



BMJ Open Association between symptoms and risk of non-ST segment elevation myocardial infarction according to age and sex in patients admitted to the emergency department with suspected acute coronary syndrome: a single-centre retrospective cohort study

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ABSTRACT

Objectives Evaluate the association between symptoms and risk of non-ST segment elevation myocardial infarction (NSTEMI) in patients admitted to an emergency department with suspected acute coronary syndrome based on sex and age.

Design Post hoc analysis of a prospective observational study conducted between September 2015 and May 2019.

Setting University hospital in Norway.

Participants 1506 participants >18 years of age (39.6% women and 31.0% 70 years of age or older).

Findings The OR for NSTEMI was 9.4 if pain radiated to both arms, 3.0 if exertional chest pain was present during the last week and 2.9 if pain occurred during activity. Men had significantly lower OR compared with women if pain was dependent of position, respiration or palpation (OR 0.17 vs 0.53, p value for interaction 0.047). Patients <70 years had higher predictive value than older patients if they reported exertional chest pain the last week (OR 4.08 vs 1.81, 95% p value for interaction 0.025) and lower if pain radiated to the left arm (OR 0.73 vs 1.67, p value for interaction 0.045).

Conclusions Chest pain with radiation to both arms, exertional chest pain during the last week and pain during activity had the strongest predictive value for NSTEMI. The differences in symptom presentation and risk of NSTEMI between sex and age groups were small.

Trial registration number WESTCOR study ClinicalTrials.gov (NCT02620202).

INTRODUCTION

The epidemiological panorama of acute myocardial infarction (AMI) has changed during the past decades with a lower rate of ST-segment elevation myocardial infarction

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Our large cohort of prospectively included patients with suspected acute non-ST segment elevation myocardial infarction (NSTEMI) is among the very few using a high-sensitivity troponin assay in establishing the final diagnoses.
- ⇒ The diagnostic performance of symptoms predicting NSTEMI was assessed in a real-life setting including patients with and without NSTEMI, compared with earlier register studies which only included NSTEMI patients.
- ⇒ The study investigated the important topic whether women with atypical symptoms have higher risk of myocardial infarction than men and assessed the impact of age in the same cohort.
- ⇒ Information about symptom presentation was gathered retrospectively and not based on a standardised symptom assessment form. Symptom descriptions in the electronic charts may have been influenced by the hospital physicians' risk assessment as they were not blinded for ECGs and first troponin measurements.
- ⇒ The results may not be representative for STEMI patients and those with non-chest pain NSTEMI.

(STEMI) versus non-STEMI (NSTEMI).¹ The decline in STEMI incidence has been attributed to improved awareness of coronary risk factors and early primary preventive measurements. Why the incidence of NSTEMI has increased in the same period may be due to demographic changes and higher prevalence of concomitant conditions like diabetes and obesity that promote

NSTEMI more than STEMI. Moreover, increasingly sensitive troponin assays tend to reclassify patients from the diagnosis of unstable angina pectoris (UAP) to NSTEMI,² which can explain the decline in the frequency of ECG changes in AMI patients over the last 50 years.³

The recent epidemiological shift may affect what symptoms we consider to be representative of AMI. Earlier studies of symptom presentation where 50%–90% of patients had ischaemic ECGs^{4–6} probably do not represent the AMI patients in today's emergency departments. The new high-sensitivity troponin assays (hs-Tn) are very sensitive, but less specific as they detect slightly increased troponin concentrations in a substantial number of non-AMI patients. Correct triage based on symptoms may help ensure early treatment in high-risk patients and possibly reduce unnecessary examinations and overtreatment in low-risk patients.

Studies suggest that symptom presentation differs by sex and age, which can influence the rate of misdiagnosis and affect prognosis. Most studies identifying sex differences are based on AMI registries, and do not compare presenting symptoms in patients with AMI to patients with non-coronary disease.^{7–11} Newer prospective studies including patients with suspected rather than confirmed coronary disease find less sex differences,^{12–16} questioning the assumption that presenting symptoms of AMI are different in men compared with women. Furthermore, women with AMI are older than men. Although most newer studies on sex differences adjust for age, few studies have compared the OR for different symptoms based on sex and age in the same cohort.

To address these unresolved issues, we assessed typical symptoms of NSTEMI in a contemporary cohort of patients presenting with suspected NSTEMI-acute coronary syndrome (ACS) and the potential impact of sex and age on these associations.

METHODS

Study design and population

The Aiming Towards Evidence-Based Interpretation of Cardiac Biomarkers in Patients Presenting with Chest Pain is a prospective observational study conducted at two university hospitals in Norway.¹⁷

The current article is a post hoc analysis of a subset of 1506 patients >18 years admitted to Haukeland University Hospital between September 2015 and May 2019 with suspected NSTEMI-ACS. Suspected NSTEMI-ACS was defined as chest pain or discomfort that triggered a cardiac evaluation consisting of ACS risk assessment, an ECG and troponin measurements. Participants gave oral consent to participate in the study at arrival, and written consents were obtained when the clinical situation was stabilised. Blood samples from patients who did not provide written consent were destroyed. Patients with ST segment elevations were excluded, as well as patients transferred from other hospitals, those unable to provide informed

consent or with a short life expectancy, for example, terminal cancer.

Data collection

Information about symptoms at presentation was collected from electronic medical records provided by ambulance personnel, referring physicians and hospital physicians at presentation. The chart reviewers were not blinded to the study hypothesis. The treating hospital physicians are instructed to report both positive and negative symptoms as part of the department's routine. However, since a symptom checker is not routinely used, the amount of available information was to some extent dependent of the treating physician's accuracy. In the very few incidences (<5 cases) where prehospital and in-hospital personnel gave conflicting information, data provided by hospital physicians were used.

Blood samples were analysed using the high-sensitivity troponin T assay from Roche Diagnostics with a limit of blank of 3 ng/L, a limit of detection of 5 ng/L and a sex-neutral 99th percentile of 14 ng/L, CV_A were 10% or lower for concentrations >4.5 ng/L. The final diagnosis was adjudicated by two independent cardiologists based on clinical data, high-sensitivity troponin T, 12-lead ECG and additional coronary examinations.¹⁷ AMI was defined according to the third universal definition for MI.¹⁸ A 20% or 50% change in troponin concentration was regarded significant if baseline cTnT concentration were >14 ng/L or ≤14 ng/L, respectively.

Chest pain characteristics

Detailed information on character, location and duration of pain was available for >80% of patients. Patients with missing information about character, location or duration were excluded from specific analyses when that information was needed, but not from the study. Additional symptoms like shortness of breath and nausea not registered at presentation were regarded negative, in line with similar studies.⁷ The fraction of unregistered symptoms (then considered negative) is available in online supplemental table 1. The additional symptoms most often not reported were pain dependent of position (85.5% unreported), palpitations (81.1%) and pain dependent of respiration (77.5%). Shortness of breath were left unregistered in 24.3%, while nausea and vomiting were not registered in 49.3% and 56.0% of patients. The majority of positive or negative symptoms were reported equally often in patients with a later diagnosis NSTEMI versus non-NSTEMI, with five exceptions: Positive or negative presence of diaphoresis/clamminess and effect of nitroglycerines were reported more often for patients with a later diagnosis of NSTEMI. Positive and negative presence of dizziness and pain triggered by respiration or palpation were reported more often in patients given a non-NSTEMI diagnosis.

Traditionally, several studies have chosen to define typical location and pain character as pain or

discomfort in chest, arm or jaw, with character being dull, heavy, tight or crushing. Atypical pain has been defined as pain located in the epigastrium, abdomen, back or any other location with character being burning, stabbing, stinging or any other character.^{12 19} When combined, pain is regarded atypical if either character or location is atypical, and typical only when both are classified as typical. The term typical and atypical symptoms of ACS is debated and should be used with caution since the frequency of reported symptoms may differ between sexes and age groups.²⁰ For simplicity reasons, we have still included these terms according to definitions described above.

Statistical analysis

Baseline characteristics for patients with and without NSTEMI was reported as means (± 2 SD) for normally distributed data, median with 25- and 75-percentiles for non-normally distributed data and frequencies with percentages for categorical data. Differences between groups were compared using two-sample t-test or Wilcoxon rank-sum test for continuous variables and Pearson χ^2 test or Fisher's exact for categorical data.

Patients were grouped by gender and age, using ≥ 70 years as the cut-off limit for age based on median age of first myocardial infarction close to 70 years in the USA²¹ and 72 years for all myocardial infarctions in Norway.²²

ORs with 95% CIs were calculated for all specific symptoms within sex and age groups. Sensitivity, specificity, positive and negative predictive value (PPV and NPV), positive and negative likelihood ratio (LR), accuracy and area under receiver operating characteristic curve (ROC-AUC) were calculated for selected variables. To assess the association between symptoms and sex we made a multivariable regression model containing symptom, sex and the combined variable of symptom/sex. Age effect was similarly evaluated using symptom, age group and the combined variable of symptom/age. The p value for interactions was calculated using Wald χ^2 . The degree of interaction for sex and age was compared in order to evaluate which factor influenced the odds of having an NSTEMI if presentation was typical or atypical for NSTEMI.

Hypothesis testing were two tailed, and p values < 0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics V.26.0.0.1 and R V.4.0.3.

Patient and public involvement

The study was discussed in the patients' user committee at Haukeland University Hospital in January 2016. This committee include one representative from the national patient organisation for lung and heart diseases. The user committee was positive to the study and gave important input to the planning

and implementation. Information describing the progression and data reported from the study is available for patients online.

RESULTS

Baseline characteristics are shown in [table 1](#). A total of 175 patients (11.6%) were classified with NSTEMI, of which 96% had a type 1 infarction and 4% type 2 infarction. Women accounted for 39.6% of the included patients and 30.3% of those with NSTEMI. Corresponding numbers for patients ≥ 70 years of age was 31.0% and 43.4%. Patients with NSTEMI was on average 5.4 years older than non-myocardial infarction patients, and women were 4.7 years older than men.

Presenting symptoms are outlined in online supplemental [table 2](#). If both pain location and character were in line with what has usually been described as typical, the sensitivity and NPV for NSTEMI was 84.6 (95% CI 77.4 to 90.2) and 92.0 (95% CI 88.4 to 94.5) (see [table 2](#)). The specificity was low, and the AUC was only slightly better than neutral, 0.532.

Patients in the total cohort had significantly increased OR for NSTEMI if chest pain radiated to both arms, was triggered by physical activity or if chest pain had occurred multiple times during the last week ([tables 3 and 4](#)). In total, 50% of patients with radiation to both arms were diagnosed with NSTEMI (PPV 50.0, 95% CI 38.8 to 61.2), the highest fraction of the assessed symptoms (see [table 2](#)). Negative ORs were observed if the pain was located precordial, occurred during rest or was accompanied by dizziness.

Sex differences

Chest pain character traditionally regarded atypical was present in a higher fraction of men than women (21.8% vs 18.3%, $p=0.041$). On the other hand, chest pain location regarded atypical were present in a borderline higher fraction of women (9.4% vs 6.7%, $p=0.059$) (see [figure 1](#) and online supplemental [table 2](#)). In patients with either atypical character or location, there were no difference between women and men (19.5% of women vs 18.0% of men, $p=0.494$). Women significantly more often than men reported radiating pain and additional symptoms.

The OR for having an NSTEMI based on specific symptoms differed slightly between women and men. Men had lower OR for NSTEMI than women if additional symptoms like pain dependent on position, respiration or palpation were present (OR 0.17, 95% CI 0.07 to 0.39 vs OR 0.53, 95% CI: 0.25 to 1.11, p value for interaction 0.047) (see [table 3](#)). The difference was driven by a lower OR for positional pain (OR 0.17, 95% CI 0.04 to 0.71 for men vs OR 1.10, 95% CI 0.42 to 2.90 for women, p value for interaction 0.033).

Longer symptom duration (60 min to 24 hours) was associated with NSTEMI in women but not in men, with interaction being borderline significant ($p=0.050$).

Age differences

A higher fraction of younger (< 70 years) than older patients (≥ 70 years) presented with what has traditionally been

Table 1 Baseline characteristics by sex and age group

	All patients, (n=1506)	Women, (n=597)	Men, (n=909)	P value	Age <70, (n=1039)	Age ≥70, (n=467)	P value
Baseline characteristics							
Age, years	62.3±33.1	65.1±28.6	60.4±35.2	<0.001 (T)	54.6±20.9	79.3±29.5	<0.001 (T)
Symptom to arrival time, hours	8.6 (3.1–52.7)	8.6 (2.8–51.2)	8.9 (3.2–56.25)	0.266 (W)	9.1 (3.1–55.0)	8.3 (3.1–50.8)	0.449 (W)
Hospital stay, hours	28.0 (22–69)	26.0 (22–50)	32.0 (22–73)	<0.001 (W)	26.0 (21–62)	44.0 (24–78)	<0.001 (W)
Acute MI	175 (11.6)	53 (8.9)	122 (13.4)	0.007 (C)	99 (9.5)	76 (16.3)	<0.001 (C)
Risk factors							
Hypertension, %	616 (40.9)	266 (44.6)	350 (38.5)	0.019 (C)	337 (32.4)	279 (59.7)	<0.001 (C)
Hyperlipidaemia, known %	303 (20.1)	121 (20.3)	182 (20.0)	0.907 (C)	193 (18.6)	110 (23.6)	0.026 (C)
Hyperlipidaemia, new,* %	142 (9.4)	71 (11.9)	71 (7.8)	0.008 (C)	98 (9.4)	44 (9.4)	0.995 (C)
Diabetes mellitus, %	181 (12.0)	62 (10.4)	119 (13.1)	0.114 (C)	105 (10.1)	76 (16.3)	0.001 (C)
Insulin-dependent	51 (3.4)	18 (3.0)	33 (3.6)	0.518 (C)	26 (2.5)	25 (5.4)	0.005 (C)
Family history, %	275 (18.3)	117 (19.6)	158 (17.4)	0.276 (C)	224 (19.8)	51 (10.9)	<0.001 (C)
Current smoker, %	284 (18.9)	118 (19.8)	166 (18.3)	0.466 (C)	206 (19.8)	78 (16.7)	0.152 (C)
Previous smoker, %	658 (43.7)	248 (41.5)	410 (45.1)	0.173 (C)	445 (42.8)	213 (45.6)	0.314 (C)
Medical history							
Prior MI, %	289 (19.2)	76 (12.7)	213 (23.4)	<0.001 (C)	141 (13.6)	148 (31.7)	<0.001 (C)
Prior PCI, %	293 (19.5)	73 (12.2)	220 (24.2)	<0.001 (C)	159 (15.3)	134 (28.7)	<0.001 (C)
Prior CABG, %	111 (7.4)	18 (3.0)	93 (10.2)	<0.001 (C)	45 (4.3)	66 (14.1)	<0.001 (C)
Heart failure, %	52 (3.4)	18 (3.0)	34 (3.7)	0.451 (C)	20 (1.9)	32 (6.9)	<0.001 (C)
Stroke, %	42 (2.8)	12 (2.0)	30 (3.3)	0.137 (C)	17 (1.6)	25 (5.4)	<0.001 (C)
Peripheral vascular disease, %	29 (1.9)	9 (1.5)	20 (2.2)	0.339 (C)	11 (1.1)	18 (3.9)	<0.001 (C)
Vital parameters at admission							
Systolic BP, mm Hg	145.9±41.0	147.2±47.3	143.8±40.1	0.003 (T)	142.9±41.0	150.1±46.4	<0.001 (T)
Diastolic BP, mm Hg	84.3±25.3	81.5±26.7	85.4±24.9	<0.001 (T)	85.2±24.6	80.8±27.5	<0.001 (T)
Heart rate, bpm	72.7±32.9	75.9±32.3	74.2±38.1	0.069 (T)	74.1±31.0	76.6±25.0	0.012 (T)
BMI†	27.4±9.2	26.4±9.6	28.0±8.8	<0.001 (T)	28.0±9.4	26.2±8.3	<0.001 (T)
ECG findings							
ST segment depression, %	47 (3.1)	22 (3.7)	25 (2.8)	0.307 (C)	21 (2.0)	26 (5.6)	<0.001 (C)
T-wave inversion, %	47 (3.1)	18 (3.0)	29 (3.2)	0.848 (C)	33 (3.2)	14 (3.0)	0.854 (C)

Values are median (IQR), mean±2 SD, or n (%).

*Total cholesterol ≥6.5 ng/L at presentation.

†Data missing in 50.6% (762/1506).

BMI, body mass index; BP, blood pressure; C, chi-square; CABG, coronary artery bypass grafting; FE, Fischer's exact; MI, myocardial infarction; PCI, percutaneous coronary intervention; T, two-sample t-test; W, Wilcoxon.

regarded atypical character (22.5% vs 15.4%, $p=0.006$). Traditionally considered atypical chest pain location was present in a higher fraction of older patients (10.3% vs 6.7%, $p=0.018$) (see [figure 1](#) and online supplemental table 2). As seen with sexes, a similar fraction of younger and older patients presented with either atypical character or location (18.2% of younger patients vs 19.5% of older patients, $p=0.582$).

A few differences in the OR for NSTEMI based on specific symptoms were evident. In patients presenting with exertional chest pain during the past week, younger patients had higher OR for NSTEMI compared with older patients (OR 4.08, 95% CI 2.63 to 6.34 vs OR 1.81, 95% CI 1.03 to 3.15, p value for interaction 0.025) (see [table 4](#)). For pain radiating to the left arm, the ORs for NSTEMI were lower in younger

than older patients (OR 0.73, 95% CI 0.42 to 1.28, vs OR 1.67, 95% CI 0.93 to 3.00, p value for interaction 0.045).

DISCUSSION

Our study of suspected ACS in patients without ST elevations showed that chest pain radiating to both arms has the highest predictive value for NSTEMI regardless of sex and age. Retrosternal location, vomiting, diaphoresis, onset during physical activity and exertional chest pain prior to admission are other symptoms found to be representative of AMI. This is in line with previous studies with high percentage of patients with ST elevations, who were diagnosed with less sensitive troponin assays. The presence of symptoms like chest pain dependent of

Table 2 Diagnostic precision of selected chest pain characteristics

	Sensitivity	Specificity	PPV	NPV	Pos. LR	Neg. LR	Accuracy	AUC
Location*								
Retrosternal	61.1 (53.3–68.4)	57.1 (54.4–59.8)	15.9 (14.2–17.8)	91.7 (90.1–93.1)	1.42 (1.24–1.63)	0.68 (0.56–0.83)	57.6 (55.0–60.1)	0.591
Precordial	7.6 (4.1–12.6)	76.5 (74.1–78.8)	4.1 (2.5–6.8)	86.2 (85.6–86.8)	0.32 (0.19–0.55)	1.21 (1.15–1.27)	68.5 (66.0–70.8)	0.421
Sum typical† location	95.9 (91.8–98.4)	5.4 (4.2–6.8)	11.9 (11.5–12.2)	90.9 (82.4–95.5)	1.01 (0.98–1.05)	0.75 (0.35–1.61)	16.0 (14.2–18.0)	0.507
Sum atypical‡ location	6.4 (3.2–11.2)	92.1 (90.4–93.5)	9.7 (5.5–16.3)	88.1 (87.7–88.5)	0.80 (0.44–1.47)	1.02 (0.97–1.06)	82.0 (80.0–84.0)	0.492
Character								
Sum typical§ character	89.5 (83.0–94.1)	14.8 (12.8–17.1)	11.5 (10.9–12.2)	91.9 (87.2–95.0)	1.05 (0.99–1.12)	0.71 (0.42–1.19)	23.1 (20.7–25.6)	0.522
Sum atypical¶ character	21.8 (15.2–29.8)	74.8 (72.1–77.4)	9.7 (7.1–13.1)	88.5 (87.5–89.5)	0.87 (0.62–1.21)	1.05 (0.95–1.15)	69.0 (66.3–71.6)	0.483
Typical pain**	84.6 (77.4–90.2)	21.8 (19.4–24.3)	11.7 (10.9–12.6)	92.0 (88.4–94.5)	1.08 (1.00–1.17)	0.71 (0.47–1.17)	28.6 (26.1–31.2)	0.532
Atypical pain††	15.4 (9.8–22.6)	78.2 (75.7–80.6)	8.0 (5.5–11.6)	88.3 (87.4–89.1)	0.71 (0.47–1.07)	1.08 (1.00–1.17)	71.4 (68.8–73.9)	0.468
Radiation								
Multiple directions	27.8 (21.2–35.2)	80.9 (78.6–83.0)	15.8 (12.5–19.7)	89.7 (88.7–90.5)	1.45 (1.11–1.90)	0.89 (0.81–0.98)	74.8 (72.5–77.0)	0.543
Both arms	19.5 (13.8–26.3)	97.5 (96.5–98.3)	50.0 (38.8–61.2)	90.4 (89.7–91.0)	7.76 (4.92–12.23)	0.83 (0.77–0.89)	88.6 (86.9–90.2)	0.585
Left arm	20.7 (14.9–27.6)	80.1 (77.8–82.2)	11.8 (8.9–15.5)	88.7 (87.8–89.5)	1.04 (0.76–1.42)	0.99 (0.91–1.07)	73.3 (71.0–75.6)	0.504
Right arm	1.18 (0.1–4.2)	98.6 (97.8–99.2)	10.0 (2.53–32.2)	88.6 (88.4–88.7)	0.86 (0.20–3.68)	1.00 (0.98–1.02)	87.5 (85.7–89.1)	0.499
Any radiation	48.1 (45.4–50.9)	48.1 (45.4–50.9)	13.8 (12.4–15.4)	91.3 (89.5–92.9)	1.24 (1.10–1.41)	0.74 (0.60–0.91)	50.0 (47.4–52.6)	0.563
Additional symptoms‡‡								
Sum typical§§	66.3 (58.8–73.2)	33.2 (30.7–35.8)	11.5 (10.4–12.7)	88.2 (85.7–90.3)	0.99 (0.89–1.11)	1.02 (0.81–1.27)	37.1 (34.6–39.6)	0.497
Sum atypical¶¶	8.6 (4.9–13.7)	74.8 (72.3–77.1)	4.3 (2.7–6.8)	86.2 (85.5–86.8)	0.34 (0.21–0.56)	1.22 (1.16–1.29)	67.1 (64.6–69.4)	0.417
Last 24 hours								
Exc. chest pain >once	5.1 (2.4–9.5)	97.1 (96.0–97.9)	18.8 (10.2–31.9)	88.6 (88.3–89.0)	1.76 (0.87–3.56)	0.98 (0.94–1.01)	86.4 (84.6–88.1)	0.511
Last week								
Exertional chest pain	35.4 (28.4–43.0)	84.5 (82.5–86.4)	23.1 (19.2–27.6)	90.9 (89.9–91.8)	2.29 (1.81–2.90)	0.76 (0.68–0.85)	78.8 (76.7–80.9)	0.6

*In patients having chest pain at presentation.

†Summation of traditionally considered typical pain location like retrosternal, precordial, other parts of thorax, shoulder, arms, jaw or neck.

‡Summation of traditionally considered atypical pain location like epigastrum, abdomen, back or other locations.

§Summation of traditionally considered typical pain character like tight, crushing, dull or heavy.

¶Summation of traditionally considered atypical pain character like burning, stinging or other.

**Typical pain is defined as the combination of traditionally considered typical location and typical character.

††Atypical pain is defined as either atypical location or atypical character, or both.

‡‡If not stated considered negative.

§§Summation of traditionally considered typical additional symptoms like shortness of breath, nausea, vomiting, diaphoresis, clamminess, palpitations or dizziness.

¶¶Summation of traditionally considered atypical additional symptoms like pain dependent of position, respiration or palpation.

Accuracy, Sensitivity x prevalence + specificity x (1 - prevalence); AUC, Area under receiver operating characteristics curve; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Positive OR (95% CI) for NSTEMI by symptoms in all patients and by sex

	N of total (%)	All (n=1506)	Men (n=909)	Women (n=597)	P value for interaction
Presenting symptom					
Chest pain	1468 (97.5)	1.55 (0.47–5.09)	2.05 (0.48–8.75)	0.97 (0.12–7.76)	0.565
Location*					
Retrosternal	661 (45.0)	2.09 (1.51–2.89)	2.24 (1.51–3.34)	1.75 (0.98–3.10)	0.48
Precordial	317 (21.5)	0.27 (0.15–0.48)	0.24 (0.12–0.46)	0.30 (0.09–0.98)	0.734
Thorax, other parts	396 (27.0)	0.95 (0.67–1.37)	1.05 (0.68–1.64)	0.85 (0.45–1.60)	0.579
Shoulders or arms	34 (2.3)	0.72 (0.22–2.40)	0.74 (0.17–3.26)	0.73 (0.09–5.65)	0.989
Jaw or neck	25 (1.7)	1.45 (0.49–4.26)	3.88 (0.91–16.4)	0.64 (0.08–4.89)	0.156
Sum typical† location	1391 (94.8)	1.35 (0.61–2.98)	1.60 (0.48–5.32)	0.97 (0.33–2.83)	0.543
Epigastric or abdominal	81 (5.5)	1.07 (0.54–2.11)	0.81 (0.31–2.09)	1.67 (0.62–4.49)	0.298
Other location‡	34 (2.3)	0.22 (0.03–1.65)	–	0.56 (0.07–4.30)	0.999
Sum atypical§ location	77 (5.2)	0.79 (0.42–1.51)	0.57 (0.22–1.45)	1.29 (0.53–3.18)	0.217
Character					
Tight/crushing	960 (63.7)	1.33 (0.82–2.14)	1.44 (0.80–2.59)	1.18 (0.51–2.75)	0.706
Dull/heavy	81 (5.4)	1.16 (0.59–2.32)	0.73 (0.28–1.89)	2.37 (0.85–6.58)	0.098
Sum typical¶ character	1033 (68.6)	1.48 (0.83–2.64)	1.18 (0.62–2.26)	3.37 (0.80–14.3)	0.194
Burning	89 (5.9)	2.21 (1.27–3.83)	3.14 (1.61–6.10)	1.14 (0.39–3.38)	0.12
Stinging	218 (14.5)	0.42 (0.23–0.77)	0.34 (0.16–0.73)	0.57 (0.20–1.64)	0.448
Other atypical	2 (0.1)	–	–	–	0.999
Sum atypical** character	299 (19.9)	0.83 (0.54–1.28)	0.82 (0.49–1.37)	0.78 (0.35–1.74)	0.932
Unknown	263 (17.5)	1.40 (0.96–2.06)	1.58 (1.01–2.47)	0.95 (0.43–2.08)	0.273
Typical pain††	981 (66.8)	1.52 (0.94–2.48)	1.39 (0.78–2.50)	1.99 (0.76–5.19)	0.609
Atypical pain‡‡	224 (15.3)	0.66 (0.40–1.07)	0.72 (0.40–1.29)	0.50 (0.19–1.31)	0.609
Radiation					
Multiple directions	298 (19.8)	1.63 (1.13–2.34)	1.62 (1.00–2.61)	2.06 (1.14–3.73)	0.532
Both arms	66 (4.4)	9.40 (5.62–15.7)	8.28 (4.44–15.4)	11.7 (4.68–29.1)	0.543
Left arm	296 (19.7)	1.05 (0.71–1.56)	1.05 (0.65–1.69)	1.08 (0.54–2.17)	0.939
Right arm	20 (1.7)	0.86 (0.20–3.74)	1.65 (0.35–7.87)	–	0.999
Both shoulders	25 (1.7)	1.97 (0.73–5.31)	0.64 (0.08–5.01)	4.49 (1.36–14.9)	0.114
Left or right shoulder	92 (6.1)	0.16 (0.04–0.67)	0.14 (0.02–1.04)	0.21 (0.03–1.58)	0.776
Jaw	321 (21.3)	1.41 (0.98–2.03)	1.70 (1.06–2.70)	1.34 (0.74–2.46)	0.551
Epigastrium or abdomen	38 (2.5)	1.18 (0.46–3.07)	0.36 (0.05–2.71)	2.96 (0.95–9.29)	0.075
Back	189 (12.5)	1.42 (0.92–2.20)	1.71 (0.95–3.07)	1.41 (0.71–2.80)	0.677
Numbness upper extremities	128 (8.5)	1.12 (0.65–1.94)	1.07 (0.55–2.08)	1.21 (0.46–3.22)	0.827
Any radiation	789 (52.4)	1.69 (1.21–2.35)	1.82 (1.22–2.70)	1.77 (0.93–3.34)	0.937
Unknown	26 (1.7)	2.33 (0.92–5.88)	2.02 (0.65–6.29)	3.01 (0.61–14.9)	0.69
Additional symptoms§§					
Shortness of breath	628 (41.7)	1.06 (0.77–1.45)	1.11 (0.75–1.64)	1.05 (0.60–1.85)	0.875
Nausea	318 (21.1)	0.93 (0.63–1.37)	1.01 (0.61–1.68)	0.95 (0.50–1.80)	0.88
Vomiting	43 (2.9)	2.38 (1.15–4.93)	2.33 (0.97–5.64)	2.45 (0.68–8.89)	0.951
Diaphoresis or clamminess	287 (19.1)	1.79 (1.25–2.56)	2.01 (1.32–3.06)	1.19 (0.58–2.45)	0.218
Palpitations	174 (11.6)	0.69 (0.40–1.20)	0.90 (0.47–1.75)	0.47 (0.16–1.33)	0.298
Dizziness	226 (15.0)	0.38 (0.21–0.70)	0.43 (0.21–0.91)	0.35 (0.12–0.98)	0.732
Sum typical¶¶ add. symptoms	1005 (66.7)	0.98 (0.70–1.37)	1.11 (0.75–1.66)	0.84 (0.45–1.56)	0.452

Continued

Table 3 Continued

	N of total (%)	All (n=1506)	Men (n=909)	Women (n=597)	P value for interaction
Dependent of position	124 (8.2)	0.43 (0.20–0.94)	0.17 (0.04–0.71)	1.10 (0.42–2.90)	0.033
Dependent of respiration	149 (9.9)	0.19 (0.07–0.52)	0.13 (0.03–0.55)	0.33 (0.08–1.39)	0.384
Pain on palpation	177 (11.8)	0.38 (0.19–0.75)	0.21 (0.07–0.69)	0.69 (0.29–1.66)	0.117
Sum atypical*** add. symptoms	351 (23.3)	0.28 (0.16–0.48)	0.17 (0.07–0.39)	0.53 (0.25–1.11)	0.047
Effect of NG	268 (17.8)	1.78 (1.24–2.57)	1.49 (0.71–3.13)	1.57 (0.57–4.31)	0.936
Onset of symptoms					
During physical activity	285 (18.9)	2.91 (2.06–4.10)	2.63 (1.74–3.96)	3.29 (1.75–6.19)	0.559
After physical activity	72 (4.8)	1.27 (0.64–2.52)	1.02 (0.42–2.47)	1.86 (0.62–5.60)	0.405
Acute/chronic stress	115 (7.6)	0.26 (0.10–0.72)	0.10 (0.01–0.71)	0.62 (0.19–2.07)	0.118
During rest	1027 (68.2)	0.50 (0.36–0.69)	0.56 (0.38–0.83)	0.41 (0.23–0.73)	0.4
Unknown	18 (1.2)	2.98 (1.05–8.45)	5.30 (1.40–20.0)	1.29 (0.16–10.5)	0.264
Symptom duration					
<30 min	377 (25.0)	0.91 (0.62–1.33)	0.98 (0.62–1.55)	0.77 (0.39–1.53)	0.559
30–60 min	84 (5.6)	1.36 (0.73–2.53)	2.87 (1.45–5.69)	–	0.997
60 min to 24 hours	482 (32.0)	1.44 (1.02–2.04)	1.12 (0.74–1.71)	2.37 (1.28–4.39)	0.05
>24 hours	155 (10.3)	0.13 (0.04–0.40)	–	0.60 (0.18–2.00)	0.996
Terminated by NG					
Terminated by morphine	88 (5.8)	1.55 (0.86–2.78)	1.53 (0.76–3.05)	1.50 (0.50–4.50)	0.979
Unknown	37 (2.5)	0.88 (0.31–2.51)	1.26 (0.36–4.44)	0.52 (0.07–3.95)	0.463
Unknown	283 (18.8)	0.77 (0.50–1.18)	0.85 (0.51–1.42)	0.61 (0.27–1.38)	0.491
Intensity of pain in intervals†††	1506 (100)	1.56 (1.19–2.04)	1.84 (1.28–2.63)	1.21 (0.80–1.84)	0.141
Last 24 hours					
Exertional chest pain >once	48 (3.2)	1.80 (0.86–3.77)	1.12 (0.42–2.94)	4.36 (1.32–14.4)	0.083
Last week					
Exertional chest pain	268 (17.8)	3.00 (2.13–4.26)	2.77 (1.84–4.18)	3.25 (1.73–6.10)	0.679
Shortness of breath	60 (4.0)	1.36 (0.66–2.82)	1.20 (0.45–3.19)	1.77 (0.59–5.30)	0.607
Pain similar to previous AMI	57 (3.8)	0.72 (0.29–1.84)	0.45 (0.14–1.47)	2.09 (0.45–9.82)	0.12

Statistically significant differences highlighted

*In patients having chest pain at presentation.

†Summation of traditionally considered typical pain location like retrosternal, precordial, other parts of thorax, shoulder, arms, jaw or neck.

‡Summation of pain in the back and all other non-typical locations.

§Summation of traditionally considered atypical pain location like epigastrium, abdomen, back or other locations.

¶Summation of traditionally considered typical pain character like tight, crushing, dull or heavy.

**Summation of traditionally considered atypical pain character like burning, stinging or other.

††Typical pain is defined as the combination of traditionally considered typical location and character.

‡‡Atypical pain is defined as either atypical location or character, or both.

§§ If not stated considered negative.

¶¶ Summation of traditionally considered typical additional symptoms like shortness of breath, nausea, vomiting, diaphoresis, clamminess, palpitations or dizziness.

*** Summation of traditionally considered atypical additional symptoms like pain dependent of position, respiration or palpation.

†††Four groups; no pain; Visual analogue scale (VAS) 1–3.5; VAS 3.5–6.5; VAS >6.5.

AMI, acute myocardial infarction; NG, Nitroglycerin; NSTEMI, non-ST segment elevation myocardial infarction.

position, palpation or respiration reduced the OR for NSTEMI significantly more in men than women. Similarly, prodromes of exertional chest pain during the last week before admission was more predictive of NSTEMI in younger than older patients.

Despite improvements in biochemical diagnostics and imaging, symptom evaluation is the cornerstone in early risk stratification of patients admitted with suspected ACS.

Hs-Tn is highly efficient in identifying AMI. However, given the assays' ability to detect even slightly elevated troponin concentrations in a substantial numbers of non-AMI patients, withholding further cardiac examinations in some selected patients with low clinical suspicion of ACS could reduce the number of unwarranted complications and side effects of unnecessary investigations or treatment.

Table 4 Positive OR for NSTEMI by age group

	N of total (%)	<70 years(n=1039)	≥70 years (n=467)	P value for interaction
Presenting symptom				
Chest pain	1468 (97.5)	1.98 (1.28–3.04)	2.67 (1.60–4.44)	0.374
Location*				
Retrosternal	661 (45.0)	1.98 (1.28–3.04)	2.67 (1.60–4.44)	0.374
Precordial	317 (21.5)	0.33 (0.16–0.66)	0.20 (0.07–0.56)	0.444
Thorax, other parts	396 (27.0)	1.05 (0.65–1.70)	0.75 (0.43–1.32)	0.382
Shoulders or arms	34 (2.3)	1.00 (1.00–4.37)	0.41 (0.05–3.18)	0.485
Jaw or neck	25 (1.7)	0.79 (0.10–6.15)	1.68 (0.44–6.36)	0.546
Sum typical† location	1391 (94.8)	2.32 (0.55–9.73)	1.09 (0.41–2.94)	0.398
Epigastric or abdominal	81 (5.5)	0.21 (0.03–1.53)	1.74 (0.78–3.87)	0.052
Other location‡	34 (2.3)	0.43 (0.06–3.20)	–	0.999
Sum atypical§ location	77 (5.2)	0.27 (0.07–1.13)	1.24 (0.57–2.68)	0.068
Character				
Tight/crushing	960 (63.7)	1.06 (0.67–1.65)	0.92 (0.55–1.52)	0.323
Dull/heavy	81 (5.4)	0.39 (0.09–1.64)	1.90 (0.81–4.45)	0.074
SUM typical¶ character	1033 (68.6)	1.36 (0.68–2.71)	1.76 (0.76–4.06)	0.961
Burning	89 (5.9)	2.01 (0.98–4.10)	2.00 (0.85–4.69)	0.992
Stinging	218 (14.5)	0.41 (0.19–0.86)	0.48 (0.17–1.39)	0.829
Other atypical	2 (0.1)	1.04 (0.99–1.10)	1.02 (0.96–1.09)	0.641
Sum atypical** character	299 (19.9)	0.76 (0.43–1.34)	1.11 (0.55–2.24)	0.407
Unknown	263 (17.5)	1.45 (0.87–2.44)	1.21 (0.67–2.17)	0.638
Typical pain††	981 (66.8)	1.41 (0.75–2.68)	1.83 (0.86–3.90)	0.607
Atypical pain‡‡	224 (15.3)	0.71 (0.37–1.34)	0.55 (0.26–1.16)	0.607
Radiation				
Multiple directions	298 (19.8)	1.84 (1.17–2.89)	1.36 (0.74–2.52)	0.436
Both arms	66 (4.4)	12.50 (6.58–23.75)	5.35 (2.26–12.62)	0.119
Left arm	296 (19.7)	0.73 (0.42–1.28)	1.67 (0.93–3.00)	0.045
Right arm	20 (1.7)	0.73 (0.09–5.62)	1.03 (0.12–8.94)	0.82
Both shoulders	25 (1.7)	0.73 (0.09–5.62)	3.05 (0.87–10.68)	0.242
Left or right shoulder	92 (6.1)	0.14 (0.02–0.98)	0.20 (0.03–1.53)	0.777
Jaw	321 (21.3)	1.53 (0.97–2.41)	1.29 (0.70–2.38)	0.65
Epigastrium or abdomen	38 (2.5)	0.74 (0.17–3.16)	2.30 (0.58–9.09)	0.267
Back	189 (12.5)	1.31 (0.73–2.34)	2.59 (0.23–28.97)	0.792
Numbness upper extremities	128 (8.5)	1.15 (0.59–2.24)	1.31 (0.48–3.60)	0.843
Any radiation	789 (52.4)	1.47 (0.95–2.27)	2.25 (1.33–3.79)	0.223
Unknown	26 (1.7)	2.64 (0.72–9.62)	1.74 (0.46–6.60)	0.662
Additional symptoms§§				
Shortness of breath	628 (41.7)	1.03 (0.68–1.57)	1.14 (0.69–1.88)	0.757
Nausea	318 (21.1)	0.75 (0.43–1.29)	1.23 (0.68–2.20)	0.225
Vomiting	43 (2.9)	1.68 (0.57–4.96)	3.27 (1.15–9.27)	0.386
Diaphoresis or clamminess	287 (19.1)	1.90 (1.21–2.99)	1.86 (1.02–3.38)	0.953
Palpitations	174 (11.6)	0.61 (0.28–1.35)	0.72 (0.33–1.58)	0.777
Dizziness	226 (15.0)	0.39 (0.18–0.86)	0.38 (0.15–0.98)	0.966
Sum typical¶¶ add. symptoms	1005 (66.7)	0.97 (0.63–1.51)	1.01 (0.60–1.70)	0.898

Continued

Table 4 Continued

	N of total (%)	<70 years(n=1039)	≥70 years (n=467)	P value for interaction
Dependent of stature	124 (8.2)	0.41 (0.15–1.15)	0.50 (0.15–1.66)	0.824
Dependent of respiration	149 (9.9)	0.23 (0.07–0.73)	0.15 (0.02–1.11)	0.72
Pain on palpation	177 (11.8)	0.44 (0.19–1.03)	0.29 (0.09–0.97)	0.586
Sum atypical*** add. symptoms	351 (23.3)	0.28 (0.14–0.57)	0.28 (0.12–0.67)	0.995
Effect of NG	268 (17.8)	1.23 (0.56–2.71)	2.18 (0.87–5.50)	0.356
Onset of symptoms				
During physical activity	285 (18.9)	3.32 (2.14–5.16)	2.42 (1.39–4.22)	0.382
After physical activity	72 (4.8)	1.47 (0.64–3.34)	1.06 (0.30–3.76)	0.675
Acute or chronic psychologic stress	115 (7.6)	0.19 (0.05–0.77)	0.60 (0.14–2.63)	0.26
During rest	1027 (68.2)	0.45 (0.30–0.69)	0.52 (0.31–0.87)	0.697
Unknown	18 (1.2)	2.40 (0.50–11.47)	3.17 (0.74–13.57)	0.798
Symptom duration				
<30 min	377 (25.0)	0.86 (0.53–1.39)	1.32 (0.74–2.34)	0.333
30–60 min	84 (5.6)	1.60 (0.73–3.48)	1.18 (0.43–3.22)	0.574
60 min to 24 hours	482 (32.0)	1.36 (0.88–2.09)	1.63 (0.99–2.70)	0.748
>24 hours	155 (10.3)	0.08 (0.01–0.58)	0.20 (0.05–0.85)	0.489
Terminated by NG	88 (5.8)	1.92 (0.94–3.91)	1.24 (0.45–3.40)	0.428
Terminated by morphine	37 (2.5)	1.60 (0.46–5.53)	0.33 (0.04–2.60)	0.196
Unknown	283 (18.8)	0.86 (0.49–1.50)	0.63 (0.32–1.24)	0.494
Intensity of pain in intervals†††	1506 (100)	1.51 (1.05–2.18)	1.70 (1.14–2.55)	0.662
Last 24 hours				
Exertional chest pain >once	48 (3.2)	2.33 (0.86–6.31)	1.15 (0.38–3.50)	0.356
Last week				
Exertional chest pain	268 (17.8)	4.08 (2.63–6.34)	1.81 (1.03–3.15)	0.025
Shortness of breath	60 (4.0)	1.16 (0.40–3.34)	1.46 (0.53–4.06)	0.758
Pain similar to previous infarction	57 (3.8)	0.55 (0.13–2.32)	0.85 (0.25–2.97)	0.652

Statistically significant differences highlighted

*In patients having chest pain at presentation.

†Summation of traditionally considered typical pain location like retrosternal, precordial, other parts of thorax, shoulder, arms, jaw or neck.

‡Summation of pain in the back and all other non-typical locations.

§Summation of traditionally considered atypical pain location like epigastrium, abdomen, back or other locations.

¶Summation of traditionally considered typical pain character like tight, crushing, dull or heavy.

**Summation of traditionally considered atypical pain character like burning, stinging or other.

††Typical pain is defined as the combination of traditionally considered typical location and typical character.

‡‡Atypical pain is defined as either atypical location or atypical character, or both.

§§If not stated considered negative.

¶¶Summation of traditionally considered typical additional symptoms like shortness of breath, nausea, vomiting, diaphoresis, clamminess, palpitations or dizziness.

***Summation of traditionally considered atypical additional symptoms like pain dependent of position, respiration or palpation.

†††Four groups; no pain; Visual analogue scale (VAS) 1–3.5; VAS 3.5–6.5; VAS>6.5.

AMI, acute myocardial infarction; NG, Nitroglycerin; NSTEMI, non-ST segment elevation myocardial infarction.

Since first described as a typical symptom by Heberden,²³ radiation to the left arm has been found to be less predictive of AMI than radiation to right arm or both arms.^{24–27} Two recent studies found a relatively low OR just below 1.5 for AMI if left-sided radiation was present.^{12 13} Our neutral OR of 1.05 (95% CI 0.71 to 1.56) might be due to the exclusion of STEMI patients, but also seem part of a

trend where radiation to the left arm is less predicative of AMI than assumed some decades ago.

International guidelines including the new ESC guidelines state that women more often than men present with atypical symptoms.²⁸ Indeed, earlier studies found that women with coronary disease more often present without chest pain or report other symptoms as their main

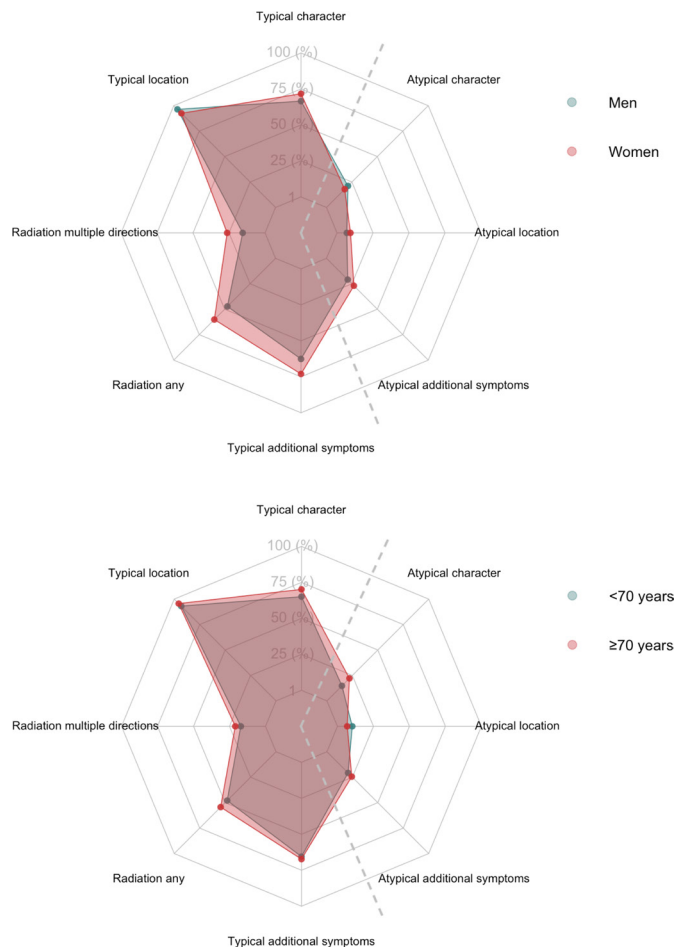


Figure 1 Incidence of traditionally considered typical and atypical chest pain symptoms in women/men and younger/older patients presenting with suspected ACS. ACS, acute coronary syndrome.

complaint.^{7 10 29 30} Studies also found that women more often than men have additional symptoms like jaw pain, back pain and nausea.^{8 9 31–33} Our study does not support that large sex differences are evident during presentation for NSTEMI, and the frequencies of what has traditionally been regarded typical symptoms in patients presenting with suspected ACS were similar across groups. Moreover, the odds of actually having an NSTEMI if the pain had both typical character and location was not lower in women. We do not find that women have higher odds of NSTEMI compared with men if they report radiating pain or additional symptoms like shortness of breath and nausea. Women with NSTEMI also reported anginal pain prior to their infarction and pain onset was just as often during activity.

In our study, we demonstrate that a few symptoms may be more or less pronounced depending on age groups. One limitation in the earlier studies were the lack of adjustment for age³¹ which makes it difficult to assess if any observed difference is a result of age or sex. The women in our study are on average 4.7 years older than men, and some symptoms suggestive of NSTEMI in women also apply for the oldest patient group. However,

for most symptoms like location, character, pain prior to admission and trigger factors the interaction between traditionally considered atypical symptoms and age is stronger than the interaction between atypical symptoms and sex. These findings suggest that older patients have higher risk of actually having an NSTEMI if traditionally considered atypical symptoms are present compared with women as a group.

None of the LRs calculated for single symptoms in our contemporary cohort are extremely high or extremely low. This probably reflects the clinical presentation of ACS showing a heterogeneous mix of symptoms being present with different intensity and frequency in individual patients. Some characteristics like chest pain radiating to both arms (LR 7.76) and any additional symptom considered atypical (LR 0.34) seem valuable for initial risk stratification. In line with previous studies our investigation shows that evaluation of symptoms should only be one of several elements to which the decision on further cardiac examinations is based on.

Strengths and limitations

The strength of this study is the inclusion of a large cohort of patients with chest pain being evaluated for AMI rather than having a confirmed diagnosis of AMI. The inclusion criteria were wide ensuring a representative patient population regarding age and co-morbidity. Diagnoses were based on a standard and robust adjudication process, and 89% of patients were observed in hospital for at least 8 hours with three or more high-sensitivity troponin measurements.

The study, however, has some limitations. Information was gathered retrospectively through digital charts. Even though information came from two or more sources (general practitioner and/or ambulance log in addition to hospital physicians at admission), the presence or absence of some additional symptoms were not reported in all patients. Symptoms not mentioned by any source were considered not present, which may have introduced a bias in particular for the five additional symptoms that were unequally reported between patients with and without NSTEMI (online supplemental table 1).

Another limitation is the lack of completely consecutive inclusion. This is a problem notified in similar studies due to the logistic challenges related to an around the clock all week inclusion in the ED. This inclusion procedure ensures that diurnal rhythm or differences between weekends and working days are unlikely to influence the results, but the lack of completely consecutive inclusion could lead to a selection bias as patients with minor disease might be easier to include during busy hours in the ED. If the data are skewed towards more patients with less severe disease (and less pronounced clinical symptoms) being included, this is more likely to underestimate our findings compared with overestimate them for example, the OR for radiation to both arms as a sign of ACS could in reality be higher than 9.4, and minor differences between gender and age groups could also be unnoticed.

The slightly lower rate of AMI seen in our compared with similar studies^{12 13} indicating that such selection bias may have influenced our data, but could also be due to not including STEMI patients. Patient characteristics is otherwise similar in our and other studies focusing on a rapid diagnosis of NSTEMI.

Since patients with STEMI were not included in the study, our findings may not be representative for this group. Few studies have compared symptoms of STEMI versus NSTEMI, but some typical signs like central location, nausea and diaphoresis may be less frequent in patients with NSTEMI compared with STEMI.²⁷ Since 97.4% of patients presented with chest pain or discomfort, our data should not be regarded valid for non-chest pain AMI. Possible sex or age differences in these subgroups should be evaluated in other studies.

We did not correct for multiple testing. If a p value of 0.01 had been regarded significant instead of 0.05, none of the observed interactions between sex and symptoms or age and symptoms had been statistically significant. This should be interpreted as strengthening the assumption that differences in symptom prediction based on group stratification is uncertain.

Finally, many cardiac centres have lately implemented sex-specific troponin T upper reference limits (URLs) for the evaluation of AMI. Our study uses a sex-neutral cut-off since this was recommended when the study was planned in 2012. Only one of the 597 female patients in our study would be reclassified from UAP to NSTEMI if URL was lowered from 14 ng/L to 9 ng/L. No male patients would be reclassified from NSTEMI to unstable angina if URL was raised from 14 ng/L to 16 ng/L. Changing the URL did not affect the observed results.

Conclusion

Chest pain with radiation to both arms has the highest predictive value for identification of NSTEMI regardless of sex and age. Presenting symptoms for NSTEMI are overall similar to those earlier reported for STEMI and vary little between sex and age groups in a contemporary cohort of patients with suspected NSTEMI-ACS assessed using a hs-Tn.

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Contributors O-TS conceived the research question, collected and analysed the data and drafted the manuscript. O-TS, KMA, KV and TO developed the study

design and contributed in data acquisition and analysis. HLT participated in data collection and provided critical revision. ROB, ØS, VVSB and ØRM took part in the early planning of the study design and provided critical revision. JL is the article guarantor, accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish. All acknowledged coauthors revised the article critically for its intellectual content and approved the final manuscript for submission.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

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