Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis

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ABSTRACT

Background
Prompt diagnosis of acute myocardial infarction or acute coronary syndrome is very important.

Aim
A systematic review was conducted to determine the accuracy of 10 important signs and symptoms in selected and non-selected patients.

Design of study
Diagnostic meta-analysis.

Method
Using MEDLINE, CINAHL, EMBASE, tracing references, and by contacting experts, studies were sought out that described one of the 10 signs and symptoms on one or both conditions. Studies were excluded if they were not based on original data. Validity was assessed using QUADAS and all data were pooled using a random effects model.

Results
Sixteen of the 28 included studies were about patients who were non-selected. In this group, absence of chest-wall tenderness on palpation had a pooled sensitivity of 92% (95% confidence interval [CI] = 86 to 96) for acute myocardial infarction and 94% (95% CI = 91 to 96) for acute coronary syndrome. Oppressive pain followed with a pooled sensitivity of 60% (95% CI = 55 to 66) for acute myocardial infarction. Sweating had the highest pooled positive likelihood ratio (LR+), namely 2.92 (95% CI = 1.97 to 4.23) for acute myocardial infarction. The other pooled LR+ fluctuated between 1.05 and 1.49. Negative LRs (LR–) varied between 0.98 and 0.23. Absence of chest-wall tenderness on palpation had a LR– of 0.23 (95% CI = 0.18 to 0.29).

Conclusions
Based on this meta-analysis it was not possible to define an important role for signs and symptoms in the diagnosis of acute myocardial infarction or acute coronary syndrome. Only chest-wall tenderness on palpation largely ruled out acute myocardial infarction or acute coronary syndrome in low-prevalence settings.

Keywords
diagnostic meta-analysis; myocardial ischemia; signs and symptoms.

INTRODUCTION

'Chest pain' is a symptom of illnesses of different organs (heart, lung, stomach and intestines, muscles, and skeleton) or of psychiatric disorders, all of which require specific treatment. Due to the high mortality and morbidity of coronary disease, in the event of chest pain, a GP will always consider the possibility of an acute myocardial infarction or unstable angina. Moreover, fast treatment — such as thrombolysis, percutaneous coronary intervention, or coronary artery bypass graft — can be life-saving and increase the patient's life expectancy and quality of life.[1]

The annual incidence of acute myocardial infarction for persons aged 30–69 years is estimated by the British Heart Foundation at 0.6% for men and at 0.1% for women.[2] In Belgium the figures are comparable: in the 45–75-year-old age group Bartholomeeussen *et al*[3] found a yearly incidence of acute myocardial infarction of 0.55% for men and 0.19% for women. The incidence of severe heart disease in people complaining of chest pain is highly dependent on the care setting: for Belgium percentages vary between 4.8% when a

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GP is contacted and 24.2% for patients in the emergency department of a university teaching hospital.[4]

Severe prolonged chest pain of acute onset is rarely a decision-making problem. Attacks of chest pain that are experienced by the patient and defined as not very severe or prolonged, but distressing enough for them to contact a GP, present a more difficult problem in diagnosis and management.[5] In the majority of European countries GPs will perform most of the triage in patients with chest pain and so can only rely on signs and symptoms. The accuracy of these signs and symptoms has already been the subject of systematic reviews. Several authors only used groups consisting of patients with known acute myocardial infarctions in their reviews;[6–8] such studies can only determine the sensitivity. The specificity, the positive or negative likelihood ratio (LR+, LR–), the positive predictive value (PPV), and the negative predictive value (NPV) cannot be determined using such samples. Consequently, the accuracy of a test cannot be described fully.

Panju *et al* only used studies concerning patients included via an emergency department or patients admitted to a hospital.[9] Mant *et al* only used articles dated before 1992 in their review on signs and symptoms,[10] while Chun and McGee only used MEDLINE for their search strategy.[11] More recent studies were included in this systematic review. Two analyses were made: one of studies of patients who were non-selected (recruited by GPs, paramedics, or emergency departments) and one of studies of patients who were selected (recruited by coronary care units and cardiologists).

Ten signs and symptoms that could be found by history taking or physical examination were investigated. The diagnostic value was examined for acute myocardial infarction or acute coronary syndrome of:

- radiating pain (left arm and/or shoulder, right arm and/or shoulder, both arms and/or shoulder, neck, back, epigastric);
- oppressive pain;
- nausea and/or vomiting;
- sweating; and
- absence of chest-wall tenderness on palpation (absence of tenderness).

How this fits in

Most information about signs and symptoms is derived from studies in coronary care units with patients who have 100% acute myocardial infarction. Those data are not similarly accurate in a primary care setting (GP surgery, emergency department, and paramedics). This study was not able to define an important role for signs and symptoms in the diagnosis of acute myocardial infarction or acute coronary syndrome. Only chest-wall tenderness on palpation largely ruled out acute myocardial infarction or acute coronary syndrome in low-prevalence settings.

METHOD

Search strategy

MEDLINE, EMBASE and CINAHL were searched. All searches were up to date as of 31 May 2006. In MEDLINE a combination of terms was used involving all possible elements, the target disease and no filters: ("Physicians, Family"[MeSH] OR "Emergency Service, Hospital"[MeSH] OR "Emergency Medical Services"[MeSH] OR "Emergency Medicine"[MeSH]) AND ("Chest Pain"[MeSH] OR "Myocardial Ischemia"[MeSH]).

An adapted version of this search string was used in CINAHL: ((Emergency-Medicine) OR (Emergency-Service) OR (Physicians-Emergency) OR (Emergencies) OR (Emergency-Care) OR (Emergency-Medical-Services) OR (Physicians-Family) OR (Prehospital-Care)) AND ((Angina-Pectoris) OR (Chest-Pain) OR (Myocardial-Infarction) OR (Myocardial- Ischemia)).

The search string used in EMBASE was: ('emergency health service' OR 'general practitioner' OR 'emergency health service' OR 'emergency ward' OR 'emergency medicine') AND ('thorax pain' OR 'heart muscle ischemia')

In addition, the reference lists of the retrieved articles were checked. A search for any unpublished study results was limited to contacting known researchers in the field.

Study selection

The study strategy was designed to include all published diagnostic accuracy studies on signs and symptoms for the diagnosis of acute myocardial infarction, unstable angina, or acute coronary syndrome. Studies were excluded if diagnostic tests were not one of the 10 selected signs or symptoms and if they were not based on original data or if the data were insufficient to construct a 2x2 table. Language restrictions were English, French, German, and Dutch. Two independent reviewers screened the titles; a third reviewer resolved any disagreements that occurred between the two. All the selected titles were studied in full text by one reviewer. A list of excluded studies and a log of reasons for exclusion are available from the authors on request. When patients were recruited by GPs, paramedics, or emergency departments, they were considered 'non-selected'. Patients recruited by coronary care units and cardiologists

were considered 'selected'.

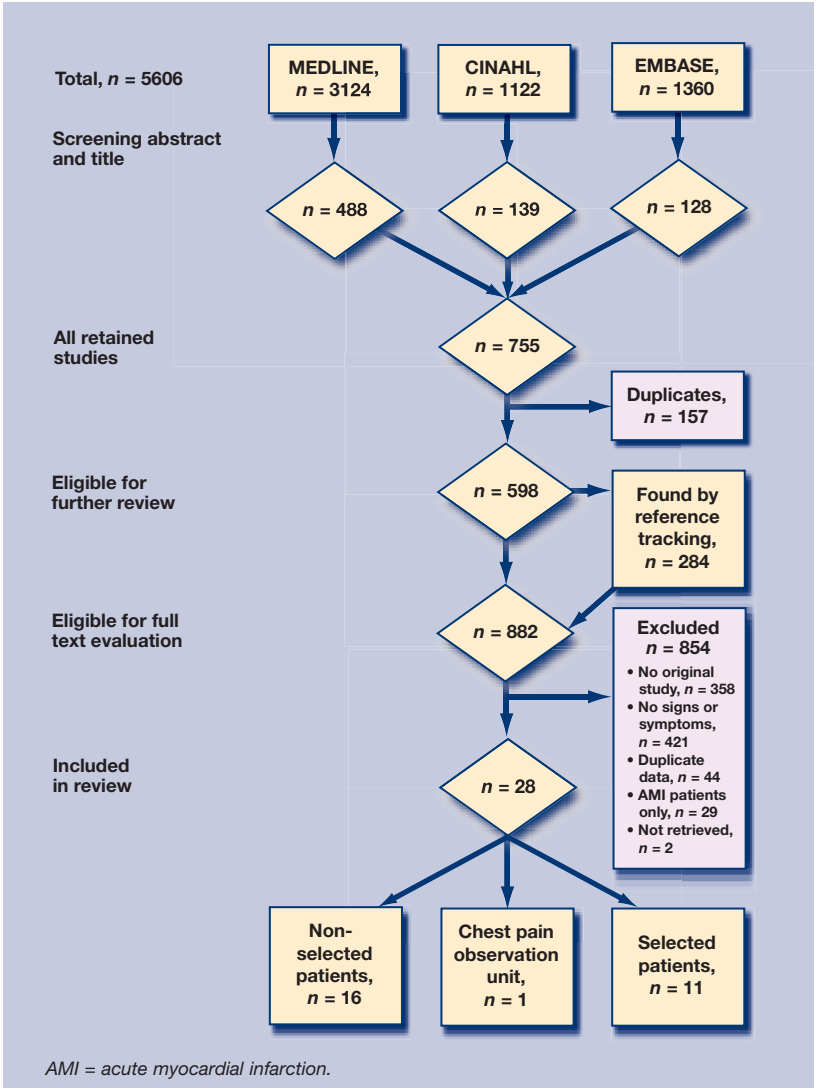
Chosen articles were retrieved in full and further included in the review after they had been assessed for quality using the QUADAS instrument, shown in Appendix 1.[12] The selection of participants and the validity of the reference standard were the most important considerations. Studies were excluded from the review if they failed on one of these two items. Studies that failed on other QUADAS questions were not excluded, not even those without blind interpretation of the other tests, as blinding is almost impossible in this case.

Data extraction

The following data were extracted (in duplicate) from the studies:

- the design: whether the data were collected prospectively or retrospectively, and whether the participants were included consecutively;
- the setting: whether participants were recruited by GPs, cardiologists, paramedics, emergency departments, chest pain observation units, or coronary care units;
- age and sex;
- index test: pain radiating to left arm and/or shoulder; to right arm and/or shoulder; to both arms and/or shoulders; to neck; to back; epigastric, oppressive pain; nausea and/or vomiting; sweating; absence of tenderness;
- the number of patients and the prevalence of the disease in the study group;
- the results from the study in absolute numbers (in the absence of the absolute numbers, they were calculated from prevalence, sensitivity and specificity);
- the inclusion and exclusion criteria; and
- the reference standard.

Figure 1. Retrieval of eligible studies: flowchart.



AMI = acute myocardial infarction.

Statistical analysis and data synthesis

Two groups were analysed separately: the patients who were non-selected and those who were selected. Standard methods recommended for the meta-analysis of diagnostic test evaluations were used.[13–15] Analyses were performed using Stata (version 8, Stata Corporation, Texas). Sensitivity, specificity, LR+ (= sensitivity/[1 — specificity]; a positive test result makes the odds of the disease 'LR+' times more possible), LR– (= [1 — sensitivity]/specificity; a negative test result makes the odds of the disease 'LR–' times less possible) and the odds ratio (OR) were pooled using a random effects model. PPV or NPV were not reported because of the heterogeneity between studies due to differences in setting and prevalence.

Heterogeneity in meta-analysis refers to the degree of variability in results across studies. Forest plots were examined and used, the χ^2 and Fisher's Exact tests were used and, in view of the low power of the χ^2 test, the I^2 statistic was also estimated to detect heterogeneity.[16] In order to keep the tables readable, only the I^2 data are reported. The potential presence of publication bias using funnel plots and the Egger test was tested for.[17–18]

RESULTS

Included studies

Figure 1 outlines the study selection process. The great majority of publications concerning acute myocardial infarction and acute coronary syndrome discuss the technical tests and treatments. The number of studies found reporting the selected signs and symptoms was not very extensive — there were 57 in all. A further 29 were excluded because only patients with confirmed acute myocardial infarctions or acute coronary syndromes

were included. Twenty-eight articles were included in the meta-analysis:[19–46] 16 studies were about patients who were non-selected, 11 studies were about patients who were selected, and one study was made in a chest pain observation unit.

Study characteristics and quality

During the selection process the inter-rater agreement between the two reviewers was very good with a κ of 0.82 (95% confidence interval [CI] = 0.79 to 0.85). There was no disagreement in items of the QUADAS instrument. The results of the studies included on the QUADAS list are outlined in Appendix 2. In an attempt to analyse subgroups for sex and age, 14 authors were contacted by e-mail and additional data were obtained for two studies. Appendices 3 and 4 present the descriptive data from the studies included.

For the final diagnosis of acute myocardial infarction the reference tests used were enzyme rises (*n* = 23), electrocardiogram (ECG) change (*n* = 22), history (*n* = 11), scintigraphy (*n* = 8), autopsy (*n* = 5), criteria of the World Health Organization or European Society of Cardiology (*n* = 4), sudden death (*n* = 3), coronary angiogram (*n* = 2), echocardiography (*n* = 2), or urgent revascularisation (*n* = 1). In some studies, at least two tests were required. History alone was always insufficient to diagnose an acute myocardial infarction.

Reference tests for unstable angina were: history (pain: frequency, worse, new) (*n* = 5), ECG changes without enzymes rises (*n* = 3), unproven acute myocardial infarction (*n* = 2), Canadian Cardiovascular Society classification criteria (*n* = 1), and clinical judgement (*n* = 1).

One study[46] gave only reference tests for acute coronary syndrome: troponin rise, cardiac death, acute myocardial infarction, new onset heart failure, life-threatening arrhythmia, or coronary revascularisation.

Prevalence

Two large studies[36,37] provided 50% of the subjects. When the results of all the studies were combined, there were 5067 (11.6%) patients with acute myocardial infarction out of a group of 43 138, and 4594 (26.3%) patients with acute coronary syndrome out of a group of 17 416. Of these 17 416, 13 108 (75.3%) belonged to a group also examined for acute myocardial infarction. There are approximately 50% more patients with unstable angina than acute myocardial infarction.

The varying prevalence of acute myocardial infarction depended on the setting and inclusion criteria. Graff *et al*'s[37] low prevalence of about 2% was caused by the very large inclusion criteria, that is, 'all patients with possible acute myocardial infarction for whom a rapid ECG was performed'. The chest pain observation unit, to which patients with unclear signs and symptoms and without clear ECG abnormalities and/or blood abnormalities were admitted, had a prevalence of 4%.[40] In other studies executed in emergency departments, prevalences of between 6% and 18% were found. The group transported by ambulance in Svenson *et al*'s study,[44] with a prevalence of 29%, situates itself between the patients seen in an emergency department and those admitted to a coronary care unit (prevalence from 36–50%). In the study of Van der Does *et al*[21] the prevalence of referred patients was as low as 7%.

Heterogeneity in the non-selected group

For acute myocardial infarction there was homogeneity in the LR+ of oppressive pain and in the LR– for tenderness. For acute coronary syndrome there was homogeneity in the LR+ of left-arm pain and the LR– for sweating and tenderness. For the other analyses, a moderate to high level of heterogeneity was found.

Indications of diagnostic accuracy in the non-selected group

Appendix 5 (for the diagnosis of acute myocardial infarction) and Appendix 6 (for a diagnosis acute coronary syndrome) (both subgroups separately) show the pooled sensitivity, specificity, LR+, LR–, and OR with their 95% CI and I^2. The sensitivity and specificity per sign or symptom varied greatly.

The sensitivity of absence of tenderness was

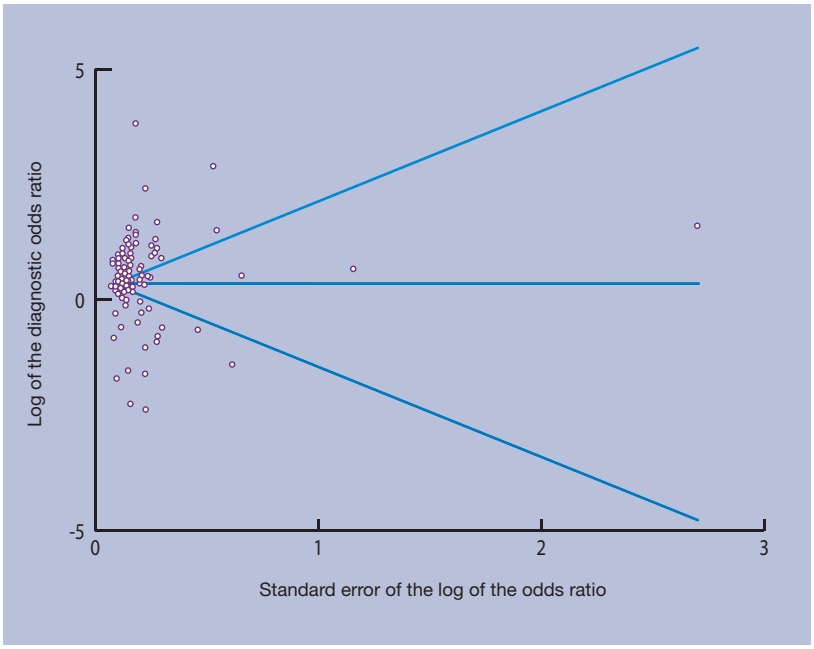


Figure 2. Funnel plot for evaluation of publication bias in all studies.

high, namely 92% (95% CI = 85.5 to 96.4) for acute myocardial infarction and 94% (95% CI = 91.4 to 96.1) for acute coronary syndrome. Oppressive pain followed with a sensitivity of 60% (95% CI = 53.7 to 66.0 for acute myocardial infarction). Sweating had the highest LR+, namely 2.92 (95% CI = 1.97 to 4.32 for acute myocardial infarction).

The LR+ of right arm or shoulder pain was 2.89 (95% CI = 1.40 to 5.98) for acute myocardial infarction (one study). The other LR+ fluctuated between 1.05 and 1.49 for acute coronary syndrome.

Absence of tenderness had a LR- of 0.23 (95% CI = 0.18 to 0.29) for acute myocardial infarction and 0.17 (95% CI = 0.11 to 0.26) for acute coronary syndrome. Other LR– varied between 0.69 (oppressive pian and sweating for acute myocardial infarction) and 0.98 (epigastric pain) for acute coronary syndrome.

Publication bias

A funnel plot, signifying publication bias, is shown in Figure 2. The plot appears symmetrical, suggesting absence of publication bias. This was confirmed by a non-significant Egger test (0.79).

DISCUSSION

Studies included

More than half of the studies dated from after Mant *et al*'s[10] selection. Sixteen new articles about several signs and symptoms that were not included in Chun and McGee's review[11] were included, indicating the necessity for a new systematic review.

Although the authors aimed to find all relevant studies, some could have been missed. However, the search strategy will have detected most studies. As only two studies were performed in a general practice setting, it was decided to look for 'primary care' studies, which were defined as settings in which patients who had not been referred by other medical practitioners were seen. In Europe and some other parts of the world this mostly concerns general practice. In the US and a number of other countries however, this frequently includes the emergency department and patients admitted by paramedics. The information on these unselected patients is certainly relevant for GPs.

Quality

A fair amount of research dates from several decades ago. It could be argued that these older studies are disadvantaged in terms of quality as empirical research on design-related bias and the STARD (Standards for Reporting of Diagnostic Accuracy) initiative to improve quality are fairly recent.[47–49] Although new research on the quality of diagnostic accuracy studies confirms that quality is still not optimal, the quality of the studies included was good according to the QUADAS criteria.

A good reference test is essential in diagnostic research. It was unclear how frequently these criteria were used for the definite diagnosis of acute myocardial infarction. The acceptance of a broad range of inclusion criteria (autopsy, sudden death, scintigraphy, echocardiography, and angiography) as reference tests increased the number of real positives at the risk of spectrum bias.[10] Verification bias was not a major problem because almost all patients received a reference standard. The increasing sensitivity of the blood tests used over the years — starting with transaminase via lactate dehydrogenase, creatine kinase (CK) and the isoenzyme CK-MB, and recently troponin T — has caused a rise in real positives. However, no increase in the prevalence of acute myocardial infarction in the emergency departments or the coronary care units was noticed over the course of time. The reference test for unstable angina was not as clearly defined as that for acute myocardial infarction because it often depended on the clinical picture and its interpretation. All of this could cause either over- or underestimation of the prevalence found.

Although 'acute myocardial infarction + unstable angina = acute coronary syndrome', a distinction was made between acute myocardial infarction and acute coronary syndrome to ensure that no data was left out of those studies that dealt only with acute myocardial infarction.

Prevalences

In 2000, the definition of acute myocardial infarction changed to: 'typical rise and gradual fall of cardiac troponin, or more rapid fall of CK-MB, with at least one of the following: ischemic symptoms; the development of pathological Q waves; ECG changes indicative of ischemia (ST-segment elevation or depression); coronary artery intervention'.[50] This definition of acute myocardial infarction will increase the sensitivity of diagnosing acute myocardial infarction and thereby increase the findings of its incidence. The increased specificity of troponin, however, should decrease the number of false-positive diagnoses. The combined effect that these two factors may have on the case-fatality rate is currently unclear.[51]

The larger number of acute myocardial infarctions in patients transported by ambulance compared to those in patients transported to the emergency department by other means has been documented previously.[4] The low prevalence of referred patients in the study by van der Does *et al*[21] is possibly

explained by the underestimation of the number of acute myocardial infarctions due to the absence of sensitive blood analyses in 1972.

It should also be noted that in most studies the true population prevalence of acute myocardial infarction was higher because patients who died at home could not be included.

Heterogeneity

Most of the pooled results were heterogeneous, due to different settings, inclusion criteria, and reference standards. The non-homogenous pooled results must be interpreted very carefully.

Diagnostic accuracy of signs and symptoms in the non-selected patients group

Absence of tenderness was highly sensitive for acute myocardial infarction (92%) and acute coronary syndrome (94%). The presence of palpation pain greatly reduces the chance of acute myocardial infarction and acute coronary syndrome with a LR– of 0.23 and 0.17 respectively. Similar pleuretic or positional thoracic pain was not selected in this study. In Mant's *et al*'s study the absence of pleuretic pain had a LR– of 0.19 and the absence of positional pain a LR– of 0.27.[10] Oppressive pain, with a pooled sensitivity of 60% and a specificity of 58% has almost no influence on the likelihood of acute myocardial infarction. The sensitivities of the other signs and symptoms were even lower and could not be used to exclude acute myocardial infarction or acute coronary syndrome. The differences in sensitivity and specificity between acute myocardial infarction and acute coronary syndrome remained small and were therefore not relevant.

It is true that, even in unselected settings such as general practice, patients have a reason for visiting their GP with chest pain. Fear of having a myocardial infarction may be one such reason. Anyone not visiting their doctor will not be diagnosed with acute myocardial infarction so the classical signs and symptoms of chest pain and irradiation are always part of the diagnostic work-up.

Clinical implications

To summarise the interpretation of signs and symptoms in the clinical context, consider a patient in a low-, intermediate-, and high-prevalence setting. For the sake of clarity the highest pooled LR+ and the lowest LR– found for acute myocardial infarction, namely sweating (LR+ 2.92, LR– 0.69), and absence of chest-wall tenderness (LR+ 1.47, LR– 0.23) were used.

In a low pre-test probability situation of 5%, which may be regarded as the prevalence in those patients who are unselected and contact a GP with chest pain, these LR+ translate to a 13% and 7% post-test probability of a positive test result.[4] In low pre-test settings the presence of the signs and symptoms listed above is insufficient to definitively confirm acute myocardial infarction. In their absence the post-test probability is lowered to 4% and 1%. Absence of sweating should scarcely affect GPs' management; the presence of chest-wall tenderness results in a post-test probability of 1.1% and so largely rules out acute myocardial infarction for clinical purposes.

In an intermediate-prevalence setting of 15%, which is the prevalence expected in a patient seen by the GP during an urgent home visit or in an emergency department, the same reasoning produces a post-test probability of 34% and 21%. If these symptoms are absent this becomes 11% and 4%. These results should barely influence GPs' treatment strategy.

In a high-prevalence setting of 40%, such as a coronary care unit the same signs or symptoms represent a post-test probability of 66% and 49% if positive, and 32% and 13% if negative. These results will also add nothing to the diagnostic process.

Each of these signs and symptoms may also trigger consideration of acute myocardial infarction or acute coronary syndrome: non-specific complaints such as back pain or vomiting/nausea can also be caused by acute myocardial infarction or acute coronary syndrome. In Goodacre *et al*'s[45] study of patients with undifferentiated chest pain (with normal ECG and without a clear clinical diagnosis of acute coronary syndrome) the final diagnosis was acute coronary syndrome in 7.9%. This group of missed acute coronary syndrome probably still has a higher mortality than patients without acute coronary syndrome.[52]

Previous meta-analyses of signs and symptoms

All the pooled results were situated within the 95% CIs of the previous investigations, except in the absence of chest-wall tenderness. Here a LR+ of 1.47 (95% CI = 1.23 to 1.75) was found, which was somewhat higher than in Mant *et al*'s[10] research (1.18; 95% CI = 1.16 to 1.22).

Limitations of the review

Some studies suggested a difference in the diagnostic accuracy of signs and symptoms according to age[27,38] or sex,[43] but there were not enough studies to perform a subgroup analysis. Although the combination of signs and symptoms,

their context, the severity, and the progression from the start influence the interpretation, it was impossible to examine this because there were almost no included studies that investigated the diagnostic accuracy of combinations of signs and symptoms. Only three of the selected studies combined different signs and symptoms: Short[22] (previous or not-previous history of acute coronary syndrome and studied signs and symptoms), Lee *et al*[23] (sharp or stabbing pain and pain pleuretic, positional or reproduced by palpation and no prior acute coronary syndrome), and Hargarten *et al*[25] (radiating pain and sweating, difficult breathing, and nausea/vomiting).

Persons with chest pain can also be subject to serious, even life-threatening, diseases other than acute myocardial infarction or acute coronary syndrome, such as pulmonary embolism, and stomach bleeding. This requires analysis with CART-type models in the individual studies. CART is a statistical package that produces decision trees using variables (coded signs and symptoms) directing to classes (diagnostic categories). At each node of the decision tree, the programme calculates which variable is the 'most discriminating' and constructs, at that node, a bifurcation of two branches. For each resulting branch, CART calculates the next most discriminating variable and continues in this way until either the subgroups or the discriminating power become 'too small'. A final statistical pruning technique results in an optimal tree, where optimality is measured by various criteria.[53–55] As far as the authors know no systematic review has been published pooling the results of such studies.

In 2005 a new multilevel method for the bivariate pooling of combined sensitivity and specificity was published.[56] This method may be superior to classic pooling. The authors were asked to do the calculations on the current study's results of the absence of chest-wall tenderness on palpation in relation to acute myocardial infarction. Because of the minimal differences, the previous calculations were not reworked.

Conclusions

Based on this meta-analysis, it was not possible to define an important role for signs and symptoms in the diagnosis of acute myocardial infarction or acute coronary syndrome. Only chest-wall tenderness on palpation largely ruled out acute myocardial infarction or acute coronary syndrome in low-prevalence settings.

Competing interests

The authors have stated that there are none

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Appendix 1. The QUADAS tool.[12]

- Was the spectrum of patients representative of patients who will receive the test in practice?
- Were selection criteria clearly described?
- Is the reference standard likely to correctly classify the target condition?
- Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
- Did the whole sample or a random selection of sample receive verification using a reference standard diagnosis?
- Did patients receive the same reference standard regardless of the index test result?
- Was the reference standard independent of the index test (that is, the index test did not form part of the reference standard?)
- Was the execution of the index test described in sufficient detail to permit replication of the test?
- Was the execution of the reference standard described in sufficient detail to permit its replication?
- Were the index test results interpreted without knowledge of the results of the reference standard?
- Were the reference standard results interpreted without knowledge of the results of the index test?
- Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
- Were interpretable intermediate test results reported?
- Were withdrawals from the study explained?

Appendix 2. Qualification of the articles with the QUADAS tool.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Säwe, 1971[19]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	yes	no
Säwe, 1972[20]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	yes	no
Van der Does, 1980[21]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes
Short, 1981[22]	yes	yes	yes	no	yes	yes	yes	no	yes	yes	no	yes	yes	yes
Lee, 1985[23]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	no
Tierney, 1986[24]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no
Hargarten, 1987[25]	yes	yes	yes	yes	yes	yes	yes	yes	no	?	no	yes	no	no
Herlihy, 1987[26]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	no	yes
Solomon, 1989[27]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	yes
Berger, 1990[28]	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	yes	no
Jonsbu, 1991[29]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	no
Gaston-Johansson, 1991[30]	yes	no	yes	yes	yes	yes	yes	yes	yes	?	?	yes	no	no
Hartford, 1993[31]	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	yes
Grijseels, 1995[32]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	yes
Everts, 1996[33]	yes	no	yes	yes	yes	yes	yes	yes	yes	?	?	yes	no	no
Pfister, 1997[34]	yes	yes	yes	yes	yes	yes	yes	no	no	yes	no	yes	no	yes
Lopez-Jiminez, 1998[35]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no
Pope, 1998[36]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	yes	no
Graff, 2000[37]	yes	yes	no	yes	?	?	yes	yes	no	?	?	yes	no	no
Milner, 2001[38]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	yes	no	yes
Herlitz, 2002[39]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	no
Goodacre, 2002[40]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	yes
Baxt, 2002[41]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	yes	no
Albarran, 2002[42]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	no	no
Vodopiutz, 2002[43]	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	?	yes	no	yes
Svensson, 2003[44]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	no	no
Goodacre, 2003[45]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	no	yes
Christenson, 2006[46]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

Appendix 3. Characteristics of acute myocardial infarction (AMI) included studies.

Study	Design	Sample size	% AMI	Mean age	% males	Setting	Inclusion	Exclusion	Reference standard AMI
Säwe, 1971[19,a]	Prospective consecutive	137	39	62	67	CCU	Central chest pain (>15 m, <48 hr) or pulmonary oedema or shock or syncope or status anginosus	Known valvular lesion, acute hypovolaemia or intoxication, syncope without ECG evidence of AMI	Q-wave and/or ST elevation or GOT, GPT, LDH changes, necropsy
Säwe, 1972[20,a]	Prospective consecutive	921	49	65	60	CCU	Central chest pain (>15 m, <48 hr) or pulmonary oedema or shock or syncope or status anginosus	Known valvular lesion, acute hypovolaemia or intoxication, syncope without ECG evidence of AMI	Q-wave and/or ST elevation or GOT, GPT, LDH changes or autopsy findings myocardial necrosis
Van der Does, *et al*, 1980[21]	Prospective consecutive	1343	7	54	55	GP	Recent chest pain or dyspnoea, palpitations or dizziness or syncope upper abdominal pain or mood changes	<25 yr women, <20 yr men	WHO criteria for AMI, at least 4 pts score: ECG typical-2pt, suspect-1pt, ditto symptoms and enzymes
Short, 1981[22]	Prospective ?	456	40	62	57	Car	One or more attacks of spontaneous chest pain and who were referred for cardiology opinion	Ill enough for hospitalisation or diagnosis of coronary disease regarded as definite	History and ECG (Minnesota code) or twice limit AAT at 24–48 hr after onset
Lee, *et al*, 1985[23]	Prospective consecutive	596	17	56	48	ED	Chief complaint of anterior, precordial or left lateral chest pain	Local trauma, abnormalities on chest X-ray, <25 yr	One of: characteristic evolution of enzyme levels (CK-MB or LDH or CK) or Q-waves of scintiscan
Tierney, *et al*, 1986[24]	Prospective ?	492	12	?	?	ED	Anterior chest pain as one of their complaints	<30 yr men, <40 yr female	When cardiac enzyme CK elevated and CK-MB >4% or LDH1> (or equal) LDH or when no enzyme: new abnormal Q-wave
Herlihy, *et al*, 1987[26]	Prospective consecutive	265	44	?	?	CCU	Chest pain and electrographic changes	Illness or medication that could produce nausea, with thrombolytic medication	CK and ECG
Solomon, *et al*, 1989[27]	Prospective consecutive	7734	14	?	50	ED	Chief complaint of anterior, precordial or left lateral chest pain	Local trauma, abnormalities on chest X-ray, <30 yr, >4 visit	One of: characteristics evolution of enzyme levels (CK-MB or LDH or CK), Q-waves, scintiscan, sudden unexplained death within 72 hr
Berger, *et al*, 1990[28]	Prospective consecutive	278	36	57	69	CCU	Admitted to the hospital, complaining chiefly of chest pain	Trauma, transferred from other hospital with a diagnosis	Chest pain, ECG changes indicating myocardial infarction, significant CK elevation
Jonsbu, *et al*, 1991[29]	Prospective consecutive	200	37	?	?	CCU	Admitted to hospital with suspected acute heart disease	Unable to give reliable medical history	Clinical history, ECD signs, enzyme activity, ventriculography, scintigraphy, autopsy
Gaston-Johansson, *et al*,1991[30]	Prospective consecutive	94	40	?	71	CCU	Chest pain suggesting AMI	>75 yr, cardiogenic shock	Two of: typical clinical symptoms and chest pain > 15 mins, AAT or CK elevations, Q waves ST elevation or T inversion

Appendix 3 continued: Characteristics of acute myocardial infarction (AMI) included studies.

Hartford, *et al*, 1993[31]	Prospective consecutive	226	48	?	?	CCU	Because of suspected AMI	Very poor clinical condition, does not understand Swedish	Two of three: chest pain > 15 min, aminotransferase, new Q-waves in two leads
Everts, *et al*, 1996[33]	Prospective consecutive	902	50	64	71	CCU	Chest pain with possible AMI	Hypotension, severe congestive heart failure, severe UA, cognitive limitation, language	Two of three: chest pain >15 min, aminotranferase, new Q-waves in two leads
Pfister, *et al*, 1997[34]	Prospective consecutive	327	18	64	65	ED	Chest pain (>10 min), irradiation (epigastric, jaw, L extremity) during angina, dyspnoea, non-traumatic or toxic cardiac arrest	<20 yr, trauma	At least two of: history, ECG, CK-MB
Lopez-Jiminez *et al*, 1998[35]	Prospective consecutive	2694	6	?	45	ED	Chief complaint of chest pain	Local trauma, abnormalities on chest X-ray, <30 yr, >4 visit, prior AMI, A, PTCA, bypass	One of: characteristics evolution of enzyme levels (CK-MB or LDH or CK), Q-waves, scintiscan, sudden unexplained death within 72 hr
Pope, *et al*, 1998[36]	Prospective consecutive	10 689	8	59	52	ED	Chief complaint chest, left arm, jaw or epigastric pain or discomfort, dyspnoea, dizziness, palpitations or other symptoms suggestive of acute ischemia	<30yr, 18yr if suspected to have used cocaine	WHO criteria for AMI
Graff, *et al*, 2000[37]	Prospective consecutive	10 678	2	?	?	ED	All patients with possible AMI were a rapid ECG was performed	No	ICD-9-CM 410. 01/11/21/31/41/ 51/61/71/81/91
Herlitz, *et al*, 2002[39]	Retrospective consecutive	930	14	71	51	Para	Chest pain or slightest suspicion of an acute coronary syndrome	No	Two of: chest pain >15 min, CK more than twice upper limit, Q-waves
Goodacre, *et al*, 2002[40]	Prospective consecutive	893	4	53	62	CPOU	Chest pain (patients at low risk)	<25 yr, trauma, new ECG changes consistent with ischemia, comorbidity necessitating hospitalisation,definite unstable angina	WHO criteria for AMI
Baxt, *et al*, 2002[41]	Prospective 16/ day	2204	6	53	40	ED	Anterior chest pain prompting an ECG	<24 yr	European Society of Cardiology criteria
Albarran, *et al*, 2002[42]	Prospective consecutive	541	48	?	68	CCU	Acute chest pain	Pain >24 hr, <18 yr, no English	Troponin I >6 ng/ml and ECG changes
Svensson, *et al*, 2003[44]	Prospective consecutive	538	29	69	58	Para	Chest pain or discomfort >15 min, within last 6 hr, dyspnoea, or any condition suggesting acute coronary syndrome	Lung disease	Two of: typical symptoms, Q-waves, CK-MB> 10 ng/ml or troponin >0.05 ng/ml

[a]*The patients of the first article are part of the second study. The signs and symptoms discussed in the two studies are different. Car = cardiologist; CCU = coronary care unit or admitted to hospital, CPOU = chest pain observation unit, ECD = electrocardiogram, ED = emergency department, Para = paramedics of an ambulance. A = angina. AAT = aspartate aminotransferase. AMI = acute myocardial infarction. CK = creatine kinase. CK-MB = CK isoenzyme. ECG = echocardiogram. GOT = aspartate aminotransferase. GPT = alanine transferase. ICD = International Classification of Diseases. LDH = lactate dehydrogenase. LDH1 = lactate dehydrogenase isoenzyme 1. UA = unstable angina. WHO = World Health Organization.*

Appendix 4. Characteristics of acute coronary syndrome = acute myocardial infarction + unstable angina included studies.

Study	Design	Sample size	% ACS	Mean age	% Males	Setting	Inclusion	Exclusion	Reference Standard
Lee, *et al*, 1985[23]	Prospective consecutive	596	41	56	48	ED	Chief complaint of anterior, precordial or left lateral chest pain	Local trauma, abnormalities on chest X-ray, <25 yr	AMI: one of characteristic evolution of enzyme levels (CK-MB, LDH, CK), Q-waves, scintiscan. UA: chest pain worse or new and diagnosis was made by a senior clinician
Hargarten, *et al*, 1987[25]	Retrospective consecutive	401	57	65	?	Para	'Stable' chest pain	Heart failure, rhythm problems, hypotension	AMI: ST-elevation followed by T-inversion (at least two leads), CPK-MB, LDH ration, autopsy pyrophosphate scan UA: no
Grijseels, *et al*, 1995[32]	Prospective consecutive	1005	42	67	54	GP	Symptoms of possible cardiac origin seen by GP and transferred	No	AMI: standard history, ECG, enzyme criteria UA: angina with increasing frequency and severity and new recent onset with documentation of ST -T changes at rest, abnormal stress test or coronary arteriogram
Pope, *et al*, 1998[36]	Prospective consecutive	10689	23	59	52	ED	Chief complaint of chest, left arm, jaw or epigastric pain or discomfort, dyspnoea, dizziness, palpitations or other symptoms suggestive of acute ischemia	<30 yr, 18 yr if suspected to have used cocaine	AMI: WHO criteria for AMI UA: Canadian Cardiovascular Society classification criteria
Milner, *et al*, 2001[38]	Prospective consecutive	531	40	60	53	ED	>45 yr and one symptom suggestive of ACS, or 18–44 yr if diabetes and two risk factors	<45 yr without diabetes or <18 yr with diabetes	AMI: elevated cardiac enzymes (CK-MB). UA: ECG changes (ST, T) and no cardiac enzymes elevation
Herlitz, *et al*, 2002[39]	Retrospective consecutive	930	30	71	51	Para	Chest pain or slightest suspicion of an acute coronary syndrome	No	AMI: two of chest pain>15 min, CK more than twice upper limit, Q-wave A: according to clinical judgement
Goodacre, *et al*, 2002[40]	Prospective consecutive	893	9	53	62	CPOU	Chest pain (patients at low risk)	<25 yr, trauma, new ECG changes consistent with ischemia, comorbidity necessitating hospitalisation, definite unstable angina	AMI: WHO criteria for AMI. ACS: present or in following 6 months: AMI, cardiac death, arrhythmia or revascularisation
Vodopiutz, *et al*, 2002[43]	Prospective at random	92	47	62	48	CCU	Admitted because of chest pain as main symptom	Refused, too sick, language problems	AMI: angio, autopsy, scintigraphy, echocardio, ECG and enzyme kinetics UA: no

Appendix 4 continued. Characteristics of acute coronary syndrome = acute myocardial infarction + unstable angina included studies.

Svensson, *et al*, 2003[44]	Prospective consecutive	538	57	69	58	Para	Due to chest pain or discomfort >15 min, within last 6 hr, dyspnoea, or any condition suggesting acute CS	Lung disease	AMI: two of: typical symptoms, Q-waves, CK-MB >10 ng/ml or troponin >0.05 ng/ml Myocardial ischemia: dynamic changes ECG, no increase biochemical markers
Goodacre, *et al*, 2003[45]	Prospective consecutive	972	8	50	64	ED	'Undifferentiated chest pain' all patients attending with chest pain or related complaint (low risk)	Evidence of ACS (ECG or clear clinical) requiring admission, clear non-cardiac cause no informed consent	ACS: any elevation of T (after 2 days) or after 30 days: cardiac death, non-fatal myocardial infarction, new-onset heart failure, life-threatening arrhythmia or coronary revascularisation procedure
Christenson, *et al*, 2006[46]	Prospective 7am–10pm	769	21	58	62	ED	Primary complaint of anterior or lateral chest pain	<25 yr, traumatic or XR- evident cause, enrolled in study 30 days previously, communication problems, no fixed address in British Columbia, without available telephone contact	AMI: one of 1) CK-MB increase definite for AMI (specific hospital criteria) or troponin I >1.0 μg/l 2) troponin I increase (<1.0) and ECG changes (ischemia), coronary angiogram >70% lesion, positive stress test or urgent revascularisation 3) ECG evolution consistent AMI 4) fibrinolytic therapy or angioplasty with clinical diagnosis of AMI 5) death with no other definite cause. UA: chest pain of 20 min at least and one of: 1) troponin I increase to 0.99 maximum and no other AMI criteria 2) dynamic ECG changes (ischemia) (ST or T), but not persistent ST elevation 3) coronary angiogram (70% lesions) and hospital admission 4) positive stress test and hospital admission

Car = cardiologist; CCU = coronary care unit or admitted to hospital, CPOU = chest pain observation unit, ECD = electrocardiogram, ED = emergency department, Para = paramedics of an ambulance. ACS = acute coronary syndrome. AMI = acute myocardial infarction. CK = creatine kinase. CK-MB = CK isoenzyme. CS = coronary syndrome. ECG = echocardiogram. LDH = lactate dehydrogenase. UA = unstable angina. WHO = World Health Organization. XR = X-rays.

Appendix 5. Pooled sensitivity, specificity, positive and negative likelihood ratios, odds ratios of signs and symptoms for acute myocardial infarction in patient groups.

Symptom		Acute myocardial infarction Non-selected patients	95% CI	I^{2a} (%)	Acute myocardial infarction Selected patients	95%CI	I^{2a} (%)
Pain in left arm and/or shoulder							
Not selected[41]	Sensitivity	33	25.4 to 41.8	–	54	50.2 to 56.9	0
Selected[19,28,30,33,42]	Specificity	76.3	74.5 to 78.2	–	65	56.4 to 72.8	87
	LR+	1.42	1.10 to 1.83	–	1.49	1.20 to 1.85	71
	LR–	0.87	0.77 to 0.99	–	0.76	0.66 to 0.88	57
	OR	1.631	12 to 2.39	–	2.00	1.39 to 2.88	65
Pain in right arm and/or shoulder							
Not selected[24]	Sensitivity	15	5.9 to 23.7	–	32	25.1 to 40.8	77
Selected[19,28,30,33,42]	Specificity	95	92.8 to 97.0	–	86	78.4 to 91.2	85
	LR+	2.89	1.40 to 5.98	–	2.35	1.44 to 3.84	80
	LR–	0.90	0.81 to 1.00	–	0.81	0.66 to 1.00	96
	OR	3.22	1.41 to 7.36	–	3.09	1.63 to 5.85	80
Pain in both arms							
Not selected (n/a)	Sensitivity				32	25.1 to 40.8	77
Selected[19]	Specificity				86	78.4 to 91.2	85
	LR+				2.35	1.44 to 3.84	80
	LR–				0.81	0.66 to 1.00	96
	OR				3.09	1.63 to 5.85	80
Pain in neck							
Not selected[41]	Sensitivity	14	8.2 to 20.4	–	24	18.3 to 30.2	65
Selected[30,33,42]	Specificity	90	89.0 to 91.6	–	75	71.6 to 77.7	0
	LR+	1.48	0.94 to 2.31	–	0.99	0.83 to 1.17	0
	LR–	0.95	0.88 to 1.02	–	1.00	0.95 to 1.07	0
	OR	1.55	0.92 to 2.61	–	0.98	0.78 to 1.23	0
Pain in back							
Not selected (n/a)	Sensitivity				25	22.0 to 28.2	0
Selected[30,33,42]	Specificity				71	66.4 to 75.6	45
	LR+				0.84	0.62 to 1.14	59
	LR–				1.07	0.96 to 1.19	60
	OR				0.78	0.52 to 1.19	59
Epigastric pain							
Not selected[23]	Sensitivity	10	3.9 to 15.3	–	5	2.1 to 10.8	89
Selected[34,36,37,39]	Specificity	93	91.1 to 95.2	–	91	85.0 to 95.4	99
	LR+	1.44	0.73 to 2.83	–	0.73	0.61 to 0.87	0
	LR–	0.97	0.91 to 1.04	–	1.04	1.02 to 1.05	0
	OR	1.49	0.71 to 3.12	–	0.69	0.57 to 0.85	0
Oppressive pain							
Not selected[23,24,27,35,41]	Sensitivity	60	53.7 to 66.0	77	77	71.3 to 81.2	0
Selected[28,29,31]	Specificity	58	55.0 to 60.2	87	35	28.7 to 41.3	48
	LR+	1.42	1.32 to 1.53	36	1.79	1.07 to 1.30	0
	LR–	0.69	0.61 to 0.80	64	0.70	0.52 to 0.86	0
	OR	2.06	1.60 to 2.53	51	1.77	1.25 to 2.51	0
Vomiting and/or nausea							
Not selected[24,36,39,41]	Sensitivity	34	25.3 to 44.1	84	29	12.5 to 51.5	97
Selected[20,22,26,28,29]	Specificity	77	71.1 to 81.3	97	81	76.6 to 85.1	73
	LR+	1.41	1.17 to 1.72	64	1.42	0.76 to 2.64	92
	LR–	0.83	0.83 to 0.96	52	0.82	0.66 to 1.03	94
	OR	1.62	1.22 ro 2.14	59	1.73	0.71 to 4.12	93
Sweating							
Not selected[21,24,27,39,41,44]	Sensitivity	45	36.0 to 54.0	91	41	22.9 to 60.5	95
Selected[20,22,29,31]	Specificity	84	78.6 to 88.0	97	85	69.2 to 94.7	98
	LR+	2.92	1.97 to 4.32	95	2.44	1.42 to 4.20	81
	LR–	0.69	0.60 to 0.78	81	0.72	0.56 to 0.91	90
	OR	4.54	2.47 to 8.36	94	3.81	1.88 to 7.70	83
Absence of chest wall tenderness							
Not selected[23,24,27,35]	Sensitivity	92	85.5 to 96.4	89			
Selected (n/a)	Specificity	36	20.5 to 51.8	99			
	LR+	1.47	1.23 to 1.75	97			
	LR–	0.23	0.18 to 0.29	0			
	OR	0.17	0.12 to 0.23	26			

[a]I^2 = 100% x (Q-df)/Q, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. LR+ = positive likelihood ratio. LR– = negative likelihood ratio. OR = odds ratio.

Appendix 6. Pooled sensitivity, specificity, positive and negative likelihood ratios, odds ratios of signs and symptoms for acute coronary syndrome in patients groups.

		Acute coronary syndrome Non-selected patients			Acute coronary syndrome Selected patients		
Symptom			95% CI	I^{2a} (%)		95%CI	I^{2a} (%)
Pain in left arm and/or shoulder							
Not selected[38,45,46]	Sensitivity	38	18.6 to 59.5	95			
Selected (n/a)	Specificity	71	56.9 to 82.6	97			
	LR+	1.30	1.13 to 1.47	0			
	LR–	0.88	0.78 to 1.00	58			
	OR	1.50	1.19 to 1.90	0			
Pain in right arm and/or shoulder							
Not selected[45]	Sensitivity	18	9.6 to 26.2	–	23	10.6 to 35.9	–
Selected[43]	Specificity	95	93.8 to 96.1	–	94	87.2 to 100	–
	LR+	3.78	2.17 to 6.60	–	3.80	1.12 to 12.91	–
	LR–	0.86	0.77 to 0.96	–	0.82	0.98 to 0.98	–
	OR	4.40	2.29 to 8.48	–	46.5	1.19 to 18.20	–
Pain in neck							
Not selected[46]	Sensitivity	35	27.9 to 42.4	–			
Selected (n/a)	Specificity	76	72.2 to 79.1	–			
	LR+	1.44	1.12 to 1.86	–			
	LR–	0.86	0.76 to 0.97	–			
	OR	1.69	1.16 to 2.44	–			
Pain in back							
Not selected[38,45]	Sensitivity	13	2.8 to 34.3	86	29	15.3 to 43.2	–
Selected[43]	Specificity	76	26.7 to 98.6	98	49	35.0 to 63.0	–
ACS[38,43,45]	LR+	1.49	0.62 to 3.56	80	0.57	0.33 to 0.99	–
	LR–	0.93	0.77 to 1.13	87	1.44	1.02 to 2.04	–
	OR	1.59	0.58 to 4.37	80	0.40	0.17 to 0.90	–
Epigastric pain							
Not selected[23,36,39,45]	Sensitivity	12	5.4 to 20.8	97			
Selected (n/a)	Specificity	89	82.9 to 94.1	98			
	LR+	1.05	0.35 to 3.20	97			
	LR–	0.98	0.88 to 1.08	97			
	OR	1.08	0.31 to 3.74	97			
Oppressive pain[56]							
Not selected[23]	Sensitivity	56	49.7 to 62.1	–	79	66.9 to 91.2	–
Selected[43]	Specificity	67	61.8 to 71.7	–	39	25.1 to 52.4	–
	LR+	1.68	1.40 to 2.02	–	1.29	0.99 to 1.69	–
	LR–	0.66	0.56 to 0.77	–	0.54	0.27 to 1.06	–
	OR	2.54	1.82 to 3.56	–	2.39	0.94 to 6.08	–
Vomiting and/or nausea							
Not selected[25,36,38,39,44,45]	Sensitivity	26	20.7 to 32.2	91			
Selected (n/a)	Specificity	82	74.1 to 88.4	98			
	LR+	1.32	1.09 to 1.65	68			
	LR–	0.93	0.89 to 0.96	35			
	OR	1.43	1.14 to 1.81	63			
Sweating							
Not selected[32,38,39,44]	Sensitivity	43	32.2 to 64.9	98			
Selected (n/a)	Specificity	68	44.0 to 86.5	99			
	LR+	1.34	1.09 to 1.65	76			
	LR–	0.85	0.79 to 0.92	40			
	OR	1.65	1.39 to 1.95	0			
Absence of chest-wall tenderness							
Not selected[23,24]	Sensitivity	94	91.4 to 96.1	0			
Selected (n/a)	Specificity	33	19.7 to 47.9	96			
	LR+	1.41	1.12 to 1.78	94			
	LR–	0.17	0.11 to 0.26	0			
	OR	0.12	7.0 to 21.0	34			

Note: Pain in both arms — not applicable. [a]I^2=100% x (Q-df)/Q, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. ACS = acute coronary syndrome. LR+ = positive likelihood ratio. LR– = negative likelihood ratio. OR = odds ratio.