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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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4 **The prognostic utility and diagnostic efficacy of intracoronary electrocardiogram**
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6 **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

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4 sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and
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6 diagnostic odds ratio with 95% CIs of ST-segment elevation were 0.83 (0.74-0.89), 0.87
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8 (0.79-0.93), 6.57 (4.01-10.76), 0.20 (0.13-0.29), and 33.37 (19.36-57.52) respectively.
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11 **Conclusions**

12
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14 These findings provide quantitative data supporting that IC-ECG had good
15
16 diagnostic efficacy for local myocardial injury, and could predict clinical outcomes.
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22 **Key words:** intracoronary electrocardiogram, prognostic utility, diagnostic efficacy,
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24 meta-analysis.
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27 **Strengths and limitations of this study**

28 Strengths

- 29 1. There were large number of patients analyzed.
- 30 2. We performed meta-regression and heterogeneities analysis to find out the source
31 of heterogeneities.

32 Limitations

- 33 1. Limited by the published studies, we could only perform meta-analysis of
34 observational studies.
- 35 2. We did not perform sensitivity analysis of the timing when the IC-ECG was recorded,
36 limited by the number of studies.

37 **Key questions**

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4 **What is already known about this subject?** Invasive diagnostic tools are
5
6 recommended for guiding PCI by the guidelines, but these tools are not always
7
8 available. In some cases, the catheters or pressure wires, may not pass through the
9
10 lesions or may be damaged. The cost are also important additional considerations. IC-
11
12 ECG might be an alternative choice, but need to be assessed its prognostic utility and
13
14 diagnostic efficacy.
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19 **What does this study add?** This up-to-date meta-analysis of published studies was
20
21 conducted to evaluate the prognostic utility and diagnostic efficacy of IC-ECG recorded
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23 during PCI. And we found that IC-ECG had good diagnostic efficacy for local myocardial
24
25 injury, and could predict clinical outcomes.
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30 **How might this impact on clinical practice?** Our results indicated that IC-ECG had
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32 potential value for guiding PCI. Further researches should consider the correlation
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34 between the timing when the IC-ECG was recorded and clinical outcomes.
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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

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4 rates, EF during following-up, and the diagnostic efficacy of IC-ECG. The true-positive,
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6 true-negative, false-positive, and false-negative values were also estimated, using the
7
8 data we extracted from the studies.
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10

11 **Patient and Public Involvement**

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14 Patients or the public WERE NOT involved in the design, or conduct, or reporting,
15
16 or dissemination plans of our research.
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19 **Statistical analysis**

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22 We directly extracted ORs from each study, or indirectly estimated ORs by
23
24 calculating event rates. And then we pooled ORs using a random-effects meta-analysis
25
26 method. For EF, we pooled unstandardized mean difference using a random-effects
27
28 meta-analysis method. Summary sensitivities, specificities, diagnostic odds ratios,
29
30 positive and negative likelihood ratios with their 95% CIs of IC-ECG were obtained
31
32 using random effect models with DerSimonian Laird methods[19]. Summary receiver-
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34 operating-characteristic (SROC) curves were constructed and the areas under the
35
36 SROC curves (AUC) was performed to assess the diagnostic accuracy of IC-ECG.
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43 To perform quality assessment, two authors independently assessed the
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45 prognostic studies' qualities by using the Downs-Black criteria[20] and the diagnostic
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47 studies' qualities by using the Quality Assessment Tool for Diagnostic Accuracy Studies
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49 (QUADAS) tool[21]. The Downs-Black criteria devised an instrument consisting of 27
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51 questions that evaluate reporting, external validity, internal validity (bias and
52
53 confounding), and statistical power. All questions received scores 0 or 1, with the
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55 exception of question 5, which ranged from 0 to 2, depending on whether the
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4 statistical power of the survey was explicitly stated in the article as being at least 80%.
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6 Thus, the maximum score achievable by an article was 27 points. The QUADAS tool
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8 contained 14 questions which could be used for assessing the quality of diagnostic
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10 studies. Disagreements were resolved by consensus.
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14 Statistical heterogeneities between studies were evaluated with the I^2
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16 statistic[22], which estimates the percentage of total variation across studies due to
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18 true between-study differences rather than chance, with I^2 values of 25, 50, and 75%
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20 representing low, medium, and high heterogeneities, respectively. We explored
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22 sources of heterogeneities through Galbraith plot[23] and meta-regression analysis.
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24 The Begg asymmetry tests[24] for clinical outcomes and Deeks' asymmetry test[25]
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26 for the diagnostic studies were performed to assess the publication bias. P values that
27
28 were less than 0.05 were considered statistically significant. All statistical analyses
29
30 were carried out with STATA, version 16.0 (Stata Corp, College Station, Texas).
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37 **Results**

38 **Literature search**

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40 The details of search steps are shown in Figure 1. We identified and screen 480
41
42 articles from our preliminary search. After screening abstracts, 440 articles were
43
44 excluded because the study objects were not IC-ECG. 16 articles were excluded
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46 because they were not clinical trials. Bigler's study compared deep learning with
47
48 manually obtained IC-ECG results[26], and was excluded. 23 articles were identified
49
50 for full review. Among these articles, 2 duplicated studies were excluded. 9 articles
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52 were excluded because they did not report ORs, diagnostic accuracy, or data
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4 necessary to calculate these. Finally, there were 12 studies included in our meta-
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6 analysis. 7 studies reported the clinical outcomes and 6 studies reported the
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8 diagnostic efficacy of IC-ECG.
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10 11 **Study characteristics**

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14 The characteristics of included studies are shown in Table 1 and Supplement
15
16 table 1. There were 6 cohort studies, 1 case-control study and 5 diagnostic studies in
17
18 our meta-analysis. There were 1198 cases included in our meta-analysis totally.
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20 Among these cases, 821 cases and 485 cases were included in the meta-analysis for
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22 clinical outcomes and diagnostic efficacy of IC-ECG respectively. The proportion of
23
24 men was 68.8%. The inclusion criteria of the included articles was CAD patients,
25
26 including stable or unstable angina pectoris, and myocardial infarction. The clinical
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28 outcomes reported in these studies were mainly MACEs, cardiac death, myocardial
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30 infarction, repeat revascularization, and EF. The reference standards reported in the
31
32 diagnostic studies were varied, including FFR[5, 13], echocardiogram[14], surface
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34 ECG[12], and troponin[15, 16].
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43 **The correlation between clinical outcomes and ST-segment elevation recorded** 44 45 **by IC-ECG**

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48 Pooled OR for MACE is shown in Figure 2a. The inclusion criteria of these studies
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50 were patients with angina and stable conditions. MACEs were defined as cardiac death,
51
52 myocardial infarction, revascularization, and hospitalization for heart failure in
53
54 Ikenaga's study[10]. In Uetani's study[11] and Balian's study[12], MACEs were defined
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56 as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG
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4 after PCI procedures was significantly associated with higher risk of MACE (OR 4.65,
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6 95%CI 1.69-12.77). There were mild heterogeneities among studies ($I^2=30.1\%$,
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8 $p=0.239$). And there was no publication bias (the result was shown in Supplement
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10 figure 1a, $p=0.602$).
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14 Pooled ORs for cardiac death, myocardial infarction, and revascularization are
15
16 shown in Figure 2b-2d. The inclusion criteria of these studies were patients with
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18 angina or non ST-segment elevation myocardial infarction (NSTEMI). In the meta-
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20 analysis for cardiac death, Ikenaga's study[10] was excluded because there were no
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22 events. ST-segment elevation recorded by IC-ECG after PCI procedures was
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24 significantly associated with higher risk of myocardial infarction (OR 5.08, 95%CI 1.10-
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26 23.44), but not cardiac death (OR 4.53, 95%CI 0.79-25.90) nor revascularization (OR
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28 1.83, 95%CI 0.93-3.62). There were no heterogeneities among studies (cardiac death,
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30 $I^2=0\%$, $p=0.494$; myocardial infarction, $I^2=0\%$, $p=0.567$; revascularization, $I^2=0\%$,
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32 $p=0.642$). And there were no publication bias (cardiac death, $p=0.317$; myocardial
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34 infarction, $p=0.317$; revascularization, $p=0.602$, and the results were shown in
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36 Supplement figure 1b-1d).
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45 **The correlation between EF and different results recorded by IC-ECG during** 46 47 **follow-up** 48 49

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51 The correlation between EF and different results recorded by IC-ECG are shown
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53 in Figure 3. We divided the included studies into 2 subgroups according to the
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55 different evaluation methods reported by the studies. One was ST-segment resolution,
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57 and the other one was ST-segment elevation. In the subgroup of ST-segment
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4 resolution, inclusion criteria were patients with ST-segment elevation myocardial
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6 infarction (STEMI). The pooled weighted mean difference (WMD) was 6.49, with
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8 95%CI 3.84-9.14. There were no heterogeneities ($I^2=0%$, $p=0.525$). And there was no
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10 publication bias (the result was shown in Supplement figure 2a, $p=0.317$). The
11
12 inclusion criteria of ST-segment elevation subgroup were patients with NSTEMI
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14 (Hishikari, et al[7]) or anterior myocardial infarction (Yajima, et al[9]). The pooled
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16 WMD was 0.86, with 95%CI -8.55-10.26. There were heterogeneities ($I^2=86.3%$,
17
18 $p<0.01$), but no publication bias (the result was shown in Supplement figure 2b,
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20 $p=0.317$).

21 22 23 24 25 26 27 **Diagnostic efficacy of ST-segment elevation recorded by IC-ECG**

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30 The pooled diagnostic efficacy is shown in Table 2 and the forest plots are shown
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32 in Supplement figure 3. The SROC curve is shown in Figure 4a. All the included studies
33
34 compared ST-segment elevation recorded by IC-ECG to reference standards. Among
35
36 these 6 diagnostic studies, 5 studies[5, 12, 13, 15, 16] studied the diagnostic efficacy
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38 for myocardial injury or ischemia. The other one studied the diagnostic efficacy for
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40 myocardial viability[14]. The pooled sensitivity, specificity, positive likelihood ratio,
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42 negative likelihood ratio, and diagnostic odds ratio were 0.83 (95%CI 0.74-0.89), 0.87
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44 (95% 0.79-0.93), 6.57 (95%CI 4.01-10.76), 0.20 (95%CI 0.13-0.29), and 33.37 (95%CI
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46 19.36-57.52) respectively. The AUC of SROC was 0.92 (95%CI 0.89-0.94). There were
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48 heterogeneities ($I^2=67%$, $p=0.024$), but no publication bias ($p=0.97$, the result was
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50 shown in Supplement figure 4).

51 52 53 54 55 56 57 **Meta-regression and heterogeneities analysis of the diagnostic studies**

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4 The Galbraith (radial) plot[23] for diagnostic studies is shown in Figure 4b. Abaci's
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6 study [14] was located outside the 95% boundaries in the Galbraith plot, indicating
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8 that this study was the source of heterogeneities. We also performed meta-regression
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10 and the results are shown in Supplement table 2. Significant heterogeneities were
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12 found when year of publication was 2003, location was Turkey, and reference
13
14 standard was echocardiogram. These results all indicated that Abaci's study was the
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16 main source of heterogeneities. After omitting Abaci's study, the pooled sensitivity,
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18 specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio
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20 were 0.78 (95%CI 0.72-0.84), 0.89 (95% 0.82-0.94), 7.4 (95%CI 4.40-12.30), 0.24
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22 (95%CI 0.19-0.32), and 30 (95%CI 16-56) respectively. The AUC of SROC was 0.86
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24 (95%CI 0.82-0.88), and $I^2=0\%$. The results of diagnosis were also the source of
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26 heterogeneities. There were 3 studies[5, 12, 15] studied the diagnostic efficacy for
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28 myocardial injury. The pooled sensitivity and specificity of these 3 studies were
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30 0.76(0.70-0.83) and 0.92(0.87-0.96), respectively.
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40 **Quality assessment**

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42 Results of quality assessment adapted from Downs-Black criteria were shown in
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44 Supplement table 3. Studies could reach the maximum of 27 points, but no study
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46 reached this limit. Only 3 studies[6, 7, 11] reported the confounders. 2 studies[6, 12]
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48 did not report the adverse events. Most of the studies reported the characteristics of
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50 patients lost to follow-up, except 2 studies[9, 11]. We could hardly evaluate the
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52 external validity of all the studies, because none of them described the proportion of
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54 the source population from which the patients are derived. No studies tried to blind
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4 study subjects to the intervention they received, while 4 studies[6-8, 10] blinded
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6 reviewers to the results of measurements between different groups. No studies had
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8 randomized design. Only 2 studies [7, 11] performed adjustment for confounders in
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10 the analysis of main outcomes, and 3 studies [7, 8, 12] reported the numbers of
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12 patients lost to follow-up.
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17 Results of quality assessment adapted from QUADAS tool were shown in
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19 Supplement table 4. All the studies clearly described the methods. No studies
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21 described whether they blinded reviewers to the results of IC-ECGs, while 3 studies
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23 [12-14] blinded reviewers to the results of reference standards. Only 2 studies[12, 14]
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25 reported the intermediate results, and 2 studies[5, 12] explained the withdrawals.
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29 30 **Discussion**

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32 Our results from the meta-analysis of observational studies indicated that ST-
33
34 segment elevation recorded by IC-ECG after PCI procedures for stable angina patients
35
36 linked to worse MACE outcomes. For angina or NSTEMI patients, ST-segment
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38 elevation was significantly associated with higher risk of myocardial infarction during
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40 follow-up, but not cardiac death nor revascularization. ST-segment resolution
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42 recorded by IC-ECG after PCI procedures for STEMI patients was significantly
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44 associated with increased EF during follow-up. But ST-segment elevation during PCI
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46 procedures did not significantly link to increased or decreased EF. After meta-
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48 regression analysis, ST-segment elevation recorded by IC-ECG showed good diagnostic
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50 efficacy for myocardial injury or ischemia.
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58 ST-segment shift pattern recorded by ECG during acute myocardial infarction was
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4 reported 100 years ago [27]. And ST-segment deviation recorded by surface ECG was
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6 a part of the universal definition of myocardial infarction[28]. However, surface ECG
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8 was not reliable for detecting local myocardial ischemia during PCI procedures in real
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10 time. In this case, IC-ECG was more reliable and sensitive for detecting ischemia[29].
11
12 Moreover, impaired microvascular perfusion during PCI might lead to periprocedural
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14 myocardial infarction, indicating worse outcomes. IC-ECG could detect local ischemia,
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16 which was found to be well associated with impaired microvascular perfusion[10].
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18 Although there were several invasive diagnostic tools for guiding PCI, IC-ECG appeared
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20 to be potential tools for detecting myocardial ischemia in real time and guiding PCI.
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27 The results from this meta-analysis indicated that ST-segment elevation recorded
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29 by IC-ECG after PCI procedure was significantly associated with worse MACE outcomes
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31 and higher risk of myocardial infarction in angina or NSTEMI patients, but not
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33 significantly associated with cardiac death nor revascularization. Although there were
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35 trends that the risks of cardiac death and revascularization were higher when ST-
36
37 segment elevation was observed, more cases might be needed to prove this
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39 hypothesis. ST-segment elevation recorded by IC-ECG might be observed when higher
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41 pressure or longer duration balloon inflation was performed, indicating local ischemia.
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43 Local myocardial ischemia could be confirmed by testing myocardial biomarkers.
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45 Interestingly, IVUS guided stent overexpansion was associated with higher
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47 periprocedural creatine kinase-MB isoenzyme level, but lower risk of target lesion
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49 revascularization and mortality at 1 year[30]. Therefore, IC-ECG might provide useful
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51 information for guiding stent expansion[10]. Moreover, Ikenaga found more plaque
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4 rupture and vulnerable plaque when ST-segment elevation was observed on IC-
5 ECG[10]. IC-ECG could help to distinguish the plaque, and might be a potential tool for
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9 guiding PCI.

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11 According to our meta-analysis, EF was significantly higher during follow-up when
12 ST-segment resolution was observed on IC-ECG in STEMI patients. ST-segment
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17 resolution on surface ECG which was observed 90 minutes after the initial therapy was
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20 found to be significantly associated with smaller infarct size and fewer deaths[31]. But
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23 surface ECG could not explore some small infarct zone sometimes[8]. Furthermore,
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26 restoration of coronary flow didn't mean normal myocardial perfusion nor better
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29 outcomes[32]. IC-ECG could provide real time ST-segment information, and was found
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31
32 to be well associated with microvascular obstruction and infarct size[6]. In our meta-
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35 analysis, ST-segment resolution recorded by IC-ECG was significantly associated with
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38 higher EF, meaning better recovery of heart function. This finding was similar to
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41 previous studies. In the subgroup of ST-segment elevation, there were heterogeneities
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44 between 2 studies. In Hishikari's study[7], ST-segment elevation recorded by IC-ECG
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47 was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's
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50 study[9], the result was different in anterior myocardial infarction patients. The
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52
53 possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-
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56 ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was
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59 performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI
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62 procedure might indicate prolonged local myocardial ischemia and worse outcome, as
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64
65 we described above. The result of Hishikari's study that lower EF was observed in ST-

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4 segment elevation group, was one of these evidence. On the other hand, there might
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6 be myocardium stun after acute myocardial infarction[33]. The results of Yajima's
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8 study showed that ST-segment elevation recorded by IC-ECG after balloon inflation
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10 could predict myocardial viability and better outcomes[9]. These findings showed that
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12 IC-ECG might help to optimize PCI procedure by providing real time information, which
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14 could predict clinical outcomes.
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19 After heterogeneities analysis and omitting 1 study, the pooled sensitivity was
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21 0.78 (95%CI 0.72-0.84), and specificity was 0.89 (95% 0.82-0.94) for diagnosing
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23 myocardial injury or ischemia. And the AUC of SROC was 0.86 (95%CI 0.82-0.88).
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25 Although the pooled likelihood ratios [7.4 (95%CI 4.40-12.30) for positive, and 0.24
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27 (95%CI 0.19-0.32) for negative likelihood ratios] or diagnostic odds ratio [30 (95%CI
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29 16-56)] were not very satisfactory, the results still indicated that IC-ECG had good
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31 diagnostic efficacy. These results indicated that IC-ECG could be used for diagnosing
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33 myocardial injury or ischemia. Comparing to surface ECG, IC-ECG had higher diagnostic
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35 efficacy. Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be
36
37 easily performed and produce real time information. Although Abaci's study was
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39 omitted after meta-regression analysis, this study still produced important results.
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41 Like Yajima's study which was mentioned above, Abaci's study recorded IC-ECG after
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43 balloon inflation, not PCI procedures. Both of these 2 studies found a good correlation
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45 between ST-segment elevation during PCI procedures and myocardial viability. In
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47 short, IC-ECG had potential value for guiding PCI.
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58 The strengths of our study were the large number of patients analyzed. However,
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4 there were limitations to our study. First, limited by the published studies, we could
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6 only perform meta-analysis of observational studies. Second, not all the included
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8 studies performed blind methods, adjustments for confounders, or reports of patients
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10 lost to follow-up. Thus the results of quality assessment were not so satisfactory. Third,
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12 there were some heterogeneities of our results. But after heterogeneities analysis,
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14 these heterogeneities could be eliminated or explained. Forth, we did not perform
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16 sensitivity analysis of the timing when the IC-ECG was recorded, limited by the number
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18 of studies. But we found that recording IC-ECG in different phases of PCI procedures
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20 might produce different information which might help decision making. Further
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22 researches should consider the correlation between the timing when the IC-ECG was
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24 recorded and clinical outcomes.
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32 **Conclusions**

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34 IC-ECG had good diagnostic efficacy for local myocardial injury, and could predict
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36 clinical outcomes, which could be easily performed and produce real time information
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38 during and after PCI procedures. IC-ECG could be an alternative tool for guiding PCI.
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52

53 **Contributorship Statement**

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55 **Design and Planning** Pan Yizhi MD, PhD
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57

58 **Data collection** Huang Jiankai, MD, PhD; Fan Jun, MD, PhD
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4 **Data analysis** Li Weiji, MD, PhD; Chen Pingan, MD, PhD; He Jialin, MBBS
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6 **Statistics and Conduct** Li Weiji, MD, PhD; He Jialin, MBBS
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9 **Drafting article and Reporting** Li Weiji, MD, PhD; He Jialin, MBBS; Fan Jun, MD, PhD
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11 **Guarantor** Pan Yizhi MD, PhD
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17 **Ethics committee approval**
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19 We do not need ethics committee approval for our study because it is meta-analysis
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21 and we did not access primary patient/animal data nor interact with any
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23 patients/animals. We collected and synthesized data from previous studies published
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25 on MEDLINE database.
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32 **Sources of Funding**
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34 Not applicable.
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40 **Disclosure**
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42 None.
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48 **References**
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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,

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4 2011; ⑥ Vassilev, et al, 2016. SENS, sensitivity; SPEC, specificity; SROC, summary
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6 receiver-operating-characteristic; AUC, areas under the SROC curves; IC-ECG,
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8 intracoronary electrocardiogram.
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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.

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|----|------------------|-------|----------------------|-----|------|-----------|------|---------------------|
| 1 | | | | | | | | |
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| 4 | Yajima, et al. | 2001, | Cohort study, single | 65 | 75.4 | 61.3±7.0 | 1 | N/A |
| 5 | | | | | | | | |
| 6 | Japan[9] | | center | | | | | |
| 7 | | | | | | | | |
| 8 | Balian, et al. | 2006, | Cohort study, single | 108 | 87.3 | 61.7±10.0 | 12±5 | Surface ECG |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
| 11 | Italy[12] | | center | | | | | |
| 12 | | | | | | | | |
| 13 | Balian, et al. | 2011, | Diagnostic study | 48 | 52.0 | 65.0±9.0 | N/A | FFR |
| 14 | | | | | | | | |
| 15 | Italy[13] | | | | | | | |
| 16 | | | | | | | | |
| 17 | Abaci, et al. | 2003, | Diagnostic study | 71 | 84.5 | 54.0±11.0 | N/A | Low-dose dobutamine |
| 18 | | | | | | | | |
| 19 | Turkey[14] | | | | | | | echocardiography |
| 20 | | | | | | | | |
| 21 | FIESTA. | 2018, | Diagnostic study | 37 | 69.0 | 65.0±10.0 | N/A | FFR |
| 22 | | | | | | | | |
| 23 | Bulgaria[5] | | | | | | | |
| 24 | | | | | | | | |
| 25 | Wang, et al. | 2011, | Diagnostic study | 86 | 67.4 | 54.5±10.2 | N/A | Troponin T |
| 26 | | | | | | | | |
| 27 | China[15] | | | | | | | |
| 28 | | | | | | | | |
| 29 | Vassilev, et al. | 2016, | Diagnostic study | 135 | 59.2 | 65.1±10.0 | N/A | Troponin I |
| 30 | | | | | | | | |
| 31 | Bulgaria[16] | | | | | | | |
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* 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(0.04-0.79) | 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(0.10-0.40) | 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.

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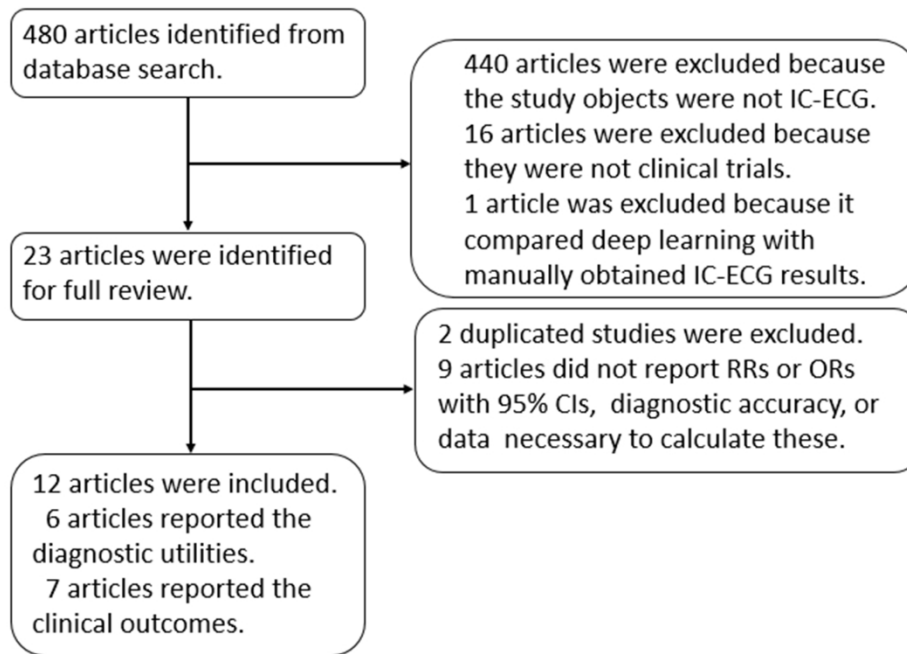


Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

125x93mm (1200 x 1200 DPI)

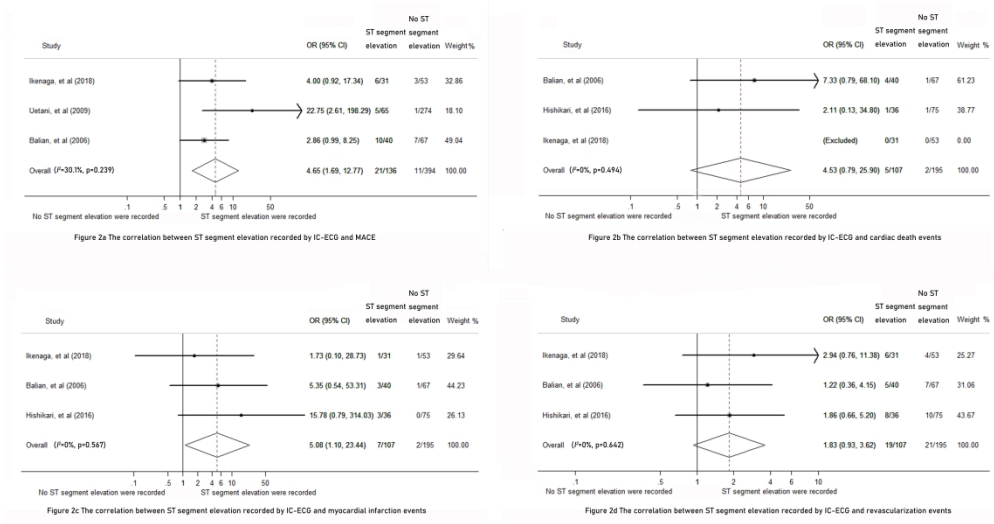


Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during 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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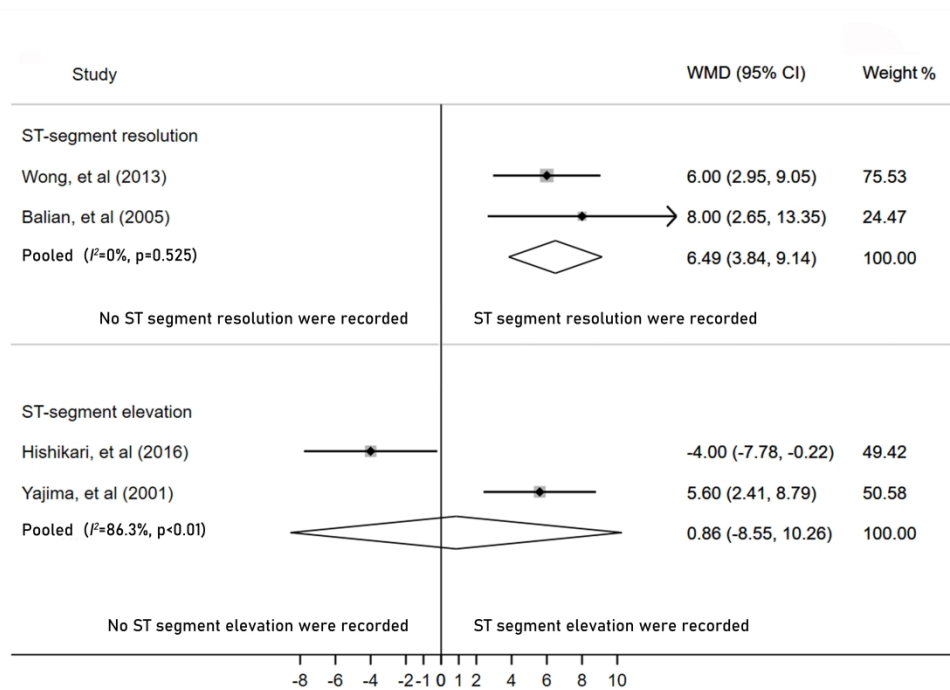


Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG,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

420x303mm (300 x 300 DPI)

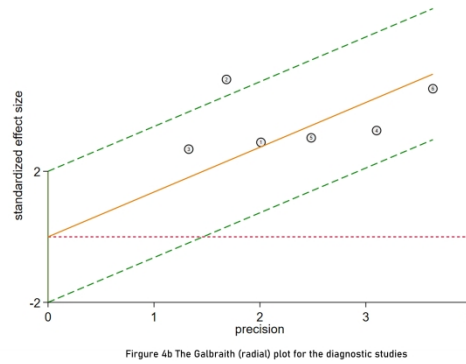
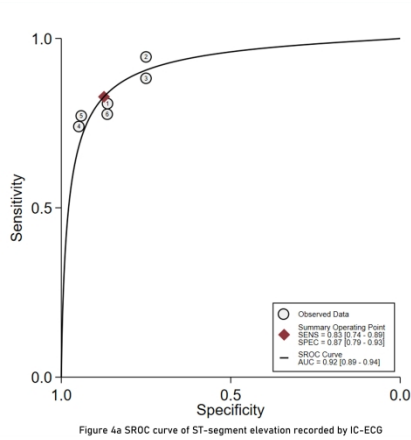


Figure 4 The SROC curve of ST-segment elevation recorded by IC-ECG and the Galbraith (radial) plot for the diagnostic studies. The SROC curve and the AUC showed a good diagnostic accuracy for ST-segment elevation recorded by IC-ECG. And the Galbraith plot showed that Abaci's study was the main source 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

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Supplement Table 1 Characteristic of included studies.

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| 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 1.73m ²). 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 $\geq 4\text{mm}$ expected
 limitation in FD-OCT evaluation
 and angiographic evidence of
 coronary dissection or major
 side branch ($>1\text{mm}$) 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

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contraindications to CMR (e.g., by CMR 4 days after primary-
 pacemaker implantation or PCI.
 claustrophobia) and
 contraindication to
 gadopentetate dimeglumine
 (e.g., known hypersensitivity to
 gadopentetate dimeglumine or
 creatinine clearance \leq 60
 mL/min/1.73 m²).

Hishikari, et al. 2016, Japan[7] Patients' symptoms of coronary (1) age<21 years, (2) STEMI, (3) In hospital: ventricular
 ischemia that were worsening or history of MI, (4) history of PCI, arrhythmias, congestive heart
 occurring at rest for more than 10 (5) renal insufficiency with a failure, cardiogenic shock, and
 min within the past 12 hours, baseline serum creatinine cardiac death. Follow-up:
 unequivocal changes on an level >1.8 mg/dL (133 μ mol/L), Adverse events included fatal

admission ECG elevated cardiac (6) multivessel CAD or left main arrhythmias, cardiac death, biomarkers and no CAD, (7) patients in whom the nonfatal MI, revascularization contraindication for PCI absence of significant CAD or or congestive heart failure culprit lesion could not be requiring hospitalization. identified according to the angiogram, and (8) major (>1.5 mm) side branch occlusion after PCI.

Uetani, et al. 2009 Japan[11] Consecutive patients who 1) emergency coronary Post-procedure cardiac underwent apparently successful angioplasty within 24 h of biomarkers and in hospital elective coronary stent onset; 2) elevated pre-major adverse cardiac event, implantations. All had angina, procedural cardiac biomarker; which was defined as cardiac documented myocardial ischemia, 3) active congestive heart death and MI. or both. failure; 4) severe lesion

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 4 characteristics not suitable for
 5
 6 soft-tip guidewire; 5)
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 8 angioplasty with debulking
 9
 10 device (directional coronary
 11
 12 atherectomy or rotational
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 14 atherectomy); 6) Thrombolysis
 15
 16 In Myocardial Infarction (TIMI)
 17
 18 flow grade 1 to 2 of target
 19
 20 vessel at the end of procedure;
 21
 22 and 7) multivessel stenting in a
 23
 24 single procedure.
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32 Balian, et al. 2005, Italy[8]

33 Absence of cardiogenic shock, Patients with previous AMI, Left ventricular ejection
 34 adequacy of echocardiographic ventricular conduction fraction and infarct zone wall
 35
 36 window, IRA occlusion (TIMI flow disturbances on standard ECG, motion score index.
 37
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4 grade 0-1) or patency (TIMI flow or ventricular pacing were.
5
6 grade 2) with a severe (>90%)
7
8 stenosis, and a successful primary
9
10 stenting.
11
12
13
14 Yajima, et al. 2001, Japan[9] Patients with a first episode of contraindication of coronary coronary events, clinical
15 anterior myocardial infarction angiogram, >50% stenosis in outcomes, left ventriculogram
16
17 underwent emergency coronary the left main coronary measurements and myocardial
18
19 angioplasty within 12 hours of artery, >75% stenosis in viability
20
21 onset.
22 another major coronary artery,
23
24 prior myocardial infarction,
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26 cardiogenic shock,
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28 cardiomyopathy, and right or
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30 left bundle branch block on the
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38 ECG.
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|--------------------------------|--|--|--|
| Balian, et al. 2006, Italy[12] | <p>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.</p> | <p>Unstable patients, patients with ventricular conduction disturbances on standard ECG or ventricular pacing, and those who had procedural complications were excluded.</p> | <p>Adverse events included death, nonfatal MI, or a new coronary revascularization procedure. Major coronary events included death or nonfatal MI.</p> |
| Balian, et al. 2011, Italy[13] | <p>Patients undergoing elective coronary angiography with single-vessel intermediate stenosis (40–70% diameter narrowing) on</p> | <p>prior ST segment elevation myocardial infarction, prior coronary revascularization, ostial stenosis, presence of left</p> | N/A |

quantitative assessment were 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; Patients with poor acoustic window, postinfarction angina, regional wall motion abnormality; active congestive heart failure, single, non-occlusive significant bundle branch block, atrial stenosis ($\geq 70\%$ by quantitative fibrillation, valvular disease, N/A

measurements) in the IRA; and significant stenosis in the non-scheduled revascularization of the IRA, and collateral filling to the IRA for angiographic and clinical IRA.

reasons.

FIESTA. 2018, Bulgaria[5]

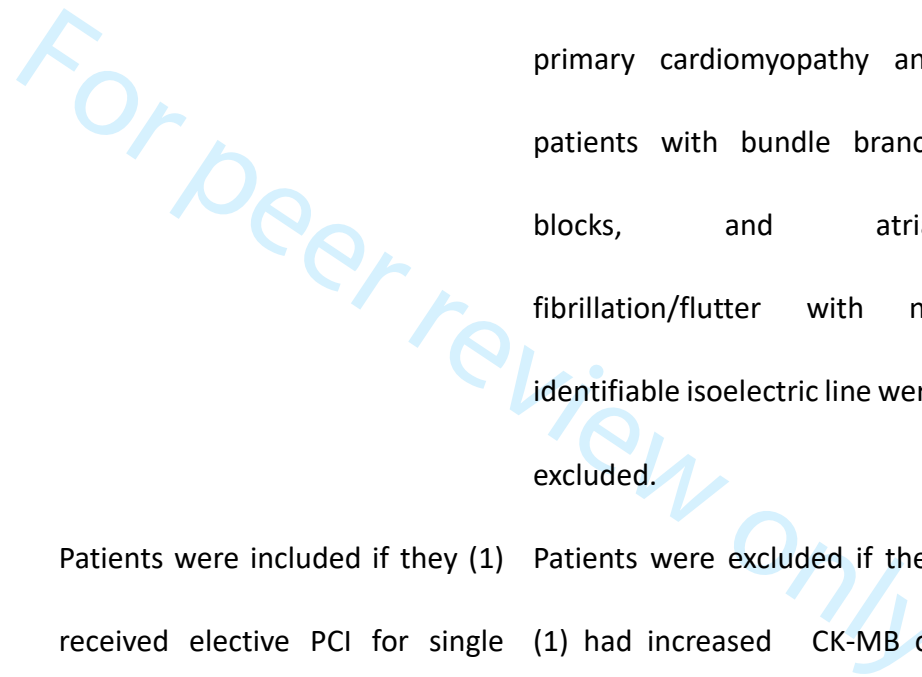
Patients with stable or unstable patients with ST-segment N/A
angina were included. The elevation myocardial infarction
inclusion criterion was and those with non-cardiac
angiographic bifurcation lesions in comorbid conditions with a life
a native coronary artery with a expectancy of less than one
diameter ≥ 2.5 mm and ≤ 4.5 year. In addition, patients with
mm and an side branch diameter left main coronary artery
 ≥ 2.0 mm. 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



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troponin T before PCI; (3) had ideal fibrillation found on ECG; (3) results during the procedure. 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

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4 artery stenosis, 2) total
5
6 occlusion before occurrence of
7
8 SB, 3) lesion of interest located
9
10 at infarct-related artery, 4)
11
12 subjects with left ventricular
13
14 ejection fraction < 30%, 5)
15
16 subjects with moderate or
17
18 severe degree valvular heart
19
20 disease or primary
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22 cardiomyopathy, and 6)
23
24 patients with bundle branch
25
26 blocks, atrial fibrillation patient
27
28 with ST-segment elevation
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30 myocardial infarction and those
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4 with non-cardiac co-morbid
5 conditions with life expectancy
6 <1 year. The following patients
7 were also excluded: 1) left main
8 coronary artery stenosis, 2)
9 total occlusion before
10 occurrence of SB, 3) lesion of
11 interest located at infarct-
12 related artery, 4) subjects with
13 left ventricular ejection fraction
14 < 30%, 5) subjects with
15 moderate or severe degree
16 valvular heart disease or
17 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 | Ajima, 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 |

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|----|---------------------|----|---------------------|----|---------------------|----|---------------------|----|---------------------|----|---------------------|----|---------------------|
| 11 | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine |
| 12 | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine | to | Unable to determine | to | 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 |

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|-------|---------------------|---------------------|-----|---------------------|-----|-----|-----|
| 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 | Yes | Yes |
| Total | 18 | 18 | 21 | 18 | 19 | 19 | 17 |
| score | | | | | | | |

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 |

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|----|--|-----|-----|-----|-----|-----|-----|
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| 2 | | | | | | | |
| 3 | | | | | | | |
| 4 | 2. Were selection criteria clearly described? | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | | | | | | | |
| 6 | 3. Is the reference standard likely to correctly | Yes | Yes | Yes | Yes | Yes | Yes |
| 7 | | | | | | | |
| 8 | classify the target condition? | | | | | | |
| 9 | | | | | | | |
| 10 | | | | | | | |
| 11 | 4. Is the time period between reference | Yes | Yes | Yes | Yes | Yes | Yes |
| 12 | | | | | | | |
| 13 | standard and index test short enough to be | | | | | | |
| 14 | | | | | | | |
| 15 | reasonably sure that the target condition did | | | | | | |
| 16 | | | | | | | |
| 17 | not change between the two tests? | | | | | | |
| 18 | | | | | | | |
| 19 | | | | | | | |
| 20 | 5. Did the whole sample or a random | Yes | Yes | Yes | Yes | Yes | Yes |
| 21 | | | | | | | |
| 22 | selection of the sample, receive verification | | | | | | |
| 23 | | | | | | | |
| 24 | using a reference standard of diagnosis? | | | | | | |
| 25 | | | | | | | |
| 26 | | | | | | | |
| 27 | 6. Did patients receive the same reference | Yes | Yes | Yes | Yes | Yes | Yes |
| 28 | | | | | | | |
| 29 | standard regardless of the index test result? | | | | | | |
| 30 | | | | | | | |
| 31 | | | | | | | |
| 32 | 7. Was the reference standard independent | Yes | Yes | Yes | Yes | Yes | Yes |
| 33 | | | | | | | |
| 34 | of the index test (i.e. the index test did not | | | | | | |
| 35 | | | | | | | |
| 36 | | | | | | | |
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4 form part of the reference standard)?

5
6 8. Was the execution of the index test Yes Yes Yes Yes Yes Yes Yes

7
8 described in sufficient detail to permit

9
10 replication of the test?

11
12 9. Was the execution of the reference Yes Yes Yes Yes Yes Yes Yes

13
14 standard described in sufficient detail to

15
16 permit its replication?

17
18 10. Were the index test results interpreted Yes Yes Yes Unaware Unaware Unaware

19
20 without knowledge of the results of the

21
22 reference standard?

23
24 11. Were the reference standard results Unaware Unaware Unaware Unaware Unaware Unaware

25
26 interpreted without knowledge of the results

27
28 of the index test?

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30 12. Were the same clinical data available Yes Yes Yes Yes Yes Yes Yes

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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

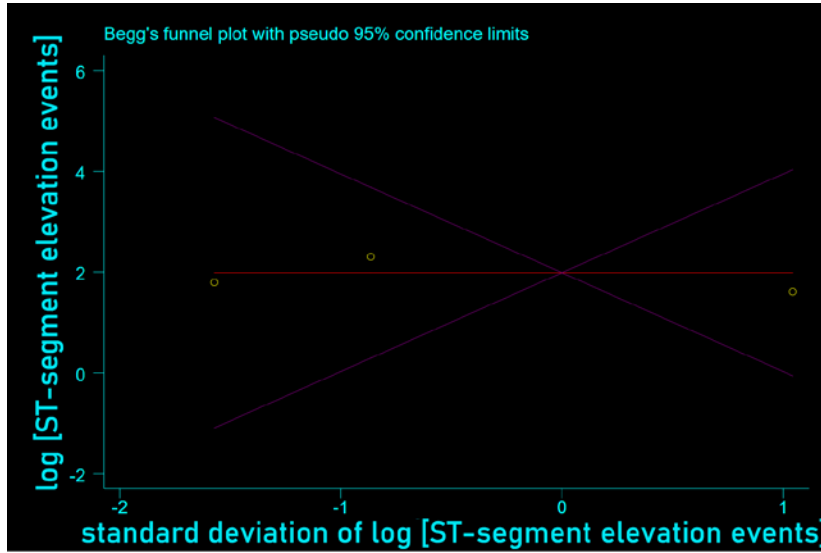
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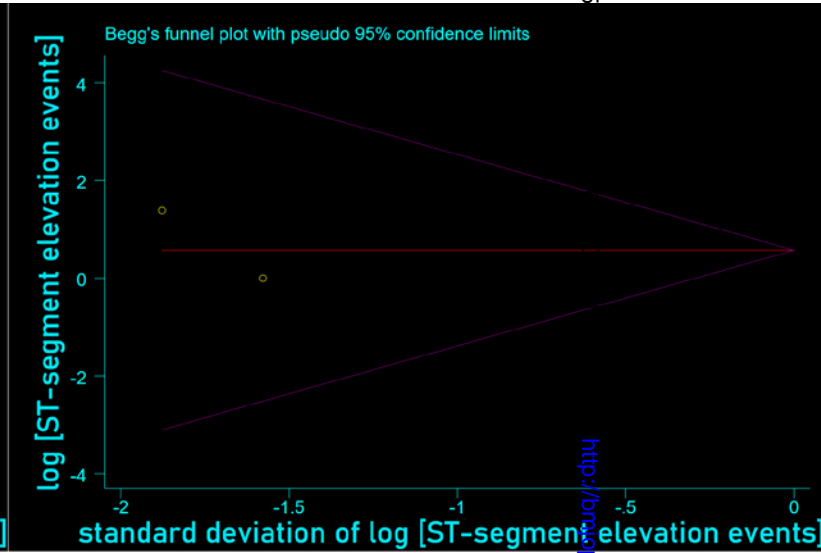
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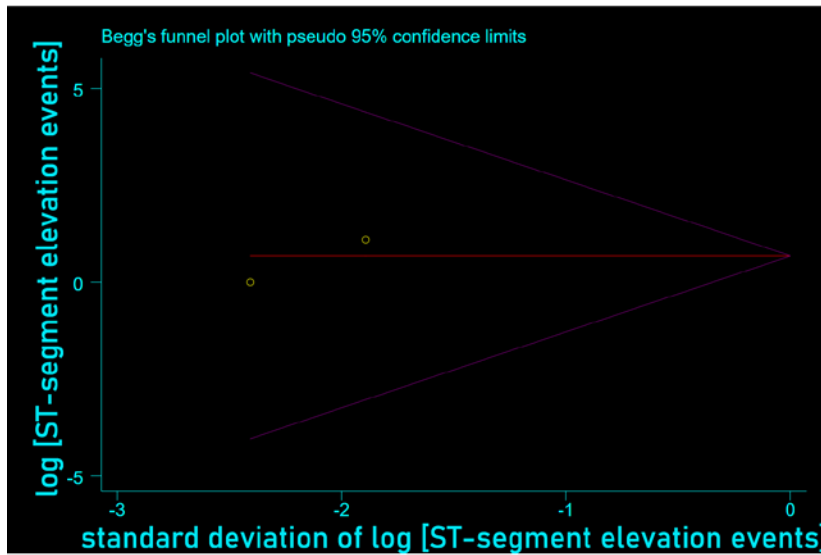
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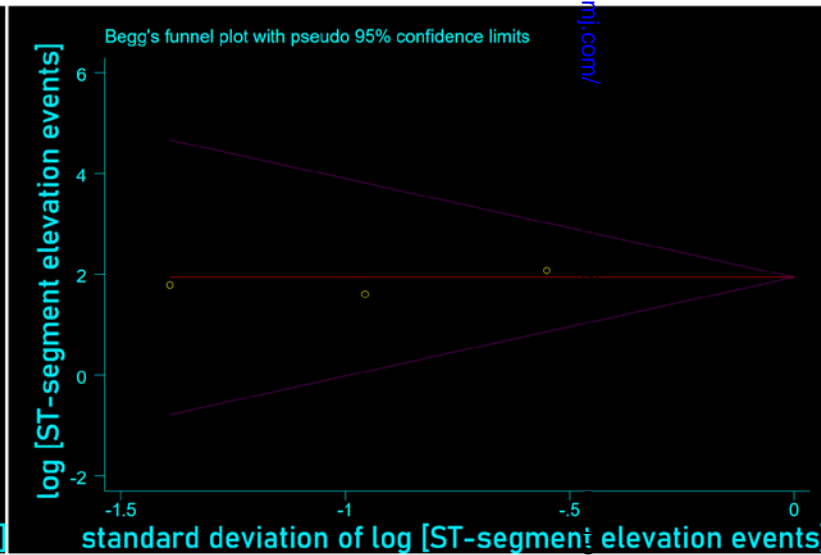
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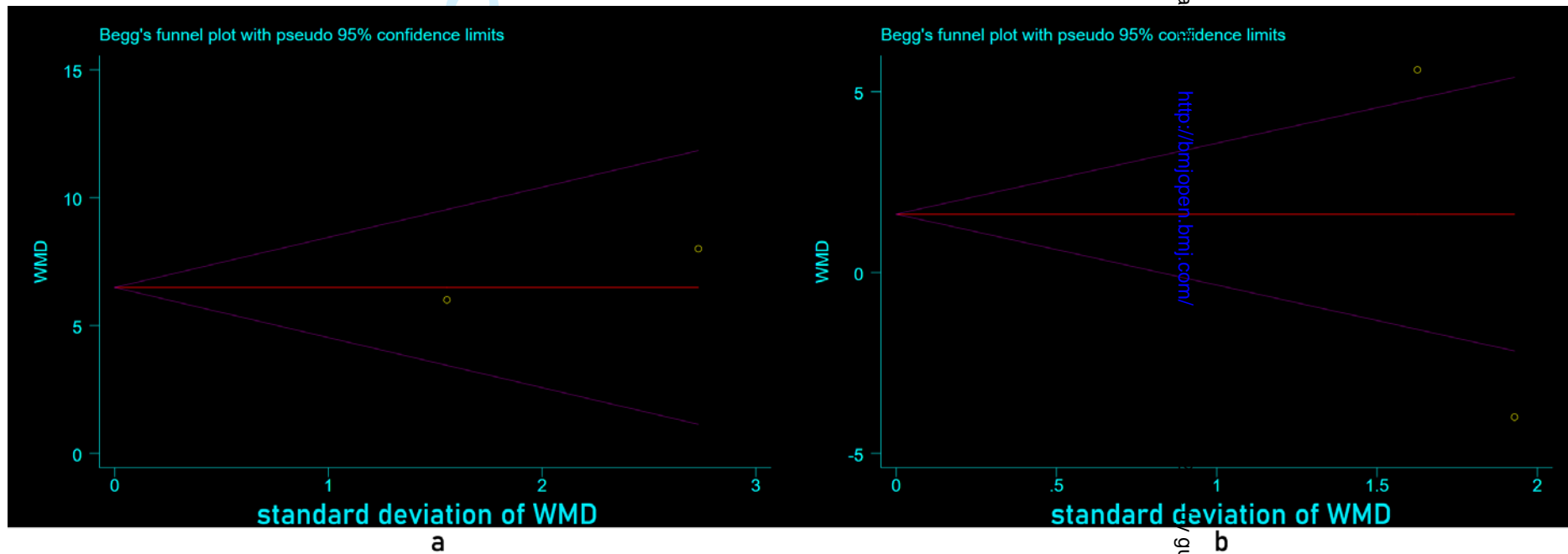


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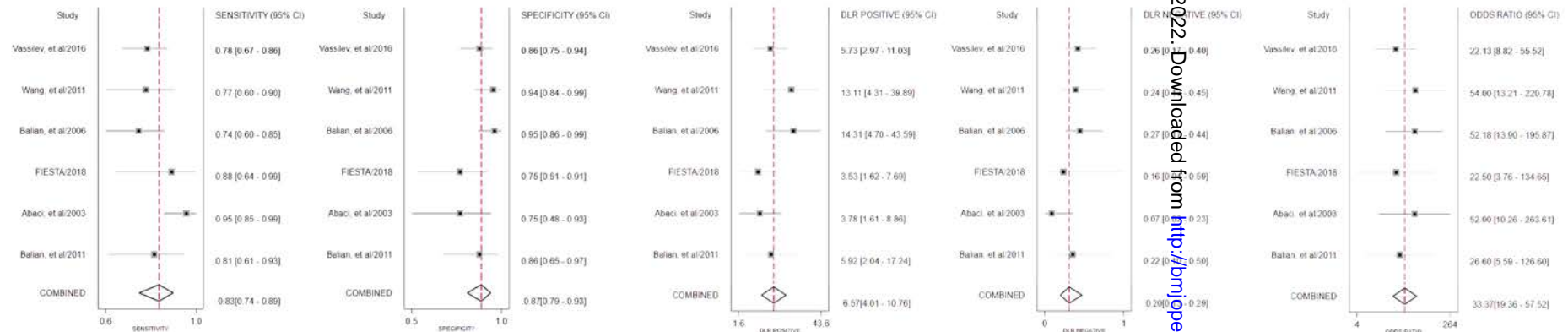
Supplement Figure 1 Publication bias assessment for studies reported clinical outcomes. Using Begg asymmetry test, we found no publication bias in the meta-analysis for the clinical outcomes of (a) major adverse cardiac event, (b) cardiac death, (c) myocardial infarction, and (d) revascularization, with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



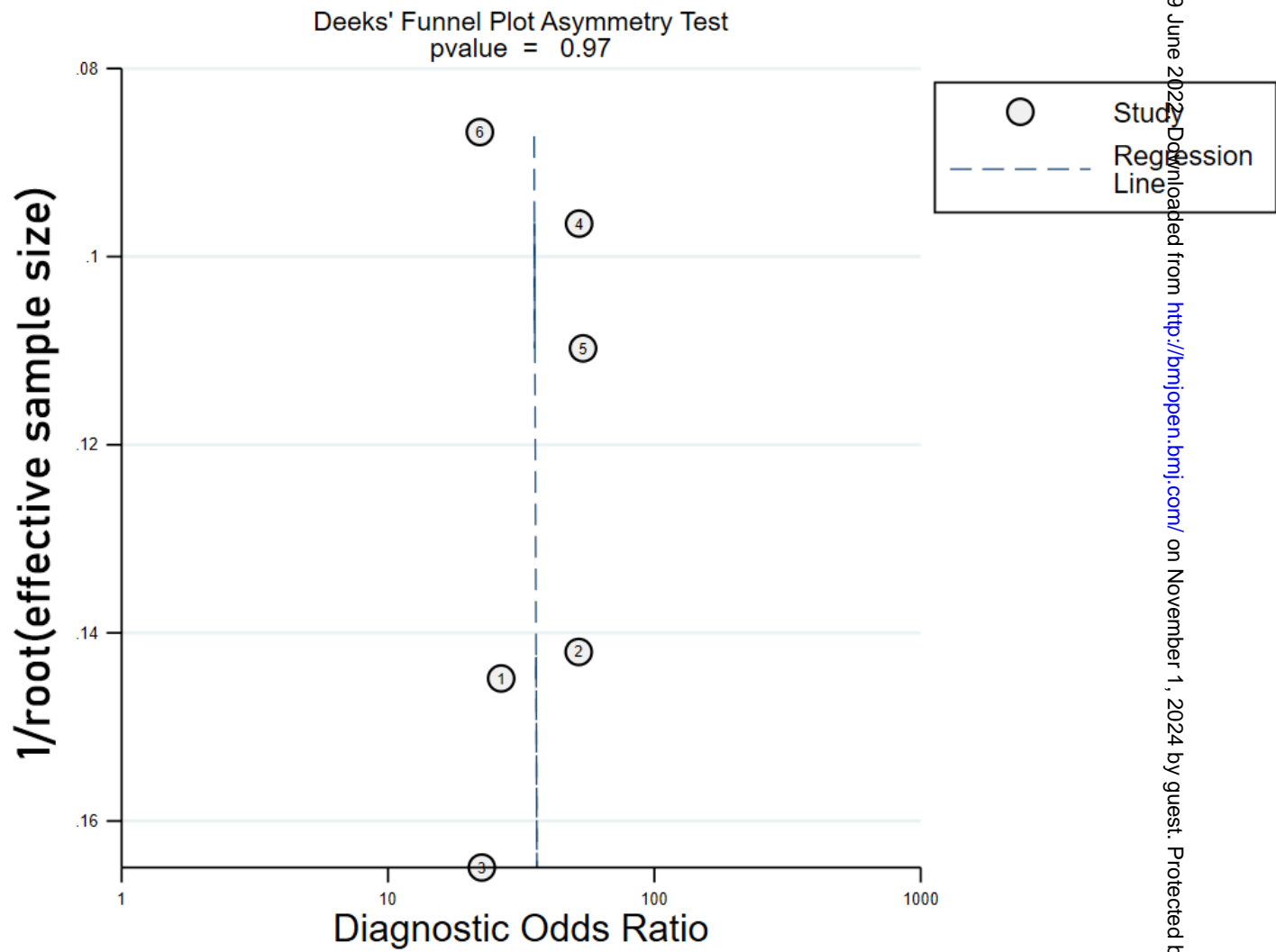
Supplement Figure 2 Publication bias assessment for studies reported ejection fraction. Using Begg asymmetry test, we found no publication bias in the meta-analysis for (a) ST-segment resolution recorded by IC-ECG, and (b) ST-segment elevation. Both p values were 0.317. WMD,

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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%CI 0.74-0.89), specificity was 0.87 (95% 0.79-0.93), positive likelihood ratio was 6.57 (95%CI 4.01-10.76), negative likelihood ratio was 0.20 (95%CI 0.13-0.29), and diagnostic odds ratio was 33.37 (95%CI 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 Abad, et al, 2003; ③ FIESTA, 2018; ④

Balian, et al, 2006; ⑤ Wang, et al, 2011; ⑥ Vassilev, et al, 2016.

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PRISMA 2020 Checklist

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| 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

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| 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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4 **The prognostic and diagnostic accuracy of intracoronary electrocardiogram**
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6 **recorded during percutaneous coronary intervention—a Meta-Analysis**
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35 Word count: 3039; Figure number: 4; Table number: 1.

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40 **Disclaimers**

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45 Hospital, Guangzhou Medical University.

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48 **Source of support**

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51 There were no sources of support for this study.

52
53 **Disclosure**

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56 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%CI

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4 3.84-9.14) for ejection fraction when ST-segment resolution was recorded, and 0.86
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6 (95%CI -8.55-10.26) when ST-segment elevation was recorded. The pooled sensitivity
7
8 and specificity of ST-segment elevation were 0.78 (95% credibility intervals 0.64-0.89)
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10 and 0.87 (95% credibility intervals 0.75-0.94) respectively.
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14 **Conclusions**

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17 These findings provide quantitative data supporting that IC-ECG had promising
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19 diagnostic ability for local myocardial injury, and could predict clinical outcomes.
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25 **Key words:** intracoronary electrocardiogram, prognostic accuracy, diagnostic
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27 accuracy, meta-analysis.
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31 **Strengths and limitations of this study**

32 Strengths

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38 1. There were relatively large number of patients analyzed.
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40 2. We used Bayesian meta-analysis to reduce the bias when assessing the diagnostic
41
42 accuracy.
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45 Limitations

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48 1. Limited by the published studies, we could only perform meta-analysis of
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50 observational studies.
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52 2. We did not perform sensitivity analysis of the timing when the IC-ECG was recorded,
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54 and different types of CADs, limited by the number of studies.
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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

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4 or median age, inclusion criteria, exclusion criteria, reference standard, ORs or event
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6 rates, EF during following-up, and the diagnostic accuracy of IC-ECG. The true-positive,
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8 true-negative, false-positive, and false-negative rates were also estimated, using the
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10 data we extracted from the studies.
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13 14 **Patient and Public Involvement**

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16
17 Patients or the public WERE NOT involved in the design, or conduct, or reporting,
18
19 or dissemination plans of our research.
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21

22 **Statistical analysis**

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25 We directly extracted ORs from each study, or indirectly estimated ORs by
26
27 calculating event rates. And then we pooled ORs using a random-effects meta-analysis
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29 method. For EF, we pooled unstandardized mean difference using a random-effects
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31 meta-analysis method. Summary sensitivity and specificity with their 95% credibility
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33 intervals of IC-ECG were obtained by using Bayesian bivariate random effects meta-
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35 analysis[19-21]. Bayesian summary receiver-operating-characteristic (SROC) curves
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37 were constructed and the areas under the Bayesian SROC curves (AUC) were
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39 performed to assess the diagnostic accuracy of IC-ECG[20,21].
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46 To perform quality assessment, two authors independently assessed the
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48 prognostic studies' qualities by using the Newcastle-Ottawa Scale (NOS)[22] and the
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50 diagnostic studies' qualities by using the Quality Assessment Tool for Diagnostic
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52 Accuracy Studies (QUADAS) tool [23]. The NOS evaluated 3 parameters (selection,
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54 comparability, and outcome) divided across 8 items. Each item was scored from 0 to
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56 1 star, except for comparability, which could be adapted to the specific topic of
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4 interest to score up to 2 stars. Thus, the maximum score for each study was 9. Studies
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6 with <3 stars were at a high risk of bias and would be excluded. The QUADAS tool
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8 contained 14 questions which could be used for assessing the qualities of diagnostic
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10 studies. Disagreements were resolved by consensus.
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14 Statistical heterogeneities between prognostic studies were evaluated with the
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16 I^2 statistic [24], which estimates the percentage of total variation across studies due
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18 to true between-study differences rather than chance, with I^2 values of 25, 50, and 75%
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20 representing low, medium, and high heterogeneities, respectively. We performed
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22 conflict of evidence analysis for diagnostic studies by extending the random effects
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24 distribution, using a scale mixture of normal distributions per random effect[20]. After
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26 splitting the studies' weights, we could find out the heterogeneities if the posterior
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28 probabilities of studies were greater than 0.7. The Begg asymmetry tests[25] for
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30 studies which reported clinical outcomes were performed to assess the publication
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32 bias. P values that were less than 0.05 were considered statistically significant.
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34 Statistical analyses were carried out with STATA, version 16.0 (Stata Corp, College
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36 Station, Texas), and R statistical software with "bamdit" packages[20].
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45 **Results**

46 **Literature search**

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49 The details of search steps are shown in Figure 1. We identified and screen 480
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51 articles from our preliminary search. After screening abstracts, 440 articles were
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53 excluded because the study objects were not IC-ECG. 16 articles were excluded
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55 because they were not clinical trials. Bigler's study compared deep learning with
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4 manually obtained IC-ECG results[26], and was excluded. 23 articles were identified
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6 for full review. Among these articles, 2 duplicated studies were excluded. 9 articles
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8 were excluded because they did not report ORs, diagnostic accuracy, or data
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10 necessary to calculate these. Finally, there were 12 studies included in our meta-
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12 analysis. 7 studies reported the clinical outcomes and 6 studies reported the
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14 diagnostic accuracy of IC-ECG.
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18 19 **Study characteristics**

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21
22 The characteristics of included studies are shown in Table 1 and Supplement
23
24 table 2. There were 7 cohort studies and 6 diagnostic studies in our meta-analysis.
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26 There were 1198 cases included in our meta-analysis totally. Among these cases, 821
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28 cases and 485 cases were included in the meta-analysis for prognostic and diagnostic
29
30 accuracy of IC-ECG respectively. The proportion of men was 68.8%. The inclusion
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32 criteria of the included articles were CAD patients, including stable or unstable angina
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34 pectoris, and myocardial infarction. The clinical outcomes reported in these studies
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36 were mainly MACEs, cardiac death, myocardial infarction, repeat revascularization,
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38 and EF. The reference standards reported in the diagnostic studies were varied,
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40 including FFR[5,13], echocardiogram[14], and troponin[12,15,16].
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48 **The correlation between clinical outcomes and ST-segment elevation recorded** 49 50 **by IC-ECG**

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53 Pooled OR for MACE is shown in Figure 2a. The inclusion criteria of these studies
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55 were patients with angina and stable conditions. MACEs were defined as cardiac death,
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57 myocardial infarction, revascularization, and hospitalization for heart failure in
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4 Ikenaga's study[10]. In Uetani's study[11] and Balian's study[12], MACEs were defined
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6 as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG
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8 after PCI procedures was significantly associated with higher risk of MACE (OR 4.65,
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10 95%CI 1.69-12.77). There were mild heterogeneities among studies ($I^2=30.1\%$,
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12 $p=0.239$). And there was no publication bias (the result is shown in Supplement figure
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14 1a, $p=0.602$).

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19 Pooled ORs for cardiac death, myocardial infarction, and revascularization are
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21 shown in Figure 2b-2d. The inclusion criteria of these studies were patients with
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23 angina or non ST-segment elevation myocardial infarction (NSTEMI). In the meta-
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25 analysis for cardiac death, Ikenaga's study[10] was excluded because there were no
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27 events. ST-segment elevation recorded by IC-ECG after PCI procedures was
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29 significantly associated with higher risk of myocardial infarction (OR 5.08, 95%CI 1.10-
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31 23.44), but not cardiac death (OR 4.53, 95%CI 0.79-25.90) nor revascularization (OR
32
33 1.83, 95%CI 0.93-3.62). There were no heterogeneities among studies (cardiac death,
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35 $I^2=0\%$, $p=0.494$; myocardial infarction, $I^2=0\%$, $p=0.567$; revascularization, $I^2=0\%$,
36
37 $p=0.642$). And there were no publication bias (cardiac death, $p=0.317$; myocardial
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39 infarction, $p=0.317$; revascularization, $p=0.602$, and the results are shown in
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41 Supplement figure 1b-1d).

50 **The correlation between EF and different results recorded by IC-ECG during** 51 52 **follow-up** 53

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56 The correlation between EF and different results recorded by IC-ECG are shown
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58 in Figure 3. We divided the included studies into 2 subgroups according to the
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4 different evaluation methods reported by the studies. One was ST-segment resolution,
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6 and the other one was ST-segment elevation. In the subgroup of ST-segment
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8 resolution, inclusion criteria were patients with ST-segment elevation myocardial
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10 infarction (STEMI). The pooled weighted mean difference (WMD) was 6.49, with
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12 95% CIs 3.84-9.14. There were no heterogeneities ($I^2=0\%$, $p=0.525$). And there was no
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14 publication bias (the result is shown in Supplement figure 2a, $p=0.317$). The inclusion
15
16 criteria of ST-segment elevation subgroup were patients with NSTEMI (Hishikari, et
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18 al[7]) or anterior myocardial infarction (Yajima, et al [9]) . The pooled WMD was 0.86,
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20 with 95% CIs -8.55-10.26. There were heterogeneities ($I^2=86.3\%$, $p<0.01$), but no
21
22 publication bias (the result is shown in Supplement figure 2b, $p=0.317$).
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30 **Diagnostic accuracy of ST-segment elevation recorded by IC-ECG**

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32 Abaci's study reported the diagnostic accuracy for myocardial viability[14], while
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34 the other 5 diagnostic studies reported the diagnostic accuracy for myocardial injury
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36 or ischemia. Therefore, we excluded Abaci's study when we performed Bayesian
37
38 meta-analysis for diagnostic studies. The pooled diagnostic accuracy and the
39
40 predictive posterior rates are shown in Supplement figure 3. The Bayesian SROC curve
41
42 and the AUC are shown in Figure 4. The pooled sensitivity and specificity were 0.78
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44 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94),
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46 respectively. And predictive posterior sensitivity and specificity were 0.76 (95%
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48 credibility intervals 0.39-0.96) and 0.85 (95% credibility intervals 0.50-0.98),
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50 respectively. The AUC of Bayesian SORC was 0.65 (95% credibility intervals 0.56-0.69).
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58 After splitting the studies' weights, there were no heterogeneities and the posterior
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4 probabilities of studies were all smaller than 0.7. The posterior distributions of the
5
6 component weights are shown in Supplement figure 4.
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8 9 **Quality assessment**

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11 Results of quality assessment adapted from NOS are shown in Supplement table
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13 3. All the studies reached over 3 stars, but no study reached the maximum score.
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15 Considering all the studies included CAD patients, no study got scored in the fourth
16
17 item of selection section. Only 3 studies[6,7,11] reported the confounders and were
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19 scored 2 stars in the comparability section. Two studies[9,11] reported the in-hospital
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21 outcomes and did not report the patients lost to follow-up, therefore, they were not
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23 scored in the second and third items of outcome section.
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30 Results of quality assessment adapted from QUADAS tool are shown in
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32 Supplement table 4. All the studies clearly described the methods. No studies
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34 described whether they blinded reviewers to the results of IC-ECGs, while 3
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36 studies[12-14] blinded reviewers to the results of reference standards. Only 2
37
38 studies[12,14] reported the intermediate results, and 2 studies[5,12] explained the
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40 withdrawals.
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45 **Discussion**

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48 Our results from the meta-analysis of observational studies indicated that ST-
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50 segment elevation recorded by IC-ECG after PCI procedures for stable angina patients
51
52 linked to worse MACE outcomes. For angina or NSTEMI patients, ST-segment
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54 elevation was significantly associated with higher risk of myocardial infarction during
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56 follow-up, but not cardiac death nor revascularization. ST-segment resolution
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4 recorded by IC-ECG after PCI procedures for STEMI patients was significantly
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6 associated with increased EF during follow-up. But ST-segment elevation during PCI
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8 procedures did not significantly link to increased or decreased EF. After Bayesian
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10 meta-analysis, ST-segment elevation recorded by IC-ECG showed promising diagnostic
11
12 ability for myocardial injury or ischemia.
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16
17 ST-segment shift pattern recorded by ECG during acute myocardial infarction was
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19 reported 100 years ago [27]. And ST-segment deviation recorded by surface ECG was
20
21 a part of the universal definition of myocardial infarction[28]. However, surface ECG
22
23 was not reliable for detecting local myocardial ischemia during PCI procedures in real
24
25 time[29]. In this case, IC-ECG was more reliable and sensitive for detecting local
26
27 ischemia[30]. For instance, in Vassilev's study, they found that when they pulled back
28
29 the guidewire, the elevated ST-segment would suddenly normalize if the wire tip
30
31 exited the border of ischemic territory[16]. Although IC-ECG was more sensitive than
32
33 surface ECG when assessing left ascending artery and circumflex territory, It should be
34
35 noted that IC-ECG was less sensitive when assessing right coronary artery
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37 territory[31,32]. On the other hand, impaired microvascular perfusion during PCI
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39 might lead to periprocedural myocardial infarction, indicating worse outcomes. IC-
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41 ECG could detect local ischemia, which was found to be well associated with impaired
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43 microvascular perfusion[10]. For instance, in Sato's study, the prolongation of ST-
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45 segment elevation time recorded by IC-ECG was associated with higher max-lipid core
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47 burden index 4mm detected by near-infrared spectroscopy with IVUS in stable angina
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49 patients, which might indicate distal embolization and microvascular disease[33].
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4 The results from this meta-analysis indicated that ST-segment elevation recorded
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6 by IC-ECG after PCI procedure was significantly associated with worse MACE outcomes
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8 and higher risk of myocardial infarction in angina or NSTEMI patients, but not
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10 significantly associated with cardiac death nor revascularization. Although there were
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12 trends that the risks of cardiac death and revascularization were higher when ST-
13
14 segment elevation was observed, more cases might be needed to prove this
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16 hypothesis. ST-segment elevation recorded by IC-ECG might be observed when higher
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18 pressure or longer duration balloon inflation was performed, indicating local ischemia.
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20 Local myocardial ischemia could be confirmed by testing myocardial biomarkers.
21
22 Vassilev's study found that the maximal ST-segment elevation during inflation
23
24 significantly correlated with final absolute ST-segment elevation and creatine kinase-
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26 MB isoenzyme increase post PCI, but not with troponin[16]. Interestingly, IVUS guided
27
28 stent overexpansion was associated with higher periprocedural creatine kinase-MB
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30 isoenzyme level too, but lower risk of target lesion revascularization and mortality at
31
32 1 year[34]. Therefore, IC-ECG might provide useful information for guiding stent
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34 expansion[10]. Moreover, Ikenaga and Sato found more plaque rupture, vulnerable
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36 plaque or higher lipid core burden when ST-segment elevation was observed, even
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38 persisted on IC-ECG[10,33]. IC-ECG could help to distinguish the plaque, optimizing
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40 medical therapies or PCI strategies. For instance, we could use vasodilators, loading
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42 dose of statin, or embolic protection devices to reduce distal embolization[33]. And,
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44 Vassilev's studies found that IC-ECG had good correlation with FFR, which might be
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46 used in guiding bifurcation PCI procedures[5,16].
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4 According to our meta-analysis, EF was significantly higher during follow-up when
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6 ST-segment resolution was observed on IC-ECG in STEMI patients. ST-segment
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8 resolution on surface ECG which was observed 90 minutes after the initial therapy was
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10 found to be significantly associated with smaller infarct size and fewer deaths[35]. But
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12 surface ECG could not explore some small infarct zone sometimes[8]. Furthermore,
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14 restoration of coronary flow didn't mean normal myocardial perfusion nor better
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16 outcomes[36]. IC-ECG could provide real time ST-segment information, and was found
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18 to be well associated with microvascular obstruction and infarct size[6]. In our meta-
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20 analysis, ST-segment resolution recorded by IC-ECG was significantly associated with
21
22 higher EF, meaning better recovery of heart function. This finding was similar to
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24 previous studies. In the subgroup of ST-segment elevation, there were heterogeneities
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26 between 2 studies. In Hishikari's study[7], ST-segment elevation recorded by IC-ECG
27
28 was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's
29
30 study[9], the result was different in anterior myocardial infarction patients. The
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32 possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-
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34 ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was
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36 performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI
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38 procedure might indicate prolonged local myocardial ischemia and worse outcome, as
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40 we described above. The result of Hishikari's study that lower EF was observed in ST-
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42 segment elevation group, was one of these evidences. On the other hand, there might
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44 be myocardium stun after acute myocardial infarction[37]. The results of Yajima's
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46 study showed that ST-segment elevation recorded by IC-ECG after balloon inflation
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4 could predict myocardial viability and better outcomes[9]. These findings showed that
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6 IC-ECG might help to optimize PCI procedure by providing real time information, which
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8 could predict clinical outcomes.
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11 The diagnostic studies included in our study reported 3 reference standards.
12
13 After excluding Abaci's study, there were still 2 reference standards. And the
14
15 reference standards (FFR and troponin) for diagnosing myocardial ischemia or injury
16
17 were not perfect. Also, there were too few studies included in our meta-analysis.
18
19 Considering these situations, we used Bayesian meta-analysis to assess the pooled
20
21 diagnostic accuracy of IC-ECG. There were already several papers illustrated this
22
23 method to reduce the bias which came from the different or imperfect reference
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25 standards[20,21,38,39]. The results of our Bayesian meta-analysis showed the
26
27 promising diagnostic ability of IC-ECG for diagnosing myocardial ischemia or injury.
28
29 Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be easily
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31 performed and produce real time information. Although Abaci's study was excluded
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33 when performing the meta-analysis, this study still provided important results. Like
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35 Yajima's study which was mentioned above, Abaci's study recorded IC-ECG after
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37 balloon inflation, not PCI procedures. Both of these 2 studies found a good correlation
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39 between ST-segment elevation and myocardial viability. In short, IC-ECG had potential
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41 value for guiding PCI.
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52 The strengths of our study were the relatively large number of patients analyzed.
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54 And we used Bayesian meta-analysis to reduce the bias when assessing the diagnostic
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56 accuracy. However, there were limitations to our study. First, limited by the published
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4 studies, we could only perform meta-analysis of observational studies. And the wide
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6 CIs of ORs were the results of low event rates reported in the studies, especially in the
7
8 no ST-segment elevation group. Second, not all the included studies performed
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10 adjustments for confounders, or reports of patients lost to follow-up. Thus, the results
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12 of quality assessment were not so satisfactory. Third, there were varied and imperfect
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14 reference standards reported in the diagnostic studies. Therefore, we chose Bayesian
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16 meta-analysis to assess the pooled diagnostic accuracy, reducing the bias. Forth, we
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18 did not perform sensitivity analysis of the timing when the IC-ECG was recorded, and
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20 different types of CADs, limited by the number of studies. But in the meta-analysis of
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22 clinical outcomes, there were no heterogeneities or publication bias. These results
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24 indicated that different types of CADs had little influence on the ORs. And we found
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26 that recording IC-ECG in different phases of PCI procedures might produce different
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28 information which might help decision making. Further researches should consider
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30 whether the correlation between IC-ECG measures and clinical outcomes depend on
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32 the timing of the IC-ECG.
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Conclusions

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

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4 **Design and Planning** Pan Yizhi MD, PhD

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

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

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

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

16
17 **Guarantor** Pan Yizhi MD, PhD

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22 **Acknowledgements**

23
24 The authors thank Dr. Wu Suhua, who is from department of Cardiology, The First
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Affiliated Hospital, Sun Yat-Sen University, for his help.

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33 **Registration and protocol**

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

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44 **Competing interests**

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46 The authors have declared that no competing interests exist.

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52 **Availability of data, code and other materials**

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

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4 collection forms, data extracted from included studies, data used for all analyses, and
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6 analytic code used in the study are not publicly available.
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10 11 **Ethics committee approval**

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13 We do not need ethics committee approval for our study because it is meta-analysis
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15 and we did not access primary patient/animal data nor interact with any
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17 patients/animals. We collected and synthesized data from previous studies published
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19 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-

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

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

China[15]

| | | | | | |
|---|-----|------|-----------|-----|------------|
| Vassilev, et al. 2016, Diagnostic study | 135 | 59.2 | 65.1±10.0 | N/A | Troponin I |
|---|-----|------|-----------|-----|------------|

Bulgaria[16]

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

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

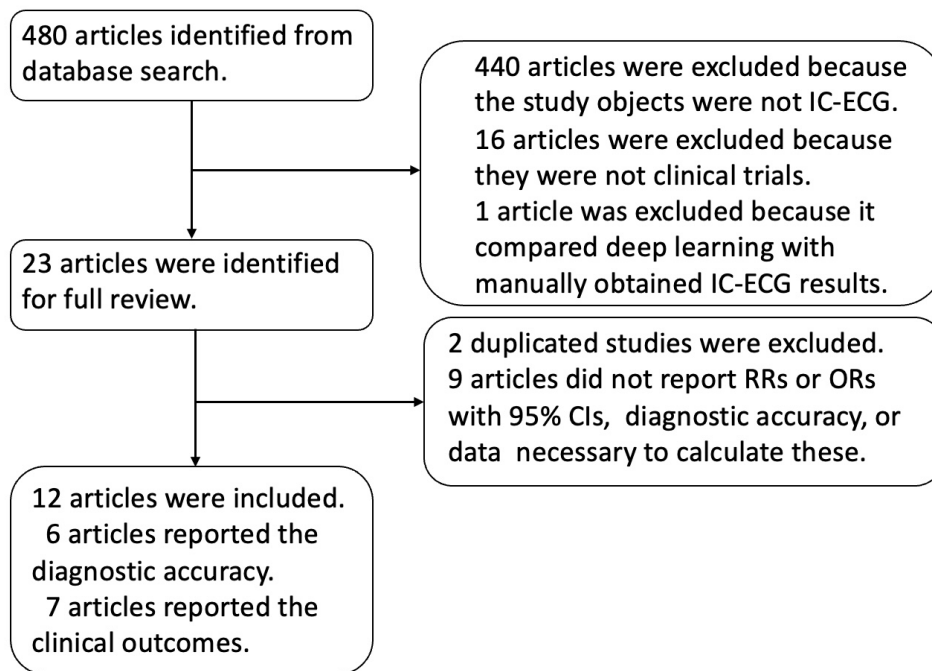


Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

236x165mm (144 x 144 DPI)

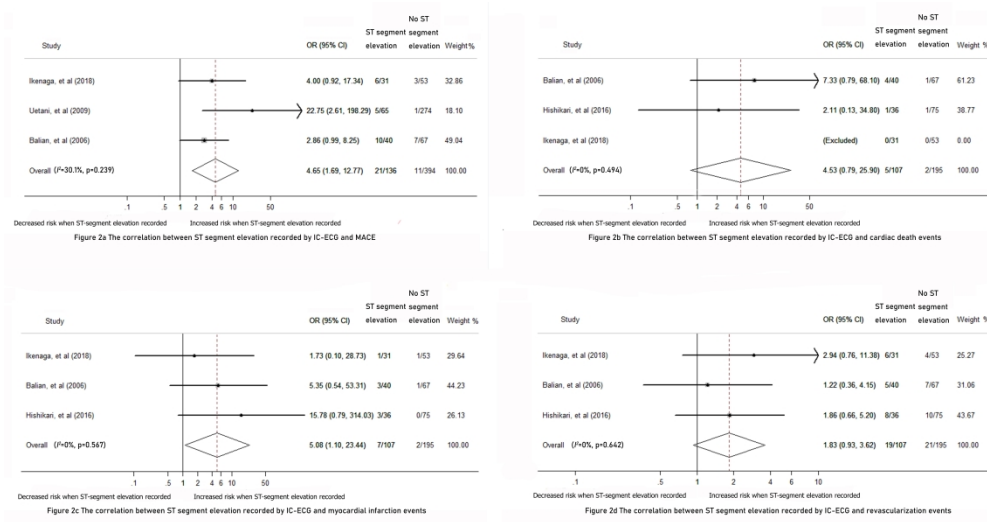


Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during 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.

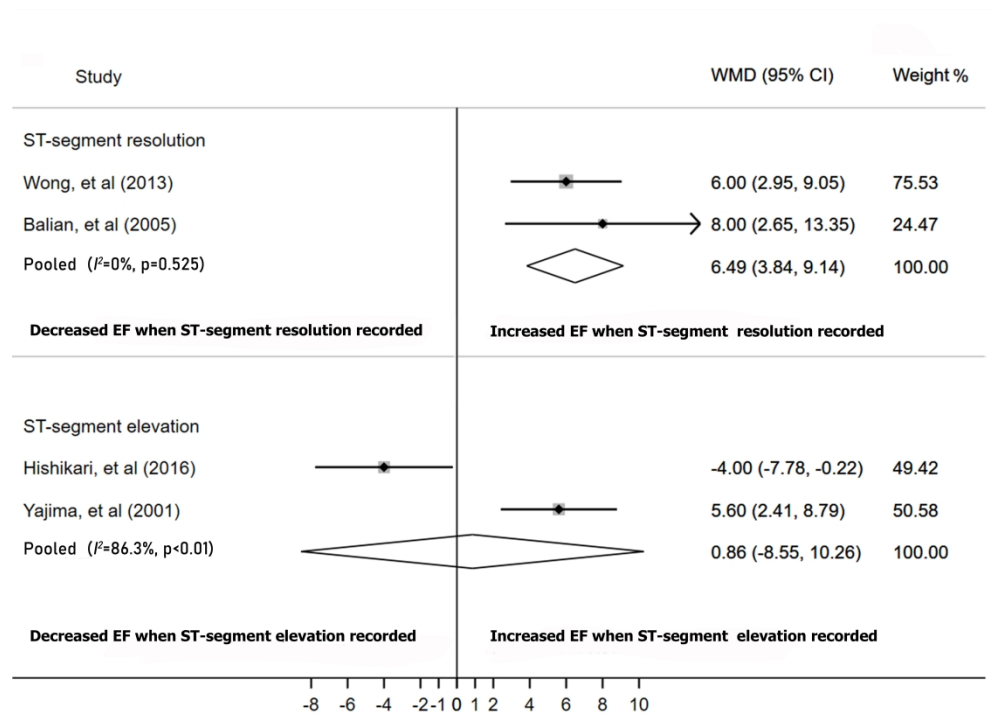


Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, 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.

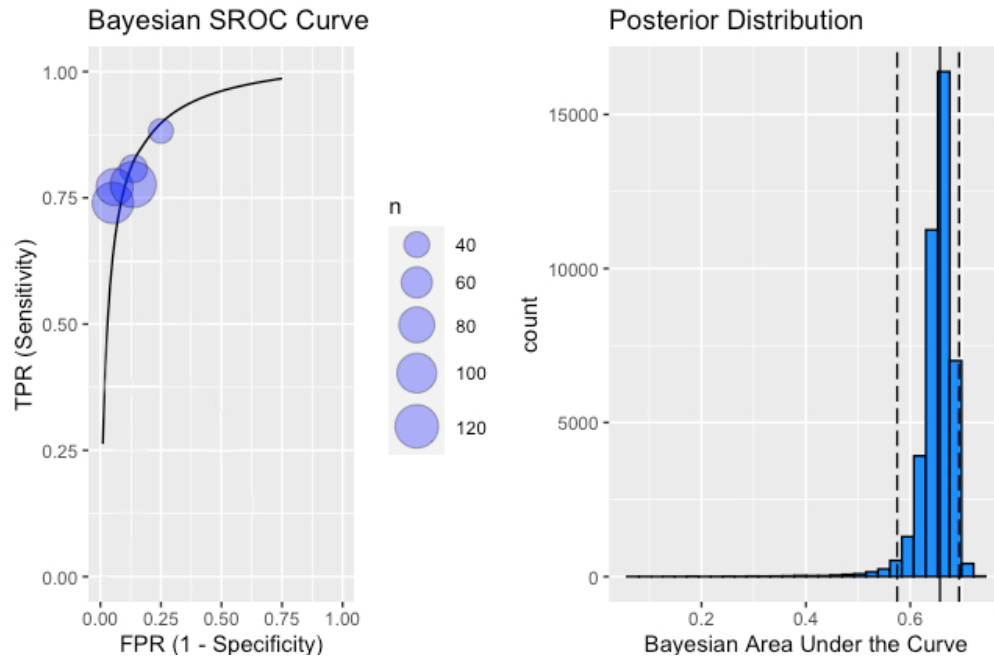


Figure 4 The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and the posterior distribution of AUC. Each circle identifies the true positive rate versus the false positive rate of each study. The AUC was 0.65 (95% credibility intervals 0.56-0.69). TPR, true positive rate; FPR, false positive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

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] | <p>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.</p> | <p>(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</p> | <p>Major adverse cardiac event (MACE), which was defined as cardiac death, MI, repeat revascularization and/or hospitalization for heart failure.</p> |

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4 expected difficulty in advancing
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6 soft-tip guidewire or the FD-
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8 OCT catheter, severe calcified
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10 lesions needed for debulking
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12 device, target vessel reference
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14 diameter of ≥ 4 mm expected
15
16 limitation in FD-OCT evaluation
17
18 and angiographic evidence of
19
20 coronary dissection or major
21
22 side branch (>1 mm) occlusion
23
24 after the procedure.
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32 Wong, et al. 2013, Australia[6]

33 Patients with acute STEMI who
34
35 underwent primary-PCI.

36 patients aged <18 years,
37
38 previous myocardial infarction
39
40 in the same territory,

41 The relationship between
42
43 intracoronary ST-segment
44
45 resolution and MVO assessed
46

contraindications to CMR (e.g., by CMR 4 days after primary-
 pacemaker implantation or PCI.
 claustrophobia) and
 contraindication to
 gadopentetate dimeglumine
 (e.g., known hypersensitivity to
 gadopentetate dimeglumine or
 creatinine clearance \leq 60
 mL/min/1.73 m²).

Hishikari, et al. 2016, Japan[7] Patients' symptoms of coronary (1) age<21 years, (2) STEMI, (3) In hospital: ventricular
 ischemia that were worsening or history of MI, (4) history of PCI, arrhythmias, congestive heart
 occurring at rest for more than 10 (5) renal insufficiency with a failure, cardiogenic shock, and
 min within the past 12 hours, baseline serum creatinine cardiac death. Follow-up:
 unequivocal changes on an level >1.8 mg/dL (133 μ mol/L), Adverse events included fatal

admission ECG elevated cardiac (6) multivessel CAD or left main arrhythmias, cardiac death,
 biomarkers and no CAD, (7) patients in whom the nonfatal MI, revascularization
 contraindication for PCI absence of significant CAD or or congestive heart failure
 culprit lesion could not be requiring hospitalization.
 identified according to the
 angiogram, and (8) major (>1.5
 mm) side branch occlusion after
 PCI.

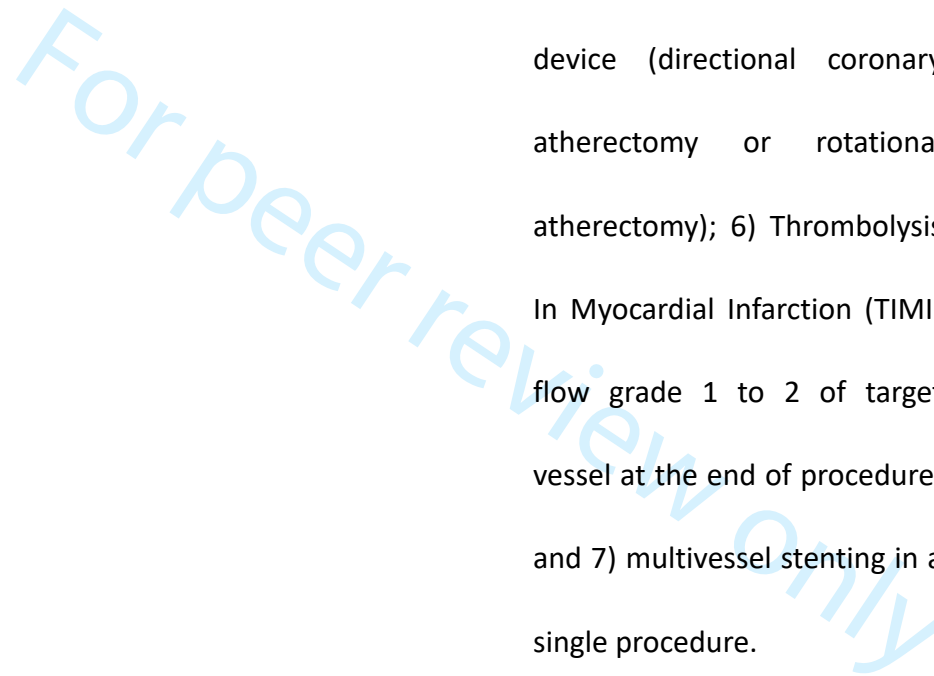
Uetani, et al. 2009 Japan[11]

Consecutive patients who 1) emergency coronary Post-procedure cardiac
 underwent apparently successful angioplasty within 24 h of biomarkers and in hospital
 elective coronary stent onset; 2) elevated pre-major adverse cardiac event,
 implantations. All had angina, procedural cardiac biomarker; which was defined as cardiac
 documented myocardial ischemia, 3) active congestive heart death and MI.
 or both. 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 procedure; and 7) multivessel stenting in a single procedure.

Balian, et al. 2005, Italy[8]

Absence of cardiogenic shock, Patients with previous AMI, Left ventricular ejection adequacy of echocardiographic ventricular conduction fraction and infarct zone wall window, IRA occlusion (TIMI flow disturbances on standard ECG, motion score index.



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grade 0-1) or patency (TIMI flow or ventricular pacing were.

grade 2) with a severe (>90%)

stenosis, and a successful primary

stenting.

Yajima, et al. 2001, Japan[9]

Patients with a first episode of contraindication of coronary coronary events, clinical

anterior myocardial infarction angiogram, >50% stenosis in outcomes, left ventriculogram

underwent emergency coronary the left main coronary measurements and myocardial

angioplasty within 12 hours of artery, >75% stenosis in viability

onset. another major coronary artery,

prior myocardial infarction,

cardiogenic shock,

cardiomyopathy, and right or

left bundle branch block on the

ECG.

| | | | |
|--------------------------------|--|--|--|
| Balian, et al. 2006, Italy[12] | <p>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.</p> | <p>Unstable patients, patients with ventricular conduction disturbances on standard ECG or ventricular pacing, and those who had procedural complications were excluded.</p> | <p>Adverse events included death, nonfatal MI, or a new coronary revascularization procedure. Major coronary events included death or nonfatal MI.</p> |
| Balian, et al. 2011, Italy[13] | <p>Patients undergoing elective coronary angiography with single-vessel intermediate stenosis (40–70% diameter narrowing) on</p> | <p>prior ST segment elevation myocardial infarction, prior coronary revascularization, ostial stenosis, presence of left</p> | N/A |

quantitative assessment were 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; Patients with poor acoustic window, postinfarction angina, regional wall motion abnormality; active congestive heart failure, single, non-occlusive significant bundle branch block, atrial stenosis ($\geq 70\%$ by quantitative fibrillation, valvular disease, N/A

measurements) in the IRA; and significant stenosis in the non-scheduled revascularization of the IRA, and collateral filling to the IRA for angiographic and clinical IRA.

reasons.

FIESTA. 2018, Bulgaria[5]

Patients with stable or unstable patients with ST-segment N/A
 angina were included. The elevation myocardial infarction
 inclusion criterion was and those with non-cardiac
 angiographic bifurcation lesions in comorbid conditions with a life
 a native coronary artery with a expectancy of less than one
 diameter ≥ 2.5 mm and ≤ 4.5 year. In addition, patients with
 mm and an side branch diameter left main coronary artery
 ≥ 2.0 mm. 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 fibrillation found on ECG; (3) results during the procedure. 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

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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

1
2
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4 with non-cardiac co-morbid
5 conditions with life expectancy
6 <1 year. The following patients
7 were also excluded: 1) left main
8 coronary artery stenosis, 2)
9 total occlusion before
10 occurrence of SB, 3) lesion of
11 interest located at infarct-
12 related artery, 4) subjects with
13 left ventricular ejection fraction
14 < 30%, 5) subjects with
15 moderate or severe degree
16 valvular heart disease or
17 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 | | Assessment | 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 | |
| | | | | | | | | | |

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|----|---------------------------|---|---|---|----|---|---|---|---|
| 1 | | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | Ikenaga, et al. 2018[10] | * | * | * | | * | * | * | 6 |
| 4 | | | | | | | | | |
| 5 | Wong, et al. 2013[6] | * | * | * | ** | * | * | * | 8 |
| 6 | | | | | | | | | |
| 7 | Hishikari, et al. 2016[7] | * | * | * | ** | * | * | * | 8 |
| 8 | | | | | | | | | |
| 9 | Uetani, et al. 2009[11] | * | * | * | ** | * | | | 6 |
| 10 | | | | | | | | | |
| 11 | Balian, et al. 2005[8] | * | * | * | | * | * | * | 6 |
| 12 | | | | | | | | | |
| 13 | Yajima, et al. 2001[9] | * | * | * | | * | | | 4 |
| 14 | | | | | | | | | |
| 15 | Balian, et al. 2006[12] | * | * | * | | * | * | * | 6 |
| 16 | | | | | | | | | |

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 |

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representative of the patients who will receive the test in practice?

2. Were selection criteria clearly described? Yes Yes Yes Yes Yes Yes Yes

3. Is the reference standard likely to correctly classify the target condition? Yes 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 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 Yes

6. Did patients receive the same reference standard regardless of the index test result? Yes Yes Yes Yes Yes Yes Yes

| | | | | | | | |
|----|--|---------|---------|---------|---------|---------|---------|
| 1 | | | | | | | |
| 2 | | | | | | | |
| 3 | | | | | | | |
| 4 | 7. Was the reference standard independent | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | | | | | | | |
| 6 | of the index test (i.e. the index test did not | | | | | | |
| 7 | | | | | | | |
| 8 | form part of the reference standard)? | | | | | | |
| 9 | | | | | | | |
| 10 | | | | | | | |
| 11 | 8. Was the execution of the index test | Yes | Yes | Yes | Yes | Yes | Yes |
| 12 | | | | | | | |
| 13 | described in sufficient detail to permit | | | | | | |
| 14 | | | | | | | |
| 15 | replication of the test? | | | | | | |
| 16 | | | | | | | |
| 17 | | | | | | | |
| 18 | | | | | | | |
| 19 | 9. Was the execution of the reference | Yes | Yes | Yes | Yes | Yes | Yes |
| 20 | | | | | | | |
| 21 | standard described in sufficient detail to | | | | | | |
| 22 | | | | | | | |
| 23 | permit its replication? | | | | | | |
| 24 | | | | | | | |
| 25 | | | | | | | |
| 26 | | | | | | | |
| 27 | 10. Were the index test results interpreted | Yes | Yes | Yes | Unaware | Unaware | Unaware |
| 28 | | | | | | | |
| 29 | without knowledge of the results of the | | | | | | |
| 30 | | | | | | | |
| 31 | reference standard? | | | | | | |
| 32 | | | | | | | |
| 33 | | | | | | | |
| 34 | | | | | | | |
| 35 | 11. Were the reference standard results | Unaware | Unaware | Unaware | Unaware | Unaware | Unaware |
| 36 | | | | | | | |
| 37 | interpreted without knowledge of the results | | | | | | |
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of the index test?

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 Yes Unaware Yes Unaware Unaware Unaware

results reported?

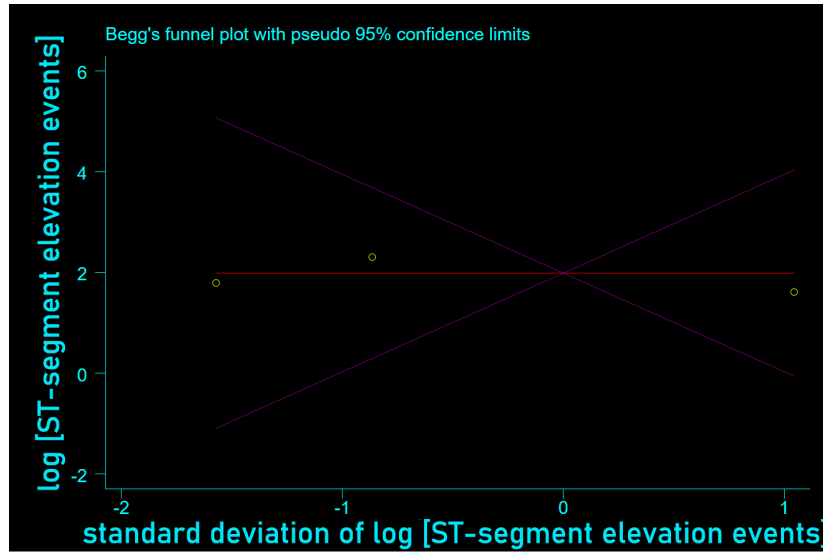
14. Were withdrawals from the study Yes Unaware Unaware Yes Unaware Unaware

explained?

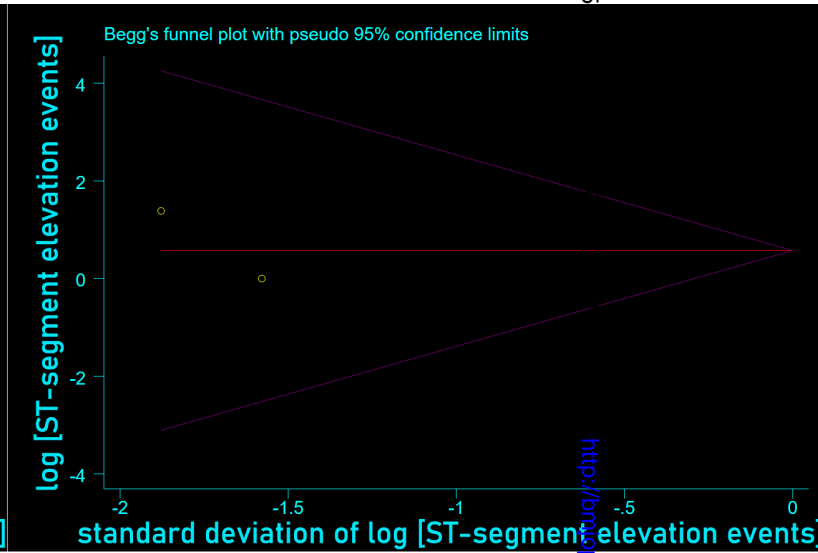
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Supplemental Figures and Figure Legends

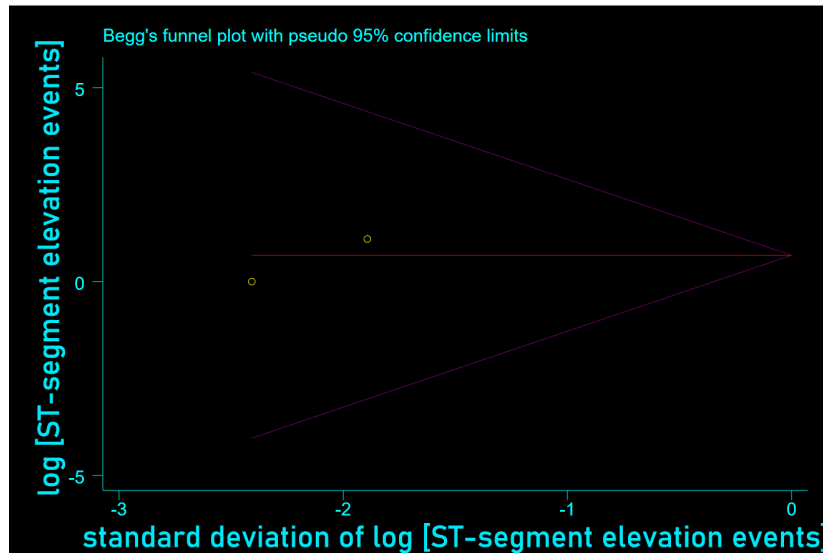
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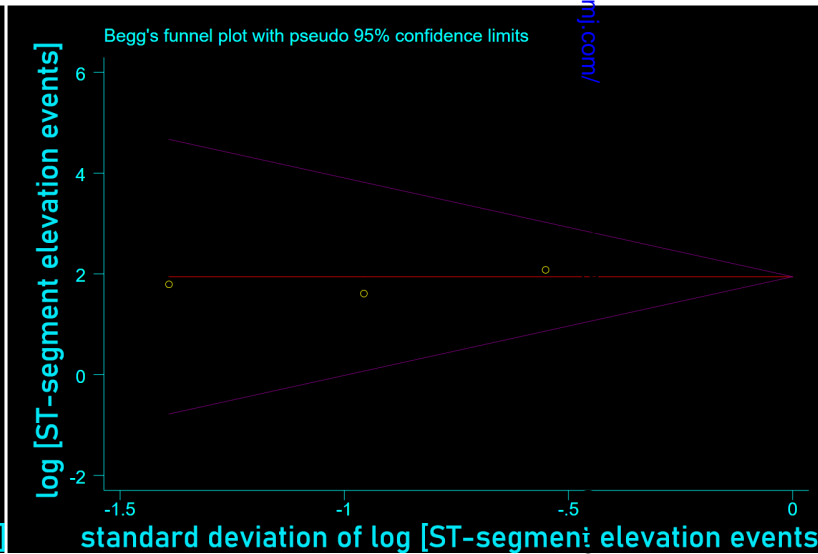
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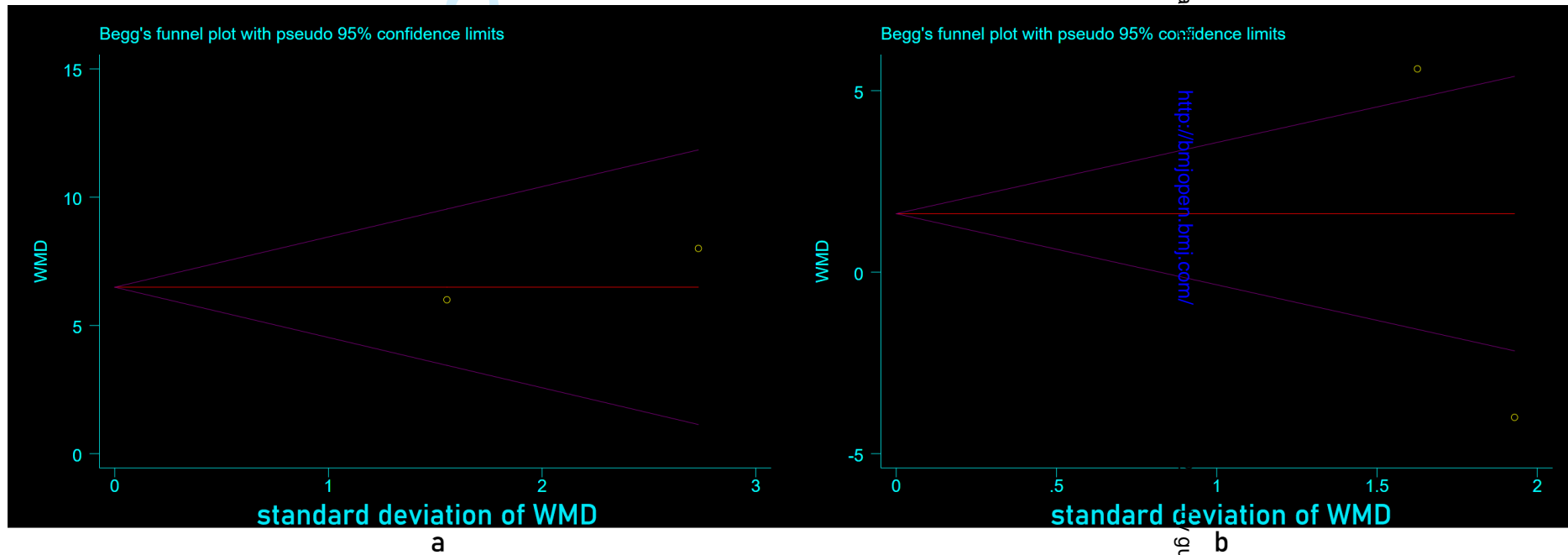
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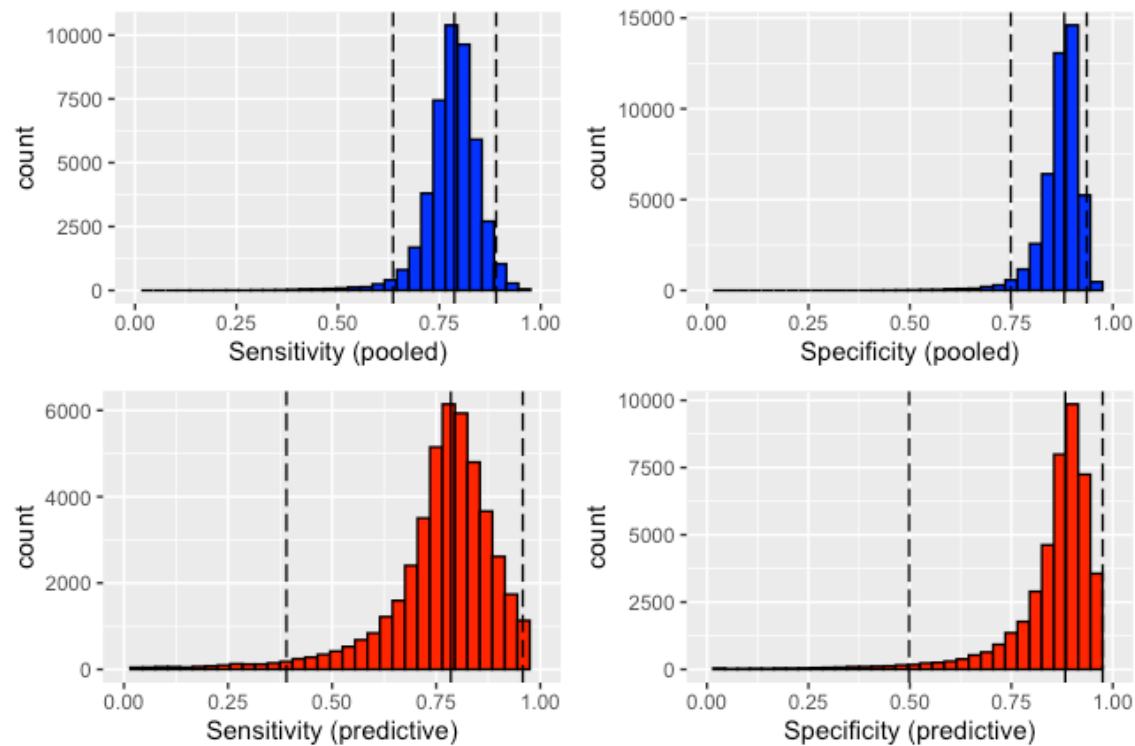
Supplement Figure 1 Publication bias assessment for studies reported clinical outcomes. Using Begg asymmetry test, we found no publication bias in the meta-analysis for the clinical outcomes of (a) major adverse cardiac event, (b) cardiac death, (c) myocardial infarction, and (d) revascularization, with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

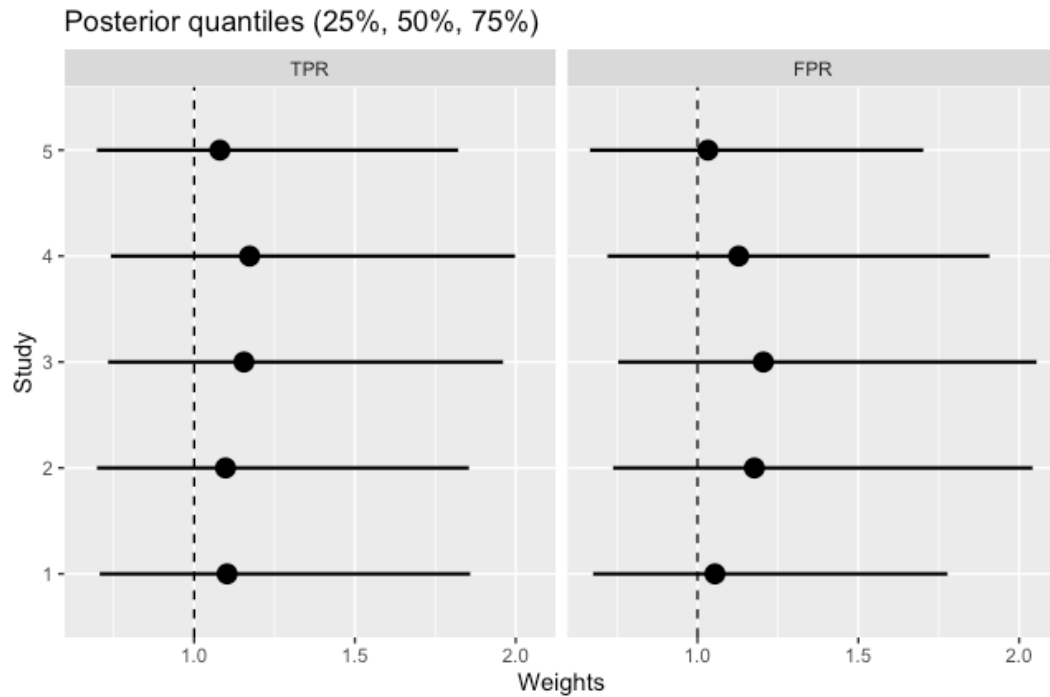
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weighted mean difference. IC-ECG, intracoronary electrocardiogram.



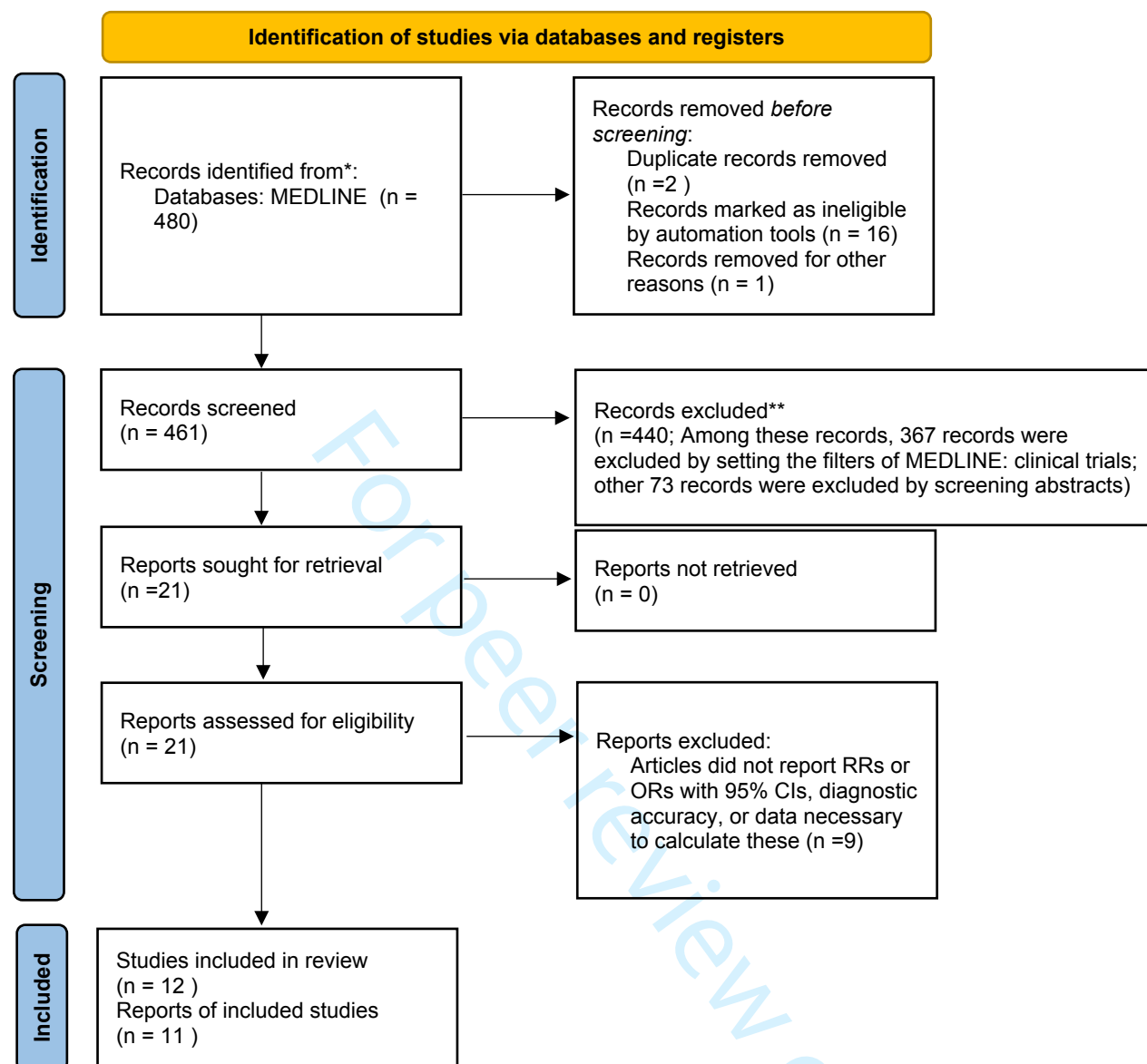
Supplement Figure 3 Posterior distributions for the pooled sensitivity and specificity and their predictive posteriors. The pooled sensitivity and specificity (upper) were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94), respectively. And predictive posterior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

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| 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

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

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

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|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2021-055871.R2 |
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1 **The prognostic and diagnostic accuracy of intracoronary electrocardiogram**
2 **recorded during percutaneous coronary intervention—a Meta-Analysis**

3
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14
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20 **Disclosure**

21 Please refer to the ICMJE disclosure form we submitted.

1 **Abstract**

2 **Objective**

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

9 **Methods**

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

16 **Results**

17 Of the 12 included studies, 7 studies reported the clinical outcomes (821 patients)
18 and 6 studies reported the diagnostic accuracy (485 patients) of IC-ECG. The pooled
19 odds ratios with 95% confidence intervals (CIs) of ST-segment elevation recorded by
20 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-
21 3.62) for major adverse cardiac events, myocardial infarction, cardiac death, and
22 revascularization, respectively. The weighted mean difference were 6.49 (95%CIs

1 3.84-9.14) for ejection fraction when ST-segment resolution was recorded, and 0.86
2 (95%CI -8.55-10.26) when ST-segment elevation was recorded. The pooled sensitivity
3 and specificity of ST-segment elevation were 0.78 (95% credibility intervals 0.64-0.89)
4 and 0.87 (95% credibility intervals 0.75-0.94) respectively.

5 **Conclusions**

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

8
9 **Key words:** intracoronary electrocardiogram, prognostic accuracy, diagnostic
10 accuracy, meta-analysis.

11 12 **Strengths and limitations of this study**

13 Strengths

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

17 Limitations

- 18 1. Limited by the published studies, we could only perform meta-analysis of
19 observational studies.
- 20 2. We did not perform sensitivity analysis for the timing when the IC-ECG was recorded,
21 different types of CADs, different definitions of significant ST-segment changes on IC-
22 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,

1 2021, in the MEDLINE database.

2 **Search strategy**

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

9 **Inclusion and exclusion criteria**

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

19 **Data extraction**

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

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4 1 or median age, inclusion criteria, exclusion criteria, reference standard, ORs or event
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6 2 rates, EF during following-up, and the diagnostic accuracy of IC-ECG. The true-positive,
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9 3 true-negative, false-positive, and false-negative rates were also estimated, using the
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11 4 data we extracted from the studies.

5 **Patient and Public Involvement**

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

8 **Statistical analysis**

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

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

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

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

14 **Results**

15 **Literature search**

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

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

4 **Study characteristics**

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

17 **The correlation between clinical outcomes and ST-segment elevation recorded** 18 **by IC-ECG**

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

1 as cardiac deaths and myocardial infarction. ST-segment elevation recorded by IC-ECG
2 after PCI procedures was significantly associated with higher risk of MACE (OR 4.65,
3 95%CI 1.69-12.77). There were mild heterogeneities among studies ($I^2=30.1\%$,
4 $p=0.239$).

5 Pooled ORs for cardiac death, myocardial infarction, and revascularization are
6 shown in Figure 2b-2d. The inclusion criteria of these studies were patients with
7 angina or non ST-segment elevation myocardial infarction (NSTEMI). In the meta-
8 analysis for cardiac death, Ikenaga's study [10] was excluded because there were no
9 events. ST-segment elevation recorded by IC-ECG after PCI procedures was
10 significantly associated with higher risk of myocardial infarction (OR 5.08, 95%CI 1.10-
11 23.44), but not cardiac death (OR 4.53, 95%CI 0.79-25.90) nor revascularization (OR
12 1.83, 95%CI 0.93-3.62). There were no heterogeneities among studies (cardiac death,
13 $I^2=0\%$, $p=0.494$; myocardial infarction, $I^2=0\%$, $p=0.567$; revascularization, $I^2=0\%$,
14 $p=0.642$).

15 **The correlation between EF and different results recorded by IC-ECG during** 16 **follow-up**

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

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4 1 95%CI 3.84-9.14. There were no heterogeneities ($I^2=0\%$, $p=0.525$). The inclusion
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6 2 criteria of ST-segment elevation subgroup were patients with NSTEMI (Hishikari, et al
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9 3 [7]) or anterior myocardial infarction (Yajima, et al [9]) . The pooled WMD was 0.86,
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11 4 with 95%CI -8.55-10.26. There were heterogeneities ($I^2=86.3\%$, $p<0.01$).

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

6 Abaci's study reported the diagnostic accuracy for myocardial viability [14], while
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8 the other 5 diagnostic studies reported the diagnostic accuracy for myocardial injury
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10 or ischemia. Therefore, we excluded Abaci's study when we performed Bayesian
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12 meta-analysis for diagnostic studies. The inclusion criteria of included studies were
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14 angina patients with stable conditions. The pooled diagnostic accuracy and the
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16 predictive posterior rates are shown in Supplement figure 1. The Bayesian SROC curve
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18 and the AUC are shown in Figure 4. The pooled sensitivity and specificity were 0.78
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20 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94),
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22 respectively. The AUC of Bayesian SROC was 0.65 (95% credibility intervals 0.56-0.69).
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24 And there were no heterogeneities. The posterior distributions of the component
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26 weights which were used for conflict of evidence analysis are shown in Supplement
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28 figure 2.
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48 **Quality assessment**

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

4 Results of quality assessment adapted from QUADAS tool are shown in
5 Supplement table 4. All the studies clearly described the methods. No studies
6 described whether they blinded reviewers to the results of IC-ECGs, while 3 studies
7 [12-14] blinded reviewers to the results of reference standards. Only 2 studies [12,14]
8 reported the intermediate results, and 2 studies [5,12] explained the withdrawals.

9 **Discussion**

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

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

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

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

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

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

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4 1 previous studies. In the subgroup of ST-segment elevation, there were heterogeneities
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6 2 between 2 studies. In Hishikari's study [7], ST-segment elevation recorded by IC-ECG
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8 3 was associated with lower EF during follow-up in NSTEMI patients, while in Yajima's
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10 4 study [9], the result was different in anterior myocardial infarction patients. The
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12 5 possible explanation might be the timing of recording IC-ECG. In Hishikari's study, IC-
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14 6 ECG was performed after the PCI procedure while in Yajima's study, IC-ECG was
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16 7 performed after the balloon inflation. On IC-ECG, ST-segment elevation after PCI
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18 8 procedure might indicate prolonged local myocardial ischemia and worse outcome, as
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20 9 we described above. The result of Hishikari's study that lower EF was observed in ST-
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22 10 segment elevation group, was one of these evidences. On the other hand, there might
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24 11 be myocardium stun after acute myocardial infarction [36]. The results of Yajima's
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26 12 study showed that ST-segment elevation recorded by IC-ECG after balloon inflation
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28 13 could predict myocardial viability and better outcomes [9]. These findings showed that
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30 14 IC-ECG might help to optimize PCI procedure by providing real time information, which
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32 15 could predict clinical outcomes.

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43 16 The diagnostic studies included in our study reported 3 reference standards.
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45 17 After excluding Abaci's study, there were still 2 reference standards. And the
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47 18 reference standards (FFR and troponin) for diagnosing myocardial ischemia or injury
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49 19 were not perfect. Also, there were too few studies included in our meta-analysis.
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51 20 Considering these situations, we used Bayesian meta-analysis to assess the pooled
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53 21 diagnostic accuracy of IC-ECG. There were already several papers illustrated this
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55 22 method to reduce the bias which came from the different or imperfect reference
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1 standards [20,21,37,38]. The results of our Bayesian meta-analysis showed the
2 promising diagnostic ability of IC-ECG for diagnosing myocardial ischemia or injury.
3 Furthermore, comparing to other invasive diagnostic tools, IC-ECG could be easily
4 performed and produce real time information. But some details might affect the
5 diagnostic accuracy when performing IC-ECG. One of the details was the type of guide
6 wire used. Vassilev found out that the exact size of recording electrode is the last 3 cm
7 of every workhorse guidewire [16]. And Uetani found that the waveforms of IC-ECG
8 were different in the same position between conventional uninsulated guidewires and
9 polymer-covered wires [11]. However, we could not perform sensitivity analysis for
10 different guide wires, limited by the included studies, to verify the hypothesis that
11 different types of guide wires would affect the diagnostic accuracy of IC-ECG. The
12 other one detail was the position of the wire tip. The convenient way of performing
13 IC-ECG was putting the wire tip in the distal position of the target vessel, just like what
14 the most included studies did. In most situation, IC-ECG could detect local ischemia in
15 the pertinent area of target vessels by using this method. But Vassilev found that when
16 they pulled back the guidewire, the elevated ST-segment would suddenly normalize if
17 the wire tip exited the border of ischemic territory [16]. And they explored a method
18 to detect and define the ischemic territory. Further researches should consider how
19 these details affect the diagnostic accuracy of IC-ECG in order to guide the PCI
20 procedures better. Although Abaci's study was excluded when performing the meta-
21 analysis, this study still provided important results. Like Yajima's study which was
22 mentioned above, Abaci's study recorded IC-ECG after balloon inflation, not PCI

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4 1 procedures. Both of these 2 studies found a good correlation between ST-segment
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6 2 elevation and myocardial viability. In short, IC-ECG had potential value for guiding PCI.

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9 3 The strengths of our study were the relatively large number of patients analyzed.

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11 4 And we used Bayesian meta-analysis to reduce the bias when assessing the diagnostic

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13 5 accuracy. However, there were limitations to our study. First, limited by the published

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15 6 studies, we could only perform meta-analysis of observational studies. And the wide

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17 7 CIs of ORs were the results of low event rates reported in the studies, especially in the

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19 8 no ST-segment elevation group. Second, not all the included studies performed

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21 9 adjustments for confounders, or reports of patients lost to follow-up. Thus, the results

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23 10 of quality assessment were not so satisfactory. Third, there were varied and imperfect

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25 11 reference standards reported in the diagnostic studies. Therefore, we chose Bayesian

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27 12 meta-analysis to assess the pooled diagnostic accuracy, reducing the bias. Forth, we

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29 13 did not perform sensitivity analysis for the timing when the IC-ECG was recorded,

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31 14 different types of CADs, different definitions of significant ST-segment changes on IC-

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33 15 ECG or different guide wires used in the studies, limited by the number of studies. But

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35 16 in the meta-analysis of clinical outcomes, there were no heterogeneities. These results

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37 17 indicated that these subgroups might have little influence on the ORs. And we found

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39 18 that recording IC-ECG in different phases of PCI procedures might produce different

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41 19 information which might help decision making. Further researches should consider

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43 20 whether the correlation between IC-ECG measures and clinical outcomes depend on

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45 21 the timing of the IC-ECG. Fifth, we did not report publication bias, because given the

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47 22 small numbers of included studies, it was not possible to meaningfully assess

1 publication bias.

2 **Conclusions**

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

7 8 **Contributorship Statement**

9 **Design and Planning** Pan Yizhi MD, PhD

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

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

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

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

14 **Guarantor** Pan Yizhi MD, PhD

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18 Affiliated Hospital, Sun Yat-Sen University, for his help.

19

20 **Registration and protocol**

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

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6 2 **Competing interests**7
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9 3 The authors have declared that no competing interests exist.
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14 5 **Availability of data, code and other materials**15
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17 6 The original template data collection forms, data extracted from included studies,
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19 7 data used for all analyses, and analytic code used in the study are not publicly available.
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2122 8 If these original materials are needed, please contact the authors.
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27 10 **Ethics committee approval**28
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30 11 We do not need ethics committee approval for our study because it is meta-analysis
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32 12 and we did not access primary patient/animal data nor interact with any
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34 13 patients/animals. We collected and synthesized data from previous studies published
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36 14 on MEDLINE database.
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4 **Figure legends**
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6 **Figure 1** Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR,
7 risk ratio; OR, odds ratio; CI, confidence interval.
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10 **Figure 2** The correlation between ST-segment elevation recorded by IC-ECG and
11 clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-
12 segment elevation recorded by IC-ECG after PCI procedures was significantly
13 associated with higher risk of MACE and myocardial infarction during follow-up, but
14 was not significantly associated with cardiac death nor revascularization. OR, odds
15 ratio; CI, confidence interval; IC-ECG, intracoronary electrocardiogram; MACE, major
16 adverse cardiac event.
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30 **Figure 3** The differences in ejection fraction between different results recorded by IC-
31 ECG during follow-up. We pooled unstandardized mean difference using a random-
32 effects meta-analysis method. Ejection fraction was significantly higher during follow-
33 up when ST-segment resolution was observed on IC-ECG, while we could not find
34 similar result when ST-segment elevation was recorded. WMD, weighted mean
35 difference; CI, confidence interval; EF, ejection fraction; IC-ECG, intracoronary
36 electrocardiogram.
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48 **Figure 4** The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and
49 the posterior distribution of AUC. Each circle identifies the true positive rate versus
50 the false positive rate of each study. The AUC was 0.65 (95% credibility intervals
51 0.56-0.69). TPR, true positive rate; FPR, false positive rate; SROC, summary receiver-
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- 1 operating-characteristic; AUC, areas under the Bayesian SROC curve; IC-ECG,
- 2 intracoronary electrocardiogram.

For peer review only

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

China[15]

| | | | | | |
|---|-----|------|-----------|-----|------------|
| Vassilev, et al. 2016, Diagnostic study | 135 | 59.2 | 65.1±10.0 | N/A | Troponin I |
|---|-----|------|-----------|-----|------------|

Bulgaria[16]

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

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

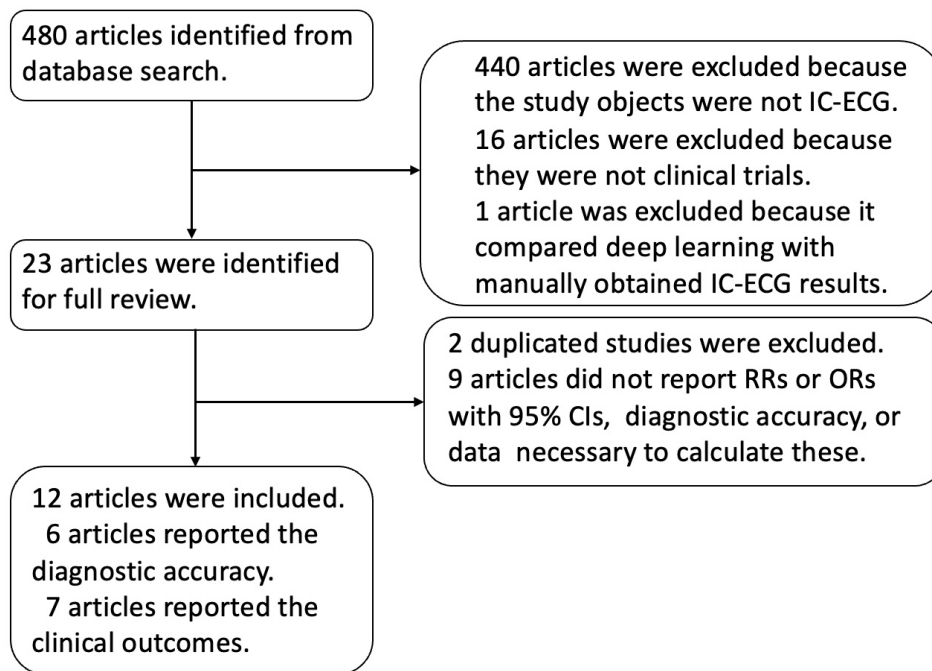


Figure 1 Selection of included studies. IC-ECG, intracoronary electrocardiogram; RR, risk ratio; OR, odds ratio; CI, confidence interval.

236x165mm (144 x 144 DPI)

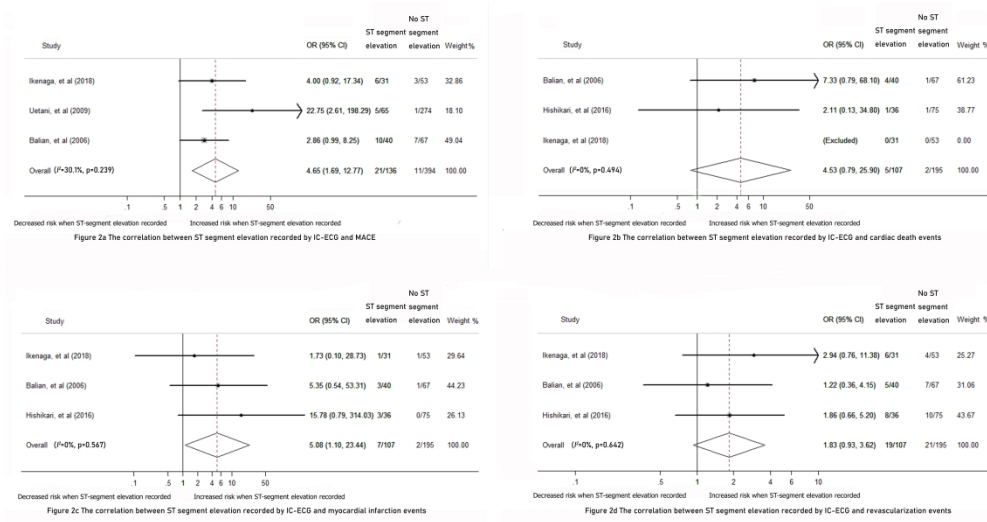


Figure 2 The correlation between ST-segment elevation recorded by IC-ECG and clinical outcomes. We pooled ORs using a random-effects meta-analysis method. ST-segment elevation recorded by IC-ECG after PCI procedures was significantly associated with higher risk of MACE and myocardial infarction during 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.

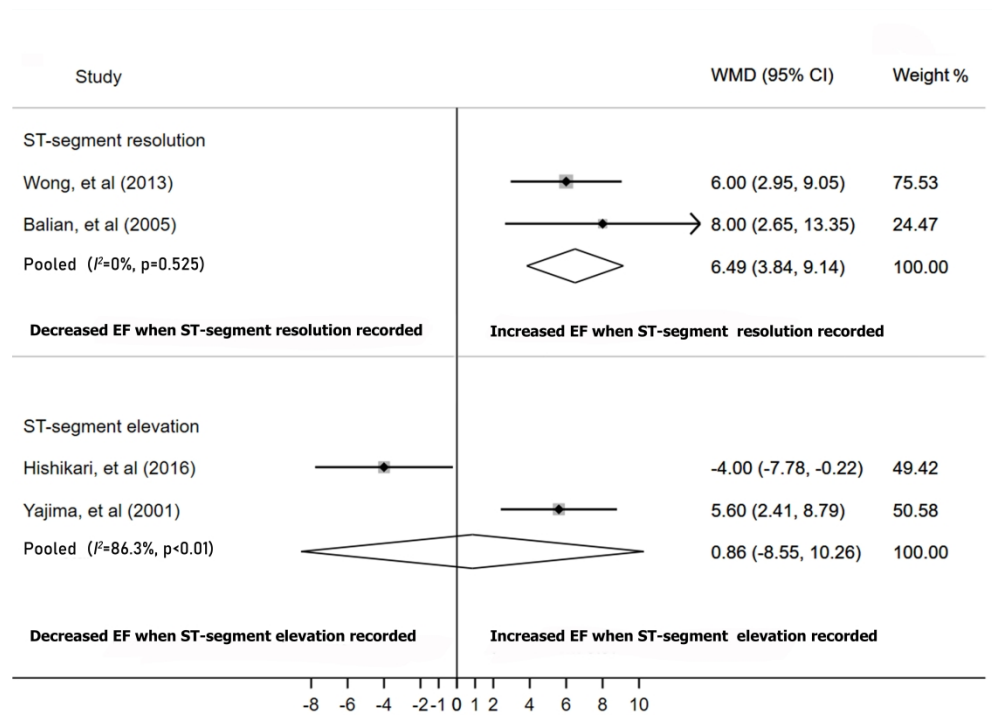


Figure 3 The differences in ejection fraction between different results recorded by IC-ECG during follow-up. We pooled unstandardized mean difference using a random-effects meta-analysis method. Ejection fraction was significantly higher during follow-up when ST-segment resolution was observed on IC-ECG, 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.

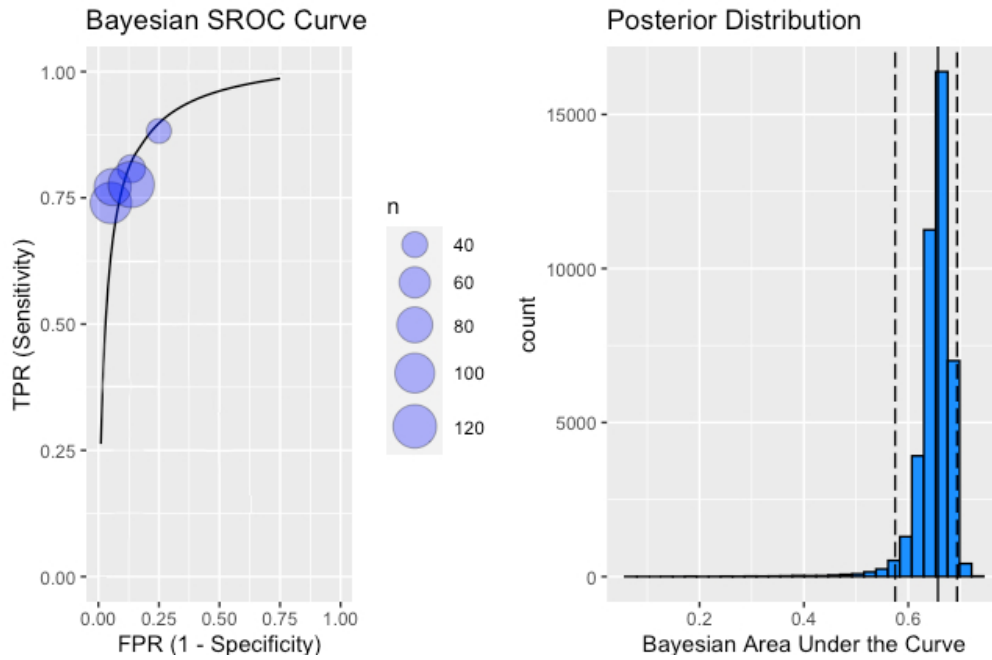


Figure 4 The Bayesian SROC curve of ST-segment elevation recorded by IC-ECG and the posterior distribution of AUC. Each circle identifies the true positive rate versus the false positive rate of each study. The AUC was 0.65 (95% credibility intervals 0.56-0.69). TPR, true positive rate; FPR, false positive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

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, repeat revascularization and/or hospitalization for heart failure. | ST-segment elevation on IC-ECG was defined as ST-segment elevation ≥ 1 mm from baseline. |

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4 territory of previous MI,
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8 ostium lesions, extremely
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10 tight lesions or tortuous
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12 vessels where we
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14 expected difficulty in
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16 advancing
17
18 soft-tip guidewire or the
19
20 FD-OCT catheter, severe
21
22 calcified lesions needed
23
24 for debulking device,
25
26 target vessel reference
27
28 diameter of ≥ 4 mm
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38 expected limitation in FD-
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OCT evaluation and
angiographic evidence of
coronary dissection or
major side branch
(>1mm) occlusion after
the procedure.

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

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 12 gadopentetate
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 14 dimeglumine or
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 16 creatinine clearance \leq
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 18 60 mL/min/1.73 m²).
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 25 Hishikari, et al. 2016, Patients' symptoms of (1) age<21 years, (2) In hospital: ventricular The ST-segment elevation
 26 Japan[7] coronary ischemia that STEMI, (3) history of MI, arrhythmias, congestive on the IC-ECG was
 27 were worsening or (4) history of PCI, (5) renal heart failure, cardiogenic defined as >0.1 mV
 28 occurring at rest for more insufficiency with a shock, and cardiac death. elevation compared with
 29 than 10 min within the past baseline serum creatinine Follow-up: Adverse the corresponding
 30 12 hours, unequivocal level >1.8 mg/dL (133 events included fatal isoelectric line.
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changes on an admission (mmol/L), (6) multivessel arrhythmias, cardiac
 ECG elevated cardiac CAD or left main CAD, (7) death, nonfatal MI,
 biomarkers and no patients in whom the revascularization or
 contraindication for PCI absence of significant congestive heart failure
 CAD or culprit lesion requiring hospitalization.
 could not be identified
 according to the
 angiogram, and (8) major
 (>1.5 mm) side branch
 occlusion after PCI.

Uetani, et al. 2009 Consecutive patients who 1) emergency coronary Post-procedure cardiac The study defined
 Japan[11] underwent apparently angioplasty within 24 h of biomarkers and in persistent ST-segment
 successful elective coronary onset; 2) elevated pre-hospital major adverse elevation in the IcECG as
 stent implantations. All had procedural cardiac cardiac event, which was an ischemic change.

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4 angina, documented biomarker; 3) active defined as cardiac death
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6 myocardial ischemia, or congestive heart failure; and MI.
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9 both. 4) severe lesion
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11 characteristics not
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13 suitable for soft-tip
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15 guidewire; 5) angioplasty
16
17 with debulking device
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19 (directional coronary
20
21 atherectomy or rotational
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23 atherectomy); 6)
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25 Thrombolysis In
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27 Myocardial Infarction
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29 (TIMI) flow grade 1 to 2 of
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31 target vessel at the end of
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| | | 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 $\geq 50\%$ 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 events, coronary angiogram, | clinical outcomes, left ventriculogram | ST-segment elevation on IC-ECG was defined as ST-segment elevation ≥ 0.2 |

emergency coronary stenosis in the left main measurements and mV from baseline.

angioplasty within 12 hours coronary artery, >75% myocardial viability

of onset. stenosis in another major

coronary artery, prior

myocardial infarction,

cardiogenic shock,

cardiomyopathy, and

right or left bundle

branch block on the ECG.

Balian, et al. 2006, Italy[12] Men and women who were Unstable patients, Adverse events included Intracoronary ST
 at least 18 years old, had patients with ventricular death, nonfatal MI, or a deviation (elevation or
 normal CK-MB and cardiac conduction disturbances new coronary depression) was
 troponin I (cTnI) values on standard ECG or revascularization considered significant if
 before the procedure and ventricular pacing, and procedure. Major ≥ 1 mm compared with

were in stable condition, those who had coronary events included the corresponding
 without angina in the procedural complications death or nonfatal MI. baseline value.
 previous 48 hours. Further were excluded.

criteria for inclusion were
 that the PCI procedure was
 successful and an optimal
 final result was obtained.

| | | |
|--------------------------------|---|--|
| Balian, et al. 2011, Italy[13] | <p>Patients undergoing prior ST segment N/A elective coronary elevation myocardial angiography with single- infarction, prior coronary vessel intermediate revascularization, ostial stenosis (40–70% diameter stenosis, presence of left narrowing) on quantitative bundle branch block, assessment were non-sinus rhythm or</p> | <p>Compared to baseline, an IC-ECG ST-segment deviation (elevation or depression) ≥ 1 mm during adenosine infusion was considered significant.</p> |
|--------------------------------|---|--|

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 \geq |
|--------------------------------|--|--|-----|---|

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

a diameter ≥ 2.5 mm and one year. In addition,
 ≤ 4.5 mm and an side patients with left main
branch diameter ≥ 2.0 coronary artery stenosis,
mm. 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. | | |
| 1 | Vassilev, et al. | 2016, | At least 18 years old, with | patient with ST-segment | N/A |
| 2 | | | stable or unstable angina, | elevation myocardial | |
| 3 | Bulgaria[16] | | angiographic bifurcation | infarction and those with | |
| 4 | | | lesions located in a native | non-cardiac co-morbid | |
| 5 | | | coronary artery with | conditions with life | |
| 6 | | | diameter of \geq 2.5 mm | expectancy <1 year. The | |
| 7 | | | and \leq 4.5 mm and side | following patients were | |
| 8 | | | branch with diameter of \geq | also excluded: 1) left | |
| 9 | | | 2.0 mm. | main coronary artery | |
| 10 | | | | stenosis, 2) total | |
| 11 | | | | occlusion before | |
| 12 | | | | occurrence of SB, 3) | |
| 13 | | | | | An 0.5 mV ST-segment |
| 14 | | | | | elevation or depression |
| 15 | | | | | above or below J-point |
| 16 | | | | | was accepted as |
| 17 | | | | | threshold for defining of |
| 18 | | | | | ischemia occurrence. |

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4 lesion of interest located
5
6 at infarct-related artery,
7
8 4) subjects with left
9
10 ventricular ejection
11
12 fraction < 30%, 5)
13
14 subjects with moderate
15
16 or severe degree valvular
17
18 heart disease or primary
19
20 cardiomyopathy, and 6)
21
22 patients with bundle
23
24 branch blocks, atrial
25
26 fibrillation patient with
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28 ST-segment elevation
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30 myocardial infarction and
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4 those with non-cardiac
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6 co-morbid conditions
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8 with life expectancy <1
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10 year. The following
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12 patients were also
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14 excluded: 1) left main
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16 coronary artery stenosis,
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18 2) total occlusion before
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20 occurrence of SB, 3)
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16 fibrillation/flutter with no
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28 PCI, percutaneous coronary intervention. FD-OCT, frequency-domain optical coherence tomography. IC-ECG, intracoronary electrocardiogram.
29
30 CAD, coronary artery disease. MI, myocardial infarction. STEMI, ST-segment elevation myocardial infarction. MVO, microvascular obstruction.
31
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33 CMR, cardiac magnetic resonance. ECG, electrocardiogram. FFR, fractional flow reserve. IRA, infarct-related artery. TIMI, thrombolysis in
34
35 myocardial infarction. CK-MB, creatine kinase-myoglobin. LVEF, left ventricular ejection fraction.
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Supplement Table 3 Quality assessment adapted from the Newcastle-Ottawa Scale for studies reported clinical outcomes.

| Study | Selection | | | Demonstration of outcome of interest was not present at start of study | Comparability | | Assessment of outcome | Outcome | | Total score |
|---------------------------|--|-------------------------------------|---------------------------|--|---|---|-----------------------|----------------------------------|---|-------------|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | | Comparability of cohorts on the basis of the design or analysis | 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 |

1
2
3
4 selection of the sample, receive verification

5
6 using a reference standard of diagnosis?

7
8
9 6. Did patients receive the same reference Yes Yes Yes Yes Yes Yes Yes

10 standard regardless of the index test result?

11
12
13 7. Was the reference standard independent Yes Yes Yes Yes Yes Yes Yes

14 of the index test (i.e. the index test did not

15 form part of the reference standard)?

16
17
18 8. Was the execution of the index test Yes Yes Yes Yes Yes Yes Yes

19 described in sufficient detail to permit

20 replication of the test?

21
22
23 9. Was the execution of the reference Yes Yes Yes Yes Yes Yes Yes

24 standard described in sufficient detail to

25 permit its replication?

26
27
28 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 Unaware Unaware Unaware Unaware Unaware Unaware Unaware

interpreted without knowledge of the results of the index test?

12. Were the same clinical data available Yes Yes Yes Yes Yes Yes Yes

when test results were interpreted as would be available when the test is used in practice?

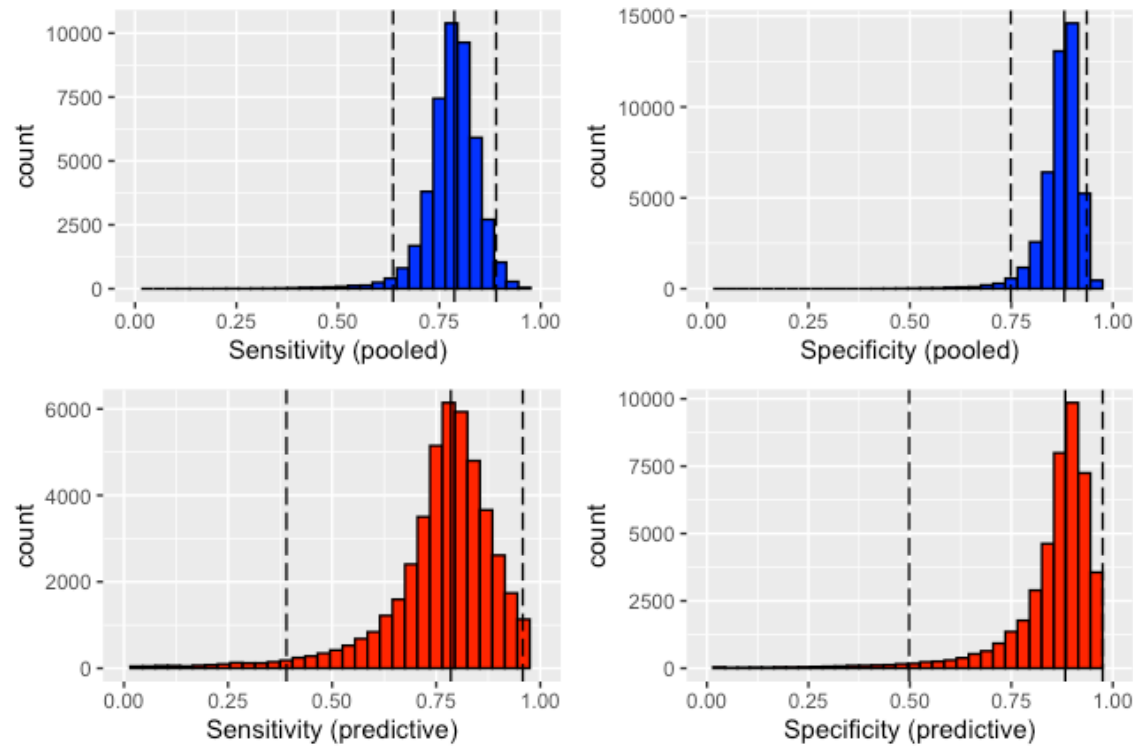
13. Were uninterpretable/ intermediate test results reported? Yes Unaware Yes Unaware Unaware Unaware Unaware

14. Were withdrawals from the study explained? Yes Unaware Unaware Yes Unaware Unaware Unaware

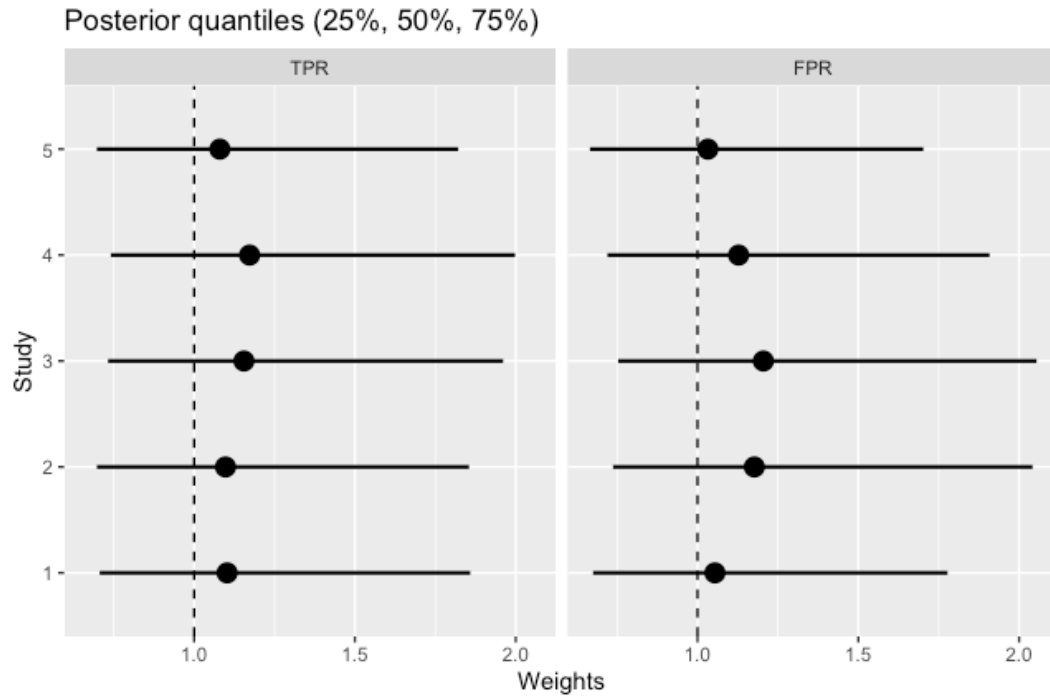
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Supplemental Figures and Figure Legends

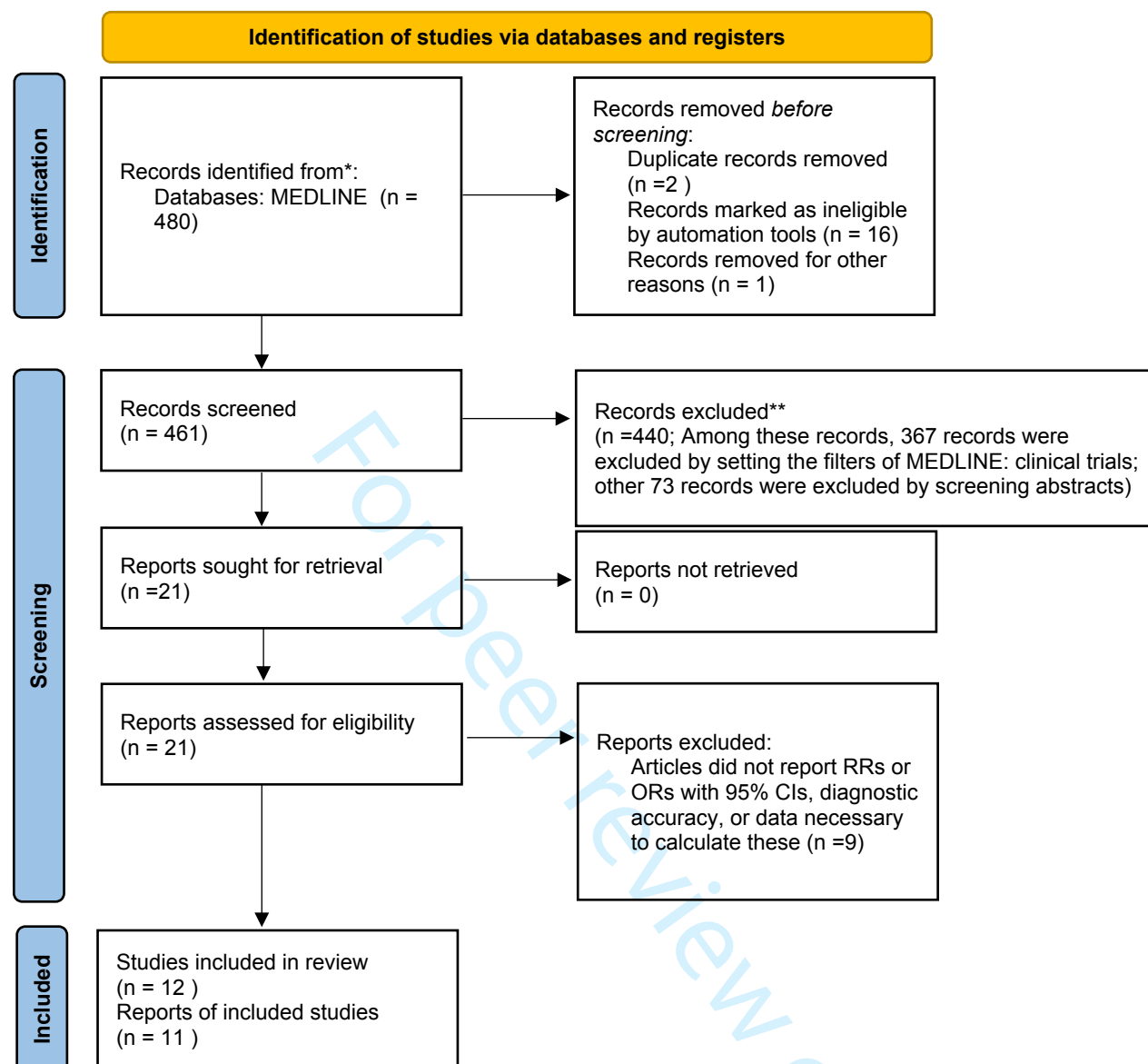


Supplement Figure 1 Posterior distributions for the pooled sensitivity and specificity and their predictive posteriors. The pooled sensitivity and specificity (upper) were 0.78 (95% credibility intervals 0.64-0.89) and 0.87 (95% credibility intervals 0.75-0.94), respectively. And predictive posterior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

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| 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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