Prognosis of unrecognized myocardial infarction determined by electrocardiogram or cardiac magnetic resonance imaging: systematic review and meta-analysis

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RESEARCH

Prognosis of unrecognized myocardial infarction determined by electrocardiogram or cardiac magnetic resonance imaging: systematic review and meta-analysis

Brief Title: Prognosis of unrecognized myocardial infarction

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Abstract

Objectives Unrecognized myocardial infarction (UMI) is highly prevalent, however, whether screening UMI can improve cardiovascular outcomes remains controversial. We evaluated the prognosis of UMI determined by electrocardiogram (UMI-ECG) or cardiac magnetic resonance imaging (UMI-CMR).

Design Meta-analysis of prospective studies.

Data sources Electronic databases (PubMed, EMBASE and Google Scholar).

Study selection Prospective cohort studies were included if adjusted relative risks (RRs) for all-cause mortality or cardiovascular outcomes of UMI compared with non-myocardial infarction (MI) were reported.

Data extraction and synthesis The primary outcomes were composite major adverse cardiac outcomes (MACEs), all-cause and cardiovascular mortality associated with UMI-ECG and UMI-CMR respectively. The secondary outcomes were the risks of recurrent coronary heart disease/MI, stroke, heart failure, and atrial fibrillation. Pooled RRs or hazard ratios (HRs) and 95% confidence intervals (CIs) were reported when appropriate. The heterogeneity for outcomes between clinically recognized MI (RMI) and UMI were compared.

Results Thirty studies comprising 253,425 participants with 1,621,920 participant-years of follow-up were included. Compared with non-MI, UMI-ECG was associated with increased risks of all-cause mortality (RR 1.50, 95% CI 1.30 to 1.73), cardiovascular mortality (HR 2.33, 95% CI 1.66 to 3.27) and MACEs (HR 1.61, 95% CI 1.38 to 1.89). UMI-CMR was also associated with increased risks of all-cause

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mortality (HR 2.16, 95% CI 1.39 to 3.35), cardiovascular mortality (HR 10.79, 95% CI 4.09 to 28.42), and MACEs (HR 3.23, 95% CI 2.10 to 4.95). No significant heterogeneity was observed for any primary outcomes between RMI and UMI-ECG or RMI and UMI-CMR. Compared with non-MI, the absolute risk difference for all-cause mortality, cardiovascular mortality and MACEs were 7.50 (95% CI 4.50 to 10.95), 11.04 (95% CI 5.48 to 18.84) and 27.45 (95% CI 17.1 to 40.05) per 1000 person-years in UMI-ECG, and 32.49 (95% CI 6.32 to 91.58), 37.2 (95% CI 11.7 to 104.20) and 51.96 (95% CI 25.63 to 92.04) per 1000 person-years in UMI-CMR.

Conclusions UMI, detected by either ECG or CMR, is associated with an adverse long-term prognosis similar to that of RMI. Screening for UMI may be useful for risk stratification among patients with a high risk of cardiovascular disease.

Key Words: Unrecognized myocardial infarction, electrocardiogram, cardiac magnetic resonance imaging, prognosis, cardiac outcomes

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What is already known on this topic

Unrecognized myocardial infarction (UMI) is highly prevalent, especially in patients with diabetes and those of older age.

It also remains unclear whether identification of UMI offers any additional prognostic value over important traditional cardiovascular risk factors.

Contemporary academic guidelines for cardiovascular disease prevention have raised great concerns about the significance of screening for myocardial ischaemia in asymptomatic individuals.

What this study adds

UMI was associated with increased risks of all-cause mortality and multiple adverse cardiovascular outcomes compared with the absence of myocardial infarction.

Electrocardiogram and cardiac magnetic resonance can provide different information, and each modality has unique clinical value in the detection of UMI.

Screening for UMI may be useful for risk stratification in the management of patients with a high risk of cardiovascular disease.

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Introduction

Unrecognized myocardial infarction (UMI) is defined as myocardial infarction (MI) that was not detected during the acute phase due to the lack of typical symptoms, but later discovered by finding of pathological Q waves on electrocardiogram (ECG), myocardial imaging evidence, or pathological findings on autopsy.[1 2] Prior studies have shown that UMI accounts for one-third to one-half of all MIs,[1-4] especially in patients with diabetes and those of older age.[5 6]

Some epidemiological studies have shown that UMI detected by ECG (UMI-ECG) is associated with subsequent increased risks of all-cause mortality, recurrent cardiovascular disease (CVD), and heart failure,[7-9] although other studies found null associations.[10-12] Furthermore, it also remains unclear whether identification of UMI-ECG offers any additional prognostic value over important conventional cardiovascular risk factors.[10 11] Therefore, contemporary academic guidelines for CVD prevention have raised great concerns about the significance of screening for myocardial ischaemia in asymptomatic individuals using ECG, even in those with a high risk of CVD.[13 14] In recent years, late gadolinium enhancement (LGE) cardiac magnetic resonance imaging (CMR) has also been employed to detect UMI.[1 15] However, the diagnostic consistency between ECG and CMR has not been thoroughly explored. The high cost and time-consuming nature of CMR have so far also limited its clinical application and use in large cohort studies, although a handful of studies have shown that UMI detected by CMR (UMI-CMR) is associated with an increased risk of mortality.[11 16]

Due to these inconsistencies, we performed a systematic review and

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meta-analysis of prospective cohort studies to synthesize available data on the prognostic value of UMI-ECG and UMI-CMR. Two key questions were explored in our study: 1) Is UMI-ECG or UMI-CMR associated with a poorer prognosis in terms of CVD and mortality than the absence of MI? 2) Is the prognosis of UMI different from that of clinically recognized MI (RMI)?

Methods

Search strategy and selection criteria

Following the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group,[17] several electronic databases (PubMed, EMBASE, and Google Scholar) were searched for prospective studies up to 30 June 2019. The search was restricted to human studies, but no restrictions were placed on language or publication form. Reference lists were manually checked to identify other potential studies. The detailed method that was used to search PubMed is presented in Online Supplementary File 1.

Studies were included in the analysis if they met the following criteria: (1) prospective cohort studies with adult participants (age of ≥18 years), (2) UMI and other cardiovascular risk factors were detected at baseline, and (3) adjusted relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs) reported for all-cause death or cardiovascular outcomes (including cardiovascular mortality, composite major adverse cardiac outcomes [MACEs], new coronary heart disease [CHD]/MI, stroke, heart failure, and atrial fibrillation)

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associated with UMI versus those without MI. UMI was defined as signs of MI shown by ECG or CMR without a documented history of acute MI. All reading mechanisms (computerized process, visual inspection or combination of both) for interpreting UMI-ECG were considered. RMI was defined as a documented clinical history of MI. Non-MI was defined as not having RMI or ECG-/CMR-positive findings of MI.

Studies were excluded if (1) the diagnosis of UMI was not based on ECG or CMR, (2) only unadjusted risks were reported for associated events, and (3) identical outcomes were derived from the same cohort. For multiple articles reporting identical outcomes from the same cohort, only the most recently published paper was included in the analysis.

Patient and public involvement

Patients and the public were not involved in setting the research question, in the outcome measures, in the design, or in the implementation of the study. No patients were asked to advice on interpretation or writing up of results.

Data extraction and quality assessment

Two reviewers (Y.Y. and W.L.) independently conducted the literature searches and screened the studies according to the pre-defined criteria. Quality assessment of the included studies was based on the Newcastle–Ottawa Quality Assessment Scale for cohort studies,[18] in which a study is judged based on selection (four items, one point each), comparability (one item, up to two points), and exposure/outcome (three items,

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one point each). In the present analysis, the quality of all included studies was graded as good (≥7 points), fair (4–6 points), or poor (<4 points).[19 20]

We also evaluated whether the studies had been adequately adjusted for potential confounders (at least six of the following seven factors: sex, age, smoking, hypertension or blood pressure or antihypertensive treatment, diabetes mellitus or fasting plasma glucose or hemoglobin A_{1c}, body mass index or overweight/obesity, and serum cholesterol or hypercholesterolemia) or whether they had been adjusted for risk scores for prediction of CVD (e.g. Framingham Risk Score), calculated from these metrics, with reference to previous studies.[21 22]

Statistical analysis

The primary outcomes were the risks of MACEs, all-cause and cardiovascular mortality associated with UMI-ECG and UMI-CMR, compared with non-MI. The secondary outcomes were the risks of recurrent CHD/MI, stroke, heart failure, and atrial fibrillation. To explore whether the prognosis of UMI differs from that of clinical RMI, the aforementioned outcomes for RMI compared with non-MI were also extracted.

Outcomes adjusted for multiple variables were extracted for the meta-analysis. If a study reported multiple results based on different numbers of covariates included in statistical adjustments, the results that adjusted for the most number of variables were extracted for the meta-analysis. We combined the ln RRs and corresponding standard errors (SEs) by the inverse variance approach. When HRs were available for all

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studies, they were directly used in the meta-analysis to calculate the overall HR estimates. If outcomes were presented as ORs, data were converted to RRs by the formula (RR = OR / ([1 − pRef] + [pRef × OR]) for analysis, where pRef is the prevalence of the outcome in the reference group.[23] We calculated the absolute risk difference for all-cause mortality and cardiovascular outcomes associated with UMI by multiplying the assumed comparator risk of each outcome of interest by the estimated RR-1, according to the recommendation by the Cochrane guidelines.[24] The median risks of outcomes in the non-MI individuals across studies were regarded as the assumed comparator risks. Absolute risk differences were expressed in events per 1,000 person years.

We used I^2 statistics to test heterogeneity. An I^2 value of >50% was considered to indicate significant heterogeneity. However, even when no statistically significant heterogeneity was found, we used the DerSimonian and Laird random-effects models as the primary approach to pool results across studies rather than the fixed-effects model, due to underlying clinical and methodological heterogeneity (e.g., baseline characteristics of the patients, adjustment for confounders, and follow-up duration). Subgroup analyses of the primary outcomes were conducted according to sex (men *vs.* women), ethnicity (Asian *vs.* non-Asian), age (average of <65 *vs.* ≥65 years), enrolment from a community-based population (yes *vs.* no), presence of diabetes (yes *vs.* no), follow-up duration (<6 *vs.* ≥6 years), adjustment for confounders (adequate *vs.* inadequate), and study quality (good *vs.* fair) if appropriate. To explore the potential impact of study characteristics (including sample size, average age,

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follow-up duration, prevalence of UMI, study quality score and absolute event rate in the original cohort) on the associations between UMI and outcomes, meta-regression analysis was performed if data were reported in more than 10 studies according to Cochrane guidelines.[25] Publication bias was evaluated by inspecting funnel plots for primary outcomes and further tested using Begg's test and Egger's test. To assess the impact of individual studies on the estimated risk, a sensitivity analysis was conducted in which the pooled RR was recalculated by omitting one study at a time.

To assess whether screening with ECG or CMR can add additional predictive value on top of traditional cardiovascular risk factors, we reviewed and summarized studies with data regarding improvement of risk prediction (e.g., change with area under the receiver operating characteristic curve, net reclassification improvement [NRI] or integrated discrimination improvement [IDI]). The NRI assesses changes in the estimated events prediction probabilities that imply a change from one category to another, while the IDI assesses changes in the estimated events prediction probabilities as a continuous variable.[26]

We also compared the difference in diagnostic efficacy between ECG and CMR for detection of UMI. Data from studies used both ECG and CMR to detect UMI were extracted. With CMR regarded as the gold standard, pooled sensitivity and specificity of ECG for diagnosing UMI were estimated by a random-effects model. [27]

Analyses were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA), RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and Meta-Disc version 1.4 software programs. [28] All *P* values are two-tailed, and

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statistical significance was set at 0.05.

Results

Studies retrieved and characteristics

Our initial search returned 17,687 articles. After screening the titles and abstracts, 116 articles qualified for a full text review (Figure 1). Finally, 30 published papers involving 253,425 participants were included in the analysis.[7 10-12 16 29-53] According to the Newcastle–Ottawa quality assessment, only two studies were graded as fair quality; all other studies were graded as good quality. The details of the quality assessment are presented in Online Supplementary File 2.

UMI-ECG and health outcomes

Twenty studies reported outcomes data associated UMI-ECG.[7 10-12 29-44] The key characteristics of the included studies are presented in Online Supplementary File 3. The studies comprised 250,407 participants with a mean follow-up duration of 6.4 years (range, 2.3–17 years). Fifteen studies were derived from the general population, two studies included patients with chronic kidney disease, two studies included patients with diabetes, and one study included patients with suspected stable coronary artery disease. ECG interpretation methods (computerized process, visual inspection or combination of both) were presented in Online Supplementary File 3. All studies defined UMI based on a major Q wave abnormality by Minnesota code, while with different modification across studies. The prevalence of UMI-ECG in the cohorts

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ranged from 0.3% to 36.0% (median 5.4%) and constituted 22.9%-61.7% for all MIs. In general population studies, the median prevalence of UMI-ECG was 5.0%. According to the pre-defined criteria, seven studies were not adequately adjusted for potential confounders, while all others were adequately adjusted (Online Supplementary File 4).

One included study reported adjusted ORs for all-cause mortality associated with UMI-ECG and were converted to RRs for meta-analysis,[32] and all others studies reported the HRs for all evaluated events. Therefore, the risk of all-cause mortality associated with UMI-ECG was reported as RRs while all other pooled outcomes were reported as HRs. Random-effects model analyses showed that compared with non-MI, UMI-ECG was associated with increased risks of all-cause mortality (RR 1.50, 95% CI 1.30 to 1.73), cardiovascular mortality (HR 2.33, 95% CI 1.66 to 3.27), and MACEs (HR 1.61, 95% CI 1.38 to 1.89) (Figure 2). Furthermore, UMI-ECG was also associated with increased risks of new CHD/MI (HR 1.66, 95% CI 1.25 to 2.20) and heart failure (RR 1.50, 95% CI 1.22 to 1.85), but not stroke (HR 1.55, 95% CI 0.75 to 3.19) or atrial fibrillation (HR 1.44, 95% CI 0.61 to 3.39) (Figure 3). No publication bias was detected based on inspection of the funnel plot (Online Supplementary File 5) or Begg's test and Egger's test (both $P > 0.05$).

The absolute risks of primary outcomes in non-MI and UMI-ECG across studies were presented in Online Supplementary File 6. Compared with non-MI, the absolute risk difference in UMI-ECG for all-cause mortality, cardiovascular mortality and MACEs is 7.50 (95% CI 4.50 to 10.95), 11.04 (95% CI 5.48 to 18.84) and 27.45

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(95% CI 17.1 to 40.05) per 1000 person-years, respectively.

UMI-CMR and health outcomes

Ten studies among 3,018 participants reported the prognostic outcomes of UMI-CMR.[16 45-53] The key characteristics of the included studies are summarized in Online Supplementary File 7. The mean follow-up duration was 6.4 years (range, 1.3–11 years). Two studies were derived from the general population, two studies included patients with acute MI, three studies included patients with diabetes/impaired fasting glucose, and three studies included patients with suspected stable coronary artery disease and without history of MI. All studies determined the present of hyper-enhancement in the LGE-CMR by visual inspection, and four studies further calculate the myocardial mass of LGE, two of them by manual inspection, two by a semiautomatic detection method. Two studies categorized LGE as either typical MI (involving the subendocardium) or atypical (subepicardial, patchy midwall, or diffuse circumferential subendocardial pattern), six studies defined UMI in present of subendocardial LGE. In two studies including patients with AMI, UMI was defined as present of subendocardial LGE in the non-acute infarcted area other than the acute infarcted area. The prevalence of UMI-CMR in the cohorts ranged from 8.2% to 31.0% (median 22.5%) and constituted 51% to 83.3% for all MIs. In general population studies, the median prevalence of UMI-CMR was 10.8%. Three studies were not adequately adjusted for potential confounders, while all others were adequately adjusted (Online Supplementary File 4).

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Random-effects model analyses showed that compared with non-MI, UMI-CMR was associated with increased risks of all-cause mortality (HR 2.16, 95% CI 1.39 to 3.35), cardiovascular mortality (HR 10.79, 95% CI 4.09 to 28.42), and MACEs (HR 3.23, 95% CI 2.10 to 4.95). Each 1% and 10% increase in left ventricular mass of LGE was associated with a 9% and 77% increase in MACEs, respectively (Figure 4). One study showed that compared with the non-MI, UMI-CMR was associated with increased risks of future MI (HR 1.87, 95% CI 1.28 to 2.73) and heart failure (HR 1.40, 95% CI 1.00 to 2.00) after adjusting for multiple risk factors. [45] Possible publication bias could not be excluded as detected by the funnel plot for the MACEs (Online Supplementary File 8) and as also showed by Begg's test ($P = 0.01$) and Egger's test ($P = 0.03$). However, applying the trim-and-fill adjustment method produced no change in the overall effect estimate for MACEs associated with UMI-CMR.

The absolute risks of primary outcomes in non-MI and UMI-CMR across studies were presented in Online Supplementary File 9. Compared with non-MI, the absolute risk difference in UMI-CMR for all-cause mortality, cardiovascular mortality and MACEs is 32.49 (95% CI 6.32 to 91.58), 37.2 (95% CI 11.7 to 104.20) and 51.96 (95% CI 25.63 to 92.04) per 1000 person-years respectively.

Comparison of prognosis between UMI and clinical RMI

When cardiovascular outcomes or mortality associated with UMI and clinical RMI were reported in the same study, data were pooled to explore whether the prognosis

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differed between UMI and RMI. Compared with the non-MI, no significant heterogeneity was observed between UMI-ECG and RMI for the risks of all-cause mortality, cardiovascular mortality, MACEs, or stroke, although the risks of recurrent CHD/MI and heart failure were higher in RMI (Figure 5a). No significant heterogeneity was observed for health outcomes (including all-cause mortality, MACEs, recurrent CHD/MI and heart failure) between RMI and UMI-CMR when compared with non-MI respectively (Figure 5b).

Subgroup analyses, meta-regression analyses and sensitivity analyses

The pre-defined subgroup analyses showed that compared with non-MI, UMI-ECG was associated with increased risks of all-cause mortality and cardiovascular mortality among all subgroup comparisons, except in female patients (all-cause mortality, HR 1.19, 95% CI 0.91 to 1.56; cardiovascular mortality, HR 2.10, 95% CI 0.78 to 5.56) (Online Supplementary File 10). However, there were no significant heterogeneity observed between male and female groups on all primary outcomes (all $P > 0.1$). CMR-UMI was associated with increased risks of all primary outcomes among all subgroup comparisons (Online Supplementary File 11). We did not perform subgroup analyses for the other cardiac outcomes because of limited studies available. In 13 studies reported the risk of all-cause mortality associated with UMI-ECG, meta-regression analysis showed no significant associations among study characteristics and risk of all-cause mortality (all $P > 0.05$, Online Supplementary File 12). The sensitivity analyses confirmed that the association between primary endpoint events and UMI-ECG or UMI-CMR did not change with the use of random-effects

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models or fixed-effects models for the meta-analysis or with recalculation of the RRs by omitting one study at a time.

Additional predictive effects for health outcomes of UMI

Few studies reported the additional predictive effects of ECG-UMI.[11 16 36] The United Kingdom Prospective Diabetes Study showed that in patients with type 2 diabetes, UMI-ECG was associated with small but statistically significant improvement in all-cause mortality (IDI, 0.0025 [0.001 to 0.0039]) and fatal MI risk stratification (IDI, 0.0043 [0.0016 to 0.007]) in multivariable adjusted model.[36] However, other studies showed that the addition of UMI-ECG did not improve the risk prediction for future recurrent MI or mortality using the Framingham Risk Score.[10 11] Three studies consistently showed that UMI-CMR can improve the risk prediction for all-cause mortality or MACEs (Table 1).

Difference in diagnostic efficacy between ECG and CMR for detection of UMI

Five studies reported diagnostic efficacy between ECG and CMR for UMI detection.[11 16 47 51 53] Pooled data from 1731 participants showed that when CMR was used as gold standard, ECG for diagnosing UMI was with low sensitivity (13.2%, 95%CI 9.7 to 17.5%), while with high specificity (95.7%, 94.5 to 96.7%) (Figure 6). The pooled positive likelihood ratio was 2.78 (95% CI 1.47 to 5.25), which indicated that the probability of a UMI patient with ECG positive finding was about 2.8 folds compared with the probability of a healthy person with positive testing (Online

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Supplementary File 13).

Discussion

Principal findings

To our knowledge, this is the first comprehensive systematic review and meta-analysis to examine the mortality and cardiovascular outcomes associated with UMI, stratified by detection with ECG or CMR. Three key findings in our study are as follows. 1) Compared with the absence of MI, UMI-ECG and UMI-CMR were associated with increased risks of all-cause mortality and multiple cardiovascular outcomes. 2) The risks of all-cause mortality, cardiovascular mortality and MACEs were similar in UMI and clinical RMI. 3) ECG screening for UMI is of low sensitivity but high specificity, and may add additional predictive values for mortality and new MI; however, the results are inconsistent. In contrast, screening with CMR can significantly increase the predictive values for mortality and CVD.

Meaning of the study and Future research

Our results provide robust evidence that although asymptomatic, UMI is associated with a poorer long-term prognosis compared with non-MI, and similarly to clinical RMI. The median prevalence of UMI-ECG was 5.4% in all included studies and 5.0% in general population cohorts, UMI-CMR was 22.5% in all included studies and 10.8% in general population respectively. Furthermore, the UMI-ECG and UMI-CMR constituted 22.9% to 61.7% and 51% to 83.3% for all MIs respectively. Considering the high prevalence and significant adverse long-term prognosis associated with UMI,

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it is with important clinical impacts to screen and proper manage these patients.

Academic guidelines' recommendations on ECG screening

The use of ECG to screen asymptomatic adults for CVD is controversial. Although screening with ECG is safe, it may lead to higher downstream cardiac testing use, more specialist consultations, and potentially higher rates of adverse events, including excess radiation exposure and procedural complications of angiography.[54] Therefore, the United States Preventive Services Task Force (USPSTF) suggests against ECG screening in patients at low risk for CVD (10-year event risk of <10%). In patients with elevated risk for CVD, the USPSTF cited that the current evidence is insufficient to assess the balance of benefits and harms of screening with ECG.[13] However, the American College of Cardiology/American Heart Association (ACC/AHA) guideline considered ECG screening to be 'reasonable' in asymptomatic people with hypertension or diabetes and that it 'may be considered' in those without hypertension or diabetes.[55] The 2019 European Society of Cardiology (ESC) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases stated that 'resting ECG is recommended in patients with diabetes mellitus with hypertension or suspected CVD.[56] However, both the ACC/AHA and ESC guidelines acknowledged the lack of data to support this expert consensus (level of evidence: C). Therefore, the robust evidence in the current study, which showed that UMI-ECG was associated with adverse outcomes, is supportive for developing strategies for screening and preventing CVD in high risk patients. However, limited data showed that ECG can add additional predictive values for mortality and new MI, and the results were

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inconsistent. These inconsistencies may arise from the fact that most of the studies included patients with a low risk of CVD. In this context, further studies are needed to evaluate the impact of ECG on incremental improvements in risk stratification in high-risk patients. A large-scale registry study from Spain showed that although the positive predictive value of asymptomatic Q waves for diagnosing UMI was 29.2% overall, it was much higher (75%) in participants with a 10-year CHD risk of ≥10% than in lower-risk participants.[3] Therefore, we agree with the Canadian diabetes guideline's proposal that screening ECG should be performed in patients with a high risk of CVD. This screening can not only provide information on baseline cardiac ischemia but can also provide information for comparison with future ECG data.[57] A repeat resting ECG may detect changes that result from UMI, leading to earlier detection of critical CVD.

How to screen for UMI

Although ECG is the most widely used non-invasive technique for cardiovascular assessment, it has been questioned for its limited sensitivity for screening UMI. It is known that Q waves can resolve with time, and patients with non-ST segment elevation MI do not have characteristic Q waves on ECG.[58] Our study also showed that the use of ECG to detect UMI has a low sensitivity (13.2%), but has a high specificity (95.7%). Therefore, it is important to develop more precise, sensitive and sophisticated ECG-based models for estimating UMI. This is possible given the availability of digital ECG data, which provide hundreds of waveform measurements and development of machine learning technology.[59]

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Not surprisingly, CMR can detect more cases of UMI than ECG. However, the high cost and time-consuming nature of CMR limit its application in clinical practice. Furthermore, the intravenous gadolinium used in CMR may pose a risk of nephrogenic systemic fibrosis in patients with kidney disease.[60] Therefore, we should note that ECG and CMR can provide different information, and each modality has unique clinical value in the detection of UMI. Further studies are needed to explore how to integrate ECG and CMR rather than replace one with the other to screen and manage patients with a risk of myocardial ischemia. We also propose that if UMI is identified by ECG in routine clinical care, CMR could be performed to identify the presence and extent of actual myocardial damage and guide treatment decisions.[61]

How to manage patients with UMI

Two randomized trials showed that compared with simply control of cardiovascular risk factors, screening for silent ischemia with a stress test does not improve the prognosis in patients with diabetes.[62 63] Although these studies had limited samples and were under-powered, they emphasized the importance of controlling cardiovascular risk factors in the treatment of asymptomatic coronary artery disease. In real clinical practice, however, many patients with UMI are undertreated. In the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, the percentage of patients with UMI received treatment of aspirin, β-blockers, and statins was only 44.4%, 25.8%, and 33.9%, respectively; which was significantly lower than that of patients with clinical RMI.[64] Similar results were observed in the ICELAND MI study and were attributed to the high mortality of patients with UMI.[11] Therefore,

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further efforts should be made to increase the adherence to guidelines recommendations for prevention of CVD in patients with UMI. However, to our knowledge, there is no currently evidence showing that patients' therapeutic strategies would be changed after been identified with UMI. Further studies are needed to fill this gap. In selected patients, adjunctive coronary revascularization is worthy of prospective testing. A recently cohort study of 9,897 patients with silent ischemia showed that compared with medical treatment, coronary revascularization was associated with a 19% and 42% reduction of death and MI, respectively, during a median follow-up duration of 4.6 years.[65]

Strengths and limitations of study

Our study has several major strengths. First, we included and stratified studies of ECG or CMR, which are the most prevalent methods for screening UMI. Second, only prospective cohort studies with adjusted RRs were included. Most of the included studies were of high quality and adequately adjusted for confounders. Third, the sample size was large and the follow-up duration was long (more than 1.6 million person-years).

However, some limitations of the study should be noted. First, there was significant heterogeneity of the populations in the included studies and we had no access to individual participants' data. However, consistent results were found in the comprehensive subgroup analyses and sensitivity analyses, and meta-regression showed that the risk of all-cause mortality in UMI-ECG did not affected by the study characteristics. These characteristics may mitigate the possibility of influencing the

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association between UMI and outcomes by confounding factors. Second, most studies using CMR screening involved patients with special conditions such as diabetes or chronic kidney disease. These patients had higher risks than those included in ECG screening; thus, direct comparison of CVD risks between UMI-ECG and UMI-CMR was unavailable. Third, UMI-ECG was defined with different criteria in included studies (as descripted in supplementary file 3), which was an underlying factor for the heterogeneity among the studies.

Conclusions

Our study has shown that UMI is highly prevalent and associated with an adverse long-term prognosis, which is similar to that of clinical RMI. Screening for UMI may be useful for risk stratification among patients with a high risk of CVD. Further studies are needed to develop standard methods for screening and treating UMI.

Dissemination plans: The results from the present study will be disseminated to appropriate audiences like academia, clinicians, policy makers, and the general public through various channels, including press release, social media, e-newsletter, websites of collaborators' universities and monthly bulletins.

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Contributors: Y.Y, X.C and Yul.H were responsible for the initial plan, study design, conducting the study, data interpretation. Y.Y, W.L, H.Z, W.M, X.C and Yul.H was responsible for data collection, data extraction, statistical analysis and manuscript drafting. Y.Y, W.L, XF.P, Yun.H, C.A and Yul.H were responsible for analyzed and interpreted the data and critically revised the paper. X.C and Yul.H are guarantors and had full access to all of the data, including statistical reports and tables), and take full responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

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Transparency declaration: The lead author (Yul.H) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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Figure Legends

Figure 1. Flow of papers through review.

CIs=confidence intervals; CMR=cardiac magnetic resonance; ECG=electrocardiogram; RRs=relative risks; UMI=unrecognized myocardial infarction.

Figure 2. Forest plot of estimates for risks of primary outcomes associated with UMI-ECG.

CIs=confidence intervals; UMI-ECG=unrecognized myocardial infarction detected by electrocardiogram; MACEs= major adverse cardiac outcomes.

Figure 3. Forest plot of estimates for risks of secondary outcomes associated with UMI-ECG.

CHD=coronary heart disease; CIs=confidence intervals; MI=myocardial infarction; HRs=hazard ratios; RRs= relative risks; UMI-ECG=unrecognized myocardial infarction detected by electrocardiogram.

One included study reported adjusted odds ratio for all-cause mortality associated with UMI-ECG and were converted to RR for meta-analysis, and all others studies reported the HRs for all evaluated events. Therefore, the risk of all-cause mortality was reported as RRs, while all other pooled outcomes were reported as HRs.

Figure 4. Forest plot of estimates for risks of primary outcomes associated with UMI-CMR.

CIs=confidence intervals; UMI-CMR=unrecognized myocardial infarction detected by cardiac magnetic resonance imaging; LGE=late gadolinium enhancement

Figure 5. Heterogeneity of all-cause mortality and cardiac outcomes between UMI and RMI, compared with non-MI. (A) UMI detected by ECG; (B) UMI detected by CMR

CMR=cardiac magnetic resonance; MACEs=major adverse cardiovascular events; MI=myocardial infarction; UMI=unrecognized myocardial infarction; RMI=clinical

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recognized myocardial infarction

Figure 6. The sensitivity and specificity of ECG for detecting UMI

Cardiac magnetic resonance was regarding as gold standard in this analysis.

CI=confidence interval; ECG=electrocardiogram; UMI=unrecognized myocardial infarction

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Table 1. Risk classification comparing models with and without UMI for mortality and cardiovascular outcomes

Study and endpoint	ROC AUC	NRI (95%CI)	IDI (95%CI)
UMI-ECG			
Schelbert 2012 (All-cause mortality)			
Base Model*	-	Reference	Reference
Baseline model+UMI	-	−0.05 (−0.17-0.05)	0.000 (−0.004-0.001)
P value	-	0.35	0.71
Davis 2013 (All-cause mortality)			
Base Model#	0.699	-	Reference
Baseline model+UMI	0.701	-	0.0025 [0.001–0.0039]
P value	0.07	-	0.001
Davis 2013 (Fatal MI)			
Base Model*	0.713	-	Reference
Baseline model+UMI	0.718	-	0.0043 [0.0016–0.007]
P value	0.16	-	0.002
Ohrn 2018 (Future MI)			
Base Model†	0.681	-	-
Baseline model+UMI	0.682	-	-
P value	0.96	-	-
UMI-CMR			
Schelbert 2012 (All-cause mortality)			
Base Model*	-	Reference	Reference
Baseline model+UMI	-	0.16 (0.01-0.31)	0.008 (0.004-0.013)
P value	-	0.04	0.001
Barbier 2016 (MACEs)			
Base Model‡	0.68	Reference	Reference
Baseline model+UMI	0.75	0.67 (0.28-1.06)	0.068 (0.025-0.111)
P value	0.04	0.0007	0.002
Elliott 2019 (MACEs)			
Base Model‡	-	-	Reference
Baseline model+UMI	-	-	0.156 (0.063-0.249)
P value	-	-	0.001

*Adjusted for age, sex, diabetes, and recognized MI.

#Adjusted for age, sex, ethnicity, smoking, hemoglobin A1c, systolic blood pressure, total cholesterol/ high-density lipoprotein cholesterol ratio.

†Adjusted for age, sex, hypertension, diabetes, smoking, total cholesterol/ high-density lipoprotein

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cholesterol, cholesterol lowering medication and family history of premature MI.

‡ Adjusted for Framingham risk score

UMI-CMR=unrecognized myocardial infarction defined by cardiac magnetic resonance; UMI-ECG=unrecognized myocardial infarction defined by electrocardiography; IDI=integrated discrimination improvement; NRI= net reclassification improvement; ROC AUC= area under the curves of receiver operating characteristic curve; UMI=unrecognized myocardial infarction

The NRI assesses changes in the estimated events prediction probabilities that imply a change from one category to another, while the IDI assesses changes in the estimated events prediction probabilities as a continuous variable.

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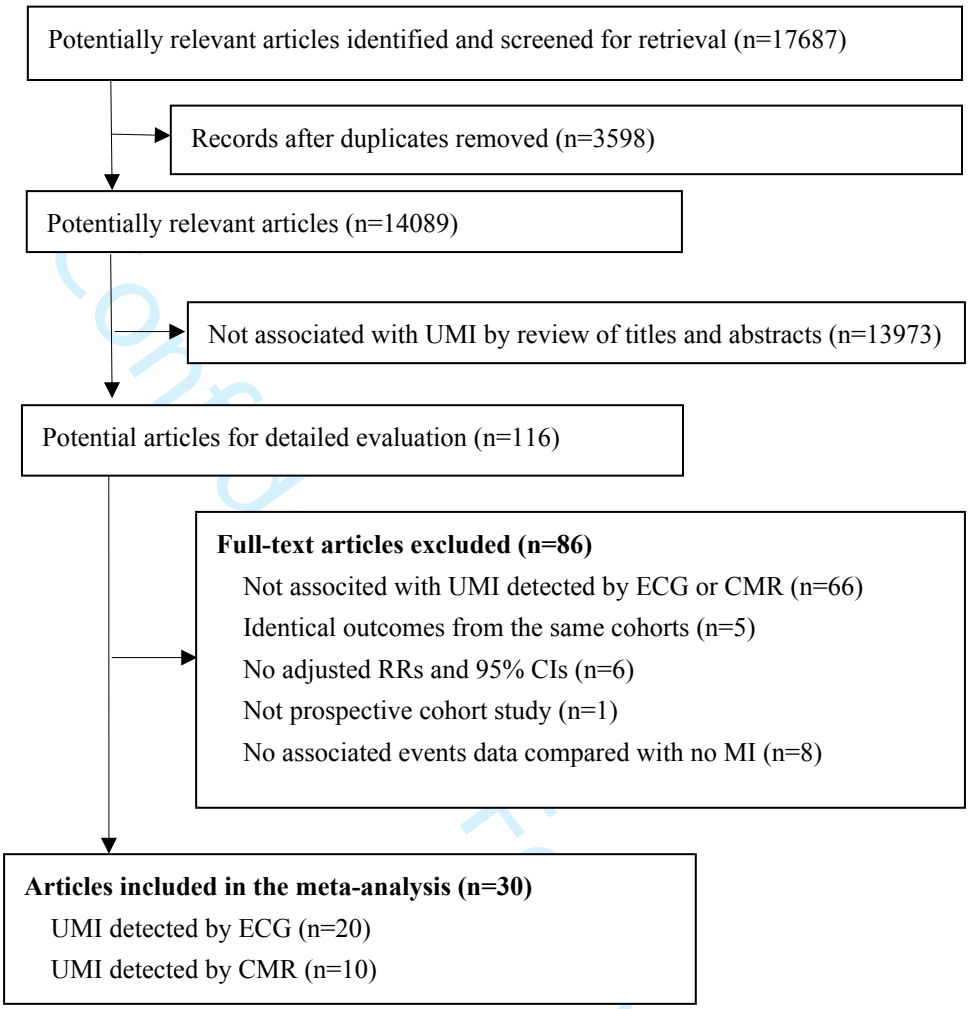

Figure 1. Flow of papers through review.

CIs=confidence intervals; CMR=cardiac magnetic resonance; ECG=electrocardiogram; RRs=relative risks; UMI=unrecognized myocardial infarction.

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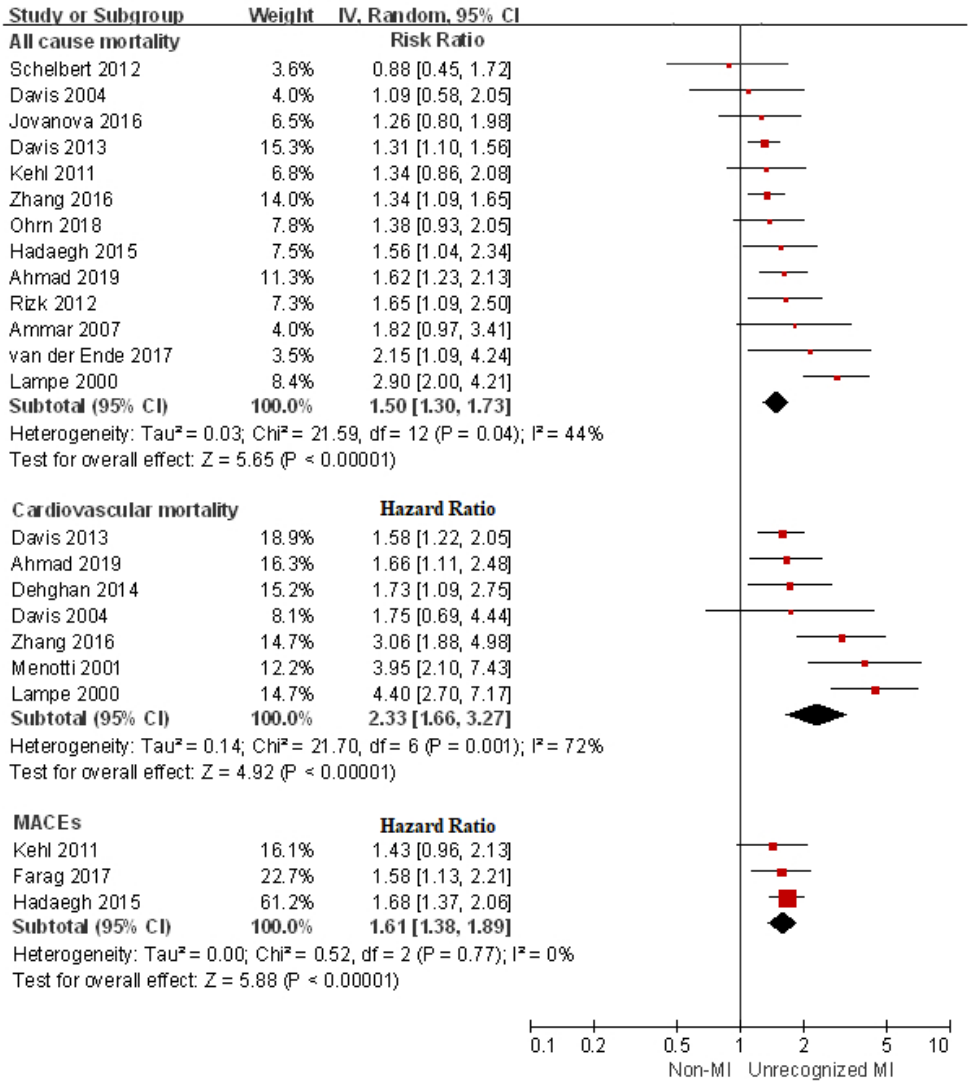
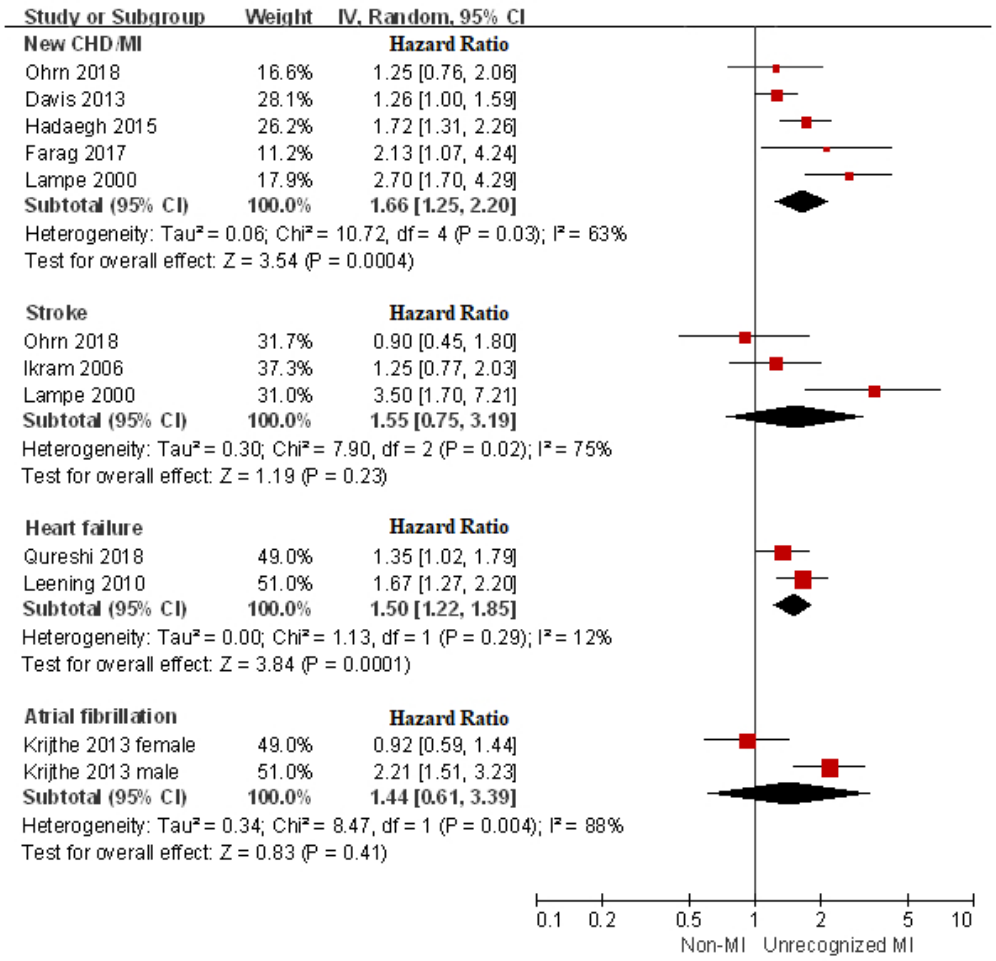


Figure 2. Forest plot of estimates for risks of primary outcomes associated with UMI-ECG. CIs=confidence intervals; UMI-ECG=unrecognized myocardial infarction detected by electrocardiogram; MACEs= major adverse cardiac outcomes.

162x182mm (96 x 96 DPI)



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One included study reported adjusted odds ratio for all-cause mortality associated with UMI-ECG and were converted to RR for meta-analysis, and all others studies reported the HRs for all evaluated events. Therefore, the risk of all-cause mortality was reported as RRs, while all other pooled outcomes were reported as HRs.

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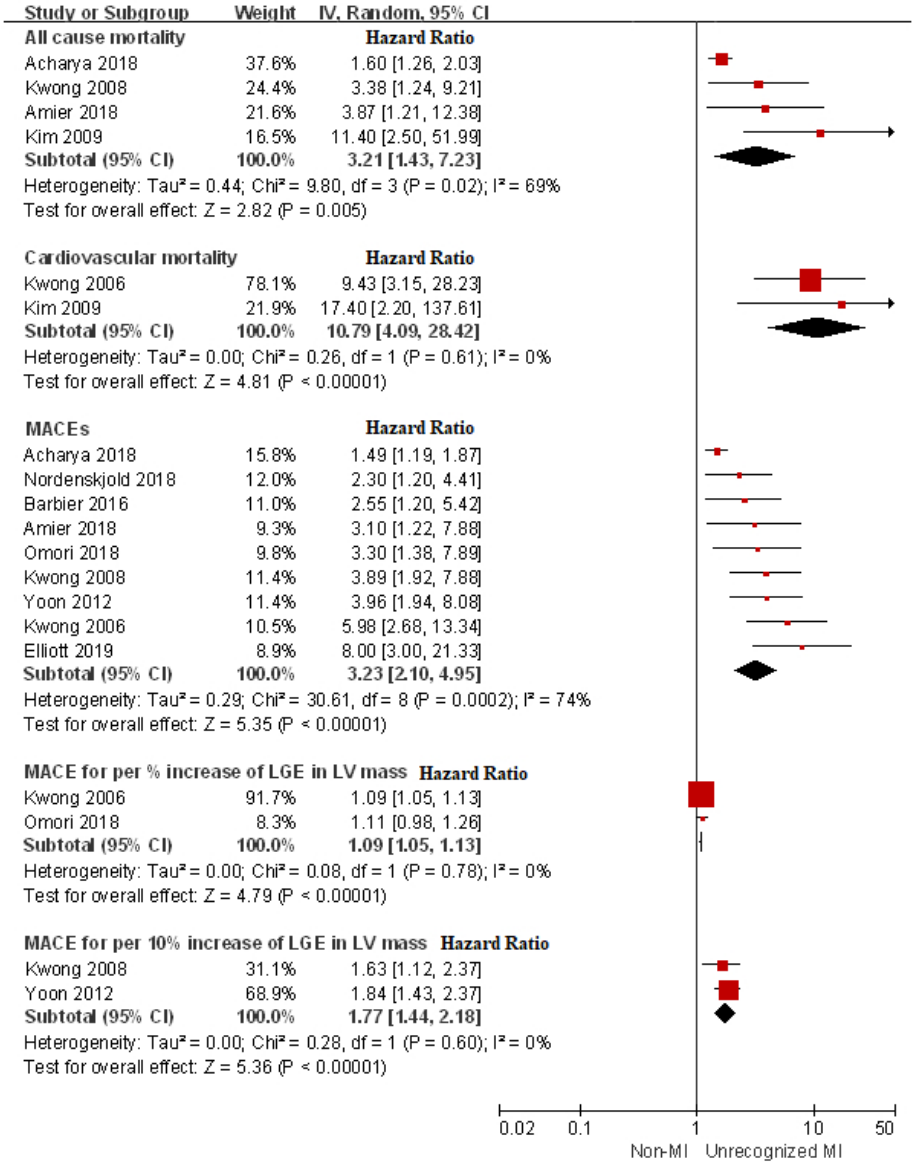

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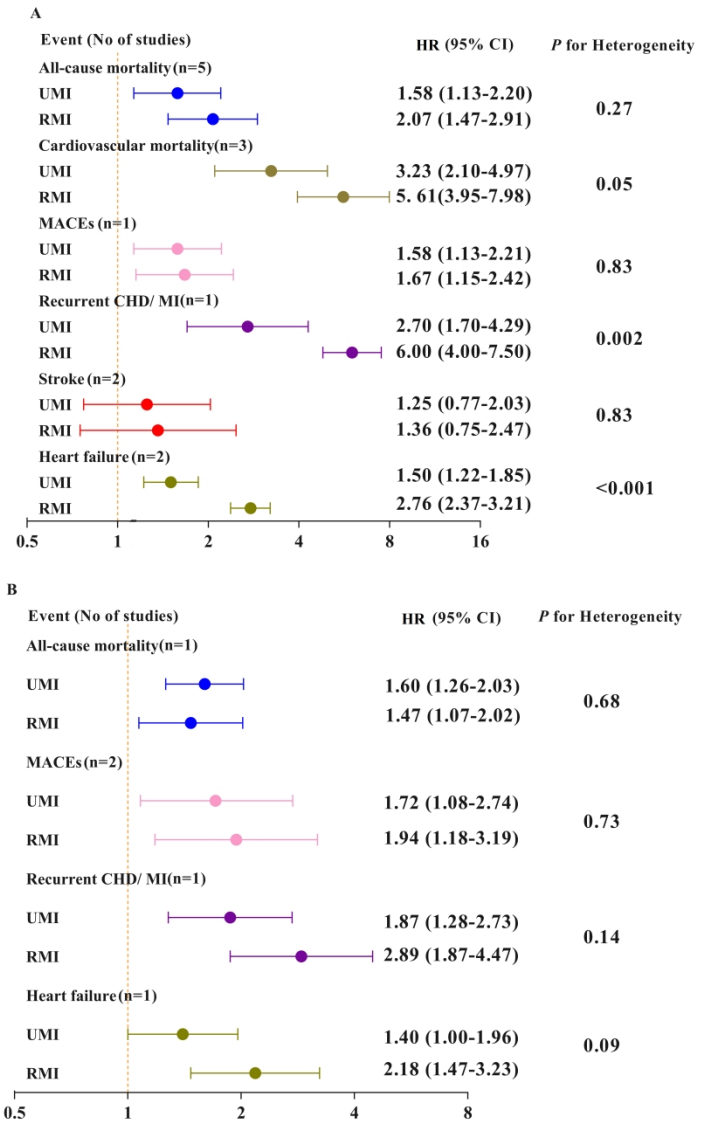
161x207mm (96 x 96 DPI)



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CMR=cardiac magnetic resonance; MACEs=major adverse cardiovascular events; MI=myocardial infarction; UMI=unrecognized myocardial infarction; RMI=clinical recognized myocardial infarction

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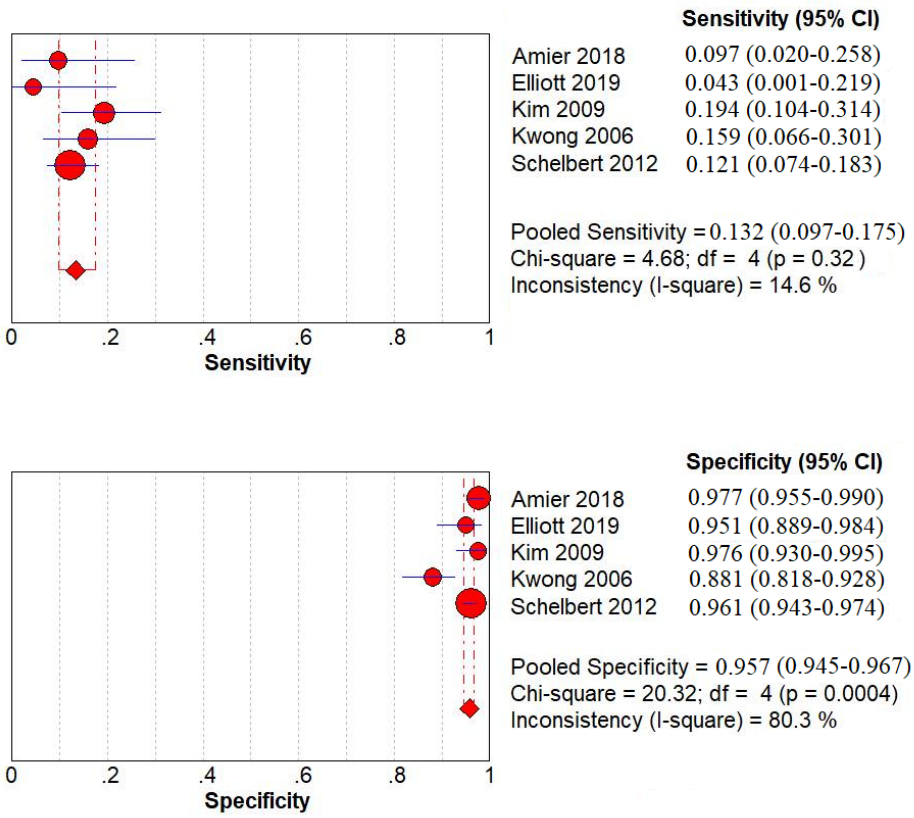

Figure 6. The sensitivity and specificity of ECG for detecting UMI
Cardiac magnetic resonance was regarding as gold standard in this analysis. CI=confidence interval; ECG=electrocardiogram; UMI=unrecognized myocardial infarction

Supplementary file 1. Literature search strategy for Pubmed

#1	(("myocardial infarction"[Mesh]) OR "myocardial ischemia"[Mesh])
#2	(("myocardial infarction"[Text Word]) OR "myocardial ischemia"[Text Word])
#3	#1 OR #2
#4	((((("unrecognized"[Text Word]) OR "silent"[Text Word]) OR " undiagnosed"[Text Word]) OR "asymptomatic"[Text Word])
#5	#3 AND #4
#6	animals[MeSH Terms]
#7	humans[MeSH Terms]
#8	#6 NOT #7
#9	**#5** NOT #8
#10	risk [Mesh]
#11	(((risk[Text Word])OR "hazard ratio"[Text Word]) OR "prognosis" [Text Word])
#12	#10 OR #11
#13	#9 AND #12

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Supplementary file 2. Quality assessment of the included studies

Study	Selection (points awarded)	Comparability (points awarded)	Outcome (points awarded)	Quality (total points)*
UMI detected by ECG				
Ahmad 2019	3	2	2	Good (7)
Qureshi 2018	3	2	3	Good (8)
Ohrn 2018	3	2	2	Good (7)
Farag 2017	2	1	2	Fair (5)
van der Ende 2017	4	1	2	Good (7)
Zhang 2016	4	2	2	Good (8)
Jovanova 2016	4	2	2	Good (8)
Hadaegh 2015	4	2	3	Good (9)
Dehghan 2014	4	2	2	Good (8)
Davis 2013	3	2	2	Good (7)
Krijthe 2013	4	2	2	Good (8)
Schelbert 2012	4	1	2	Good (7)
Rizk 2012	2	2	3	Good (7)
Kehl 2011	2	1	2	Fair (5)
Leening 2010	4	2	2	Good (8)
Ammar 2007	4	1	2	Good (7)
Ikram 2006	4	2	2	Good (8)
Davis 2004	3	2	2	Good (7)
Menotti 2001	4	2	2	Good (8)
Lampe 2000	4	1	2	Good (7)
UMI detected by CMR				
Elliott 2019	3	2	3	Good (8)
Acharya 2018	4	2	2	Good (8)
Nordenskjold 2018	3	1	3	Good (7)
Amier 2018	3	2	2	Good (7)
Omori 2018	3	2	2	Good (7)
Barbier 2016	3	2	3	Good (8)
Yoon 2012	3	2	2	Good (7)
Kim 2009	3	1	3	Good (7)
Kwong 2008	3	2	2	Good (7)
Kwong 2006	3	2	3	Good (8)

* Included studies were graded in quality as good if awarded with ≥7 points or fair if 4-6 points.

CMR=cardiac magnetic resonance; ECG=electrocardiogram; UMI=Unrecognized myocardial infarction

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Supplementary file 3. Characteristics of studies with unrecognized myocardial infarction determined by electrocardiogram

Study	Country	Patients characteristics	Sample (% Male)	Age (years) (mean/ range)	ECG interpretation method	ECG diagnositic criteria for UMI	Prevalence of UMI (%)	Proportion of UMI in all MI (%)	Follow-up duration (years)	Events for analysis
Ahmad 2019	USA	Community population	6323 (46.1)	58.4	Computerized automated process and visual inspection	A major Q wave abnormality (MC 1.1 or 1.2) or minor Q/QS wave (MC 1.3) plus major ST-T abnormality (MC 4.1, 4.2, 5.1, or 5.2)	1.5	NA	14	All-cause death; CVD mortality
Qureshi 2018	USA	Community population	9243 (42.8)	53.7	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2) or minor Q/QS wave (MC 1.3) plus major ST-T abnormality (MC 4.1, 4.2, 5.1, or 5.2)	3.4	48	13	Heart failure
Ohrn 2018	Norway	Community population	5686 (41)	63	Computerized automated process and visual inspection	Third universal definition of MI to identify prior MI on the ECG *	7.9	NA	5.5	All-cause death; MI; Stroke
Farag 2017	USA	Chronic kidney disease	1007 (58)	48	Computerized automated process and	Third Universal Definition of Myocardial Infarction	10.7	61.7	2.3	MACEs (all-cause death, MI, coronary

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					visual inspection					revascularization)
van der Ende 2017	Netherlands	Community population	152,124 (NA)	NA	Computerized automated process and visual inspection	Third Universal Definition of Myocardial Infarction	0.3	22.9	4	All-cause death
Jovanova 2016	Netherlands	Community population	4237 (45.2)	68.3	Computerized automated process and visual inspection	Pathologic Q waves and on auxiliary criteria (QR ratio and R-wave progression)	5.4	44.5	13.5	All-cause death
Zhang 2016	USA	Community population	9498 (43.1)	54.0	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2) or minor Q/QS wave (MC 1.3) plus major ST-T abnormality (MC 4.1, 4.2, 5.1, or 5.2)	3.3	45	13.2	All-cause death CHD mortality
Hadaegh 2015	Iran	Community population	1809 (47.1)	59.7	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2) or complete left bundle branch block (MC 7.1.1) or minor Q/QS wave (MC 1.3) plus major ST-T abnormality (MC 4.1, 4.2, 5.1, or 5.2)	14.9	NA	12.1	All-cause death; MACEs (all-cause death, CHD events, stroke); CHD

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Dehghan 2014	Netherlands	Community population	6534 (40.9)	69	Computerized automated process and visual inspection	Pathologic Q waves and on auxiliary criteria (QR ratio and R-wave progression)	5.7	45.8	15.6	CVD Mortality
Davis 2013	UK	Type 2 diabetes	1967 (59.8)	52.5	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2)	16.6	NA	17	All-cause death; Fatal MI; Non-fatal MI
Krijthe 2013	Netherlands	Community population	6175 (40.6)	68.6	Computerized automated process and visual inspection	Pathologic Q waves and on auxiliary criteria (QR ratio and R-wave progression)	5.4	47.6	11.7	Atrial fibrillation
Schelbert 2012	Iceland	Community population	936 (48)	76	NA	A major Q wave abnormality (MC 1.1 or 1.2)	5	33.3	6.4	All-cause death
Rizk 2012	USA	Chronic kidney disease	18864 (37.7)	64.0	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2) or minor Q/QS wave (MC 1.3) plus major ST-T abnormality (MC 4.1, 4.2, 5.1, or 5.2)	4.5	38.4	4	All-cause death
Kehl 2011	USA	Stable coronary artery disease but no history of MI	462 (79.4)	67	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2)	36	NA	6.3	MACEs (all-cause death, nonfatal MI, and stroke); All-cause

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										death
Leening 2010	Netherlands	Community population	6305 (40.9)	68.7	Computerized automated process and visual inspection	Pathologic Q waves and on auxiliary criteria (QR ratio and R-wave progression)	3.9	35.9	13.2	Heart failure
Ammar 2007	Netherlands	Community population	2029 (48.1)	62.7	Computerized automated process	A major Q wave abnormality (MC 1.1 or 1.2) or minor Q/QS wave (MC 1.3) plus major ST-T abnormality (MC 4.1, 4.2, 5.1, 5.2, 5.3)	4.0	44.5	5.5	All-cause death
Ikram 2006	Netherlands	Community population	6439 (40.4)	68.7	Computerized automated process	Pathologic Q waves and on auxiliary criteria (QR ratio and R-wave progression)	5.6	45	8.2	Stroke
Davis 2004	Australia	Type 2 diabetes	1269 (49.2)	64.1	Visual inspection	A major Q wave abnormality (MC 1.1 or 1.2)	3.9	44	7.0	All-cause death CHD mortality
Menotti 2001	Finland Netherlands Italy	Community population	1785 (100)	65-84	Visual inspection	A major Q wave abnormality (MC 1.1) or MC (1.2 + 5.1 or 5.2)	5.9	NA	10	CHD mortality
Lampe 2000	British	Community population	7715 (100)	40-59	NA	A major Q wave abnormality (MC 1.1 or 1.2)	1.7	31.6	10	All-cause death; CHD, Stroke; CVD mortality

CVD=cardiovascular disease; CHD=coronary heart disease; MACEs=major adverse cardiovascular events; MC=Minnesota code; MI=myocardial infarction; NA=not

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available; RMI=recognized myocardial infarction; UMI=unrecognized myocardial infarction

* Third universal definition of MI to identify prior MI on the ECG as: i) any Q wave in leads V2–V3 ≥0.02 s or QS complex in leads V2 and V3; ii) Q wave ≥0.03 s or QS complex in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF); or iii) R wave ≥0.04 s in V1–V2 and R/S ≥1 with a concordant positive T wave in absence of conduction defect.

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Supplementary file 4. Confounders Adjusted of the Included Studies

Study	Confounder adjusted	Adequate adjustment†
UMI detected by ECG		
Ahmad 2019	Age, sex, race, total annual income, smoking, physical activity, SBP, DBP, antihypertensive medications, diuretics, diabetes, BMI, hyperlipidemia, alcohol intake, history of gout, and eGFR.	Yes
Qureshi 2018	Age, sex, race, BMI, smoking, heart rate, SBP, antihypertensive medications, and diabetes.	Yes
Ohrn 2018	Age, sex, hypertension, diabetes, smoking, TC, HDL-C, cholesterol lowering medication and family history of premature MI.	Yes
Farag 2017	Age, sex, race, diabetes, hypertension, dyslipidemia, dialysis, and medication intake assumption	No
van der Ende 2017	Age, sex, hypertension, diabetes and heart rate	No
Jovanova 2016	Age, sex, level of education, smoking, alcohol consumption, history of stroke, diabetes and SBP.	No
Zhang 2016	Age, sex, race, study center, BMI, income, education, smoking, SBP, antihypertensive and cholesterol lowering medications, diabetes, ratio of TC/HDL-C, aspirin, family history of CAD and serum creatinine	Yes
Hadaegh 2015	Age, sex, BMI, impaired glucose regulation, hypertension, hypercholesterolemia, and smoking	Yes
Dehghan 2014	Age, sex, SBP, DBP, smoking, antihypertensive medication, TC, HDL-C, BMI, and type 2 diabetes.	Yes
Davis 2013	Age, sex, ethnicity, smoking, HbA1c, SBP, TC/HDL-C ratio	Yes
Krijthe 2013	Age, sex, SBP, DBP, smoking, antihypertensive medication, TC, HDL-C, BMI, diabetes, COPD, and heart failure.	Yes
Schelbert 2012	Age, sex, diabetes, RMI	No
Rizk 2012	Age, race, sex, region, education, income, smoking, insurance, health care, cognitive impairment, marital, SBP, anti-hypertensive medication, dyslipidemia and diabetes	Yes
Kehl 2011	Age, sex, ethnicity, smoking, heart failure, diastolic dysfunction, left ventricular ejection fraction, wall motion score, inducible ischemia	No
Leening 2010	Age, sex, SBP, DBP, antihypertensive drugs, BMI, DM, smoking, TC, HDL-C	Yes
Ammar 2007	Age, sex, diabetes, hypertension, smoking	No
Ikram 2006	Age, sex, SBP, DBP, smoking, TC, HDL-C, atrial fibrillation, diabetes, ankle–arm pressure index, cardiovascular drugs	Yes
Davis 2004	Age, sex, marital status, education, diabetes, BMI, SBP, antihypertensive medication, lipid-lowering therapy, serum creatinine, microalbuminuria, retinopathy, neuropathy, smoking, exercise	Yes
Menotti 2001	Age, BP, smoking, TC, BMI	Yes
Lampe 2000	Age	No

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UMI detected by CMR		
Elliott 2019	LVEF, Framingham risk score, diabetes type	Yes
Acharya 2018	Age, sex, diabetes, smoking, hypertension, TC, HDL-C, statin use, BMI, eGFR.	Yes
Nordenskjold 2018	Age, sex, hypertension, NT-proBNP, extent of CAD	No
Amier 2018	Age, sex, study site, pre-hospital medication, type of acute MI, number of vessel disease, reperfusion strategy, LVEF, total infarct size and microvascular obstruction.	No
Omori 2018	Age, sex, hypertension, diabetes dyslipidaemia, smoking, obesity, history of CAD, Killip classification medications, laboratory results, angiographic findings, CMR findings	Yes
Barbier 2016	Sex, Framingham Risk Score	Yes
Yoon 2012	Age, sex, hypertension, hypercholesterolemia, smoking, family history of CAD, BMI, history of CAD, revascularization, LVEF, LV wall motion abnormalities	Yes
Kim 2009	Candidate variables with $p<0.10$ from the univariable analysis (NYHA class, LVEF, non-Q-wave UMI, and revascularization during the follow-up period)	No
Kwong 2008	Age, sex, ST or T changes on ECG, and end-systolic volume index, 5-year probability of a cardiac event by the UKPDS risk model	Yes
Kwong 2006	Age, sex, race, BMI, heart rate, smoking, diabetes, hypertension, hypercholesterolemia, PCI, CABG, status of coronary stenosis on angiography, noninvasive assessment of myocardial ischemia, CMR predictors	Yes

†Adequate adjustment denoted adjustment of at least six of seven factors: sex; age; hypertension or blood pressure or antihypertensive treatment; diabetes mellitus or fasting plasma glucose or hemoglobin A1c; body mass index or overweight/obesity; cholesterol or hypercholesterolemia and smoking or adjusted for risk score calculated from these metrics (e.g Framingham Risk Score)

BMI=body mass index; CABG=Coronary Artery Bypass Grafting; CAD=coronary artery disease; COPD=chronic obstructive pulmonary disease; CMR=cardiac magnetic resonance; DBP=diastolic blood pressure; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; HDL-C= high-density lipoprotein cholesterol; MC=Minnesota code; MI=myocardial infarction; PCI=percutaneous coronary intervention; RMI=recognized myocardial infarction; SBP=systolic blood pressure; TC=total cholesterol; UMI=unrecognized myocardial infarction

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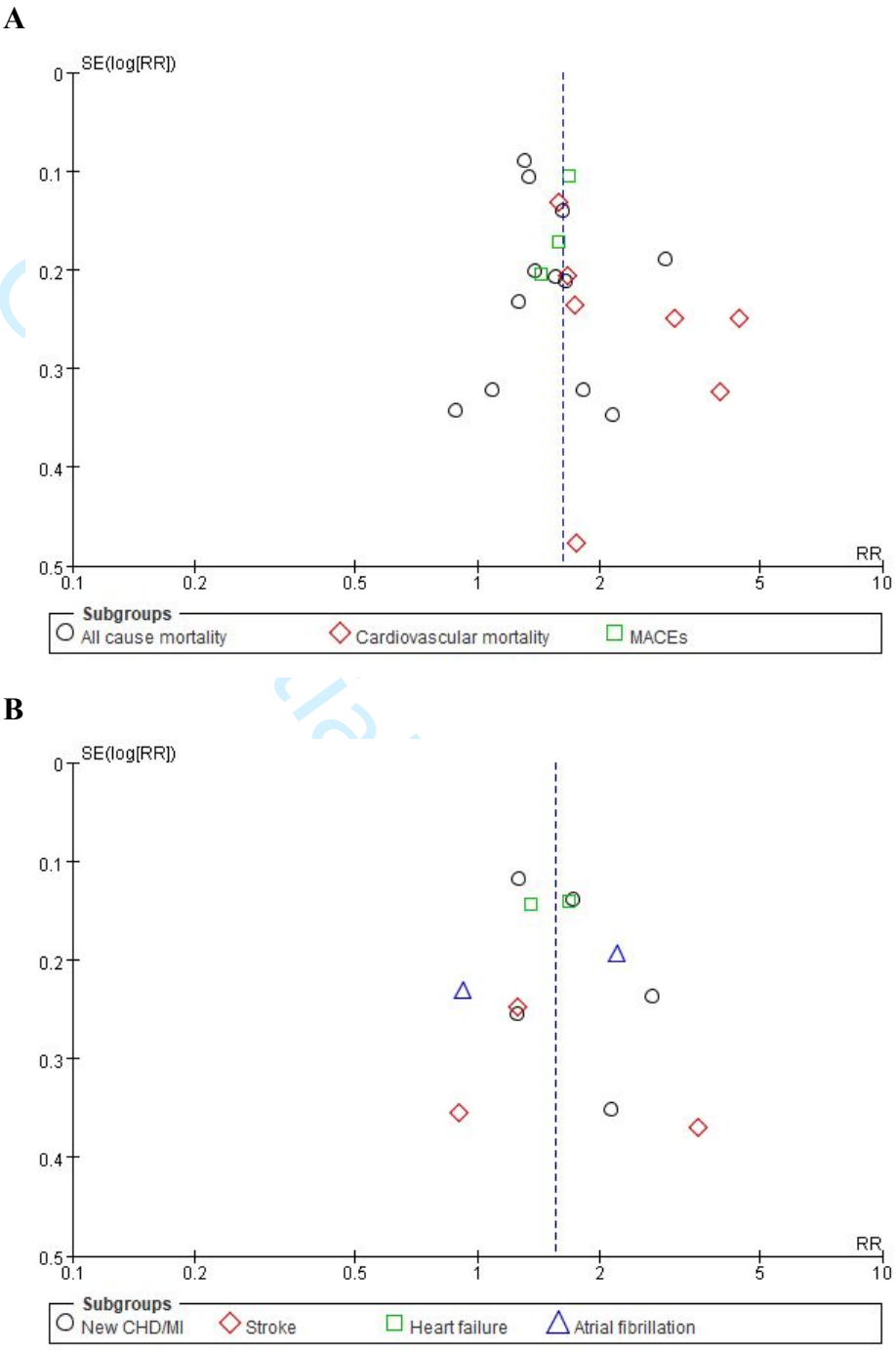

Supplementary file 5. Funnel plot of comparison.

A: primary outcomes between UMI detected by electrocardiogram and non-MI; B: Secondary outcomes between UMI detected by electrocardiogram and non-MI

CHD=coronary heart disease; MACEs=major adverse cardiovascular events; MI=myocardial infarction; UMI=unrecognized myocardial infarction

Supplementary file 6. Absolute risk of primary outcomes in UMI-ECG

Study	Event Rate* (non-MI)	Event Rate* (UMI)	Event Rate* (Total)
All-cause mortality			
Lampe 2000	7.3	25.3	9.7
Davis 2004	26	37.1	35.1
Ammar 2007	NA	NA	11.5
Kehl 2011	35	47	39.9
Rizk 2012	NA	NA	5.6
Schelbert 2012	27	NA	32.2
Davis 2013	21.3	32.6	23.3
Hadaegh 2015	8.6	17	9.5
Jovanova 2016	NA	NA	32.4
Zhang 2016	8.4	15.9	14.6
van der Ende 2017	5.5	16	25.4
Ohrn 2018	6.9	12.2	7.32
Ahmad 2019	22.7	65.6	21.6
Median	15.0	25.3	21.6
Cardiovascular mortality			
Lampe 2000	1	4.4	4.9
Menotti 2001	7	30.6	12.8
Davis 2004	8.3	14.3	14.9
Davis 2013	8.3	15.2	9.3
Dehghan 2014	11.3	18.9	12.8
Zhang 2016	0.7	3.2	1.5
Ahmad 2019	9.1	30.7	9.4
Median	8.3	15.2	9.4
MACEs			
Kehl 2011	45.0	62	48.4

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Hadaegh 2015	16.0	27.7	17.5
Farag 2017	54.0	106	63.3
Median	45.0	62	48.4

* Per 1,000 patient-years.

CHD=coronary heart disease; ECG=electrocardiogram; MACEs=major adverse composite cardiovascular events; MI= myocardial infarction; UMI=unrecognized myocardial infarction; UMI-ECG=UMI detected by electrocardiogram

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Supplementary file 7. Characteristics of studies with unrecognized myocardial infarction determined by cardiac magnetic resonance

Study	Country	Patients characteristics	Sample size (% Male)	Age (years) (mean/range)	CMR diagnositic criteria for MI	Prevalence of UMI in the cohort (%)	Proportion of UMI in all MI (%)	Follow-up duration (years)	Events for analysis
Elliott 2019	USA	Diabetes	120 (54)	52	Subendocardial LGE	19	NA	5	MACEs (All-cause death or MI)
Acharya 2018	Iceland	Community population	935 (48.3)	76	Subendocardial LGE	17	63.2	10.5	All-cause death; MACEs (all-cause death, nonfatal MI, and heart failure); New MI; Heart failure
Nordenskjold 2018	Sweden	Suspected stable CAD	235 (66)	65	Subendocardial LGE	25	NA	5.4	MACEs (cardiovascular mortality, resuscitated cardiac arrest, MI, hospitalization for angina pectoris, heart failure)
Amier 2018	Netherlands	Acute MI	392 (77)	58.3	Subendocardial LGE located in the other territories than the acute MI	8.2	NA	6.8	All-cause death; MACEs (all-cause death, reinfarction, coronary artery bypass grafting, and ischemic stroke)
Omori 2018	Japan	Acute MI	269 (78)	66	LGE located in the other territories than the acute MI	13	NA	1.8	MACEs (cardiovascular mortality, non-fatal MI, unstable angina requiring revascularization, fatal arrhythmia, and heart failure)
Barbier 2016	Sweden	Community	248	71	Subendocardial	22.2	83.3	11	MACEs (cardiovascular mortality,

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		population	(50.4)		LGE				non-fatal MI, a new diagnosis of angina pectoris, or coronary artery revascularization)
Yoon 2012	Japan	Impaired Fasting Glucose or Diabetes	332 (67.2)	68	Subendocardial LGE	31	NA	2.5	MACEs (cardiovascular mortality, new acute MI, unstable angina necessitating hospitalization, heart failure or ventricular arrhythmias necessitating an internal cardioverter and/or defibrillator)
Kim 2009	USA	Suspected stable CAD	185 (66)	60.4	Subendocardial LGE	27	NA	2.2	All-cause death; Cardiovascular mortality
Kwong 2008	USA	Diabetes	107 (63)	59 (13)	LGE	28	51.0	1.4	MACEs (all-cause death, new acute MI, unstable angina requiring hospitalization, heart failure; ventricular arrhythmias requiring internal cardioverter and/or defibrillator, and acute cerebral vascular accidents)
Kwong 2006	USA	Suspected stable CAD	195 (68)	59 (13)	LGE	22.7	NA	1.3	MACEs (cardiac death, new acute MI, unstable angina requiring hospitalization, heart failure requiring hospitalization, or ventricular arrhythmias requiring internal cardioverter and/or defibrillator) Cardiovascular mortality,

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CAD=coronary artery disease; LGE: ate gadolinium enhancement; MACEs=major adverse composite cardiovascular events; MI= myocardial infarction; UMI=unrecognized myocardial infarction

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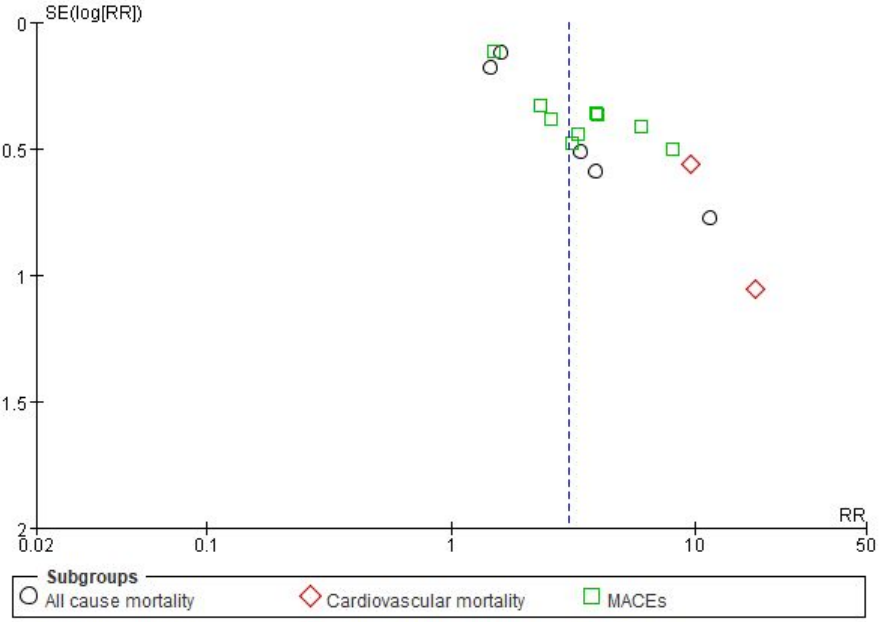

Supplementary file 8. Funnel plot of primary outcomes between UMI detected by CMR and non-MI

CMR=cardiac magnetic resonance; MACEs=major adverse cardiovascular events; MI=myocardial infarction; UMI=unrecognized myocardial infarction

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Supplementary file 9. Absolute risk of primary outcomes in UMI-CMR

Study	Event Rate* (non-MI)	Event Rate* (UMI)	Event Rate* (Total)
All-cause mortality			
Kwong 2008	NA	NA	120.2
Kim 2009	7.6	NA	39.3
Amier 2018	14.7	41.4	25.5
Acharya 2018	30.0	49	43.2
Median	14.7	45.2	41.3
Cardiovascular mortality			
Kwong 2006	NA	NA	67.1
Kim 2009	3.8	90.9	29.5
Median	3.8[#]	90.9[#]	48.3
MACEs			
Kwong 2006	NA	NA	122.3
Kwong 2008	NA	NA	253.8
Yoon 2012	NA	NA	42.2
Barbier 2016	9.0	18.2	12.5
Acharya 2018	41.1	62.8	45.3
Amier 2018	23.7	55.1	26.3
Omori 2018	37.8	127.2	49.6
Nordenskjold 2018	20.9	63.9	31.5
Elliott 2019	14.0	88.0	31.7
Median	22.3	63.4	42.2

* Per 1,000 patient-years.

[#] Data were only available in one study and regarded as the median value

CHD=coronary heart disease; CMR=cardiac magnetic resonance; MACEs=major adverse composite cardiovascular events; MI=myocardial infarction; NA=not available; UMI=unrecognized myocardial

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infarction; UMI-CMR= UMI determined by cardiac magnetic resonance

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Supplementary file 10. Subgroup analyses of the association between UMI-ECG and risk of primary outcomes

	All-cause mortality			Cardiovascular mortality			MACEs		
	Number of Studies	HR (95%CI)	*P* value* / I^2 (%)	Number of Studies	HR (95%CI)	*P* value* / I^2 (%)	Number of Studies	HR (95%CI)	*P* value* / I^2 (%)
Age									
<65 years	9	1.41 [1.27, 1.57]	0.54/0	5	2.28 [1.50, 3.46]	0.81/0	1	1.43 [0.96, 2.13]	0.77/0
≥65 years	5	1.30 [1.03, 1.65]		2	2.54 [1.13, 5.69]		2	1.65 [1.39, 1.97]	
Sex									
Male	4	1.49 [1.27, 1.75]	0.16/48.8	4	3.07 [2.11, 4.47]	0.48/0	2	1.76 [1.41, 2.20]	0.63/0
Female	4	1.19 [0.91, 1.56]		2	2.10 [0.78, 5.66]		2	1.47 [1.07, 2.02]	
Ethnicity									
Asian	1	1.56 [1.04, 2.34]	0.59/0	-	-	NA	1	1.68 [1.37, 2.06]	0.77/0
Non-Asian	12	1.39 [1.26, 1.53]		7	2.33 [1.66, 3.27]		2	1.52 [1.17, 1.96]	
Enrollment from community-based population									
Yes	9	1.58 [1.29, 1.93]	0.19/42.5	5	2.67 [1.77, 4.02]	0.04/77.5	1	1.68 [1.37, 2.06]	0.77/0
No	4	1.34 [1.16, 1.55]		2	1.59 [1.24, 2.04]		2	1.52 [1.17, 1.96]	
All participants with diabetes									
Yes	3	1.30 [1.11, 1.54]	0.13/56.8	2	1.59 [1.24, 2.04]	0.04/77.5	1	1.11 [0.73, 1.68]	0.10/63.4
No	11	1.57 [1.33, 1.85]		5	2.67 [1.77, 4.02]		2	1.62 [1.35, 1.95]	
Follow-up duration									
<6 years	4	1.62 [1.27, 2.06]	0.50/0	-	-	NA	1	1.58 [1.13, 2.21]	0.77/0
≥6 years	9	1.46 [1.22, 1.74]		7	2.33 [1.66, 3.27]		2	1.62 [1.35, 1.95]	
Adjustment of confounders									
Adequate†	7	1.39 [1.25, 1.55]	0.41/8.1	6	2.05 [1.54, 2.74]	0.008/85.6	1	1.68 [1.37, 2.06]	0.77/0
Inadequate	6	1.63 [1.13, 2.35]		1	4.40 [2.70, 7.17]		2	1.52 [1.17, 1.96]	

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* For heterogeneity among subgroups. †Adequate adjustment denoted adjustment of at least six of seven factors: sex; age; hypertension or blood pressure or antihypertensive treatment; diabetes mellitus or fasting plasma glucose or hemoglobin A1c; body mass index or overweight/obesity; cholesterol or hypercholesterolemia and smoking or adjusted for risk score calculated from these metrics

UMI-ECG=unrecognized myocardial infarction detected by electrocardiogram; MACEs=major adverse cardiovascular events; NA=not applicable

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Supplementary file 11. Subgroup analyses of the association between UMI-CMR and risk of primary outcomes

	All-cause mortality			Cardiovascular mortality					
	Number of Studies	HR (95%CI)	*P* value* / I^2 (%)	Number of Studies	HR (95%CI)	*P* value* / I^2 (%)	Number of Studies	HR (95%CI)	*P* value* / I^2 (%)
Age									
<65 years	3	4.52 [2.29, 8.90]	0.005/87.5	2	10.79 [4.09, 28.42]	NA	4	4.76 [3.13, 7.22]	0.02/80.7
≥65 years	1	1.60 [1.26, 2.03]		-	-		5	2.37 [1.54, 3.65]	
Ethnicity									
Asian	-	-	NA	-	-	NA	2	3.68 [2.12, 6.39]	0.68/0
Non-Asian	4	3.21 [1.43, 7.23]		2	10.79 [4.09, 28.42]		7	3.15 [1.90, 5.23]	
Enrollment from community-based population									
Yes	1	1.60 [1.26, 2.03]	0.005/87.5	-	-	NA	2	1.72 [1.08, 2.74]	0.005/87.4
No	3	4.52 [2.29, 8.90]		2	10.79 [4.09, 28.42]		7	3.80 [2.82, 5.12]	
All participants with diabetes									
Yes	1	3.38 [1.24, 9.21]	0.99/0	-	-	NA	3	4.43 [2.71, 7.23]	0.13/55.9
No	3	3.41 [1.11, 10.48]		2	10.79 [4.09, 28.42]		6	2.64 [1.66, 4.20]	
Follow-up duration									
<6 years	2	4.89 [2.12, 11.29]	0.01/83.2	2	10.79 [4.09, 28.42]	NA	3	3.93 [2.80, 5.52]	0.02/82.2
≥6 years	2	1.66 [1.31, 2.10]		-	-		6	1.95 [1.21, 3.12]	
Adjustment of confounders									
Adequate†	2	1.97 [1.02, 3.81]	0.08/67.7	1	9.43 [3.15, 28.23]	0.61/0	7	3.47 [2.02, 5.98]	0.42/0
Inadequate	2	5.92 [2.10, 16.67]		1	17.40 [2.20, 137.61]		2	2.54 [1.49, 4.32]	

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* For heterogeneity among subgroups. †Adequate adjustment denoted adjustment of at least six of seven factors: sex; age; hypertension or blood pressure or antihypertensive treatment; diabetes mellitus or fasting plasma glucose or hemoglobin A1c; body mass index or overweight/obesity; cholesterol or hypercholesterolemia and smoking or adjusted for risk score calculated from these metrics

UMI-CMR=unrecognized myocardial infarction detected by cardiac magnetic resonance; MACEs= major adverse cardiovascular events; NA=not applicable

No data available for subgroup analysis for sex.

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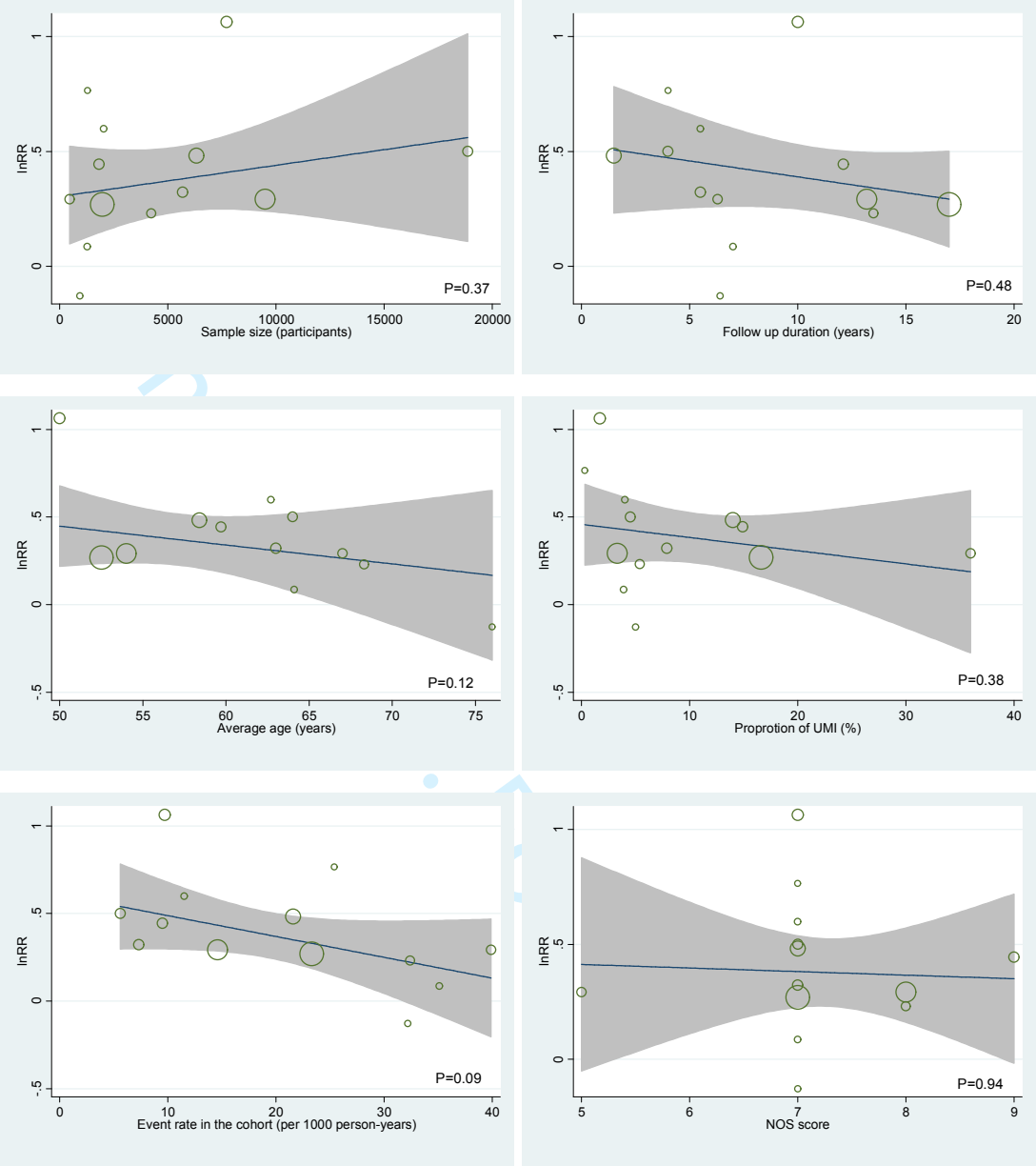
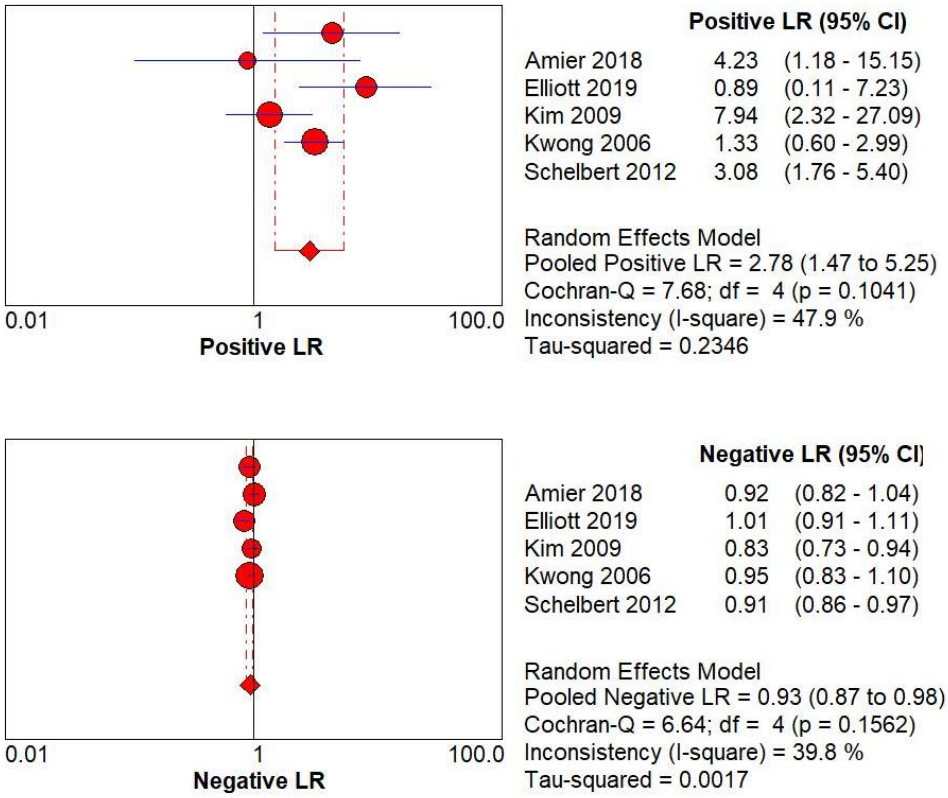


Supplementary File 12. The associations among study characteristics and risk of all-cause mortality in UMI-ECG

NOS=Newcastle–Ottawa Quality Assessment Scale for cohort studies; UMI=unrecognized myocardial infarction; UMI-ECG=unrecognized MI detected by electrocardiogram



Supplementary File 13. Difference in diagnostic efficacy between ECG and CMR for detection of UMI

CMR=cardiac magnetic resonance; ECG=electrocardiogram; LR=likelihood ratio; UMI=unrecognized myocardial infarction

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