ECG. One of the details was the type of guide wire used. Vassilev found out that the exact size of recording electrode is the last 3 cm of every workhorse guidewire [16]. And Uetani found that the waveforms of IC-ECG were different in the same position between conventional uninsulated guidewires and polymer-covered wires [11]. However, we could not perform sensitivity analysis for different guide wires, limited by the included studies, to verify the hypothesis that different types of guide wires would affect the diagnostic accuracy of IC-ECG. The other one detail was the position of the wire tip. The convenient way of performing IC-ECG was putting the wire tip in the distal position of the target vessel, just like what the most included studies did. In most situation, IC-ECG could detect local ischemia in the pertinent area of target vessels by using this method. But Vassilev found that when they pulled back the guidewire, the elevated ST-segment would suddenly normalize if the wire tip exited the border of ischemic territory [16]. And they explored a method to detect and define the ischemic territory. Further researches should consider how these details affect the diagnostic accuracy of IC-ECG in order to guide the PCI procedures better. Although Abaci's study was excluded when performing the meta-analysis, this study still provided important results. Like Yajima's study which was mentioned above, Abaci's study recorded IC-ECG after balloon inflation, not PCI

procedures. Both of these 2 studies found a good correlation between ST-segment elevation and myocardial viability. In short, IC-ECG had potential value for guiding PCI.

The strengths of our study were the relatively large number of patients analyzed. And we used Bayesian meta-analysis to reduce the bias when assessing the diagnostic accuracy. However, there were limitations to our study. First, limited by the published studies, we could only perform meta-analysis of observational studies. And the wide CIs of ORs were the results of low event rates reported in the studies, especially in the no ST-segment elevation group. Second, not all the included studies performed adjustments for confounders, or reports of patients lost to follow-up. Thus, the results of quality assessment were not so satisfactory. Third, there were varied and imperfect reference standards reported in the diagnostic studies. Therefore, we chose Bayesian meta-analysis to assess the pooled diagnostic accuracy, reducing the bias. Forth, we did not perform sensitivity analysis for the timing when the IC-ECG was recorded, different types of CADs, different definitions of significant ST-segment changes on IC-ECG or different guide wires used in the studies, limited by the number of studies. But in the meta-analysis of clinical outcomes, there were no heterogeneities. These results indicated that these subgroups might have little influence on the ORs. And we found that recording IC-ECG in different phases of PCI procedures might produce different information which might help decision making. Further researches should consider whether the correlation between IC-ECG measures and clinical outcomes depend on the timing of the IC-ECG. Fifth, we did not report publication bias, because given the small numbers of included studies, it was not possible to meaningfully assess

publication bias.

Conclusions

IC-ECG had promising diagnostic ability for local myocardial injury, and could predict clinical outcomes, which could be easily performed and produce real time information during and after PCI procedures. IC-ECG could be an alternative tool for guiding PCI when other invasive tools are not available.

Contributorship Statement

Design and Planning Pan Yizhi MD, PhD

Data collection Huang Jiankai, MD, PhD; Fan Jun, MD, PhD

Data analysis Li Weiji, MD, PhD; Chen Pingan, MD, PhD; He Jialin, MBBS

Statistics and Conduct Li Weiji, MD, PhD; He Jialin, MBBS

Drafting article and Reporting Li Weiji, MD, PhD; He Jialin, MBBS; Fan Jun, MD, PhD

Guarantor Pan Yizhi MD, PhD

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Registration and protocol

Our study was not registered, and we did not prepare a protocol according to the PRISMA-P statement.

Competing interests

The authors have declared that no competing interests exist.

Availability of data, code and other materials

The original template data collection forms, data extracted from included studies, data used for all analyses, and analytic code used in the study are not publicly available. If these original materials are needed, please contact the authors.

Ethics committee approval

We do not need ethics committee approval for our study because it is meta-analysis and we did not access primary patient/animal data nor interact with any patients/animals. We collected and synthesized data from previous studies published on MEDLINE database.

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Figure legends

Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during follow-up, but was not significantly associated with cardiac death nor revascularization. OR, odds ratio; CI, confidence interval; IC-ECG, intracoronary electrocardiogram; MACE, major adverse cardiac event.

Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. WMD, weighted mean difference; CI, confidence interval; EF, ejection fraction; IC-ECG, intracoronary electrocardiogram.

Figure 4 The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and the posterior distribution of AUC. Each circle identifies the true positive rate versus the false positive rate of each study. The AUC was 0.65 (95% credibility intervals 0.56-0.69). TPR, true positive rate; FPR, false positive rate; SROC, summary receiver-

operating-characteristic; AUC, areas under the Bayesian SROC curve; IC-ECG, intracoronary electrocardiogram.

Tables

Studies	Study design	No. of cases	Male (%)	Age (years old)	Follow-up (months)	Reference standards
Ikenaga, et al. 2018, Japan[10]	Cohort study, single center	84	36.8	67.4±9.9	12	N/A
Wong, et al. 2013, Australia[6]	Cohort study, single center	64	82.8	61.0±10.0	3	N/A
Hishikari, et al. 2016, Japan[7]	Cohort study, single center	111	73.9	68.8±12.6	35*	N/A
Uetani, et al. 2009 Japan[11]	Cohort study, single center	339	66.4	69.7±8.6	In hospital	N/A
Balian, et al. 2005,	Cohort study, single	50	84.0	59.3±11.0	6	N/A

Table 1 The characteristics of included studies.

Italy[8]		center					
Yajima, et al. Japan[9]	2001,	Cohort study, single center	65	75.4	61.3±7.0	1	N/A
Balian, et al. Italy[12]	2006,	Cohort study and diagnostic study, single center	108	87.3	61.7±10.0	12±5	Troponin I
Balian, et al. Italy[13]	2011,	Diagnostic study	48	52.0	65.0±9.0	N/A	FFR
Abaci, et al. Turkey[14]	2003,	Diagnostic study	71	84.5	54.0±11.0	N/A	Low-dose dobutamine echocardiography
FIESTA. Bulgaria[5]	2018,	Diagnostic study	37	69.0	65.0±10.0	N/A	FFR
Wang, et al.	2011,	Diagnostic study	86	67.4	54.5±10.2	N/A	Troponin T

China[15]						
Vassilev, et al. 2016, Bulgaria[16]	Diagnostic study	135	59.2	65.1±10.0	N/A	Troponin I

* The median followed-up period of this study was 35 months (28-40 months).

N/A, not available. FFR, fractional flow reserve.

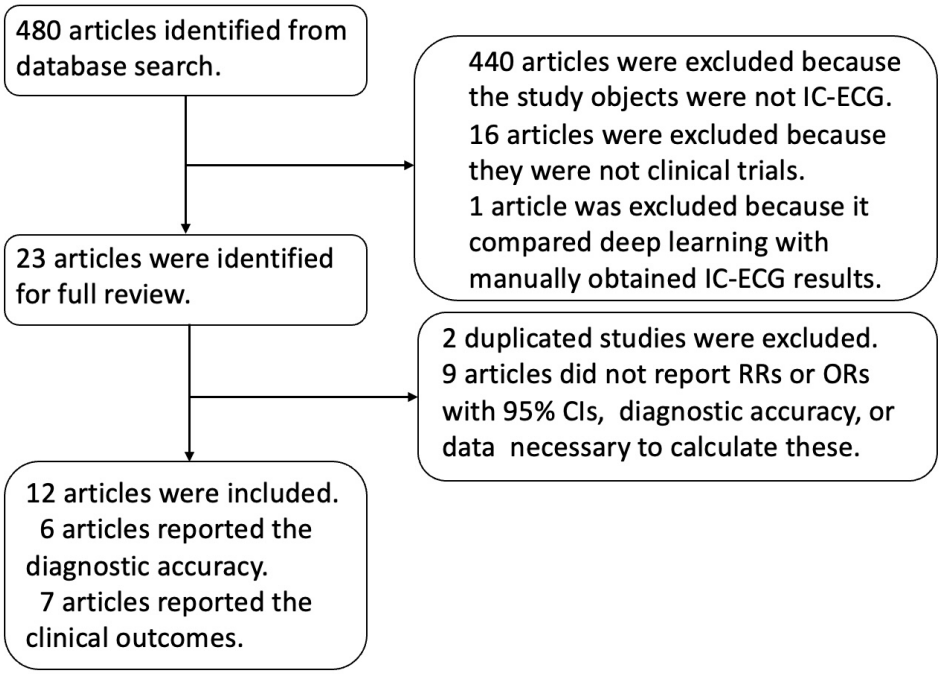

Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

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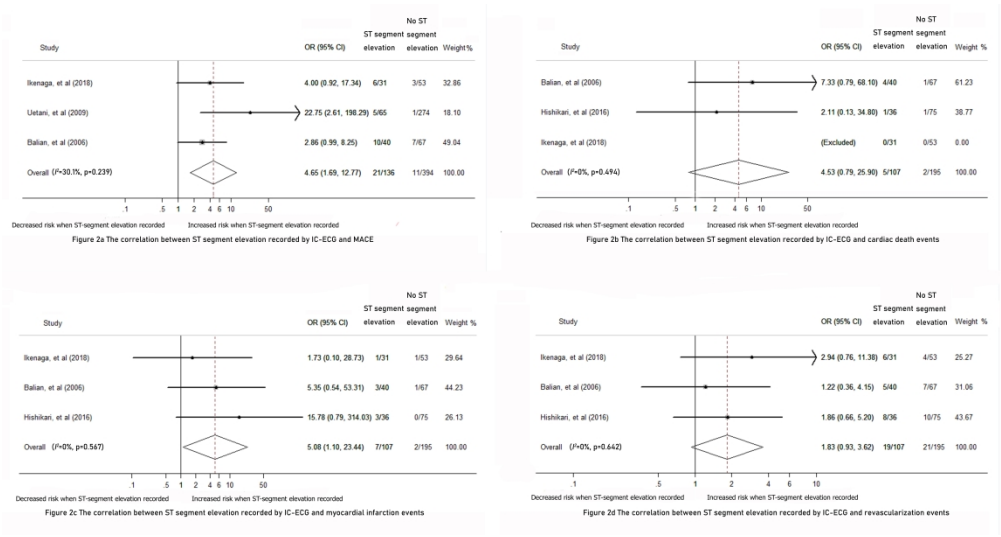

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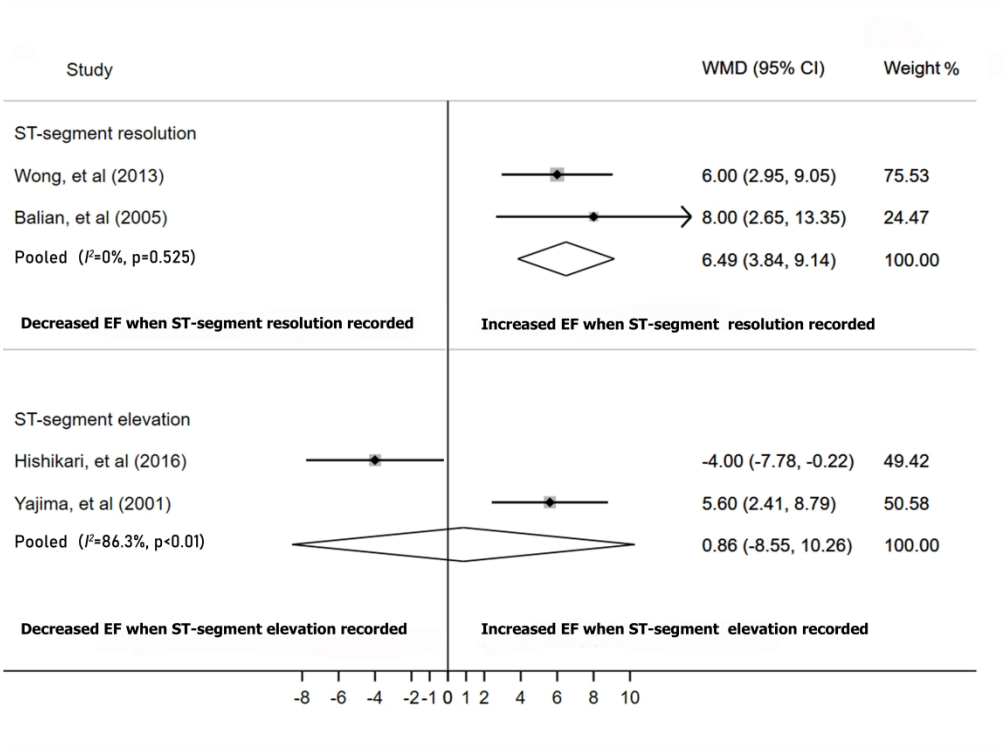


Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, while we could not find similar result when ST-segment elevation was recorded. WMD, weighted mean difference; CI, confidence interval; EF, ejection fraction; IC-ECG, intracoronary electrocardiogram.

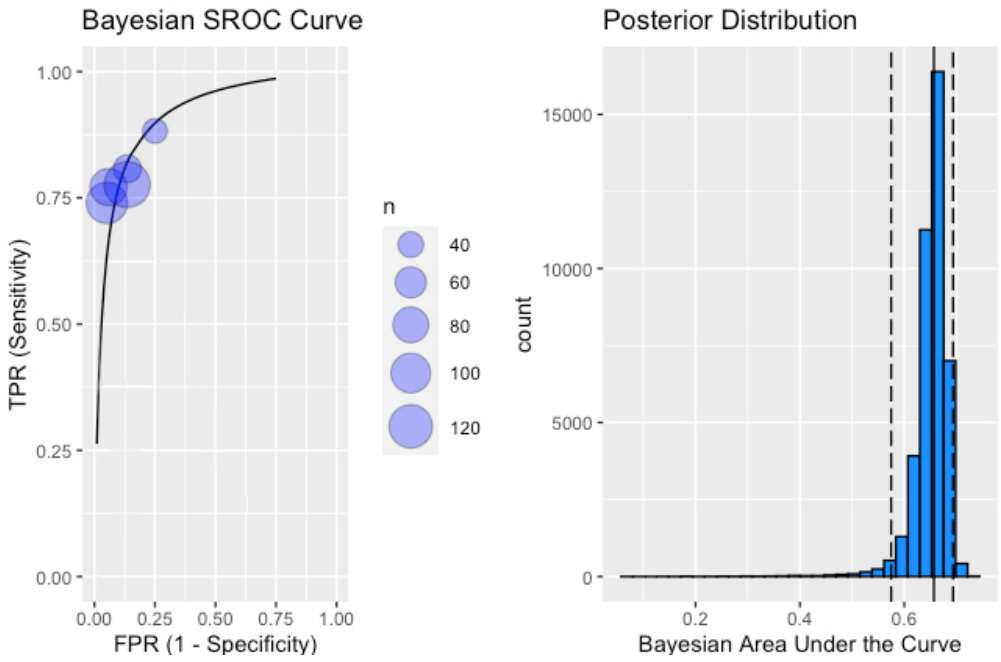


Figure 4 The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and the posterior distribution of AUC. Each circle identifies the true positive rate versus the false positive rate of each study. The AUC was 0.65 (95% credibility intervals 0.56-0.69). TPR, true positive rate; FPR, false positive rate; SROC, summary receiver-operating-characteristic; AUC, areas under the Bayesian SROC curve; IC-ECG, intracoronary electrocardiogram.

SUPPLEMENTAL MATERIAL

Supplement Table 1 Search Strategy June 19th, 2021 (PubMed)

No	Search	Hits
1	((intracoronary) AND (electrocardiogram OR ECG OR EKG)) AND (st segment)	480
2	Search 1; Filters: clinical trials	113

Note: We still screened all the articles' abstracts in case of omission.

Supplement Table 2 Characteristic of included studies.

Studies	Inclusion criteria	Exclusion criteria	Clinical endpoints	Definition of significant ST-segment changes on IC-ECG
Ikenaga, et al. 2018, Japan[10]	Patients with stable angina pectoris who underwent elective PCI for a single, native, de novo coronary lesion and performed FD-OCT and IC-ECG both at baseline and after the procedure in this study.	(i) acute coronary syndrome; (ii) elevated preprocedural cardiac biomarker; (iii) reduced renal function (Estimated glomerular filtration rate <30 mL/min per 1.73m2). Lesion-related exclusion criteria were the vessels within a myocardial	Major adverse cardiac event (MACE), which was defined as cardiac death, MI, repeat revascularization and/or hospitalization for heart failure.	ST-segment elevation on IC-ECG was defined as ST-segment elevation ⩾ 1 mm from baseline.

territory of previous MI, the left main trunk, ostium lesions, extremely tight lesions or tortuous vessels where we expected difficulty in advancing soft-tip guidewire or the FD-OCT catheter, severe calcified lesions needed for debulking device, target vessel reference diameter of ≥4mm expected limitation in FD-

		OCT evaluation and angiographic evidence of coronary dissection or major side branch (>1mm) occlusion after the procedure.		
Wong, et al. 2013, Australia[6]	Patients with acute STEMI who underwent primary-PCI.	patients aged <18 years, previous myocardial infarction in the same territory, contraindications to CMR (e.g., pacemaker implantation or claustrophobia) and	The relationship between intracoronary ST-segment resolution and MVO assessed by CMR 4 days after primary-PCI.	Improvement in IC-ECG ST-segment elevation ⩾ 1 mm immediately upon achieving TIMI 3 flow was defined as intracoronary ST-segment resolution.

		contraindication to gadopentetate dimeglumine (e.g., known hypersensitivity to gadopentetate dimeglumine or creatinine clearance ⩽ 60 mL/min/1.73 m2).		
Hishikari, et al. 2016, Japan[7]	Patients' symptoms of coronary ischemia that were worsening or occurring at rest for more than 10 min within the past 12 hours, unequivocal	(1) age<21 years, (2) STEMI, (3) history of MI, (4) history of PCI, (5) renal insufficiency with a baseline serum creatinine level >1.8 mg/dL (133	In hospital: ventricular arrhythmias, congestive heart failure, cardiogenic shock, and cardiac death. Follow-up: Adverse events included fatal	The ST-segment elevation on the IC-ECG was defined as >0.1 mV elevation compared with the corresponding isoelectric line.

	changes on an admission ECG elevated cardiac biomarkers and no contraindication for PCI	lmol/L), (6) multivessel CAD or left main CAD, (7) patients in whom the absence of significant CAD or culprit lesion could not be identified according to the angiogram, and (8) major (>1.5 mm) side branch occlusion after PCI.	arrhythmias, cardiac death, nonfatal MI, revascularization or congestive heart failure requiring hospitalization.	
Uetani, et al. 2009 Japan[11]	Consecutive patients who underwent apparently successful elective coronary stent implantations. All had	1) emergency coronary angioplasty within 24 h of onset; 2) elevated pre-procedural cardiac	Post-procedure cardiac biomarkers and in hospital major adverse cardiac event, which was	The study defined persistent ST-segment elevation in the IcECG as an ischemic change.

angina, documented myocardial ischemia, or both.	biomarker; 3) active congestive heart failure; 4) severe lesion characteristics not suitable for soft-tip guidewire; 5) angioplasty with debulking device (directional coronary atherectomy or rotational atherectomy); 6) Thrombolysis In Myocardial Infarction (TIMI) flow grade 1 to 2 of target vessel at the end of	defined as cardiac death and MI.	

		procedure; and 7) multivessel stenting in a single procedure.		
Balian, et al. 2005, Italy[8]	Absence of cardiogenic shock, adequacy of echocardiographic window, IRA occlusion (TIMI flow grade 0-1) or patency (TIMI flow grade 2) with a severe (>90%) stenosis, and a successful primary stenting.	Patients with previous AMI, ventricular conduction disturbances on standard ECG, or ventricular pacing were.	Left ventricular ejection fraction and infarct zone wall motion score index.	ST-segment resolution was defined as a ⩾50% decrease of ST-segment elevation compared to the corresponding baseline values.
Yajima, et al. 2001, Japan[9]	Patients with a first episode of anterior myocardial infarction underwent	contraindication of coronary angiogram, >50%	coronary events, clinical outcomes, left ventriculogram	ST-segment elevation on IC-ECG was defined as ST-segment elevation ⩾0.2

	emergency coronary angioplasty within 12 hours of onset.	stenosis in the left main coronary artery, >75% stenosis in another major coronary artery, prior myocardial infarction, cardiogenic shock, cardiomyopathy, and right or left bundle branch block on the ECG.	measurements and myocardial viability.	mV from baseline.
Balian, et al. 2006, Italy[12]	Men and women who were at least 18 years old, had normal CK-MB and cardiac troponin I (cTnI) values before the procedure and	Unstable patients, patients with ventricular conduction disturbances on standard ECG or ventricular pacing, and	Adverse events included death, nonfatal MI, or a new coronary revascularization procedure. Major	Intracoronary ST deviation (elevation or depression) was considered significant if ⩾1 mm compared with

	were in stable condition, without angina in the previous 48 hours. Further criteria for inclusion were that the PCI procedure was successful and an optimal final result was obtained.	those who had procedural complications were excluded.	coronary events included death or nonfatal MI.	the corresponding baseline value.
Balian, et al. 2011, Italy[13]	Patients undergoing elective coronary angiography with single-vessel intermediate stenosis (40–70% diameter narrowing) on quantitative assessment were	prior ST segment elevation myocardial infarction, prior coronary revascularization, ostial stenosis, presence of left bundle branch block, non-sinus rhythm or	N/A	Compared to baseline, an IC-ECG ST-segment deviation (elevation or depression) $\geqslant$ 1 mm during adenosine infusion was considered significant.

	considered for this study.	paced rhythm in resting ECG and a contraindication to adenosine infusion. Patients who were taking digitalis or had ST/T wave abnormalities that precluded the interpretation of ischemic ECG were also excluded.			
Abaci, et al. 2003, Turkey[14]	Recent (<1 month) Q-wave MI; angiographically documented regional wall motion abnormality; single,	Patients with poor acoustic window, postinfarction angina, active congestive heart	N/A		Significant ST-segment elevation was defined as a new or worsening ST segment elevation of ⩾

	non-occlusive significant stenosis (⩾ 70% by quantitative measurements) in the IRA; and scheduled revascularization of the IRA for angiographic and clinical reasons.	failure, bundle branch block, atrial fibrillation, valvular disease, significant stenosis in the non-IRA, and collateral filling to the IRA.		0.1 mV at 80 msec after the J-point.
FIESTA. 2018, Bulgaria[5]	Patients with stable or unstable angina were included. The inclusion criterion was angiographic bifurcation lesions in a native coronary artery with	patients with ST-segment elevation myocardial infarction and those with non-cardiac comorbid conditions with a life expectancy of less than	N/A	An ST-segment elevation >1 mm on the IC-ECG was defined as significant ischemia based on the correlation with clinical events

a diameter ⩾2.5 mm and ⩽ 4.5 mm and an side branch diameter ⩾ 2.0 mm.	one year. In addition, patients with left main coronary artery stenosis, total occlusion, lesion of interest located at an infarct-related artery, subjects with LVEF <30%, subjects with a moderate or severe degree of valvular heart disease or primary cardiomyopathy and patients with bundle branch blocks, and atrial fibrillation/flutter with no	observed in previous studies.

		identifiable isoelectric line were excluded.			
Wang, et al. 2011, China[15]	Patients were included if they (1) received elective PCI for single vessel; (2) had unstable angina, which did not onset within 48 hours, with normal CK-MB or troponin T before PCI; (3) had ideal results during the procedure.	Patients were excluded if they (1) had increased CK-MB or troponin T before PCI; (2) had intraventricular block, ventricular escape, and atrial fibrillation found on ECG; (3) had complication occurred during the procedures, including slow flow, no flow, stent thrombosis, acute	N/A		ST deviation (elevation or depression) was considered significant if >0.1 mV compared with the corresponding baseline value.

			coronary occlusion, and perforation.		
Vassilev, et al. 2016, Bulgaria[16]	At least 18 years old, with stable or unstable angina, angiographic bifurcation lesions located in a native coronary artery with diameter of ⩾ 2.5 mm and ⩽ 4.5 mm and side branch with diameter of ⩾ 2.0 mm.	patient with ST-segment elevation myocardial infarction and those with non-cardiac co-morbid conditions with life expectancy <1 year. The following patients were also excluded: 1) left main coronary artery stenosis, 2) total occlusion before occurrence of SB, 3)	N/A		An 0.5 mV ST-segment elevation or depression above or below J-point was accepted as threshold for defining of ischemia occurrence.

lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5) subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6) patients with bundle branch blocks, atrial fibrillation patient with ST-segment elevation myocardial infarction and

those with non-cardiac co-morbid conditions with life expectancy <1 year. The following patients were also excluded: 1) left main coronary artery stenosis, 2) total occlusion before occurrence of SB, 3) lesion of interest located at infarct-related artery, 4) subjects with left ventricular ejection fraction < 30%, 5)

	subjects with moderate or severe degree valvular heart disease or primary cardiomyopathy, and 6) patients with bundle branch blocks, atrial fibrillation/flutter with no identifiable isoelectric line.

PCI, percutaneous coronary intervention. FD-OCT, frequency-domain optical coherence tomography. IC-ECG, intracoronary electrocardiogram. CAD, coronary artery disease. MI, myocardial infarction. STEMI, ST-segment elevation myocardial infarction. MVO, microvascular obstruction. CMR, cardiac magnetic resonance. ECG, electrocardiogram. FFR, fractional flow reserve. IRA, infarct-related artery. TIMI, thrombolysis in myocardial infarction. CK-MB, creatine kinase-myoglobin. LVEF, left ventricular ejection fraction.

Supplement Table 3 Quality assessment adapted from the Newcastle-Ottawa Scale for studies reported clinical outcomes.

Study	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Ikenaga, et al. 2018[10]	✸	✸	✸			✸	✸	✸	6
Wong, et al. 2013[6]	✸	✸	✸		✸✸	✸	✸	✸	8
Hishikari, et al. 2016[7]	✸	✸	✸		✸✸	✸	✸	✸	8
Uetani, et al. 2009[11]	✸	✸	✸		✸✸	✸			6
Balian, et al. 2005[8]	✸	✸	✸			✸	✸	✸	6
Yajima, et al. 2001[9]	✸	✸	✸			✸			4
Balian, et al.2006[12]	✸	✸	✸			✸	✸	✸	6

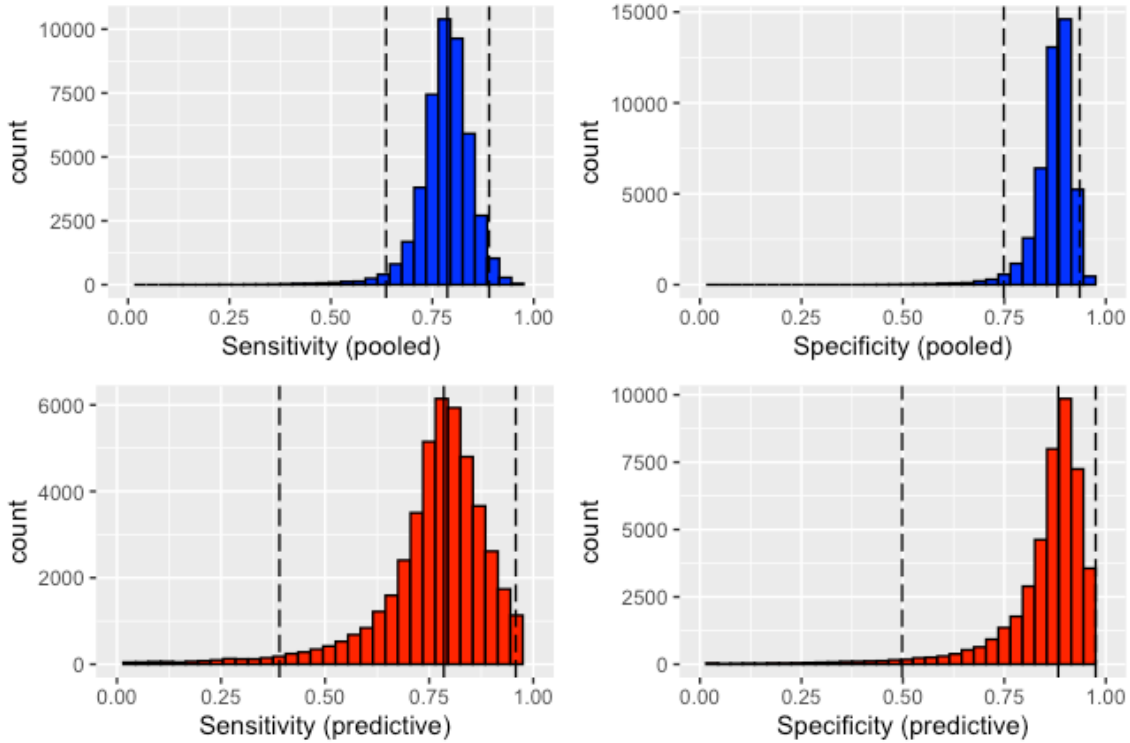
Supplement Table 4 Quality assessment adapted from QUADAS tool for diagnostic studies.

Question	Balian, et al. 2006[12]	Balian, et al. 2011[13]	Abaci, et al. 2003[14]	FIESTA. 2018[5]	Wang, et al. 2011[15]	Vassilev, et al. 2016[16]
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes	Yes	Yes
2. Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the whole sample or a random	Yes	Yes	Yes	Yes	Yes	Yes

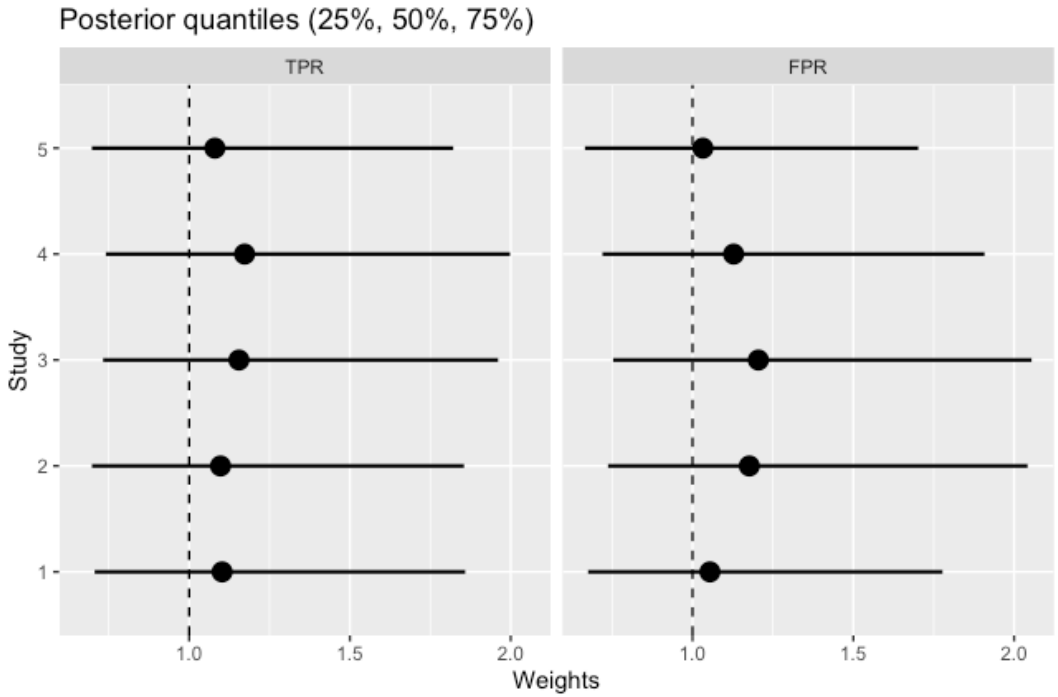
selection of the sample, receive verification using a reference standard of diagnosis?						
6. Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the index test results interpreted	Yes	Yes	Yes	Unaware	Unaware	Unaware

without knowledge of the results of the reference standard?						
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Unaware	Unaware	Unaware	Unaware	Unaware	Unaware
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes	Yes	Yes	Yes
13. Were uninterpretable/ intermediate test results reported?	Yes	Unaware	Yes	Unaware	Unaware	Unaware
14. Were withdrawals from the study explained?	Yes	Unaware	Unaware	Yes	Unaware	Unaware

Supplemental Figures and Figure Legends

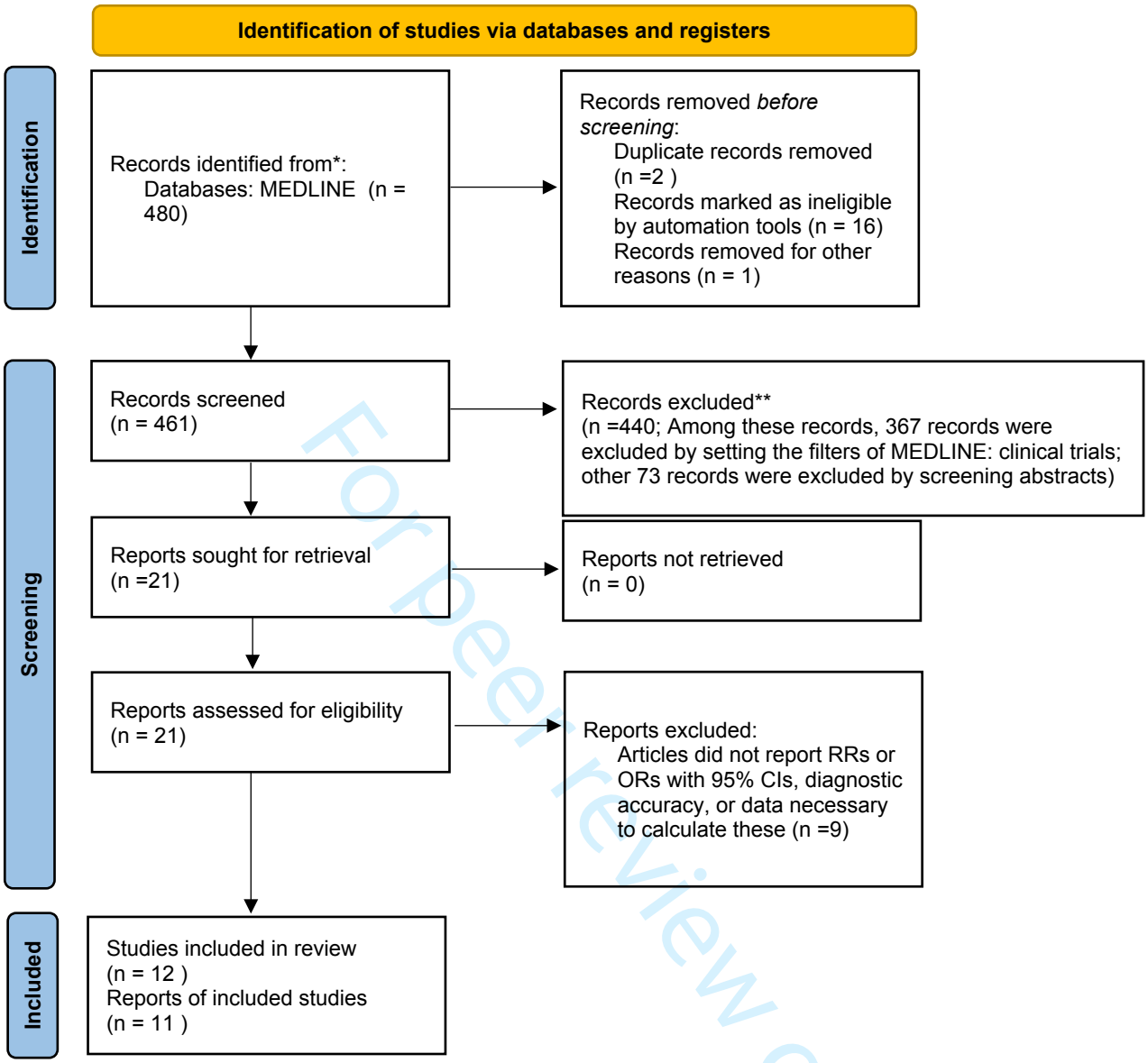


Supplement Figure 1 Posterior distributions for the pooled sensitivity and specificity and their predictive posteriors. The pooled sensitivity and specificity (upper) were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94), respectively. And predictive posterior sensitivity and specificity (lower) were 0.76 (95% credibility intervals 0.39-0.96) and 0.85 (95% credibility intervals 0.50-0.98), respectively.



Supplement Figure 2 Posterior distributions of the component weights of the diagnostic studies. Study 1: Balian, et al, 2011; Study 2: FIESTA, 2018; Study 3: Balian, et al, 2006; Study 4: Wang, et al, 2011; Study 5: Vassilev, et al, 2016. The posterior probabilities of studies were almost centered at 1.0, providing no evidence that any of the studies gave conflict of evidence in relation to the sensitivity or specificity. TPR, true positive rate; FPR, false positive rate.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	The prognostic and diagnostic accuracy of intracoronary electrocardiogram recorded during percutaneous coronary intervention—a Meta-Analysis	Title Page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4-5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5 and supplement table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7-8, and 10
Study characteristics	17	Cite each included study and present its characteristics.	Page 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8-11, and 16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 8-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 8-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 8-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 8-11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 8-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11
	23b	Discuss any limitations of the evidence included in the review.	Page 15-16
	23c	Discuss any limitations of the review processes used.	Page 15-16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 17
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 17
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 17
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Page 17
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included	Page 18

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials		studies; data used for all analyses; analytic code; any other materials used in the review.	

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