ECG-based Predictors of Re-infarction or Death on the Hospital Admission 12-Lead ECG among UA/NSTEMI Patients: A Protocol for a Systematic Review and Meta-Analysis

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Protocol

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Abstract

Background The incidence of unstable angina/ non-ST elevation MI (UA/NSTEMI) continues to rise. The electrocardiogram (ECG) remains the first-line assessment of cardiac conduction and myocardial ischemia, and is performed within the first 10-minutes of hospital presentation. Despite recent advances in treatment, in-hospital death and re-infarction continues as a result of delayed interventions. Since the ECG is a rapid test to guide treatment decisions, it is crucial emergency providers understand the prognostic value of characteristics on the admission 12-lead ECG to decide treatments which may reduce the risk of re-infarction and death. This is the first systematic review and meta-analysis to assess the significance of these ECG findings associated with in-hospital death and re-infarction.

Methods A systematic review and meta-analysis will be conducted to comprehensively assess the prognostic value of specific characteristics on the admission 12-lead ECG associated with re-infarction and death. This is the protocol for such review and meta-analysis. Electronic databases and specific cardiovascular journals will be searched using predefined search terms to identify relevant studies. Eligible studies will be peer-reviewed research articles with empirical findings on the risk re-infarction and death based on characteristics on the admission 12-lead ECG. The methodological quality of the included studies will be assessed with the Newcastle-Ottawa Quality Assessment Scale and GRADE. Citations will be managed using EndNote X9. A random effects meta-analysis will be conducted with the Meta-Essentials package and STATA.

Discussion This study will be among the first to systematically evaluate and quantitatively assess the evidence available on the prognostic value of characteristics on the admission 12-lead ECG for the risk of re-infarction and death. This study will inform clinicians about the significance of characteristics on the admission 12-lead ECG so better treatment decisions can be made, as well as inform new research opportunities in the field of cardiovascular risk stratification.

Registration This systematic review and meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42020158491).

Background

More than 65% of all myocardial infarctions in the United States are diagnosed as unstable angina/ non-ST elevation myocardial infarction (UA/NSTEMI), and the number increases annually [1]. UA/NSTEMI occurs due to the rupture or erosion of an atherosclerotic plaque causing either a partial occlusion of a coronary artery or a total occlusion of a coronary artery in the presence of collateral blood flow [2, 3]. The current diagnostic definition for UA/NSTEMI involves an emergent presentation with or without chest pain, but with electrocardiographic (ECG) changes consistent with ischemia (e.g. ST-segment changes) and elevation in cardiac biomarkers for NSTEMI only (e.g. troponin) [2]. Thus, UA/NSTEMI are similar conditions which only differ in the absence (i.e. UA) or presence (i.e. NSTEMI) of detectable cardiac biomarkers [2]. The majority of patients with UA/NSTEMI present heterogeneously with non-anginal

symptoms including arm pain and back discomfort, and normal initial cardiac biomarkers [4, 5,6]. The heterogeneity in patient presentation make decisions around timing of interventions susceptible to error despite the fact that timely interventions are needed to reduce the risk of re-infarction and death [6,7,8,9].

The risk of re-infarction and death is a serious concern among UA/NSTEMI patients, and initial treatment is based on this acute risk. In the Global Registry of Acute Coronary Events (GRACE) registry of over 16,000 patients from 14 countries between 2001 and 2007, the in-hospital mortality was 3.3% and the rate of in-hospital re-infarction was 2.4% [10]. In the United States, the Worcester Heart Attack Study reported a hospital post-admission case mortality rate of nearly 10% [11]. Despite a growing emphasis on early invasive strategy to prevent re-occurring myocardial ischemia, in-hospital mortality rates have not significantly decreased [12]. This may be due to an initial underestimation of ischemic injury at presentation [7,8,9].

The admission 12-lead ECG is known to carry similar or even better prognostic information than cardiac biomarker measurements for UA/NSTEMI [13]. The 12-lead ECG is inexpensive, noninvasive and completed within the first 10 minutes of patient presentation per current American Heart Association/ American College of Cardiology (AHA/AACC) guidelines [2]. This means the ECG can be used to *rapidly* risk stratify patients. Frontline emergency care provider can quickly and efficiently use characteristics on the admission 12-lead ECG to risk stratify suspected UA/NSTEMI patients for risk of re-infarction and death. Emergency care providers are in a unique position to initiate efforts to decrease time to initial treatment for UA/NSTEMI patients and quickly determine those at highest risk whom require more invasive interventions [14,15]. However, emergency care providers need information on the prognostic significance of specific characteristics on the admission 12-lead ECG in order to guide these initiatives.

This protocol aims to conduct a systematic review and meta-analysis to identify specific characteristics on the admission 12-lead ECG prognostic of re-infarction and death among patients presenting to the emergency department for UA/NSTEMI, and summarize the research in this field. This would be the first systematic review and meta-analysis on this topic. This systematic review and meta-analysis will inform emergency care providers about the prognostic value of the admission 12-lead ECG, and advance the science of risk stratification in UA/NSTEMI.

Methods

The following protocol has been written in accordance to the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines [16, 17]. The PRISMA-P checklist is seen in Figure 1. The protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42020158491) [18].

The proposed systematic review and meta-analysis is part of a larger project entitled “Development and Validation of TIB: A Total Ischemic Burden Score for the Rapid Risk Stratification of NSTEMI.” The aims of research are (1) to assess the prognostic value of characteristics on the admission 12-lead ECG for in-

hospital re-infarction and death; and, (2) to build a rapid risk stratification tool called Total Ischemic Burden (TIB) based solely on significant characteristics on the admission 12-lead ECG for risk assessment of in-hospital re-infarction and death; and, (3) to evaluate the impact of TIB on emergency triage, pre-hospital ECG interpretation and, ultimately, patient care at a large academic medical center.

Research Question

The PIOT (Population, Indicator, Outcome, Time) research question guiding this systematic review and meta-analysis is: Among UA/NSTEMI patients (Population), do specific characteristics on the admission 12-lead ECG (Indicator) for the prediction of re-infarction and death (Outcome) in the first 24 hours of patient presentation (Time)? No comparison component will be used.

Independent Variables

The independent variables for this protocol are specific characteristics on the 12-lead ECG. Previous research and medical expertise in this area of inquiry hypothesize the following characteristics will most likely be included: ST-segment depression, T-wave inversion, and pathological Q waves. However, we will not limit our search to just these three well known characteristics. It is also important to recognize that there may be measurement differences across studies. Although these characteristics have standardized measurements and corresponding normal values, individual studies may deviate from these published standards [19]. We will record details on the measurement of these characteristics in this review and meta-analysis.

Dependent Variable

The dependent variable of interest for this systematic review and meta-analysis is in-hospital re-infarction and death after initial presentation for UA/NSTEMI. In-hospital re-infarction will be defined in accordance to the forth universal definition of myocardial infarction, and is defined as an acute myocardial infarction that reoccurs dependent of ST-elevation or depression $\geq$ 1 mm, new pathognomonic Q waves appear in at least two contiguous leads, particularly when associated with ischemic symptoms, and a >20% increase of the cardiac troponin biomarker value in the second sample compared to the first sample collected at initial presentation [20]. If there is a difference in the definition in re-infarction in individual studies, we will record this difference as this may introduce bias and heterogeneity in this study.

Moderator Variables

Age and sex are important potential moderating variables which may influence the presenting ECG [1,19,23]. Thus, we will collect information on the age and sex distribution of the samples used in individual studies.

Data Sources, Search Terms, and Search Strategy

This literature review and meta-analysis will be based on systematic searches in multiple electronic literature databases, including Medline/PubMed, Web of Science, Embase, and CINAHL. Since ECG research appears in cardiovascular specific journals, specific searches to expand capture of relevant studies will be performed using the same key words in over 20 other cardiology and emergency medicine journals including: Circulation, Heart Rhythm, Journal of Electrocardiology, Annals of Noninvasive Electrocardiology, Journal of Cardiovascular Nursing, Journal of Emergency Nursing, European Heart Journal, The American Journal of Cardiology, EP Europace, and American Journal of Emergency Medicine (Table 1). Lastly, we will search ClinicalTrials.gov for potential grey literature. All journals and search terms are listed in Table 1. Systematic searches will be conducted by combining every possible combination of five categories of keywords. The librarian and principal investigator will be responsible for conducting searches in electronic literature databases. The librarian will be responsible for conducting searches in the electronic databases and ClinicalTrials.gov. The principal investigator will be responsible for conducting searches in cardiovascular journals. Reference lists included articles will be checked to identify any potentially eligible studies. This in-depth and librarian guided systematic procedure substantiates that the literature search comprises all published studies [33]. The use of a librarian and the search of grey literature will also help reduce the risk of selection and detection bias [31]. The search results will be exported to Endnote X9 (Clarivate Analytics, PA, USA). The librarian will save the search results in an Endnote file on an encrypted, frequently backed-up computer system as a historical record.

Inclusion and Exclusion Criteria

The inclusion criteria for this study will be: 1) full-text peer-reviewed publications; 2) English language; 3) adult ($\geq$ 18 years) patient presenting with confirmed UA/NSTEMI to the emergency department; 4) standard, resting 12-lead ECG performed in the supine position at time of admission, only, and 5) use of odds ratio (ORs) or risk ratio (RR) and the corresponding 95% confidence interval as the statistical outcome measure or the data necessary to calculate these measures. The 12-lead ECG must be in the supine position due to position effects which may distort the accuracy of the tracing [21].

For the meta-analysis portion additional inclusion criteria will be a quality score of $\geq$5 on the Newcastle-Ottawa Quality Assessment Scale and a moderate rating on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) score described below [22-24]. We used two scales in this systematic review because of their two different objectives. The objective of the Newcastle-Ottawa Quality Assessment Scale is to evaluate the quality of individual case-control or cohort design studies, whereas GRADE is for the systematic appraisal of research with the goal to advise evidence-based recommendations. Since the aims of this systematic review and meta-analysis was two-part: summarize the existing literature and develop guidelines for frontline emergency care providers, we felt two quality scales were necessary. The Newcastle-Ottawa Quality Assessment Scale varies from 0 to 9 and rates studies as poor (score of 0) to excellent quality (score of 9), correlating to the Agency for Healthcare Research and Quality (AHRQ) standards [22]. For this study, inclusion in the meta-analysis will require an overall score of $\geq$5 which corresponds to good quality research [22]. GRADE is a widely recommended transparent framework for developing and presenting summaries of evidence and provides a systematic

approach for making clinical practice recommendations [23,24]. A score of moderate will be necessary for inclusion [24]. Moderate is defined as the authors of this review believe that the true effect is probably close to the estimated effect, thus filtering out erroneous results [25].

Exclusion criteria will include: 1) serial, 12-lead ECG; and continuous 3-lead, 5-lead or 12-lead ECG monitoring. There will be no upper restrictions on age or sex distribution for this study; however, age and sex will be moderators in the meta-analysis portion of this study (see below). There is no limitation in terms of geographic region or racial background. The search period will be from the beginning of the computerization of the ECG, January 1st, 1990 to June 1, 2020 [26].

Participants

The study population will be adults (18 years or older) presenting to emergency departments with suspected UA/NSTEMI. No restrictions will be placed on participants' gender, ethnicity, or other demographic characteristics. Since the aim of the study is to determine associations between characteristics on the admission 12-lead ECG and in-hospital re-infarction and death, factors influential on patient outcomes including age and sex will be recorded and used as moderators in meta-analyses (see below) [25,31].

Data Extraction and Assessment of Methodological Quality

Following the search, all identified citations will be collected and uploaded into EndNote X8 to remove duplicates. After removing all duplicates, titles and abstracts the articles will be screened against the inclusion and exclusion criteria. The full text and citation of potential studies will be retrieved and imported into EndNote X8 with the corresponding citation. Potential articles will be assessed in detail against the inclusion criteria by the principal investigator and the senior investigator. Any disagreements that arise between the reviewers will be resolved through discussion and, when deemed necessary, a content expert (PhD-prepared cardiac nurse) will be invited as a third reviewer to make the ultimate decision. Reasons for excluded studies will be recorded and reported in the final manuscript.

After deciding which articles to include, all data entry will be completed by the principal investigator and verified by the senior investigator of this protocol who is a PhD-prepared research nurse scientist with background in ECG. The principal investigator and senior investigator will use a standardized data extraction form to ensure consistent data retrieval from the included studies (Table 2). The data extracted will include specific details about the population, context, study methods, and critical statistical findings relevant to the purpose of this review. The data extraction was piloted tested using 5 articles with an interrater reliability of 95% between the principal investigator and the senior investigator. A third reviewer was not necessary during this pilot testing. If necessary, modifications to the standardized data extraction form will be reported in detail in the full report. If required, we will contact the authors of included studies to request missing or additional data. We will record attempts to contact authors for missing or additional data. Periodic data checking and entry will be conduct to ensure accuracy.

To assess quality of articles, the Newcastle-Ottawa Quality Assessment Scale and the GRADE score will be used. The Newcastle-Ottawa Quality Assessment Scale was developed to assess the quality of non-randomized studies such as case-control and cohort studies [22]. The following characteristics will be assessed: (1) representativeness of the cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of the study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; (8) adequacy of follow-up of cohorts [22]. This scale varies from 0 to 9 indicating that studies were graded as poor to good quality, and correlates to the AHQR standards [22]. The principal investigator and senior investigator will score each article independently using the scale. Afterwards, the two will discuss their independent evaluations and provide a justification. If a discrepancy between quality score arises, a third independent reviewer (a PhD-prepared cardiac registered nurse) will provide a score and the average of all three reviewer scores will be used to determine study inclusion in the meta-analysis section of this study. Inclusion in the meta-analysis will require an overall score of $\geq$5 which corresponds to good quality research. Kappa will be calculated to quantify the level of inter-rater agreement (e.g. Kendall's tau) [22].

GRADE is a recommended transparent framework for examining existing evidence in a systematic approach for making clinical practice recommendations [23.24]. The domains of GRADE include risk of bias, imprecision, inconsistency, indirectness, and publication bias [23,24]. We will use the GRADE handbook published by Cochrane to inform our evaluation of individual studies. The same protocol as described above will be followed for determine a GRADE score.

Meta-Analytic Approach

A random-effects meta-analytic power analysis was conducted to determine the necessary number of studies and study participants to answer the research question and achieve the specific aims of this protocol [27]. Though, some have argued that a minimum number of studies to be included in a meta-analysis is two [27]. Assuming a small effect size (Cohen's d of 0.2), average number of participants per group (n=150 participants), and high study heterogeneity, a minimum of 1,050 study participants distributed across 7 individual studies will be necessary to achieve a type I and type II error rate of 5% and 10%, respectively [27]. A small effect size was assumed because each individual ECG characteristics will be evaluated individually in this meta-analysis reducing the overall ES. This proposal will target 12 individual studies for inclusion. This meta-analysis will calculate RR as the main ES estimate. RR is a total and stable measure of hazard functions; however, many studies will report an OR which can overestimate the risk ratio when the incidence of an outcome is common in a study population (>10%) [28]. For this reason, we will convert OR to RR as described by Zhang and Yu [28]. This is a simple method to approximate a RR and derive an estimate of an effect size that better represents the true RR not dependent on the frequency of the outcome [28]. All RR values will be log transformed to satisfy normal distribution assumptions. Confidence interval of each outcome measure resembles the precision of the RR estimate as an indirect measure of sample size. To correct for precision, primary studies will be weighted by the inverse of their variance. To account for known methodological differences among

included studies, the heterogeneity of RR measures will be treated as a covariate by using a random-effect model. Heterogeneity between studies will be determined using Cochran Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled ES across studies.

This analysis will assess whether or not the variation in effect sizes among pooled studies falls within expected sampling error. If this assumption is violated, then age and sex subgroup moderator analysis will be conducted. Age and sex were chosen to be moderators because they are important risk factors for UA/NSTEMI outcomes [25, 31]. If this occurs, studies will be coded as either (1) younger population (mean age<65 years) or older population (mean age >65 years) and (2) male-dominant ($\geq$65% men) or female-dominant ($\geq$65% women) [25,31]. The subgroup moderator analysis will inform whether age and sex influence prognostic ability of the ECG for death and mortality in UA/NSTEMI [25,31]. If the study fails to report a mean age, we will not be able to include it in this moderator analysis due to the skewed nature of the data. Instead, an additional data and analysis table will be used for studies which report medians. Depending on the number of studies, a subgroup comparison analysis will be completed between UA and NSTEMI to determine if there are ECG characteristics which differ between the two conditions. This will better inform about ECG changes specific to UA and NSTEMI.

Additionally, the I^2 statistic from the standard X^2 test will be computed to describe the percentage of variability across studies that is due to heterogeneity rather than chance alone. Lastly, to evaluate publication bias stemming from missing studies or search limitations, the trim-and-fill funnel plot method will be used. This method evaluates for the asymmetry of distribution of studies around their weighted mean. All analyses will be performed using Meta-Essentials in Excel, and STATA 16 (STATA Software, TX) [29,30].

Discussion

This systematic review and meta-analysis will evaluate and analyze the evidence available on the prognostic characteristics on the 12-lead ECG for in-hospital re-infarction and death. We believe this systematic review and meta-analysis will inform frontline emergency care providers on the prognostic significant of specific characteristics on the admission 12-lead ECG and result in more informed clinical decision making to reduce the incidence of in-hospital re-infarction and death. Moreover, this study will provide a much-needed overview of existing studies to inform future research in this area including our existing project which aims to

We hypothesize that multiple investigators have reported significant findings of common (e.g. ST-segment changes) and novel (e.g. QRS complex duration) characteristics which can predict in-hospital re-infarction and death, though this will be the first to summarize and synthesize these individual findings. Most of the studies may be older secondary due to well-known large and robust cardiovascular clinical trials such as GRACE [10]. We also hypothesize that there will be differences between males and females because cardiovascular studies tend to recruit more males [27]. Our protocol adjusts for this potential

limitation by including *a priori* subgroup analyses. In addition to informing frontline emergency care providers, this systematic review and meta-analysis will also inform our current project “Development and Validation of TIB: A Total Ischemic Burden Score for the Rapid Risk Stratification of NSTEMI.” The aims of this work are to (1) to assess the prognostic value of characteristics on the admission 12-lead ECG for in-hospital re-infarction and death; and, (2) to build a rapid risk stratification tool called TIB based solely on significant characteristics on the admission 12-lead ECG for in-hospital re-infarction and death. By knowing the current state of the science, we will have a better direction in assessing the importance and relevancy of specific characteristics on the admission 12-lead ECG, and how it may be weighted for clinical decision making. Finally, to our knowledge, this is the only systematic review and meta-analysis on characteristics on the admission 12-lead ECG, and one of the few in ECG overall.

Limitations

This systematic review will only include full-text peer reviewed published articles and will exclude other types of scholar works such as presentation abstracts, non-published studies and doctoral dissertations. Although some researchers have encouraged the inclusion of unpublished literature in systematic reviews and meta-analyses, the inclusion of data from unpublished studies can introduce bias [32]. Unpublished studies may provide insufficient data to be extracted for a systematic review and meta-analysis to be conducted, and may be of lower methodological quality than published studies [32]. In a study of 60 meta-analyses that included published and unpublished studies it was found that unpublished studies were more likely to be less rigorous compared to their published counterparts [33]. Moreover, a 2017 study concluded that the inclusion of non-published data had a non-significant effect on effect size estimates [32]. As the planned review will be based on a comprehensive literature search of studies published in peer reviewed journals and be accompanied by a librarian, the scientific quality of the included studies will be ensured. The robustness of the findings will also be indicated by publication bias analyses. The inclusion of a librarian to this systematic review also decreases bias, improves robustness, and correlates with a higher score in the literature searching component of systematic reviews [33, 34].

Protocol amendments

If the present protocol is substantially amended after an initiation that may impact on the conduct of the study (including eligibility criteria, study objectives, study design, study procedures, and analysis), then this amendment will be agreed upon by all collaborators prior to the implementation and will be documented in a note to a later publication or a report under the section titled “Differences between protocol and review”.

Dissemination

The results of this review will be submitted for peer-reviewed publication and will be presented at relevant cardiology conferences. The project team has commenced searching relevant studies in the relevant databases. This review is expected to be complete by December 2020.

List Of Abbreviations

ACC: American College of Cardiology

AHA: American Heart Association

AHQR: Agency for Healthcare Research and Quality

ECG: Electrocardiogram

GRACE: Global Registry of Acute Coronary Events

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

MOOSE: Meta-Analyses and Systematic Reviews of Observational Studies

NSTEMI: Non-ST Elevation Myocardial Infarction

OR: Odds Ratio

PROSPERO: International Prospective Register of Systematic Reviews

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RR: Risk Ratio

TIB: Total Ischemic Burden (Score)

UA: Unstable Angina

Declarations

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable. Data and materials are available for reviewers upon request.

Availability of Data and Materials

The datasets created and analyzed during the current study will be available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no competing interests.

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Authors' Contributions

DJD is the principal investigator and responsible for conceiving the review, designing search strategy, modifying data extraction tool, selecting the appropriate tool for quality appraisal, conducting the journal-specific searches, and drafting the protocol. He is the guarantor of this review, and initiated the publication of this protocol. DHM is the librarian responsible for refining the search strategy, conducting the database searches, initially designing the data extraction tool, and providing librarian support. MGC is the senior investigator who provided content expertise on the topic, study assessment and appraisal, and reviewed the methodology. All authors read, reviewed, edited, and approved the final manuscript.

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Tables

Table 1. Search Strategy for Protocol for ECG-based Predictors of Re-infarction or Death on the Hospital Admission 12-Lead ECG among UA/NSTEMI Patients .

Medline	((“Emergency Service, Hospital”[Mesh] OR emergency department*[tiab] OR “emergency nursing”[tiab] OR “emergency medicine”[tiab] OR “triage”[tiab] OR “cardiovascular nursing”[tiab]) AND (“Myocardial Infarction”[Mesh] OR “Non-ST Elevated Myocardial Infarction”[Mesh] OR “Myocardial Ischemia”[Mesh] OR “Myocardial Reperfusion”[Mesh] OR “Myocardial Revascularization”[Mesh] OR “Ischemic Preconditioning”[Mesh] OR “Acute Coronary Syndrome”[Mesh] OR “Angina, Unstable”[Mesh] OR “Angina Pectoris”[Mesh] OR “Coronary Artery Disease”[Mesh] OR “Coronary Vessels”[Mesh] OR “Coronary Circulation”[Mesh] OR “myocardial infarction”[tiab] OR “Non-ST elevated myocardial infarction”[tiab] OR “myocardial ischemia”[tiab] OR “myocardial reperfusion”[tiab] OR “myocardial revascularization”[tiab] OR “ischemic pre-conditioning”[tiab] OR “acute coronary syndrome”[tiab] OR “unstable angina”[tiab] OR “chest pain”[tiab] OR “chest pains”[tiab] OR “angina pectoris”[tiab] OR “atherosclerosis”[tiab] OR “coronary artery disease”[tiab] OR “coronary arteries”[tiab] OR “coronary artery”[tiab] OR “coronary circulation”[tiab] OR “UA/NSTEMI”[tiab]) AND (“12 lead ECG”[tiab] OR “12 lead electrocardiogram”[tiab] OR “Electrocardiography”[Mesh] OR “Electrocardiography”[tiab] OR “ECG”[tiab] OR “EKG”[tiab] OR “electrocardiogram”[tiab] OR “electrocardiography”[tiab] OR “diagnostic tests, routine”[MeSH Terms] OR “diagnostic measure”[tiab] OR “diagnostic procedure”[tiab] OR “diagnostic procedures”[tiab] OR “diagnostic test”[tiab] OR “diagnostic tests”[tiab] OR “diagnostic techniques”[tiab])) AND (“Death”[Mesh] OR “Fatal Outcome”[Mesh] OR “Cause of Death”[Mesh] OR “Mortality”[Mesh] OR “dead”[tiab] OR “death”[tiab] OR “fatality”[tiab] OR “fatal outcome”[tiab]) AND (“Sensitivity and Specificity”[Mesh] OR “Prognosis”[Mesh] OR “risk ratio”[tiab] OR “odds ratio”[tiab] OR “risk”[tiab] OR “probability”[tiab] OR “harm reduction”[tiab] OR “populations at risk”[tiab] OR “population at risk”[tiab]))
ience	TS= (“emergency service*” OR “emergency room” OR emergency department* OR “emergency nurs*” OR emergency medicine OR triage OR “cardiovascular nurs*”) TS=(“myocardial infarction” OR “Non-ST elevated Myocardial infarction” OR “myocardial ischemia” OR “acute coronary syndrome” OR “unstable angina” OR “ Angina Pectoris” OR “coronary artery disease” OR “coronary vessels” OR “coronary circulation” OR “ atherosclerosis” OR “chest pain*” OR “coronary artery” OR “UA/NSTEMI”) TS=(“12 lead ECG” OR “12 lead electrocardiogram” OR “twelve lead ECG” OR “twelve lead electrocardiogram” OR “electrocardiogram” OR “electrocardiography” OR “ECG” OR “EKG” OR “diagnostic test*” OR “diagnostic measure*” OR “diagnostic procedure*” OR “diagnostic techniques”) TS=(“death” OR “death” OR “mortality” OR “cause of death” OR “fatal outcome” OR “died” OR “die” OR “fatality” OR “fatal”) TS=(“sensitivity and specificity” OR “prognosis” OR “risk ratio” OR “risk” OR “odds ratio” OR “probability” OR “harm reduction” OR “population* at risk”) (#5 AND #4 AND #3 AND #2 AND #1)
	(‘emergency service, hospital’/exp OR ‘emergency service, hospital’ OR ‘emergency department,’:ti,ab OR ‘emergency departments’:ti,ab OR ‘emergency nursing’:ti,ab OR ‘emergency medicine’:ti,ab OR triage:ti,ab OR ‘cardiovascular nursing’:ti,ab OR ‘coronary care nursing’:ti,ab) AND (‘myocardial infarction’:ti,ab OR ‘non st segment elevation myocardial infarction’:ti,ab OR ‘myocardial ischemia’:ti,ab OR ‘acute coronary syndrome’:ti,ab OR ‘unstable angina’:ti,ab OR ‘chest pains’:ti,ab OR ‘angina pectoris’:ti,ab OR ‘atherosclerosis’:ti,ab OR ‘coronary artery disease’:ti,ab OR ‘coronary arteries’:ti,ab OR ‘coronary circulation’:ti,ab OR ‘ua/nstemi’:ti,ab OR ‘heart infarction’/exp OR ‘non st segment elevation myocardial infarction’/exp OR ‘heart muscle ischemia’/exp OR ‘heart muscle reperfusion’/exp OR ‘heart muscle revascularization’/exp OR ‘ischemic preconditioning’/exp OR ‘acute coronary syndrome’/exp OR ‘unstable angina pectoris’/exp OR ‘angina pectoris’/exp OR ‘coronary artery disease’/exp OR ‘coronary blood vessel’/exp) AND (‘12 lead ecg’:ti,ab OR ‘twelve lead electrocardiogram’:ti,ab OR ‘twelve lead ecg’:ti,ab OR ‘ecg’:ti,ab OR ‘ekg’:ti,ab OR ‘diagnostic test’:ti,ab OR ‘diagnostic procedure’:ti,ab OR ‘diagnostic measure’:ti,ab OR ‘diagnostic test’/exp OR ‘12 lead electrocardiogram’/exp OR ‘electrocardiogram’/exp OR ‘electrocardiography’/exp) AND (‘death’/exp OR ‘fatality’/exp OR ‘cause of death’/exp OR ‘fatal outcome’:ti,ab OR ‘morality’:ti,ab OR ‘death’:ti,ab OR ‘dead’:ti,ab) AND (‘sensitivity and specificity’/exp OR ‘prognosis’/exp OR ‘risk ratio’/exp OR ‘odds ratio’/exp OR ‘risk’/exp OR ‘probability’/exp OR ‘harm reduction’/exp OR ‘population at risk’/exp)
	1 ((MH “Emergency Service+”) OR (MH “Emergency Medical Services+”) OR “emergency services” OR (MH “Cardiovascular Nursing+”) OR “cardiovascular nurse” OR (MH “Triage”) OR (MH “Coronary Care Nursing”)) AND 2 (MH “Myocardial Infarction+”) OR (MH “Myocardial Ischemia+”) OR (MH “Myocardial Reperfusion”) OR (MH “Myocardial Revascularization+”) OR (MH “Ischemic Preconditioning, Myocardial”) OR (MH “Angina, Unstable”) OR (MH “Angina Pectoris+”) OR (MH “Acute Coronary Syndrome”) OR “non-st- segment-elevation acute coronary syndrome” OR (MH “Coronary Arteriosclerosis”) OR AB “chest pains” OR “atherosclerosis” OR “coronary arteries” OR “coronary circulation” OR “heart infarction” OR heart muscle ischemia” OR “heart muscle revascularization” OR “unstable Angina Pectoris” OR “coronary blood vessel” AND 3 (MH “Electrocardiography+”) OR AB “electrocardiogram” OR “ecg” OR “ekg” OR “12 lead electrocardiogram” OR “12 lead ecg” OR “twelve lead ecg” OR “twelve lead electrocardiogram” AND 4 (MH “Death+”) OR (MH “Fatal Outcome”) OR (MH “Cause of Death”) OR (MH “Mortality+”) AND 5 (MH “Sensitivity and Specificity”) OR (MH “Prognosis+”) OR (MH “Odds Ratio”) OR (MH “Harm Reduction”) OR AB “”risk ratio” OR “risk” OR “probability” OR “population at risk” 1 AND 2 AND 3 AND 4 AND 5
ASA Journals	“ECG OR EKG OR Electrocardiogram” AND “Non-ST Elevation Myocardial Infarction OR Unstable Angina” AND “Risk Stratification OR Risk Management” AND “Patient Outcomes”
rthm	Electrocardiogram OR ECG OR EKG AND Non-ST Elevation Myocardial Infarction OR NSTEMI OR Unstable Angina OR UA
rdiography/ the American Cardiology/ Heart Journal/ Journal of // International Cardiology/ The Journal of y Medicine/	(ECG OR EKG OR Electrocardiogram) AND (Non-ST Elevation Myocardial Infarction OR Unstable Angina) AND (Risk Stratification OR Risk Management) AND (Patient Outcomes) AND (Odds Ratio OR Risk Ratio)

spanola de a (English)/ ıtion/ The Annals ic Surgery/ : Vascular The American : Medicine	
' Noninvasive rdiography/ :y Medicine/ The Journal of Cardiology/ ardiology/ :y Triage	"ECG OR EKG OR Electrocardiogram" and "Non-ST Elevation Myocardial Infarction OR NSTEMI" OR "Unstable Angina OR UA" and "Risk Stratification OR Risk Management"
: Cardiovascular	ECG OR Electrocardiogram OR NSTEMI OR NSTEMI OR Unstable Angina OR UA AND Risk Stratification
.ung	ECG in All Content OR EKG in All Content OR Electrocardiogram in All Content AND Non ST Elevation Myocardial Infarction in All Content AND Unstable Angina in All Content AND Risk
Heart Journal/ ace/ cular Research/ Heart Journal ents/ European rnal- Quality of Clinical Outcomes	ECG OR Electrocardiogram OR EKG AND Non ST Elevation Myocardial Infarction AND Unstable Angina AND Risk Management
Heart Journal	ECG OR Electrocardiogram OR EKG AND Non ST Elevation Myocardial Infarction AND Unstable Angina AND Risk Management
Journal of :y Medicine	Non-ST Elevation Myocardial Infarction OR Unstable Angina OR Acute Coronary Syndrome AND 12 lead electrocardiogram AND Finding present on electrocardiogram AND Patient Outcome Assessment AND Cardiac risk management
ials.gov	Unstable Angina AND NSTEMI; Also searched for non-ST elevation myocardial infarction and Non ST Elevated Myocardial Infarction

Table 2. Data Extraction Form for Protocol for ECG-based Predictors of Re-infarction or Death on the Hospital Admission 12-Lead ECG among UA/NSTEMI Patients.

Author
Year
Title of the Study
Study Aim
Country
Sample Size
Mean Age (± Standard Deviation) or Median Age (Interquartile Range)
Percentage Male
Percentage of Included Patients with Known Cardiovascular Disease
Other Patient Population Characteristics
Percentage of Patients who Underwent Early Invasive Intervention
ECG Characteristics of Interest (i.e. ST-Segment Depression, T Wave Inversion, etc.)
Definition of ECG Characteristics of Interest
Primary & Secondary Endpoint
Definition of Endpoints
Associated Statistic (i.e. Risk Ratio, Odds Ratio)
Statistic 95% Confidence Interval
Sensitivity, Specificity, Positive and Negative Predictive Value
Length of Follow-Up
Covariates Adjusted
Study Design
Key Conclusions
Comments

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P 2015 Checklist

Table 3. PRISMA-P 2015 Checklist for Electrocardiogram-based Predictors of Re-infarction or Death on the Admission 12-Lead ECG among UA/NSTEMI Patients: A Systematic Review and Meta-Analysis

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		3,4, 45, 139
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		60, 144
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		6-21; 376-381
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		366-374
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		334-337
Sponsor	5b	Provide name for the review funder and/or sponsor		X	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		353-357
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		95-134
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		150-154
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		185-216
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		165-184

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		180,181
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		209-217; 229-244
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		218-228
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		156-179
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		166-175
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		209-226
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		190-208
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		285-278; 307-324
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		307-324
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		X	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		284-322

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		261-283