Diagnostic accuracy of signs and symptoms in acute coronary syndrome and acute myocardial infarction: a meta-analysis.

Lotte Nees, KU Leuven

Promotor: Prof Bert Vaes, KU Leuven

Master of Family Medicine
Masterproef Huisartsgeneeskunde
Academiejaar: 2022-2023

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Abstract

Aim To discover the diagnostic value of 13 signs and symptoms suggestive for acute coronary syndrome (ACS) and acute myocardial infarction (AMI).

Methods Conducting searches in MEDLINE, EMBASE and CINAHL and reference tracking from June 2006 to April 2022. Including studies that displayed at least one of the 13 signs or symptoms in patients in the emergency department or primary care setting. We used the bivariate random effects model to calculate the positive and negative likelihood ratio (LR+, LR-) and the diagnostic odds ratio (DOR) of two subgroups (ACS and AMI). Quality was assessed using QUADAS-2.

Results 24 studies were included, with a total of 72,992 patients. In the ACS subgroup, the most significant test was absence of chest wall tenderness (DOR = 7.73) and pain in right arm/shoulder (DOR = 3.90). In the AMI subgroup, the most useful tests were sweating (DOR = 5.75), pain in right arm/shoulder (DOR = 5.16), absence of chest wall tenderness (DOR = 3.51) and pain in both arms (DOR = 2.95).

Conclusion Separate signs and symptoms can not completely rule in or rule out AMI and ACS. They can, however, serve as a guide and raise suspicion for these two life threatening conditions. Especially chest wall tenderness by palpation can make these conditions less likely.

Abstract

Context Acuut myocardinfarct en acuut coronair syndroom (ACS) zijn een belangrijke bron van morbiditeit, mortaliteit en hoge gezondheidskosten. Onmiddellijke behandeling van deze aandoeningen kan de uitkomst verbeteren, daarom is het belangrijk dat we mogelijke vertraging in de diagnose tot een minimum beperken. In de meeste Europese landen spelen huisartsen een belangrijke rol bij de vroegtijdige zorg voor acute MI en zijn zij vaak de eerste hulpverlener met wie de patiënt in contact komt.
Pijn op de borst wordt ervaren door 1-3% van de patiënten die contact opnemen met een huisarts. Dit symptoom kan verschillende oorzaken hebben, waarvan vele niet-cardiaal. Het is belangrijk dat de huisarts onderscheid kan maken tussen de verschillende oorzaken.

Onderzoeksvraag De diagnostische waarde achterhalen van 13 individuele symptomen die kunnen wijzen op acuut coronair syndroom (ACS) en acuut myocardinfarct (AMI).
De 13 symptomen die verder onderzocht werden zijn:

- Uitstralende pijn in linkerarm/schouder, rechterarm/schouder, beide armen, nek of rug
- Epigastrische pijn
- Drukkende pijn
- Afwezigheid van thoracale drukpijn
- Braken
- Misselijkheid
- Braken en/of misselijkheid
- Zweten
- Zweten en/of misselijkheid

Methoden MEDLINE, EMBASE en CINAHL werden doorzocht van juni 2006 tot april 2022. Studies opgezet in de spoedgevallendienst of in de eerstelijnszorg werden geïncludeerd. We gebruikten het bivariate random effects-model om de positieve en negatieve likelihood ratio (LR+, LR-) en de diagnostische odds ratio (DOR) van twee subgroepen (ACS en AMI) te berekenen. De kwaliteit werd beoordeeld met behulp van QUADAS-2.

Resultaten Er werden 24 studies geïncludeerd, met in totaal 72.992 patiënten. Het meest significante symptoom in de ACS-subgroep was de afwezigheid van thoracale drukpijn (DOR = 7,73) en pijn in de rechterarm of schouder (DOR = 3,90). In de AMI-subgroep waren de meest significante symptomen zweten (DOR = 5,75), pijn in de rechterarm of schouder (DOR = 5,16), afwezigheid van thoracale drukpijn (DOR = 3,51) en pijn in beide armen (DOR = 2,95).

Conclusie Afzonderlijke symptomen kunnen AMI en ACS niet volledig aantonen of uitsluiten. Ze kunnen echter als leidraad dienen en argwaan wekken voor deze twee levensbedreigende aandoeningen. Vooral thoracale drukpijn kan deze aandoeningen minder waarschijnlijk maken.

Introduction

Acute myocardial infarction (AMI) is a life threatening disease[1]. In the USA, the number one cause of death is heart disease[2], and AMI in particular is one of the leading causes with approximately 735,000 myocardial infarction events every year[3]. In the UK, there is one hospital admission every five minutes due to AMI[4]. In total, 1,3 % of the Belgian population suffered from angina in 2018 and in people over 65 years old, this percentage was about three times higher (3,8%). In 2016, the yearly incidence of AMI in Belgium was 177 per 100,000 inhabitants[5]. In short, acute coronary syndrome (ACS) and AMI are an important source of morbidity, mortality and high healthcare costs.
Acute coronary syndrome comprises both unstable angina (UA) and acute myocardial infarction. In this meta-analysis we treat these two conditions separately[6].

Immediate treatment of AMI can improve the outcome[1], therefore it's important that we minimize possible delay in the diagnosis. First, the patient delay needs to be reduced. This is the time between symptom-onset and a call for help. Therefore, knowledge of these symptoms in the general population is crucial[7]. Second, the doctor delay needs to be as short as possible[8]. In most European countries, general practitioners (GPs) play a major role in the early care of acute MI and are often the first caregiver to be contacted by the patient[9].

Chest pain is experienced by 1-3% of the patients who contact a GP. This symptom can have several different causes, a lot of them are non-cardiac. In the study of Andersson et al[9], 10-18% of the patients with chest pain in Sweden turned out to have an underlying ischaemic heart disease, of which 2-4% due to myocardial infarction or unstable angina. It's important that the GP is able to differentiate between the different causes.

In the diagnostic meta-analysis of Bruyninckx et al[10] in 2006 the authors concluded that signs and symptoms did not have a relevant role in the diagnosis of AMI or ACS. In low-prevalence settings, only chest-wall tenderness on palpation widely ruled out AMI. However, since this meta-analysis, there have been a lot of new diagnostic publications about AMI and ACS. For this reason, we conducted a new meta-analysis. We investigated the diagnostic value of the 13 signs and symptoms suggestive for AMI or ACS, based on the signs and symptoms of Bruyninckx et al[10].

Methods:

Study design

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines[11] (Appendix 1). Before data extraction and analysis were performed, this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42022329976).

Search strategy

For this meta-analysis, we replicated the search strategy of the meta-analysis of Bruyninckx et al[10] in 2006.

We conducted our search from June 2006 to April 2022 in MEDLINE, CINAHL and EMBASE.

The search methodology used was:

- MEDLINE: *("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]).*

- CINAHL: (*"emergency medicine" OR "emergency service" OR "emergency physicians" OR "emergencies or emergency" OR "emergency care" OR "emergency medical services" OR "family physician" OR "prehospital care" AND "angina pectoris" OR "chest pain" OR "myocardial infarction" OR "myocardial ischemia") In this search we excluded Medline records.*

- EMBASE:*('general practitioner' OR 'emergency health service' OR 'emergency ward' OR 'emergency medicine') AND ('thorax pain' OR 'heart muscle ischemia') This search was limited to terms indexed in the article as 'major focus'.*

In addition, we also searched by reference tracking. This way, we wanted to find additional studies.

All references were screened in Rayyan by the executive researcher (LN) on title and abstract. The articles were divided in three groups: inclusion, doubt or exclusion. The second researcher (BV) screened the inclusion and in doubt group of articles independently and screened a random number of the articles that were excluded by LN. If there was a disagreement, a third reviewer would be engaged. Full text of the included articles and the articles in doubt was obtained and were screened by both researchers (LN and BV). A list of the excluded articles is available, including the reason for exclusion, which can be asked for. If there was a disagreement between the two researchers, the article was read by a third researcher.

We also included articles that were included in the meta-analysis of Bruyninckx et al[10] for screening full text.

Study selection

We included studies about the diagnostic accuracy of at least one of the 13 signs or symptoms in patients who were registered in primary care or emergency department with possible AMI or ACS. The different settings of the included studies were the emergency department (ED), primary care call center, ambulance service and the GPs office.
The 13 signs and symptoms are:

- Radiating pain in: left arm/shoulder, right arm/shoulder, both arms, neck and back.
- Epigastric pain
- Oppressive pain
- Absence of chest wall tenderness
- Vomiting
- Nausea
- Vomiting and/or nausea
- Sweating
- Sweating and/or nausea

We also included studies from the meta-analysis of Bruyninckx et al[10]. In this meta-analysis, there were two subgroups:

- Non-selected: patients were recruited in primary care or ED
- Selected: studies with patients recruited in the CCU

In our meta-analysis, we only focussed on a non-selected population and included these studies from Bruyninckx et al[10] that corresponded to our inclusion and exclusion criteria.

Studies were excluded for the following reasons:

- If the studied condition was not AMI or ACS
- If the study population did not represent the primary care population. For example only including patients with elevated cardiac enzymes or ECG changes
- If the study was conducted in the coronary care unit (CCU) (selected population)
- It the study didn't include one of the 13 signs or symptoms
- If the data were not original or not sufficient to construct a 2×2 table
- If the language was not English or Dutch

Data extraction

The following data was obtained from the included studies by one researcher (LN):

- The study methodology
- The sample size and prevalence of the disease
- Patients characteristics (age and sex)
- The setting in which the study was conducted
- The index test
- The reference test
- The absolute numbers for constructing a 2x2 table (or calculated from sensitivity, specificity, or percentages)
- The inclusion and exclusion criteria

Quality assessment

The quality was assessed by one researcher (LN) using the Quality Assessment of Diagnosis Accuracy Studies-2 (QUADAS-2) instrument in Review Manager (RevMan version 5.4, Cochrane training) to evaluate the risk of bias.
QUADAS-2 consists of four domains:

- Patient selection: assessment on how patients were selected for the study and the risk of selection bias
- Index test: interpretation of the 13 signs and symptoms
- Reference standard: execution and interpretation of the reference test
- Flow and timing: investigating the sequence in which the index and reference test were performed

Each domain was scored “high”, “unclear” or “low” to determine the risk of bias and applicability[12,13].

Data analysis

We divided the patients in two subgroups (AMI and ACS) on which analysis was performed independently. We used the random effect model by Reitsma et al[14] because of the heterogeneity between the different studies[15]. The analysis was performed with the Mada package in R and was based on the pooled positive likelihood ratio (LR+), negative likelihood ratio (LR-) and the diagnostic odds ratio (DOR)[16].

The LR+ can be calculated as sensitivity/(1-specificity) and can be interpreted as the ratio of patients with ACS or AMI to patients without ACS or AMI when the symptom is present[17].
The DOR can be interpreted as the odds of a positive index test (here the presence of a symptom) in patients with the disease relative to the odds of a positive test in patients without the disease. Statistically, the DOR is the ratio of LR+ to LR-[18].
Like sensitivity and specificity, the LR+, LR- and DOR are not affected by the prevalence of the disease. In contrast to positive predictive value (PPV) and negative predictive value (NPV), which respectively increase and decrease with higher disease prevalence[19].
In this meta-analysis, the prevalence between the included studies had a wide range so PPV and NPV were not reported[20].

Results

Included studies

During the study selection process, our search yielded 8876 results. After screening by title and abstract, only 55 articles remained, because the majority focused on the treatment of AMI and ACS. We included the 16 articles with non-selected patients from Bruyninckx et al[9] and one article by reference searching and screened the full text of the remaining articles. We ended up with 24[21-44] included articles. According to PRISMA 2020 standards[11], the selection process is outlined in figure 1. During this process, there was no disagreement between the two reviewers.

Study characteristics

Table 1 displays the descriptive study characteristics. The 24 studies included in this meta-analysis reflected 72,992 patients in total. The number of included patients ranged from 121 patients[38] to 22,717 patients[30] with a mean of 3041 patients.
The majority of the studies (n = 14) were conducted in the ED, other settings were the ambulance service (n = 4), the primary care or the emergency call centre (n = 4) and the GP's office (n = 2).
Cardiac biomarkers (n = 17) and electrocardiogram (ECG) (n = 15) were most frequently used to diagnose AMI and ACS. A combination of ECG, cardiac biomarkers and other reference tests were also used, like symptoms (n = 7), diagnosis from medical file (n = 4), death (n = 4), scintiscan (n = 4), coronary angiography (n = 3), stress test (n = 3), percutaneous coronary intervention (PCI) (n = 2), WHO (World Health Organisation) criteria (n = 2), stress echocardiography (n = 1), cardiac MRI (n = 1), autopsy (n = 1), history (n = 1) and European Society of Cardiology (ESC) criteria (n = 1).

In total, 11 articles conducted research about ACS, ten articles about AMI and three studies researched both conditions. Respectively, 32,102 and 40,890 patients were included in the analysis of ACS and AMI, with a prevalence ranging from 8.3% to 57% for ACS and 0.85% to 36% for AMI.

Some index tests were described differently in the included articles. For example, pain radiating to the jaw was also classified as neck pain. Oppressive pain was described as pressing, heavy, tightening, crushing, squeezing or pressure-like pain. Burning, indigestion-like pain or abdominal pain were examples of epigastric pain. Last, some studies described patients that were cold and clammy, which was classified in our study as sweating.

Quality

A summary of the quality assessment using the QUADAS-2 tool is shown in table 2. Overall, the quality of the studies was reasonable. Some studies date from over 30 years ago, with the oldest study from 1980 by Van der Does[21], when there was less focus on quality assessment and these studies used reference tests that are now obsolete.

Diagnostic accuracy of the signs and symptoms

Table 3 displays the pooled LR+, LR- and DOR separately for AMI and ACS subgroups. The most significant DOR was the index test 'Absence of chest wall tenderness': 7.73 (95% CI = 2.19 to 19.9) in the ACS subgroup with a LR- of 0.24 (95% CI = 0.10 to 0.51). In the AMI subgroup we found this symptom to be less significant, namely a DOR of 3.51 (95% CI = 1.64 to 6.61).

For the diagnosis of myocardial infarction, the symptoms 'Sweating' and 'Pain in the right arm/shoulder' had a DOR of respectively 5.75 (95% CI = 2.51 to 11.30) and 5.16 (95% CI = 1.77 to 11.90) and a LR+ of 3.57 (95% CI = 1.75 to 6.90) and 3.95 (95% CI = 1.67 to 7.51) Also pain in both arms had a LR+ of 2.95 (95% CI = 1.57 to 5.06), but this was based on only 1 study of Body et al[37], with a sample size of 796 patients. All other index tests had a LR+ less than 2.

In the ACS subgroup, only 'Pain in right arm/shoulder' had a LR more than 2, namely 2.92 (95% CI = 0.72 to 7.37) with a DOR of 3.90 (95% CI = 0.70 to 12.60).

Forest plots of the DOR of ACS and AMI by symptoms are shown in figure 2 and 3.

Discussion

In this meta-analysis, we focused on the accuracy of separate symptoms for diagnosing AMI and ACS. Our analysis showed that the absence of chest wall tenderness by palpation had the highest accuracy (DOR 7.73). This means that a patient with ACS was almost eight times more likely to not have chest wall tenderness on palpation compared to a patient without ACS and patients with chest wall tenderness were less likely to have ACS.
The analysis of pain radiating to the right arm (LR+: 3.95) and sweating (LR+: 3.57) also showed that the odds of having an AMI is almost four times higher if one of these symptoms was present.
None of these signs and symptoms alone could diagnose or exclude AMI or ACS with sufficient certainty, but they could raise suspicion for these conditions or make it less likely to occur.

Pain by chest wall palpation was also mentioned in two previously conducted meta-analyses (Bruyninckx et al[10] in 2006 and Haasenritter et al[45] in 2008), with a diagnostic accuracy that is comparable to our findings. Since 2008, we had not found a new diagnostic accuracy meta-analysis conducted.
The meta-analysis of Bruyninckx et al[10] had a similar design because our study was an update. However, our inclusion and exclusion criteria were slightly different. For example, the article of Goodacre et al[46] in 2003 excluded patients with clear evidence for ACS. Therefore, this study was excluded in our analysis. They also included patients in the CCU (selected patients). Another reason for conducting a new meta-analysis, is the statistics that were used. We used the bivariate model of Reitsma et al[14], in comparison with the classic pooling method used in the study of Bruyninckx et al[10]. Since 2005, the model of Reitsma et al[14] has been the most commonly used method in diagnostic accuracy studies[47].

In 2008, Haasenritter et al[45] conducted a similar meta-analysis about the accuracy of individual signs and symptoms. The inclusion criteria in this study were less restricted. They included all chest pain patients (acute and chronic) and not only AMI and ACS were included but also stable coronary heart disease (CHD) and major cardiac events (MCE) as target diseases.
Our study protocol was more restricted and focused on a low prevalence setting and a non-selected population, because this is useful for diagnosing these conditions in primary care.

Most studies focus on risk scores instead of separate symptoms.Those risk scores, like HEART (History, ECG, Age, Risk factors, and Troponin level) and GRACE (Global Registry of Acute Coronary Events), all include ECG findings and/or cardiac enzymes and do not use any signs or symptoms. Separate symptoms are easier to use in this setting since ECG and cardiac biomarkers are often not readily available in primary care[48]. For example, there is not always an ECG available during home visits and according to the definition of AMI from ESC guidelines[49], there is need for more than one troponin measurement to diagnose AMI. In addition, the results of the troponin in the blood sample can take a few hours, which is too long with these life-threatening conditions. New point-of-care testing (POCT) of troponin could change this, but there is need for new evidence to incorporate POCT in daily clinical practice[50].

Strengths and limitations

In this study, we had a relatively large population for analysis (72,992) in a low-prevalence setting. The majority of the studies had a prospective design, which means the patients were followed from their first visit through the diagnostic process. Therefore, selection bias was less common.
We conducted research about 13 signs and symptoms which are very common and for which patients often visit the GP's office.

In some studies[29,33,34,37] there were missing data per symptom. In those cases, there was an underestimation of the prevalence of this symptom, because patients without information on the presence of the symptom were possibly wrongly interpreted as not having the symptom, which could have resulted in bias.

In the studies conducted more than 20 years ago, we saw that the reference test included creatine kinase (CK), glutamic oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT) and/or lactate dehydrogenase (LDH) instead of troponin as cardiac biomarkers. We know now that those biomarkers are not as sensitive and specific as troponin. In September 2000, serum troponin was added to the guidelines of AMI by the American College of Cardiology and ESC[51]. As seen in table 2, this was a possible source of bias.
The reference test varied between the different studies and was in some studies only based on the letter from the cardiologist[42] or the medical file[43].
Data for some index tests were extracted from only one or two studies, which resulted in a small number of patients. For example the index test 'Pain in the right arm and/or shoulder' for patients with ACS was based on only one study[38] with only 121 patients included. Same counts for 'Pain in both arms and/or shoulders', which has only been investigated in Body et al[37] with 796 patients.

Conclusion

We concluded that separate signs and symptoms can not completely rule in or rule out AMI and ACS. They can, however, serve as a guide and raise suspicion for these two life threatening conditions. Especially chest wall tenderness by palpation can make these conditions less likely.

Figures

Figure 1:

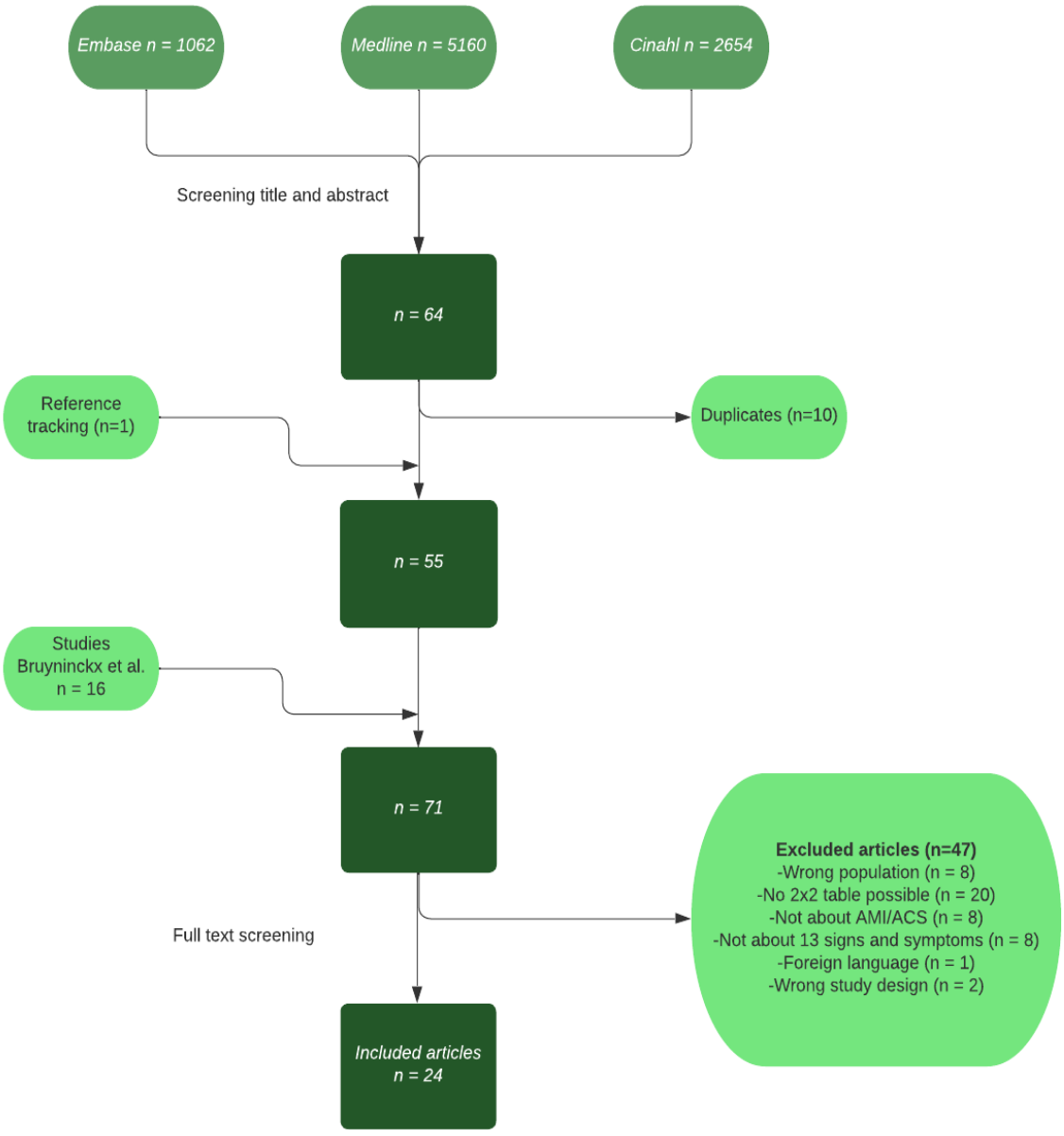


Figure 2:

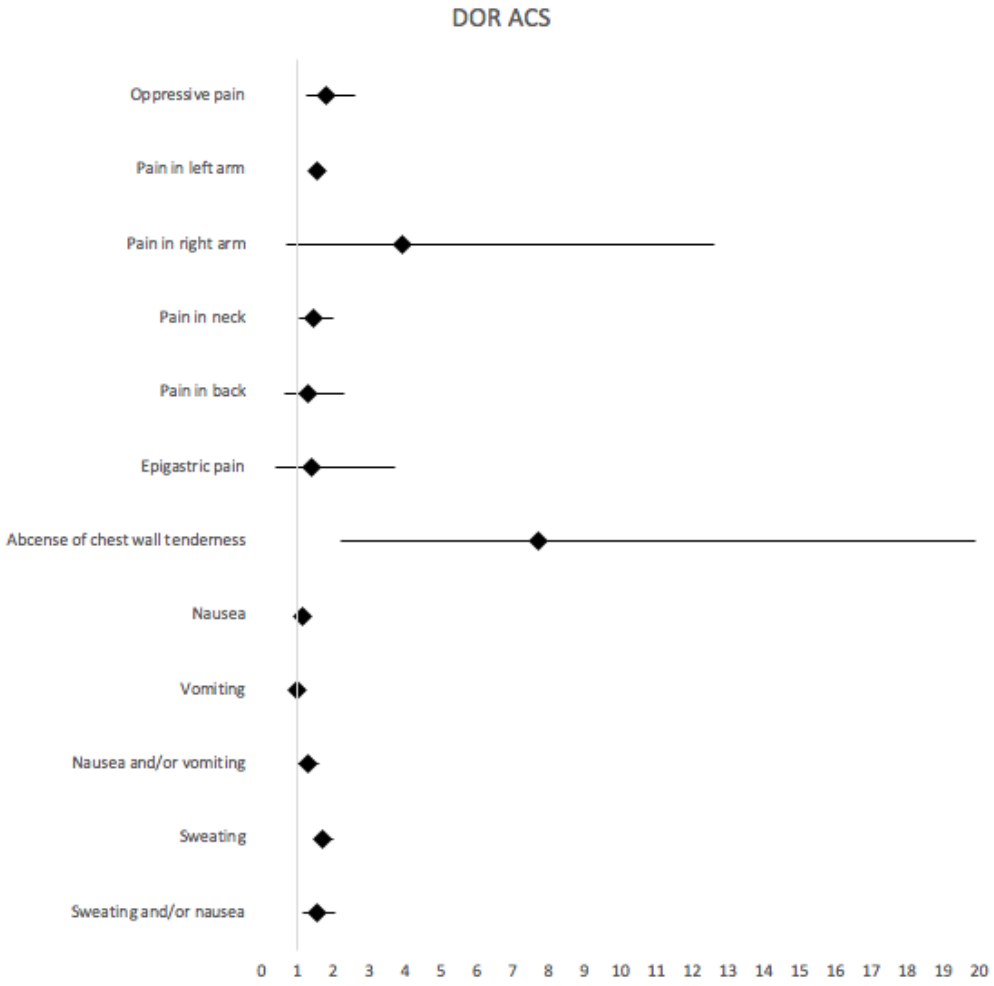
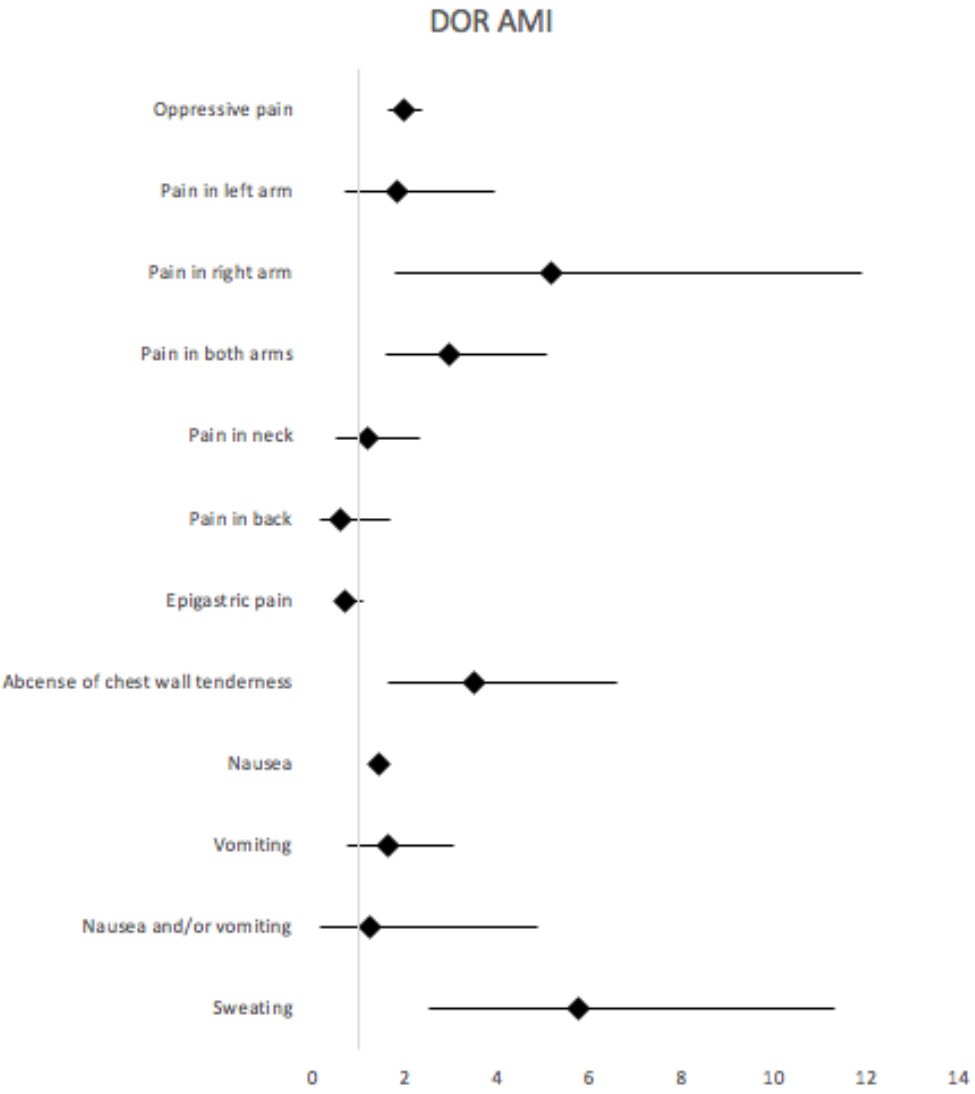

DOR ACS
Oppressive pain
Pain in left arm
Pain in right arm
Pain in neck
Pain in back
Epigastric pain
Abcense of chest wall tenderness
Nausea
Vomiting
Nausea and/or vomiting
Sweating
Sweating and/or nausea
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Figure 3:


DOR AMI
Oppressive pain
Pain in left arm
Pain in right arm
Pain in both arms
Pain in neck
Pain in back
Epigastric pain
Abcense of chest wall tenderness
Nausea
Vomiting
Nausea and/or vomiting
Sweating
0
2
4
6
8
10
12
14

Tables

Table 1:

Study	Year	Design	Sample size	% AMI/ACS	Mean age	% males	Setting	Inclusion	Exclusion	Index test	Reference test
Van der Does[21]	1980	Prosective study	1343	7% AMI	54	55%	GP	Recent chest pain or dyspnea, palpitations or dizziness or syncope, upper abdominal pain or mood changes	<25 yr women, <20 yr men	Sweating	ECG, cardiac biomarkers (a-HBDH, GOT, CK), symptoms
Lee[22]	1985	Prospecitve study	596	17% AMI 41% ACS	56	48%	ED	Chief complaint of anterior, precordial or left lateral chest pain	Local trauma, abnormalities on chest X-ray, <25 yr	Epigastric pain, oppressive pain, absence of chest wall tenderness	ECG, cardiac biomarkers (LDH, CK), scintiscan
Tierney[23]	1986	Prospective study	492	12% AMI	Not reported	Not reported	ED	Anterior chest pain as one of their complaints	<30 yr men, <40 yr female	Pain in right arm, oppressive pain, nausea and/or vomiting, sweating,	ECG, cardiac biomarkers (CK, LDH)

										absence of chest wall tenderness	
Hargarten[24]	1987	Retrospective study	401	57% ACS	65	Not reported	Ambulance service	'Stable' chest pain	Patients presenting initially with evidence of congestive heart failure, life-threatening arrhythmias/bradycardia < 50/min, second or third-degree heart block, frequent premature ventricular contractions, couplets, ventricular tachycardia), or hypotension (BP < 90 mm Hg)	Vomiting and/or nausea, sweating	ECG, cardiac biomarkers (CK, LDH), autopsy, scintiscan
Solomon[25]	1989	Prospective study	7734	14% AMI	Not reported	50%	ED	Chief complaint of anterior, precordial or left lateral chest pain	Local trauma, abnormalities on chest X-ray, <30 yr, >4 visit	Oppressive pain, sweating, absence of chest wall tenderness	ECG, cardiac biomarkers (CK, LDH), scintiscan, sudden unexplained death within 72 hr
Berger[26]	1990	Prospective study	278	36% AMI	57	69%	ED	Admitted to the hospital, complaining chiefly of chest pain	Trauma, transferred from other hospital with a diagnosis	Pain in left arm, pain in right arm, oppressive pain, vomiting and/or nausea	ECG, cardiac biomarkers (CK), symptoms
Grijseels[27]	1995	Prospective study	1005	42% ACS	67	54%	GP	Symptoms of possible cardiac origin seen by GP and transferred	No	Sweating and/or nausea	ECG, cardiac biomarkers, history, stress test, coronary angiography

Lopez-Jiminez[28]	1998	Prospective study	2694	6% AMI	Not reported	45%	ED	Chief complaint of chest pain	Local trauma, abnormalities on chest X-ray, <30 yr, >4 visit, prior AMI, PTCA, bypass	Oppressive pain, absence of chest wall tenderness	ECG, cardiac biomarkers (CK, LDH), scintiscan, sudden unexplained death within 72 hr
Pope[29]	1998	Prospective study	10689	8% AMI 23% ACS	59	52%	ED	Chief complaint chest, left arm, jaw or epigastric pain or discomfort, dyspnea, dizziness, palpitations or other symptoms suggestive of acute ischemia	<30yr, <18yr if suspected to have used cocaine	Epigastric pain, vomiting, nausea	WHO criteria
Graff[30]	2000	Prospective study	22717	0,85%AMI	Not reported	Not reported	ED	All patients with possible AMI where a rapid ECG was performed	No	Epigastric pain, pain in back, vomiting	WHO criteria
Milner[31]	2001	Prospective study	531	40% ACS	60	53%	ED	>45 yr and one symptom suggestive of ACS, or	<45 yr without diabetes or <18 yr with diabetes	Pain in left arm, pain in back, nausea and/or vomiting, sweating	ECG, cardiac biomarkers (CK)

								18–44 yr if diabetes and two risk factors			
Baxt[32]	2002	Prospective study	2204	6% AMI	53	40%	ED	Anterior chest pain prompting an ECG	<24yr	Pain in left arm, pain in neck, oppressive pain, nausea and/or vomiting, sweating	European Society of Cardiology criteria
Herlitz[33]	2002	Retrospective study	930	14% AMI	71	51%	Ambulance service	Chest pain or slightest suspicion of an acute coronary syndrome	No	Epigastric pain, nausea, vomiting, sweating	ECG, cardiac biomarkers (CK), symptoms
Svensson[34]	2003	Prospective study	538	29% AMI 57% ACS	69	58%	Ambulance service	Chest pain or discomfort >15 min, within last 6 h, dyspnoea, or any condition suggesting acute coronary syndrome	Lung disease	Sweating	ECG, cardiac biomarkers (CK, trop), symptoms
Christenson[35]	2006	Prospective study	769	21% ACS	58	62%	ED	Primary complaint of anterior or	<25 yr, traumatic or X-ray evident cause, enrolled in study 30 days previously,	Pain in left arm, pain in neck	ECG, cardiac biomarkers (CK, trop), symptoms, stress test, PCI,

								lateral chest pain	communication problems, no fixed address in British Columbia, without available telephone contact		coronary angiography, death with no other definite cause
Han[36]	2007	Retrospective study	10126	8% ACS	Not reported	44.4%	ED	> 18 yr and suspected of ACS, also chest pain, patients with dyspnea, light-headedness, dizziness, and weakness	Missing data related to gender, 12-lead ECG results, or clinical presentation, cocaine or amphetamine use, who left the ED against medical advice	Oppressive pain, pain in left arm	Cardiac biomarkers (CK, trop), death within 30 days, PCI
Body[37]	2010	Prospective study	796	19% AMI	59	60.4%	ED	Suspected cardiac chest pain, within the last 24 h	<25 yr, another medical condition requiring hospital admission, renal failure needing dialysis, significant chest trauma with suspected myocardial contusion, pregnant, did not speak English, were prisoners or if all means of follow-up would be impossible	Radiating pain in left arm/shoulder, right arm/shoulder, both arms, neck and back, epigastric pain , oppressive pain, vomiting, nausea, sweating, absence of chest wall tenderness	Cardiac biomarkers (trop)

Grani[38]	2015	Prospective, study	121	12% ACS	Not reported	60.3%	ED	Self-reported acute chest pain	<18 yr, recent thoracic surgery (<1 yr), any chronic inflammatory joint or connective tissue disease, fibromyalgia and unstable haemodynamic condition with systolic blood pressure ≤90 mm Hg or tachyarrhythmia, patients referred directly to the cardiac chest pain unit by a third party or for whom laboratory results, ECG or chest X-ray were already available at the time of enrolment	Absence of chest wall tenderness, epigastric pain, oppressive pain, radiation to left arm, right arm, back, neck, nausea, sweating	ECG, cardiac biomarkers (trop)
Rawshani[39]	2016	Retrospective study	2285	12% ACS	67	51%	Emergency call centre	Symptoms of pain or discomfort in the chest	No	Nausea/vomiting, sweating	Diagnosis from medical file

Andersson[40]	2017	Retrospective study	1702	26 % AMI	Not reported	55.9%	Ambulance service	Pain or discomfort that aroused suspicion of ACS and reported pain ≥4 on a visual analogue scale (VAS)	Systolic BP <100 mm Hg, <18yr, under the influence of alcohol or drugs, benzodiazepine abuse,, dementia or disorientation, communication problems, trauma, secondary transports	Nausea/vomiting	Diagnosis from medical file
Reuter[41]	2019	Prospective study	2485	16 % ACS	58	56.3 %	Emergency call centre	Non-traumatic chest pain	<18 yr, any difficulty in communicating	Oppressive pain	ECG, cardiac biomarkers (trop), symptoms, stress test, stress echocardiography, cardiac MRI, coronary angiography
Schols[42]	2019	Prospective study	243	18% ACS	64	52.3%	ED	Patients referred for suspected ACS	No informed consent, were not seen in person by a GP (telephone referral), or were eventually not referred to hospital	Oppressive pain, absence of chest wall tenderness	Diagnosis from medical file
Van Der Meer[43]	2019	Retrospective study	518	9% ACS	62	46.7%	Out-of-hours	Chest discomfort	<30 yr, repeated contacts, contacts that could not be retrieved	Oppressive pain, pain in back, pain in neck,	Diagnosis from medical file

							primary care calls		from the back-up system and patients without definitive diagnosis	nausea/vomiting, sweating	
Wouters[44]	2021	Retrospective study	1795	11% ACS	59	44.7%	Out-of-hours primary care calls	Chest discomfort (chest pain, pressure, tightness or discomfort)	<18 yr, pt not living in the vicinity of Utrecht, not concerned a triage call (eg, intercollegial consultation) or when the recording was of poor quality	Oppressive pain, pain in back, pain in neck, sweating, nausea/vomiting	ECG, cardiac biomarkers (trop), symptoms

AMI = acute myocardial infarction, ACS = acute coronary syndrome, GP = general practitioner, ED = emergency department, ECG = electrocardiogram, yr = year, h = hour, BP = blood pressure, PTCA = percutaneous transluminal coronary angioplasty, pt = patient, a-HBDH =a-hydroxybutyrate dehydrogenase, GOT = glutamic oxaloacetic transaminase, GPT = glutamic pyruvic transaminase, CK = creatine kinase, LDH = lactate dehydrogenase, WHO = world health organization, trop = troponin, PCI = percutaneous coronary intervention, MRI = magnetic resonance imaging

Table 2:

		ACS			AMI	
		Mean	95% CI		Mean	95% CI
Oppressive pain	LR+	1.28	1.06 to 1.61		1.39	1.30 to 1.49
	LR-	0.71	0.60 to 0.87		1.00	0.61 to 0.80
	DOR	1.82	1.22 to 2.62		1.98	1.63 to 2.39
Left arm pain	LR+	1.33	1.22 to 1.44		1,49	0.72 to 2.54
	LR-	0.87	0.78 to 0.94		0,87	0.52 to 1.04
	DOR	1.54	1.31 to 1.79		1,82	0.69 to 3.94
Sweating	LR+	1.46	1.28 to 1.67		3.57	1.75 to 6.90
	LR-	0.85	0.79 to 0.90		0.63	0.57 to 0.71
	DOR	1.71	1.46 to 2.00		5.75	2.51 to 11.30
Absence CWT	LR+	1.45	1.10 to 2.12		1.23	1.11 to 1.37
	LR-	0.24	0.10 to 0.51		0.39	0.20 to 0.68
	DOR	7.73	2.19 to 19.9		3.51	1.64 to 6.61
Epigastric pain	LR+	1.38	0.43 to 3.53		0.73	0.48 to 1.07
	LR-	1.00	0.95 to 1.13		1.02	1.00 to 1.05
	DOR	1.40	0.38 to 3.72		0.72	0.46 to 1.07
Nausea	LR+	1.11	1.04 to 1.19		1.29	1.12 to 1.50
	LR-	0.96	0.93 to 0.99		0.90	0.86 to 0.94
	DOR	1.16	1.05 to 1.28		1.43	1.20 to 1.69

Nausea and/or vomiting	LR+	1.20	1.00 to 1.46		1.12	0.43 to 3.21
	LR-	0.94	0.90 to 1.00		1.32	0.63 to 3.44
	DOR	1.28	1.00 to 1.61		1.24	0.14 to 4.89
Pain in back	LR+	1.18	0.65 to 1.85		0.60	0.15 to 1.40
	LR-	0.96	0.77 to 1.07		1.01	0.83 to 1.06
	DOR	1.27	0.62 to 2.33		0.62	0.15 to 1.70
Pain in neck	LR+	1.38	1.05 to 1.75		1.14	0.57 to 2.10
	LR-	0.94	0.85 to 0.99		1.00	0.91 to 1.12
	DOR	1.47	1.06 to 1.99		1.17	0.51 to 2.31
Pain in right arm	LR+	2.92	0.72 to 7.37		3.95	1.67 to 7.51
	LR-	0.84	0.55 to 1.03		0.81	0.62 to 0.95
	DOR	3.90	0.70 to 12.60		5.16	1.77 to 11.90
Sweating and/or nausea	LR+	1.14	1.05 to 1.25			
	LR-	0.75	0.62 to 0.91			
	DOR	1.54	1.15 to 2.03			
Vomiting	LR+	1.00	0.88 to 1.14		1.55	0.77 to 2.63
	LR-	1.00	0.99 to 1.01		0.96	0.85 to 1.01
	DOR	1.00	0.86 to 1.16		1.64	0.77 to 3.08
Pain in both arms	LR+				2.66	1.52 to 4.31
	LR-				0.91	0.84 to 0.97
	DOR				2.95	1.57 to 5.06

ACS = acute coronary syndrome, AMI = acute myocardial infarction, CI = confidence interval, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, DOR = diagnostic odds ratio, CWT = chest wall tenderness

Table 3:

		Risk of bias			Applicability concerns			
		Patient selection	Index test	Ref standard	Flow and timing	Patient selection	Index test	Ref standard
Van der Does[21]	1980							
Lee[22]	1985							
Tierney[23]	1986							
Hargarten[24]	1987							
Solomon[25]	1989							
Berger[26]	1990							
Grijseels[27]	1995							
Lopez-Jiminez[28]	1998							
Pope[29]	1998							
Graff[30]	2000							
Milner[31]	2001							
Baxt[32]	2002							
Herlitz[33]	2002							
Svensson[34]	2003							
Christenson[35]	2006							
Han[36]	2007							
Body[37]	2010							
Grani[38]	2015							
Rawshani[39]	2016							
Andersson[40]	2017							
Reuter[41]	2019							
Schols[42]	2019							
Van Der Meer[43]	2019							
Wouters[44]	2021							

High Unclear Low

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