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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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ABSTRACT

Objectives: Prompt diagnosis of acute coronary syndrome (ACS) remains a challenge, with presenting symptoms affecting the diagnosis algorithm and, consequently, management and outcomes. This study aimed to identify sex differences in presenting symptoms of ACS.

Design: Prospective cohort study (EPIHeart).

Setting: patients with confirmed diagnosis of type 1 (primary spontaneous) ACS who were consecutively admitted to the Cardiology Department of two tertiary hospitals in Portugal between August 2013 and December 2014 were included.

Participants: Presenting symptoms of 873 patients (227 women) were obtained through a face-to-face interview.

Outcome measures: Typical pain was defined according to the definition of cardiology societies. Clusters of symptoms other than pain were identified by latent class analysis. Logistic regression was used to quantify differences in presentation of ACS symptoms by sex.

Results: Chest pain was reported by 82% of patients, with no differences in frequency or location between sexes. Women were more likely to feel pain with an intensity higher than 8/10 (adjusted odds ratio [OR] 2.77, 95% confidence interval [95% CI] 1.88–4.08). Referred pain was 91% more likely in women (1.91, 1.33–2.74). The multiple symptoms cluster, which was characterized by a high probability of presenting with all symptoms, was almost 4-fold more prevalent in women (3.92, 2.21–6.98).

Conclusions: While there are no differences in the frequency or location of pain between sexes, women are more likely to feel pain of higher intensity and to present with referred pain and symptoms other than pain. Knowledge of these ACS presentation profiles is important for health policy decisions and clinical practice.

Keywords: Sex; acute coronary syndrome; women; diagnosis.

Strengths and limitations

Within a prospective cohort study, presenting symptoms of acute coronary syndrome were obtained through a structured questionnaire applied within the first 48 hours after admission.

Consecutive sampling, the detailed clinical information obtained through the questionnaire and adjustment for several confounding variables strengthens our results.

The results of this study are valid for stable patients and those that were able to answer the questionnaire in the acute phase of the acute coronary syndrome.

Some of the sex differences in presenting symptoms may be influenced by selection bias because of a higher risk of non-inclusion of women due to death in the early hours of admission.

INTRODUCTION

Acute coronary syndrome (ACS) is still one of the main causes of death worldwide and in Europe.[1,2] Coronary heart disease mortality has decreased in the last decades in developed countries because of primary prevention and improvement in treatment of patients with ACS.[2] Attainment of the maximal benefit of treatment of these patients is threatened by delayed diagnosis, partly dependent on clinical suspicion of ACS. The subjective experience of symptoms influences patients' attitudes in seeking help and professionals' interpretation of clinical presentations.[3] Early recognition of ACS may be challenging because while patients with presumed ACS have contact with healthcare providers,[4] many patients do not have an electrocardiogram before hospitalization.[5] Therefore, physicians frequently have to make decisions that are only clinically based.

Women and men generally have the same type of symptoms during an ACS episode, although the proportion presenting with different combinations of symptoms varies.[6] This conflicting evidence can be partly explained by the diverse methodology used, with few prospective studies, usually without a specific questionnaire. In prospective studies, small convenience samples were used and confounding was not always adequately addressed.[7,8] Therefore, sex-specific research on ACS presentation is a challenge and priority.[9]

This study aimed to analyse sex differences in presenting symptoms of ACS within a prospective cohort study, taking into account the contribution of multiple factors to presenting symptoms.

METHODS

Study Design and Sample Selection

The EPIHeart cohort study was designed to identify inequalities in management and outcomes of patients with ACS. This study included all consecutive patients who were admitted between August 2013 and December 2014 to the Cardiology Department of two tertiary hospitals in two regions in northern Portugal (Hospital de São João, Porto, covering the metropolitan area of Porto in the coast; and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). Eligible patients were 18 years old or older who lived in the catchment area of these hospitals (districts: Porto, Vila Real, Bragança, and Viseu), with confirmed diagnosis of type 1 (primary spontaneous) ACS. The patients were also expected to be hospitalized for at least 48 hours and not institutionalized before the event. Of 1297 patients initially

considered, in 164 the diagnosis of ACS was not confirmed, 60 were excluded due to discharge or transfer before the interview, 18 died before being invited, and 44 were unable to answer the questionnaire because of clinical instability, no understanding of Portuguese, hearing problems, or cognitive impairment. Seventy-two patients refused to participate. For this analysis, we excluded 61 patients who were not admitted because of a symptom (patients referred by a doctor, after a scheduled appointment or diagnostic exam), four with vasospastic angina, and one illicit drug user. A total of 873 patients were included. The study protocol was in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of both hospitals. All patients gave written informed consent.

Procedures and data collection

Presenting symptoms were obtained face-to-face using a structured questionnaire applied by trained interviewers, within the first 48 hours after admission, whenever possible. Over the following days, a second interview was conducted to collect data on sociodemographic characteristics and risk factors. Medical records were reviewed to extract data regarding previous medical history, admission information, and clinical data during hospitalization.

Pain, referred pain, and symptoms other than pain were measured dichotomously (yes/no). For the location of pain (direct and referred) patients were asked to point out where pain was occurring. To measure the intensity of pain, a 10-point scale (0, no pain; 10, pain of maximal intensity) was used. Symptoms other than pain included dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, and an open-ended question of "other" (12 items). Answers to the last item enabled identification of two other relatively frequent symptoms, other digestive symptoms and discomfort. Activity at the onset of the episode was measured dichotomously, including sleeping, rest, and any exertion. A stress trigger was assigned if the patient answered "yes" for at least one of following events within 24 hours preceding the episode: accident, recent diagnosis of disease, financial problems, and news of death/disease of a relative/friend.

Marital status was considered partnered for married patients or living in civil union. Education was recorded as completed years of schooling and classified into four categories: less than 4 (little formal education), 4 (elementary school), less than 12 (high school), and 12 or more years (secondary education or more). Occupations were classified into major professional groups, according to the Portuguese

Classification of Occupations 2010,[10] integrated in the International Standard Classification of Occupations (ISCO/2008).

Definition of Variables

Although symptoms of ACS have been widely described, their value for diagnosis of ACS is not unanimously recognized.[11-13] After discussion with clinical cardiologists of our team, we opted to use Cardiology Societies' position papers to define direct and referred pain locations and to select symptoms to evaluate.[14,15] Direct pain location was classified as follows: 1) typical for retrosternal, precordial, right thoracic, or bilateral thoracic pain (chest pain); 2) atypical for epigastric pain or located in the back, left arm or shoulder, right arm or shoulder, neck, or jaw; and 3) a mixture when both typical and atypical locations were present. Referred pain location was considered as follows: 1) typical if pain referred to the left arm or shoulder, right arm or shoulder, neck, or jaw; 2) atypical if pain referred to retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; and 3) a mixture for referred pain in typical and atypical locations.

Patients rarely present with a single symptom during an episode of ACS, and present with multiple symptoms instead that do not occur in isolation and may cluster.[16] There has been increasing interest in symptom cluster analysis in cardiovascular disease because it aids in assessment by enhancing recognition of patients with similar symptom profiles.[17] Groups of symptoms other than pain were obtained by latent class analysis.

The small group of non-classified (NC) patients with ACS (patients with left bundle branch block) was grouped with patients with ST elevation myocardial infarction (STEMI) (STEMI/NC ACS group). Non-ST elevation ACS (NSTEACS) included unstable angina and non-ST elevation acute myocardial infarction or subacute myocardial infarction.

Considering the possible association between coronary anatomy and clinical presentation, we grouped patients according to coronary angiography into five groups: managed conservatively; normal or near-normal coronary angiography; lesions exclusively in the anterior descending artery; lesions in the right and/or circumflex artery; and lesions in the left main coronary artery, three-vessel disease or disease both in the anterior descending artery and the right or circumflex artery.

Data Analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). Categorical variables are shown as number and percentage. To compare differences between women and men, the chi-square or Fisher's test was used for categorical variables and the t-test for continuous variables. Latent class analysis was used to identify distinct groups of individuals from a sample (clusters) who were homogeneous within the group. This was based on the fact that performance of an individual in a set of items is explained by a categorical latent variable with K classes (clusters), commonly called latent classes. The number of latent clusters was defined according to the Akaike information criterion (AIC). Starting from one single cluster and increasing one cluster at each step, the best solution was identified when an increase in the number of clusters did not lead to a decrease in the AIC.

Logistic regression was used to identify variables associated with clinical presentation. Variables with $p<0.15$ for a crude association with the endpoint were entered in the initial model and a backward strategy was used to exclude the least significant variables, based on Wald tests. We were then able to obtain the most parsimonious model with all the important determinants. Sex, age, and type of ACS were forced to remain in the model. All analyses were performed using STATA version 11.1 for Windows (Stata Corp LP, College Station, TX) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Women (n=227, 26.0%) were older (69.1 vs 64.0 years, $p<0.001$) and more frequently lived in the interior region (52.4% vs 38.7%, $p<0.001$) than men. Women were more often treated conservatively and had normal or near normal coronary arteries more frequently than men. In this sample, no difference by sex was observed in the type of ACS, where 56.6% of the patients had a discharge diagnosis of NSTEACS (Table 1).

Women more frequently had hypertension (81.5% vs 62.7%, $p<0.001$) and diabetes (38.8% vs 29.9%, $p=0.014$), and were more frequently obese (25.5% vs 18.5%, $p=0.020$) and never smokers compared with men ($p<0.001$, Table 1). Men were submitted to percutaneous coronary intervention more often than women. There were no significant differences in a previous history of renal failure, prior myocardial infarction, prior coronary artery bypass surgery, prior heart failure, and dementia by sex (Table 1).

Women were more likely to be unpartnered, disabled, less educated, and had a lower income compared with men. The median time that elapsed between admission and application of the symptom questionnaire was slightly longer in women than in men (Table 1).

Table 1. Baseline demographic, socioeconomic and clinical characteristics in the whole sample and by sex*

	Total (n = 873)	Women (n = 227)	Men (n = 646)	p
Age (years), mean (SD)	64.0 (13.0)	69.1 (12.7)	62.2 (12.7)	<0.001
Socioeconomic				
Marital status				
Partnered	667 (76.8)	133 (58.9)	534 (83.2)	<0.001
Education				
Little formal education	172 (19.9)	95 (42.4)	77 (12.0)	
Elementary school	337 (39.1)	73 (32.6)	264 (41.3)	
High school	213 (24.7)	32 (14.3)	181 (28.3)	
Secondary education or more	141 (16.3)	24 (10.7)	117 (18.3)	<0.001
Employment status				
Employed/looking after home	282 (32.6)	64 (28.3)	218 (34.1)	
Unemployed	107 (12.4)	16 (7.1)	91 (14.2)	
Retired	334 (38.6)	93 (41.2)	241 (37.7)	
Disabled	143 (16.5)	53 (23.5)	90 (14.1)	<0.001
Subjective social class				
Low	281 (32.2)	81 (35.7)	200 (31.0)	
Lower-middle	281 (32.2)	58 (25.6)	223 (34.5)	
Higher-middle/High	60 (6.9)	16 (7.1)	44 (6.8)	
No response	251 (28.8)	72 (31.7)	179 (27.7)	0.097
Household income (euros)				
<500	204 (23.4)	77 (33.9)	127 (19.7)	
501-1000	276 (31.6)	60 (26.4)	216 (33.4)	
1001 – 2000	146 (16.7)	22 (9.7)	124 (19.2)	
>2000	88 (10.1)	14 (6.2)	74 (11.5)	
No response	159 (18.2)	54 (23.8)	105 (16.3)	<0.001
Region				
Metropolitan area of Porto	504 (57.7)	108 (47.6)	396 (61.3)	
North-eastern region of Portugal	369 (42.3)	119 (52.4)	250 (38.7)	<0.001
Cardiovascular risk factors				
Smoking habit				
Never	369 (42.3)	184 (81.0)	185 (28.6)	
Current	283 (32.4)	34 (15.0)	249 (38.5)	
Former	221 (25.3)	9 (4.0)	212 (32.8)	<0.001
Hypertension	590 (67.6)	185 (81.5)	405 (62.7)	<0.001
Diabetes mellitus	281 (32.2)	88 (38.8)	193 (29.9)	0.014
Dyslipidaemia	535 (61.4)	144 (63.4)	391 (60.6)	0.454
BMI (kg/m^2)				
Median (IQR)	26.5 (18.0-44.6)	26.7 (19.5-37.9)	26.4 (18.2-39.2)	0.531
Underweight	11 (1.4)	2 (0.9)	9 (1.5)	
Normal weight	272 (33.4)	80 (37.0)	192 (32.1)	
Overweight	366 (44.9)	79 (36.6)	287 (47.9)	
Obese	166 (20.4)	55 (25.5)	111 (18.5)	0.020
Family history of CVD	303 (34.7)	73 (32.2)	230 (35.6)	0.105
Previous medical history				
Renal failure	64 (7.3)	14 (6.1)	50 (7.7)	0.434
Myocardial infarction	156 (17.9)	34 (15.0)	122 (18.9)	0.186
PCI	100 (12.4)	18 (8.4)	82 (13.8)	0.041
CABG	34 (4.2)	5 (2.3)	29 (4.9)	0.111
Heart failure	63 (7.5)	21 (9.6)	42 (6.8)	0.172
Dementia	7 (0.8)	4 (1.8)	3 (0.5)	0.060
ACS type				
STEMI/NC ACS	379 (43.4)	101 (44.5)	278 (43.0)	
NSTEACS	494 (56.6)	126 (55.5)	368 (57.0)	0.703
Coronary anatomy				
Normal or near normal	57 (6.9)	22 (10.6)	35 (5.61)	
Left anterior descending artery only	162 (19.5)	38 (18.3)	124 (19.9)	
Right and/or circumflex artery only	196 (23.6)	46 (22.1)	150 (24.0)	
Mixture	417 (50.1)	102 (49.0)	315 (50.5)	
Not submitted to coronary angiography	41 (4.7)	19 (8.4)	22 (3.4)	0.004
Symptom questionnaire application				
Time from admission (hours), median (IQR)	42.1 (25.0-68.0)	45.4 (28.5-72.3)	40.0 (24-67.4)	0.052

*Values are number and percentage unless otherwise indicated.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; CVD, cardiovascular diseases; IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/non-classifiable acute coronary syndrome.

Symptom characteristics by sex and age

Because differences in symptoms by sex and age were similar in direction and magnitude in STEMI/NC ACS and NSTEACS (Supplementary Tables 1 and 2), both types of ACS were analysed together.

Although pain was present in most patients, men presented with pain more frequently than did women (97.4% vs 94.3%, p=0.028), with no significant difference by age group in both sexes (Table 2). No difference was found in the location of pain by sex. Approximately 80% of patients felt chest pain (typical pain). Older women presented less frequently with chest pain and had chest pain and pain in other locations (mixture group) more often than did younger women (p=0.014). Referred pain was observed more frequently in women and in younger patients (only significant for men, p=0.024). Atypical and mixture referred pain were more frequent in women than in men (p<0.001), mainly in women aged ≥65 years (p=0.009). Women felt pain with higher intensity than did men (median [IQR]: 9 [8–10] vs 8 [6–9], p<0.001), without a difference by age (Table 2). Women presented with symptoms other than pain more frequently than did men (82.8% vs 68.9%, p<0.001), with no difference by age group in both sexes (Table 2).

Considering symptoms other than pain, the AIC optimum value supported a preference for a three-cluster solution (AIC 7207.508, 6869.390, 6862.476, and 6870.372 for one, two, three, and four clusters, respectively). Cluster 1 had low endorsement probabilities for all items (no symptoms cluster). Cluster 2 had a high probability for dyspnoea at rest and sweating, and a low probability for the remaining items (dyspnoea and sweating cluster). Cluster 3 had high probabilities for all items (multiple symptoms cluster). This three-cluster model made sense conceptually to cardiologists of our team. Clusters counts and probabilities of occurrence of symptoms in established clusters are shown in Supplementary Table 3. Differences in proportions of women and men in the three clusters were observed (p<0.001, Table 2). Cluster 1 was the most prevalent, in which men presented with the no symptoms cluster more frequently (76.9% vs 62.6%) and the multiple symptoms cluster less frequently (4.8% vs 15.9%) than did women. The proportion of dyspnoea and sweating cluster was similar in men and women (Table 2).

Approximately 45% of patients were at rest and 35% were under physical effort at the beginning of the episode. Older women were more frequently at rest at the beginning of the episode and younger women were more frequently under effort (p=0.011). Less than 10% of patients identified a stressful event in the previous 24 hours, with no difference by sex, but among men, a younger age was slightly associated with this trigger (p=0.045, Table 2)

Table 2. Clinical presentation of patients with acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	14 (6.2)	54 (23.8)	109 (48.0)	50 (22.0)	227 (100.0)		61 (9.4)	303 (46.9)	220 (34.1)	62 (9.6)	646 (100)		
Pain	14 (100.0)	52 (96.3)	104 (95.4)	44 (88.0)	214 (94.3)	0.229	60 (98.4)	297 (98.0)	214 (97.3)	58 (93.5)	629 (97.4)	0.228	0.028
Pain location†													
Typical	12 (85.7)	43 (82.7)	88 (85.4)	32 (72.7)	175 (82.2)		53 (89.8)	246 (83.7)	175 (82.2)	44 (75.9)	518 (83.0)		
Atypical	1 (7.1)	9 (17.3)	5 (4.9)	6 (13.6)	175 (9.9)		3 (5.1)	33 (11.2)	30 (14.1)	10 (17.2)	76 (12.2)		
Mixture	1 (7.1)	0 (0.0)	10 (9.7)	6 (13.6)	17 (8.0)	0.014	3 (5.1)	15 (5.1)	8 (3.8)	4 (6.9)	30 (4.8)	0.327	0.165
Referred pain	9 (64.3)	41 (78.8)	72 (69.2)	25 (56.8)	147 (68.7)	0.129	38 (63.3)	179 (60.3)	126 (58.9)	23 (39.7)	366 (58.2)	0.024	0.007
Radiation type‡													
Typical	8 (88.9)	20 (48.8)	28 (38.9)	7 (28.0)	63 (42.9)		28 (73.7)	114 (64.4)	67 (53.2)	10 (43.5)	219 (60.2)		
Atypical	0 (0.0)	13 (31.7)	18 (25.0)	13 (52.0)	44 (29.9)		7 (18.4)	37 (20.9)	39 (31.0)	8 (34.8)	91 (25.0)		
Mixture	1 (11.1)	8 (19.5)	26 (36.1)	5 (20.0)	40 (27.2)	0.009	3 (7.9)	26 (14.7)	20 (15.9)	5 (21.7)	54 (14.8)	0.104	<0.001
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-9)	8 (8-9)	9 (8-10)	0.170	8 (7-10)	8 (6-9)	8 (6-9)	8 (7-9)	8 (6-9)	0.095	<0.001
Symptom	11 (78.6)	45 (83.3)	91 (83.5)	41 (82.0)	188 (82.8)	0.947	43 (70.5)	209 (69.0)	151 (68.6)	42 (67.7)	445 (68.9)	0.989	<0.001
Symptom clusters‖													
Cluster 1	7 (50.0)	41 (75.9)	62 (56.9)	32 (64.0)	142 (62.6)		43 (70.5)	232 (76.6)	170 (77.3)	52 (83.9)	497 (76.9)		
Cluster 2	5 (35.7)	8 (14.8)	28 (25.7)	8 (16.0)	49 (21.6)		15 (25.6)	59 (19.5)	35 (15.9)	9 (14.5)	118 (18.3)		
Cluster 3	2 (14.3)	5 (9.3)	19 (17.4)	10 (20.0)	36 (15.9)	0.183	3 (4.9)	12 (4.0)	15 (6.8)	1 (1.61)	31 (4.80)	0.345	<0.001
Activity													
Sleep	2 (15.4)	16 (32.0)	11 (10.4)	7 (14.9)	36 (16.7)		6 (9.8)	65 (21.7)	35 (16.1)	13 (21.3)	119 (18.6)		
Rest	5 (38.5)	18 (36.0)	50 (47.2)	29 (61.7)	102 (47.2)		34 (55.7)	124 (41.3)	105 (48.2)	33 (54.1)	296 (46.3)		
Exertion	6 (46.2)	16 (32.0)	45 (42.5)	11 (23.4)	78 (36.1)	0.011	21 (34.4)	111 (37.0)	78 (35.8)	15 (24.6)	225 (35.2)	0.087	0.816
Stress trigger	2 (14.3)	6 (11.1)	11 (10.2)	3 (6.1)	22 (9.8)	0.700	11 (18.0)	23 (7.7)	15 (6.9)	6 (9.8)	55 (8.6)	0.045	0.605

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ||Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items. ¶p for age differences within each sex; #p for differences between sexes.

Multivariate models

There were no differences in the adjusted pain frequency and location between men and women. Referred pain was more likely to be experienced by women (adjusted odds ratio [OR] 1.91, 95% confidence interval [95% CI] 1.33-2.74). Moreover, women had more than double the chance of having pain radiating to typical and atypical locations (2.25, 1.32-3.84) and of feeling pain with an intensity higher than 8 (2.77, 1.88-4.08) (Table 3).

The presence of at least one symptom other than pain occurred almost two times more often in women than in men. With cluster 1 as the reference, cluster 2 and 3 were positively associated with female sex, with the latter being statistically significant. The multiple symptoms cluster was almost 4-fold more likely in women than in men (3.92, 2.21-6.98) (Table 3).

No difference in the type of patients' activities at the beginning of the episode by sex was observed (Table 3).

Table 3. Differences between women and men in clinical presentation of acute coronary syndrome (men are the reference class).

Symptoms	OR	95% CI	Adjusted for
Pain	0.61	0.26-1.42	Age , type of ACS, marital status, dyslipidaemia, CABG
Pain location*			
Typical	1	(Reference)	
Atypical	0.63	0.35-1.13	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Mixture	0.94	0.44-1.98	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	1.91	1.33-2.74	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type†			
Typical	1	(Reference)	
Atypical	1.32	0.81-2.14	Age, type of ACS, employment status, region
Mixture	2.25	1.32-3.84	Age, type of ACS, employment status, region
Pain intensity (higher than 8/10)	2.77	1.88-4.08	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.95	1.30-2.93	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters‡			
Cluster 1	1	(Reference)	
Cluster 2	1.43	0.94-2.17	Age, type of ACS, professional group, region, previous AMI
Cluster 3	3.92	2.21-6.98	Age, type of ACS, professional group, region, previous AMI
Activity group			
Sleeping	1	(Reference)	
Rest	1.09	0.69-1.72	Age, type of ACS, previous heart failure
Exertion	1.25	0.78-2.02	Age, type of ACS, previous heart failure

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; OR, odds ratio.

*Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.

†Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.

‡Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items.

DISCUSSION

In our study, no differences in the frequency and location of pain by sex were observed. Referred pain, pain radiating to typical and atypical locations, and pain of higher intensity were more likely to occur among women. Women were also more likely than men to present with symptoms other than pain. Three clusters of symptoms other than pain were identified. Women were more likely to present with the multiple symptoms cluster.

Differences between women and men in perception of symptoms of ACS might be explained by anatomical, physiological, biological, and psychosocial differences that influence each other.[8,18] We measured several variables of these different domains. Differences in symptom presentation by sex might be the result of differences in response to history-taking,[9] differences in neural receptors and pathways involved in pain, and subtle differences in the location and type of atherosclerotic lesions.[19,20] Our findings of similar ACS symptoms between women and men are consistent with previous studies,[6,21] as well as our finding that women are more likely to have atypical presentations.[8] We observed that women have a higher likelihood of atypical referred pain and of several concomitant symptoms other than pain, common to other cardiac and non-cardiac diagnoses.

In our study, chest pain was the most frequent symptom in both sexes, consistent with previous studies.[22,23] Among those with pain, typical chest pain was observed in 82% of patients, regardless of sex. The remaining patients had pain in less typical locations and were thus prone to misdiagnosis and undertreatment and, consequently, to worse outcomes.[24] Considering differences in characteristics of pain by sex, studies suggested that women, in particular older women, were less likely to have the chief complaint of chest pain associated with acute myocardial infarction.[25] Studies reported that chest pain did not differ between women and men,[8] others that women have pain in the neck and back more often than men,[26,27] without distinguishing between direct and referred pain. In our study, referred pain was observed in 61% of patients, it was more frequent in women, and typical referred pain was only observed in 33%. Notably, a study on diagnostic acuity of ACS symptoms showed that shoulder and arm pain was predictive of the diagnosis of ACS for women only.[21]

According to previous studies, with regard to other symptoms, a higher proportion of women have less typical symptoms than men.[7,27] Women have also reported other symptoms, such as indigestion, palpitations, nausea, numbness in the hands, and unusual fatigue, more frequently than men.[8] In our cohort, three symptom clusters were identified. Women had the multiple symptoms cluster more

frequently than did men, characterized by high probabilities for all symptoms. According to Rosenfeld et al. women are more likely to cluster in a similar class, called the heavy symptom burden class.[28] With regard to ACS symptom clustering, there are contradictory findings on identified clusters, the proportion of patients per cluster, and differences between clusters regarding demographic factors. In our study, cluster 1 and 3 (low and high probabilities for all symptoms, respectively) are in line with observations of other settings.[16,29] A recent systematic review of symptom clusters in cardiovascular disease[30] identified clusters with the most symptoms and clusters with the lowest number of symptoms. Our dyspnoea and sweating cluster has two common symptoms with the Riegel et al.[23] stress symptoms cluster, which includes shortness of breath, sweating, nausea, indigestion, dread, and anxiety.

Methodological differences related to sampling and measuring might explain these different results. Strengths of our study include consecutive sampling, a questionnaire with detailed clinical information was systematically applied, and we adjusted for several confounding variables.

The value of symptoms for diagnosis of ACS varies across studies.[11,12,31] Overall, the diagnostic performance of chest pain characteristics for diagnosis is limited, with likelihood ratios close to 1.[32] Sensitivity for individual symptoms of ACS, using the 13-Item Acute Coronary Syndrome Checklist, ranges from 27% to 67% for women and 14% to 72% for men. Additionally, specificity ranges from 33% to 78% for women and 34% to 78% for men, with different associations between some symptoms and diagnosis of ACS by sex.[21] However, physicians still base the likelihood of ACS mainly on symptoms and use the electrocardiogram to rule in the diagnosis.[33] Evaluation of these patients is mostly unchanged, without implementation of evidence-based assessment tools in clinical practice to improve diagnostic accuracy. Public health messages should take into account the complexity of presenting symptoms of ACS, particularly the significant proportion of women and men with ACS without typical chest pain. Additionally, there is a higher likelihood of atypical referred pain and multiple concomitant symptoms in women. These factors should be accounted for to encourage timely and appropriate care of patients with ACS.

Limitations

Participants were interviewed as soon as possible after admission, but this does not obviate the retrospective nature of data collection. The results of this study are valid for stable patients and those that were able to answer the questionnaire in the acute phase of ACS. For patients who were eligible but not

enrolled only information on sex, age and type of ACS was available. Patients who died before the interview were older (81.5±11.8 vs 64.6±13.1 years, p<0.001), were more often women (66.7% vs 26.0%, p<0.001), and more frequently had a diagnosis of STEMI (81.3% vs 43.4%, p=0.003) than did participants. Patients who were discharged or transferred to another hospital before the interview had STEMI less often (25.0% vs 43.4%, p=0.005) and patients who were not enrolled because of clinical instability or inability to understand the questionnaire were older. Patients who refused to participate were older (72.7±11.0 vs 64.0±13.0 years, p<0.001), were less often partnered (65.7% vs 76.8%, p=0.036), and had little formal education (43.1% vs 19.7%, p<0.001) compared with participants. Except for deceased patients, no difference in sex proportion was observed between participants and non-participants. We cannot exclude that some of the sex differences were caused by selection bias because of a higher risk of non-inclusion of women due to death in the early hours of admission. Considering that atypical presentation is associated with a worse prognosis, the proportion of patients with ACS presenting without typical chest pain or that of women with an atypical presentation could be even higher.[24]

CONCLUSION

This study shows no differences in the frequency and location of pain by sex, but approximately 20% of patients do not present with chest pain, regardless of sex. Women are more likely to report referred pain and multiple symptoms simultaneously. Health education messages should take into account the complexity of presentation of ACS and emphasize the possible non-chest location of pain in both sexes and the higher probability of concomitant symptoms other than pain in women. Further sex-stratified analysis of ACS presentation is required to determine the diagnostic accuracy of symptoms by sex.

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Contributors

Carla Araújo, Marta Viana and Ana Azevedo had the original idea to develop the EPIHeart cohort study and were responsible for acquiring the study grant. Carla Araújo raised the hypotheses, analysed and interpreted the data, and drafted the first version of the manuscript. Olga Laszczyńska, Milton Severo and Ana Azevedo analysed and interpreted the data. Marta Viana and Andreia Borges participated in data collection. All authors were involved in writing the paper and approved the final version of the submitted manuscript.

Data sharing

Data are available by email the corresponding author at carla-r-araujo@hotmail.com.

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Supplementary Table 1. Clinical presentation of patients with ST elevation myocardial infarction/non-classifiable acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	6 (5.9)	22 (21.8)	53 (52.5)	20 (19.8)	101 (100.0)		37 (13.3)	144 (51.8)	77 (27.7)	20 (7.2)	278 (100)		
Pain	6 (100.0)	21 (95.5)	52 (98.1)	16 (80.0)	95 (94.1)	0.039	36 (97.3)	142 (98.6)	73 (94.8)	20 (100.0)	271 (97.5)	0.338	0.106
Pain location†													
Typical	5 (83.3)	17 (81.0)	44 (84.6)	9 (56.3)	75 (78.9)		31 (88.6)	120 (85.1)	55 (76.4)	13 (65.0)	219 (81.7)		
Atypical	1 (16.7)	4 (19.0)	2 (3.8)	5 (31.3)	12 (12.6)		1 (2.9)	17 (12.1)	14 (19.4)	5 (25.0)	37 (13.8)		
Mixture	0 (0.0)	0 (0.0)	6 (11.5)	2 (12.5)	8 (8.4)	0.021	3 (8.6)	4 (2.8)	3 (4.2)	2 (10.2)	12 (4.5)	0.032	0.347
Referred pain	4 (66.7)	18 (85.7)	38 (73.1)	8 (50.0)	68 (71.6)	0.114	24 (66.7)	90 (63.4)	51 (69.9)	7 (35.0)	172 (63.5)	0.038	0.152
Radiation type‡													
Typical	3 (75.0)	8 (44.4)	17 (44.7)	1 (12.5)	29 (42.6)		19 (79.2)	53 (59.6)	26 (51.0)	3 (42.9)	101 (59.1)		
Atypical	0 (0.0)	5 (27.8)	10 (26.3)	4 (50.0)	19 (27.9)		5 (20.8)	21 (23.6)	9 (17.6)	3 (42.9)	38 (22.2)		
Mixture	1 (25.0)	5 (27.8)	11 (28.9)	3 (37.5)	20 (29.4)	0.504	0 (0.0)	15 (16.9)	16 (31.4)	1 (14.3)	32 (18.7)	0.018	0.060
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-10)	8.5 (8-9)	9 (8-10)	0.784	9 (7.5-10)	8 (7-10)	8 (6.5-9)	7.5 (6.5-9)	8 (7-10)	0.064	<0.001
Symptom	5 (83.3)	20 (90.9)	47 (88.7)	17 (85.0)	89 (88.1)	0.794	23 (62.2)	105 (72.9)	61 (79.2)	14 (70.0)	203 (73.0)	0.283	0.002
Symptom clusters‖													
Cluster 1	2 (33.3)	18 (81.8)	27 (50.9)	11 (55.0)	58 (57.4)		26 (70.3)	102 (70.8)	54 (70.1)	16 (80.0)	198 (71.2)		
Cluster 2	3 (50.0)	2 (9.1)	16 (30.2)	4 (20.0)	25 (24.8)		9 (24.3)	36 (25.0)	19 (24.7)	3 (15.0)	67 (24.1)		
Cluster 3	1 (16.7)	2 (9.1)	10 (18.9)	5 (25.0)	18 (17.8)	0.132	2 (5.4)	6 (4.2)	4 (5.2)	1 (5.0)	13 (4.7)	0.967	<0.001
Activity													
Sleep	1 (16.7)	3 (14.3)	4 (7.8)	3 (15.8)	11 (11.3)		5 (13.5)	29 (20.1)	10 (13.0)	4 (20.0)	48 (17.3)		
Rest	3 (50.0)	9 (42.9)	22 (43.1)	14 (73.7)	48 (49.5)		19 (51.4)	65 (45.1)	43 (55.8)	13 (65.0)	140 (50.4)		
Exertion	2 (33.3)	9 (42.9)	25 (49.0)	2 (10.5)	38 (39.2)	0.069	13 (35.1)	50 (34.7)	24 (31.2)	3 (15.0)	90 (32.4)	0.393	0.274
Stress trigger	1 (16.7)	2 (9.1)	4 (7.5)	3 (15.8)	10 (10.0)	0.519	5 (13.5)	11 (7.7)	6 (7.9)	2 (10.0)	24 (8.7)	0.669	0.697

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items. ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 2. Clinical presentation of patients with non-ST elevation acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	8 (6.3)	32 (25.4)	56 (44.4)	30 (23.8)	126 (100)		24 (6.5)	159 (43.2)	143 (38.9)	42 (11.4)	368 (100)		
Pain	8 (100.0)	31 (96.9)	52 (92.9)	28 (93.3)	119 (94.4)	0.864	24 (100.0)	155 (97.5)	141 (98.6)	38 (90.5)	358 (97.3)	0.073	0.131
Pain location†													
Typical	7 (87.5)	26 (83.9)	44 (86.3)	23 (82.1)	100 (84.7)		22 (91.7)	126 (82.4)	120 (85.1)	31 (81.6)	299 (84.0)		
Atypical	0 (0.0)	5 (16.1)	3 (5.9)	1 (3.6)	9 (7.6)		2 (8.3)	16 (10.5)	16 (11.3)	5 (13.2)	39 (11.0)		
Mixture	1 (12.5)	0 (0.0)	4 (7.8)	4 (14.3)	9 (7.6)	0.172	0 (0.0)	11 (7.2)	5 (3.5)	2 (5.3)	18 (5.1)	0.778	0.367
Referred pain	5 (62.5)	23 (74.2)	34 (65.4)	17 (60.7)	79 (66.4)	0.728	14 (58.3)	89 (57.4)	75 (53.2)	16 (42.1)	194 (54.2)	0.350	0.020
Radiation type‡													
Typical	5 (100.0)	12 (52.2)	11 (32.4)	6 (35.3)	34 (43.0)		9 (64.3)	61 (69.3)	41 (54.7)	7 (43.8)	118 (61.1)		
Atypical	0 (0.0)	8 (34.8)	8 (23.5)	9 (52.9)	25 (31.6)		2 (14.3)	16 (18.2)	30 (40.0)	5 (31.3)	53 (27.5)		
Mixture	0 (0.0)	3 (13.0)	15 (44.1)	2 (11.8)	20 (25.3)	0.008	3 (21.4)	11 (12.5)	4 (5.3)	4 (25.0)	22 (11.4)	0.007	0.005
Pain intensity§	9.5 (8.5-10)	9.5 (8-10)	8 (8-10)	8 (7-9)	9 (8-10)	0.224	8 (6-9)	8 (6-9)	8 (6-9)	8 (7.5-9)	8 (6-9)	0.200	<0.001
Symptom	6 (75.0)	25 (78.1)	44 (78.6)	24 (80.0)	99 (78.6)	0.992	20 (83.3)	104 (65.4)	90 (62.9)	28 (66.7)	242 (65.8)	0.278	0.007
Symptom clusters‖													
Cluster 1	5 (62.5)	23 (71.9)	35 (62.5)	21 (70.0)	84 (66.7)		17 (70.8)	130 (81.8)	116 (81.1)	36 (85.7)	299 (81.3)		
Cluster 2	2 (25.0)	6 (18.8)	12 (21.4)	4 (13.3)	24 (19.1)		6 (25.0)	23 (14.5)	16 (11.2)	6 (14.3)	51 (13.9)		
Cluster 3	1 (12.5)	3 (9.4)	9 (16.1)	5 (16.7)	18 (14.3)	0.919	1 (4.2)	6 (3.8)	11 (7.7)	0 (0.0)	18 (4.9)	0.231	<0.001
Activity													
Sleep	1 (14.3)	13 (44.8)	7 (12.7)	4 (14.3)	25 (21.0)		1 (4.2)	36 (23.1)	25 (17.7)	9 (22.0)	71 (19.6)		
Rest	2 (28.6)	9 (31.0)	28 (50.9)	15 (53.6)	54 (45.4)		15 (62.5)	59 (37.8)	62 (44.0)	20 (48.8)	156 (43.1)		
Exertion	4 (57.1)	7 (24.1)	20 (36.4)	9 (32.1)	40 (33.6)	0.032	8 (33.3)	61 (39.1)	54 (38.3)	12 (29.3)	135 (37.3)	0.180	0.768
Stress trigger	1 (12.5)	4 (12.5)	7 (12.7)	0 (0.0)	12 (9.6)	0.140	6 (25.0)	12 (7.7)	9 (6.4)	4 (9.8)	31 (8.6)	0.044	0.731

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ||Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items. ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 3. Marginal percentage of subjects with each symptom in each assigned cluster*

	Symptom clusters		
	Cluster 1* n=639	**Cluster 2†** n=167	**Cluster 3‡** n=67
Dyspnoea at rest	17.4	34.2	37.3
Exertional dyspnoea	6.0	2.1	14.5
Sweating	22.2	89.6	71.7
Nausea and vomiting	6.5	9.7	41.4
Dizziness	2.6	18.0	74.1
Blurry vision	0.6	4.4	27.5
Presyncope	1.3	11.4	42.7
Syncope	1.6	3.6	10.5
Palpitations	0.3	5.4	19.5
Weakness	7.5	17.8	64.4
"Other symptoms"	4.5	5.5	12.8
Other digestive symptoms	1.0	1.0	1.4
Discomfort	1.3	1.1	4.2

*Values are percentages.

* Cluster 1: no symptom cluster; † Cluster 2: dyspnoea and sweating cluster; ‡Cluster 3: multiple symptoms cluster.

STROBE Statement—checklist of items : ***Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **page 1 (title) and page 2 (abstract)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **page 4**
Objectives	3	State specific objectives, including any prespecified hypotheses - **page 4**
Methods		
Study design	4	Present key elements of study design early in the paper – **pages 4 and 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **pages 4-6**
Participants	6	*Cohort study:* Give the eligibility criteria, and the sources and methods of selection of participants – **pages 4 and 5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **page 6**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **pages 5 and 6**
Bias	9	Describe any efforts to address potential sources of bias - **page 6**
Study size	10	Explain how the study size was arrived at – **page 4**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why –**page 7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - **page7**
		(*b*) Describe any methods used to examine subgroups and interactions – **page 6**
		(*c*) Explain how missing data were addressed –**Patients who were unable to answer the questionnaire (with missing data on clinical presentation) were not included.**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed – **Not applicable.**
		(*e*) Describe any sensitivity analyses –**We analysed clinical presentation separately by type of acute coronary syndrome (Supplementary tables 1 and 2), but as results were similar by sex and age both types of acute coronary syndrome were analysed together.**

Continued on next page

Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed –**pages 4 and 5**
		(b) Give reasons for non-participation at each stage –**pages 4 and 5**
		(c) Consider use of a flow diagram – **Not necessary in our opinion.**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **pages 7-9**
		(b) Indicate number of participants with missing data for each variable of interest –**page 9**
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time –**pages 10 and 11**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **pages 12 and 13**
		(*b*) Report category boundaries when continuous variables were categorized – **not applicable**
Other analyses	17	Report other analyses done— eg analyses of subgroups and interactions, and sensitivity analyses – **not applicable**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **page 14**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias –**pages 15 and 16**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - **pages 14 and 15**
Generalisability	21	Discuss the generalisability (external validity) of the study results –**page 15**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based –**page 17**

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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ABSTRACT

Objectives: Prompt diagnosis of acute coronary syndrome (ACS) remains a challenge, with presenting symptoms affecting the diagnosis algorithm and, consequently, management and outcomes. This study aimed to identify sex differences in presenting symptoms of ACS.

Design: Data were collected within a prospective cohort study (EPIHeart).

Setting: Patients with confirmed diagnosis of type 1 (primary spontaneous) ACS who were consecutively admitted to the Cardiology Department of two tertiary hospitals in Portugal between August 2013 and December 2014.

Participants: Presenting symptoms of 873 patients (227 women) were obtained through a face-to-face interview.

Outcome measures: Typical pain was defined according to the definition of cardiology societies. Clusters of symptoms other than pain were identified by latent class analysis. Logistic regression was used to quantify differences in presentation of ACS symptoms by sex.

Results: Chest pain was reported by 82% of patients, with no differences in frequency or location between sexes. Women were more likely to feel pain with an intensity higher than 8/10 and this association was stronger for patients under 65 years old (interaction p=0.028). Referred pain was also more likely in women, particularly pain referred to typical and atypical locations simultaneously. The multiple symptoms cluster, which was characterized by a high probability of presenting with all symptoms, was almost 4-fold more prevalent in women (3.92, 2.21–6.98). Presentation with this cluster was associated with a higher 30-day mortality rate adjusted for the GRACE 2.0 risk score (4.9% vs 0.9% for the two other clusters, p<0.001).

Conclusions: While there are no significant differences in the frequency or location of pain between sexes, women are more likely to feel pain of higher intensity and to present with referred pain and symptoms other than pain. Knowledge of these ACS presentation profiles is important for health policy decisions and clinical practice.

Keywords: Sex; acute coronary syndrome; women; diagnosis.

Strengths and limitations

Within a prospective cohort study, presenting symptoms of acute coronary syndrome were obtained through a structured questionnaire applied within the first 48 hours after admission.

Consecutive sampling, the detailed clinical information obtained through the questionnaire and adjustment for several confounding variables strengthens our results.

The results of this study are valid for stable patients admitted to the hospital and who were able to answer the questionnaire in the acute phase of the acute coronary syndrome.

Some of the sex differences in presenting symptoms may be influenced by selection bias because of a higher risk of non-inclusion of women due to misdiagnosis or death in the early hours of admission.

INTRODUCTION

Acute coronary syndrome (ACS) is still one of the main causes of death worldwide and in Europe.[1, 2] Coronary heart disease mortality has decreased in the last decades in developed countries because of primary prevention and improvement in treatment of patients with ACS.[2] Attainment of the maximal benefit of treatment of these patients is threatened by delayed diagnosis, partly dependent on clinical suspicion of ACS. The subjective experience of symptoms influences patients' attitudes in seeking help and professionals' interpretation of clinical presentations.[3] Early recognition of ACS may be challenging because while patients with presumed ACS have contact with healthcare providers,[4] many patients do not have an electrocardiogram before hospitalization.[5] Therefore, physicians frequently have to make decisions that are only clinically based.

The population of patients with atypical ACS presentation is still not well characterized.[6] Women and men generally have the same type of symptoms during an ACS episode, although the proportion presenting with different combinations of symptoms varies.[7] This conflicting evidence can be partly explained by the diverse methodology used, with few prospective studies, usually without a specific questionnaire. In prospective studies, small convenience samples were used and confounding was not always adequately addressed.[8, 9] Therefore, sex-specific research on ACS presentation is a challenge and priority.[10]

This study aimed to analyse sex differences in presenting symptoms of ACS within a prospective cohort study, taking into account the contribution of age, socioeconomic data, previous history of coronary heart disease, risk factors, comorbidities, type of ACS and coronary anatomy to the presenting symptoms.

METHODS

Study Design and Sample Selection

The EPIHeart cohort study was designed to identify inequalities in management and outcomes of patients with ACS. This study included all consecutive patients who were admitted between August 2013 and December 2014 to the Cardiology Department of two tertiary hospitals in two regions in northern Portugal (Hospital de São João, Porto, covering the metropolitan area of Porto in the coast; and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). Eligible patients were 18 years old or older who lived in the catchment area of these hospitals (districts: Porto, Vila Real, Bragança, and Viseu),

with confirmed diagnosis of type 1 (primary spontaneous) ACS. The diagnosis of type 1 ACS and the classification in different subtypes was determined by the treating cardiologist, based on symptoms and signs at presentation, electrocardiogram findings and the increase in cardiac enzyme levels (high-sensitivity troponin I or T were used), according to the third universal definition of myocardial infarction.[11] The patients were also expected to be hospitalized for at least 48 hours and not institutionalized before the event. Of 1297 patients initially considered, in 164 the diagnosis of type 1 ACS was not confirmed, 60 were excluded due to discharge or transfer before the interview, 18 died before being invited, and 44 were unable to answer the questionnaire because of clinical instability, no understanding of Portuguese, hearing problems, or cognitive impairment. Seventy-two patients refused to participate. For this analysis, we excluded 61 patients who were not admitted because of a symptom (patients referred by a doctor, after a scheduled appointment or diagnostic exam), four with vasospastic angina, and one illicit drug user. A total of 873 patients were included (Figure 1). The study protocol was in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of both hospitals (*Comissão de Ética para a Saúde do Centro Hospitalar de S. João* and *Comissão de Ética do Centro Hospitalar de Trás-os-Montes e Alto Douro*, reference numbers of the approvals: 82/13 and 1286, respectively). All patients gave written informed consent.

Procedures and data collection

Presenting symptoms were obtained face-to-face using a structured questionnaire applied by trained interviewers, within the first 48 hours after admission, whenever possible. Over the following days, a second interview was conducted to collect data on sociodemographic characteristics and risk factors. Medical records were reviewed to extract data regarding previous medical history, admission information, and clinical data during hospitalization.

Pain, referred pain, and symptoms other than pain were measured dichotomously (yes/no). For the location of pain (direct and referred) patients were asked to point out where pain was occurring. To measure the intensity of pain, a 10-point scale (0, no pain; 10, pain of maximal intensity) was used. Symptoms other than pain included dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, and an open-ended question of "other" (12 items). Answers to the last item enabled identification of two other relatively frequent symptoms, other digestive symptoms and discomfort. Activity at the onset of the episode was measured

dichotomously, including sleeping, rest, and any exertion. A stress trigger was assigned if the patient answered "yes" for at least one of following events within 24 hours preceding the episode: accident, recent diagnosis of disease, financial problems, and news of death/disease of a relative/friend.

Marital status was considered partnered for married patients or living in civil union. Education was recorded as completed years of schooling and classified into four categories: less than 4 (little formal education), 4 (elementary school), less than 12 (high school), and 12 or more years (secondary education or more). Occupations were classified into major professional groups, according to the Portuguese Classification of Occupations 2010,[12] integrated in the International Standard Classification of Occupations (ISCO/2008).

Definition of Variables

Although symptoms of ACS have been widely described, their value for diagnosis of ACS is not unanimously recognized.[13-15] After discussion with clinical cardiologists of our team, we opted to use Cardiology Societies' position papers to define direct and referred pain locations and to select symptoms to evaluate.[16, 17] Direct pain location was classified as follows: 1) typical for retrosternal, precordial, right thoracic, or bilateral thoracic pain (chest pain); 2) atypical for epigastric pain or located in the back, left arm or shoulder, right arm or shoulder, neck, or jaw; and 3) a mixture when both typical and atypical locations were present. Referred pain location was considered as follows: 1) typical if pain referred to the left arm or shoulder, right arm or shoulder, neck, or jaw; 2) atypical if pain referred to retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; and 3) a mixture for referred pain in typical and atypical locations.

Patients rarely present with a single symptom during an episode of ACS, and present with multiple symptoms instead that do not occur in isolation and may cluster.[18] There has been increasing interest in symptom cluster analysis in cardiovascular disease because it aids in assessment by enhancing recognition of patients with similar symptom profiles.[19] Groups of symptoms other than pain were obtained by latent class analysis.

The small group of non-classified (NC) patients with ACS (patients with left bundle branch block) was grouped with patients with ST elevation myocardial infarction (STEMI) (STEMI/NC ACS group). Non-ST elevation ACS (NSTEACS) included unstable angina and non-ST elevation acute myocardial infarction or subacute myocardial infarction.

Considering the possible association between coronary anatomy and clinical presentation, we grouped patients according to coronary angiography into five groups: managed conservatively; non-obstructive coronary artery disease; lesions exclusively in the anterior descending artery; lesions in the right and/or circumflex artery; and lesions in the left main coronary artery, three-vessel disease or disease both in the anterior descending artery and the right or circumflex artery.

Data Analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). Categorical variables are shown as number and percentage. To compare differences between women and men, and by age-groups, the chi-square or Fisher's test was used for categorical variables and the t-test, Mann-Whitney or Kruskal-Wallis tests for continuous variables. Latent class analysis was used to identify distinct groups of individuals from a sample (clusters) who were homogeneous within the group. This was based on the fact that performance of an individual in a set of items is explained by a categorical latent variable with K classes (clusters), commonly called latent classes. The number of latent clusters was defined according to the Akaike information criterion (AIC). Starting from one single cluster and increasing one cluster at each step, the best solution was identified when an increase in the number of clusters did not lead to a decrease in the AIC.

Patient and system delays, severity indicators, risk stratification using calculated GRACE and CRUSADE risk scores, left ventricular systolic dysfunction and 30-day mortality rate adjusted for the GRACE 2.0 risk score,[20] were assessed according to presence of typical (chest) pain and cluster of symptoms other pain. The 30-day mortality adjusted for the GRACE 2.0 risk score was estimated based on predicted probabilities derived from logistic regression.Logistic regression was used to identify variables associated with clinical presentation. Variables with $p<0.15$ for a crude association with the endpoint were entered in the initial model and a backward strategy was used to exclude the least significant variables, based on Wald tests. We were then able to obtain the most parsimonious model with all the important determinants. Previous data support significant interaction between age and sex with clinical presentation, attenuated with advancing age, mainly in those 65 years old or older.[3] We assessed for effect measure modification by stratifying adjusted analyses based on two age groups (under 65 and 65 years old or older). Sex, age (continuous), and type of ACS were forced to remain in the models.

All analyses were performed using STATA version 11.1 for Windows (Stata Corp LP, College Station, TX) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Women (n=227, 26.0%) were older (69.1 vs 62.2 years, p<0.001) and more frequently lived in the interior region (52.4% vs 38.7%, p<0.001) than men. Women were more often treated conservatively and had non-obstructive coronary artery disease more frequently than men. In this sample, no difference by sex was observed in the type of ACS, where 56.6% of the patients had a discharge diagnosis of NSTEACS (Table 1).

Women more frequently had hypertension (81.5% vs 62.7%, p<0.001) and diabetes (38.8% vs 29.9%, p=0.014), and were more frequently obese (25.5% vs 18.5%, p=0.020) and never smokers compared with men (p<0.001, Table 1). Men were submitted to percutaneous coronary intervention more often than women. There were no significant differences in a previous history of renal failure, prior myocardial infarction, prior coronary artery bypass surgery, prior heart failure, and dementia by sex (Table 1).

Women were more likely to be unpartnered, disabled, less educated, and had a lower income compared with men. The median time that elapsed between admission and application of the symptom questionnaire was slightly longer in women than in men (Table 1).

Table 1. Baseline demographic, socioeconomic and clinical characteristics in the whole sample and by sex*

	Total (n = 873)	Women (n = 227)	Men (n = 646)	p
Age (years), mean (SD)	64.0 (13.0)	69.1 (12.7)	62.2 (12.7)	<0.001
Socioeconomic				
Marital status				
Partnered	667 (76.8)	133 (58.9)	534 (83.2)	<0.001
Education				
Little formal education	172 (19.9)	95 (42.4)	77 (12.0)	
Elementary school	337 (39.1)	73 (32.6)	264 (41.3)	
High school	213 (24.7)	32 (14.3)	181 (28.3)	
Secondary education or more	141 (16.3)	24 (10.7)	117 (18.3)	<0.001
Employment status				
Employed/looking after home	282 (32.6)	64 (28.3)	218 (34.1)	
Unemployed	107 (12.4)	16 (7.1)	91 (14.2)	
Retired	334 (38.6)	93 (41.2)	241 (37.7)	
Disabled	143 (16.5)	53 (23.5)	90 (14.1)	<0.001
Subjective social class				
Low	281 (32.2)	81 (35.7)	200 (31.0)	
Lower-middle	281 (32.2)	58 (25.6)	223 (34.5)	
Higher-middle/High	60 (6.9)	16 (7.1)	44 (6.8)	
No response	251 (28.8)	72 (31.7)	179 (27.7)	0.097
Household income (euros)				
<500	204 (23.4)	77 (33.9)	127 (19.7)	
501-1000	276 (31.6)	60 (26.4)	216 (33.4)	
1001 – 2000	146 (16.7)	22 (9.7)	124 (19.2)	
>2000	88 (10.1)	14 (6.2)	74 (11.5)	
No response	159 (18.2)	54 (23.8)	105 (16.3)	<0.001
Region				
Metropolitan area of Porto	504 (57.7)	108 (47.6)	396 (61.3)	
North-eastern region of Portugal	369 (42.3)	119 (52.4)	250 (38.7)	<0.001
Cardiovascular risk factors				
Smoking habit				
Never	369 (42.3)	184 (81.0)	185 (28.6)	
Current	283 (32.4)	34 (15.0)	249 (38.5)	
Former	221 (25.3)	9 (4.0)	212 (32.8)	<0.001
Hypertension	590 (67.6)	185 (81.5)	405 (62.7)	<0.001
Diabetes mellitus	281 (32.2)	88 (38.8)	193 (29.9)	0.014
Dyslipidaemia	535 (61.4)	144 (63.4)	391 (60.6)	0.454
BMI (kg/m^2)				
Median (IQR)	26.5 (18.0-44.6)	26.7 (19.5-37.9)	26.4 (18.2-39.2)	0.531
Underweight	11 (1.4)	2 (0.9)	9 (1.5)	
Normal weight	272 (33.4)	80 (37.0)	192 (32.1)	
Overweight	366 (44.9)	79 (36.6)	287 (47.9)	
Obese	166 (20.4)	55 (25.5)	111 (18.5)	0.020
Family history of CVD	303 (34.7)	73 (32.2)	230 (35.6)	0.105
Previous medical history				
Renal failure	64 (7.3)	14 (6.1)	50 (7.7)	0.434
Myocardial infarction	156 (17.9)	34 (15.0)	122 (18.9)	0.186
PCI	100 (12.4)	18 (8.4)	82 (13.8)	0.041
CABG	34 (4.2)	5 (2.3)	29 (4.9)	0.111
Heart failure	63 (7.5)	21 (9.6)	42 (6.8)	0.172
Dementia	7 (0.8)	4 (1.8)	3 (0.5)	0.060
ACS type				
STEMI/NC ACS	379 (43.4)	101 (44.5)	278 (43.0)	
NSTEACS	494 (56.6)	126 (55.5)	368 (57.0)	0.703
Coronary anatomy				
Non-obstructive disease	57 (6.9)	22 (10.6)	35 (5.61)	
Left anterior descending artery only	162 (19.5)	38 (18.3)	124 (19.9)	
Right and/or circumflex artery only	196 (23.6)	46 (22.1)	150 (24.0)	
Mixture	417 (50.1)	102 (49.0)	315 (50.5)	
Not submitted to coronary angiography	41 (4.7)	19 (8.4)	22 (3.4)	0.004
Symptom questionnaire application				
Time from admission (hours), median (IQR)	42.1 (25.0-68.0)	45.4 (28.5-72.3)	40.0 (24.0-67.4)	0.052

*Values are number and percentage unless otherwise indicated.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; CVD, cardiovascular diseases; IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/non-classifiable acute coronary syndrome.

Symptom characteristics by sex and age

Because differences in symptoms by sex and age were similar in direction and magnitude in STEMI/NC ACS and NSTEACS (Supplementary Tables 1 and 2), both types of ACS were analysed together.

Although pain was present in most patients, men presented with pain more frequently than did women (97.4% vs 94.3%, p=0.028), with a higher sex difference among patients with 80 or more years old (88.0% vs 93.5%). Older patients presented less often pain, but the difference by age group in both sexes was not significant (Table 2). No difference was found in the location of pain by sex. Approximately 80% of patients felt chest pain (typical pain). Older women presented less frequently with chest pain and had chest pain and pain in other locations (mixture group) more often than did younger women (p=0.014). Referred pain was observed more frequently in women and in younger patients (only significant for men, p=0.024); again in the older age group, the difference between women and men was notorious (56.8% vs 39.7%, respectively). Atypical and mixture referred pain were more frequent in women than in men (p<0.001), mainly in women aged ≥65 years (p=0.009). Women felt pain with higher intensity than did men (median [IQR]: 9 [8–10] vs 8 [6–9], p<0.001), without a difference by age (Table 2). Women presented with symptoms other than pain more frequently than did men (82.8% vs 68.9%, p<0.001), with no difference by age group in both sexes (Table 2).

Considering symptoms other than pain, the AIC optimum value supported a preference for a three-cluster solution (AIC 7207.508, 6869.390, 6862.476, and 6870.372 for one, two, three, and four clusters, respectively). Cluster 1 had low endorsement probabilities for all items (no symptoms cluster). Cluster 2 had a high probability for dyspnoea at rest and sweating, and a low probability for the remaining items (dyspnoea and sweating cluster). Cluster 3 had high probabilities for all items (multiple symptoms cluster). This three-cluster model made sense conceptually to cardiologists of our team. Clusters counts and probabilities of occurrence of symptoms in established clusters are shown in Supplementary Table 3. Differences in proportions of women and men in the three clusters were observed (p<0.001, Table 2). Cluster 1 was the most prevalent, in which men presented with the no symptoms cluster more frequently (76.9% vs 62.6%) and the multiple symptoms cluster less frequently (4.8% vs 15.9%) than did women. Higher differences of multiple symptoms cluster proportions between women and men were observed among patients in the older age group. The proportion of dyspnoea and sweating cluster was similar in men and women (Table 2).

Approximately 45% of patients were at rest and 35% were under physical effort at the beginning of the episode. Older women were more frequently at rest at the beginning of the episode and younger women were more frequently under effort (p=0.011). Less than 10% of patients identified a stressful event in the previous 24 hours, with no difference by sex, but among men, a younger age was slightly associated with this trigger (p=0.045, Table 2).

Table 2. Clinical presentation of patients with acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	14 (6.2)	54 (23.8)	109 (48.0)	50 (22.0)	227 (100.0)		61 (9.4)	303 (46.9)	220 (34.1)	62 (9.6)	646 (100)		
Pain	14 (100.0)	52 (96.3)	104 (95.4)	44 (88.0)	214 (94.3)	0.229	60 (98.4)	297 (98.0)	214 (97.3)	58 (93.5)	629 (97.4)	0.228	0.028
Pain location†													
Typical	12 (85.7)	43 (82.7)	88 (85.4)	32 (72.7)	175 (82.2)		53 (89.8)	246 (83.7)	175 (82.2)	44 (75.9)	518 (83.0)		
Atypical	1 (7.1)	9 (17.3)	5 (4.9)	6 (13.6)	175 (9.9)		3 (5.1)	33 (11.2)	30 (14.1)	10 (17.2)	76 (12.2)		
Mixture	1 (7.1)	0 (0.0)	10 (9.7)	6 (13.6)	17 (8.0)	0.014	3 (5.1)	15 (5.1)	8 (3.8)	4 (6.9)	30 (4.8)	0.327	0.165
Referred pain	9 (64.3)	41 (78.8)	72 (69.2)	25 (56.8)	147 (68.7)	0.129	38 (63.3)	179 (60.3)	126 (58.9)	23 (39.7)	366 (58.2)	0.024	0.007
Radiation type‡													
Typical	8 (88.9)	20 (48.8)	28 (38.9)	7 (28.0)	63 (42.9)		28 (73.7)	114 (64.4)	67 (53.2)	10 (43.5)	219 (60.2)		
Atypical	0 (0.0)	13 (31.7)	18 (25.0)	13 (52.0)	44 (29.9)		7 (18.4)	37 (20.9)	39 (31.0)	8 (34.8)	91 (25.0)		
Mixture	1 (11.1)	8 (19.5)	26 (36.1)	5 (20.0)	40 (27.2)	0.009	3 (7.9)	26 (14.7)	20 (15.9)	5 (21.7)	54 (14.8)	0.104	<0.001
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-9)	8 (8-9)	9 (8-10)	0.170	8 (7-10)	8 (6-9)	8 (6-9)	8 (7-9)	8 (6-9)	0.095	<0.001
Symptom	11 (78.6)	45 (83.3)	91 (83.5)	41 (82.0)	188 (82.8)	0.947	43 (70.5)	209 (69.0)	151 (68.6)	42 (67.7)	445 (68.9)	0.989	<0.001
Symptom clusters‖													
Cluster 1	7 (50.0)	41 (75.9)	62 (56.9)	32 (64.0)	142 (62.6)		43 (70.5)	232 (76.6)	170 (77.3)	52 (83.9)	497 (76.9)		
Cluster 2	5 (35.7)	8 (14.8)	28 (25.7)	8 (16.0)	49 (21.6)		15 (25.6)	59 (19.5)	35 (15.9)	9 (14.5)	118 (18.3)		
Cluster 3	2 (14.3)	5 (9.3)	19 (17.4)	10 (20.0)	36 (15.9)	0.183	3 (4.9)	12 (4.0)	15 (6.8)	1 (1.61)	31 (4.80)	0.345	<0.001
Activity													
Sleep	2 (15.4)	16 (32.0)	11 (10.4)	7 (14.9)	36 (16.7)		6 (9.8)	65 (21.7)	35 (16.1)	13 (21.3)	119 (18.6)		
Rest	5 (38.5)	18 (36.0)	50 (47.2)	29 (61.7)	102 (47.2)		34 (55.7)	124 (41.3)	105 (48.2)	33 (54.1)	296 (46.3)		
Exertion	6 (46.2)	16 (32.0)	45 (42.5)	11 (23.4)	78 (36.1)	0.011	21 (34.4)	111 (37.0)	78 (35.8)	15 (24.6)	225 (35.2)	0.087	0.816
Stress trigger	2 (14.3)	6 (11.1)	11 (10.2)	3 (6.1)	22 (9.8)	0.700	11 (18.0)	23 (7.7)	15 (6.9)	6 (9.8)	55 (8.6)	0.045	0.605

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ||Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Multivariate models

Despite the higher probability of women of both age groups to present without pain than men, no differences were observed in the adjusted pain frequency and location between men and women. Referred pain was more likely to be experienced by women (<65 years old: adjusted odds ratio [OR] 2.90, 95% confidence interval [95% CI] 1.47-5.72; >=65 years old: 1.60 (0.99-2.60), p for interaction=0.528)). Moreover, women of both age groups had a higher probability of having pain radiating to typical and atypical locations and of feeling pain with an intensity higher than 8 (Table 3). The association between intensity of pain and female sex was stronger for younger patients (interaction p=0.028) (Table 3).

The presence of at least one symptom other than pain occurred almost two times more often in women than in men. With cluster 1 as the reference, cluster 2 and 3 were positively associated with female sex, with the latter being statistically significant. The multiple symptoms cluster was almost 4-fold more likely in women than in men (3.92, 2.21-6.98 in the whole sample, interaction p=0.501) (Table 3).

No difference in the type of patients' activities at the beginning of the episode by sex was observed (Table 3).

Table 3. Differences between women and men in clinical presentation of acute coronary syndrome, by age group
(men are the reference class).

	<65 years		>=65 years			
Symptoms	**OR**	**95% CI**	**OR**	**95% CI**	**Interaction p-value**	**Adjusted for**
Pain	0.76	0.14-4.0	0.52	0.19-1.47	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)	0.97	0.44-2.14	1.71	0.90-3.23	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	2.90	1.47-5.72	1.60	0.99-2.60	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type†						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.49	0.70-3.20	1.38	0.72-2.66	0.415	
Mixture	1.77	0.73-4.29	2.75	1.36-5.57	0.606	
Pain intensity (higher than 8/10)	3.81	2.04-7.13	2.03	1.22-3.37	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.98	1.00.3.91	1.85	1.10-3.12	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters‡						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	1.07	0.53-2.15	1.67	0.97-2.87	0.246	
Cluster 3	3.14	1.15-8.62	4.23	2.03-8.81	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.68	0.33-1.38	1.38	0.74-2.57	0.284	
Exertion	0.77	0.37-1.59	1.70	0.89-3.25	0.408	

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG: coronary artery bypass surgery; CI, confidence interval; OR, odds ratio.
*Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.
†Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.
‡Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

Clinical presentation and outcomes

Patients with a diagnosis of STEMI/NC ACS who presented with atypical or mixture pain took longer to seek medical care (135 vs 85 min., p=0.012) and had longer total ischemic times (414 vs 328 min., p=0.080) than patients with chest pain (Table 4). Among patients with NSTEACS, differences in time delays according to pain location were not significant. Patients with atypical or mixture pain presented more frequently with hemodynamic instability at admission (9.7% vs 4.6%, p=0.014) and had also more often moderate to severe left ventricular systolic dysfunction (32.9 vs 24.9%, p=0.052) than patients with chest pain. The 30-day mortality adjusted for GRACE 2.0 was not significantly different between patients with chest pain and those with atypical or mixture pain (Table 4).

Among patients with STEMI/NC ACS, the total ischemic time was longer compared with patients who presented with the other symptoms clusters (533 minutes vs 321 and 384, p=0.111). Patients with the multiple symptom cluster presented more often with hemodynamic instability at admission (13.4% vs 6.4% and 4.2%, p=0.034). The mean 30-day mortality rate adjusted for the GRACE 2.0 risk score was significantly higher for patients presenting with the multiple symptom cluster (4.9% vs 0.9% for the two other clusters, p<0.001) (Table 4).

Patients with atypical or mixture chest pain and patients with the multiple symptom cluster had higher mean GRACE and median CRUSADE risk scores (Table 4).

Table 4. Patient and system delays, severity indicators, risk stratification and 30-day mortality according to clinical presentation*

	Typical (chest) pain†	Atypical or mixture pain	p	No symptom cluster ‡	Dyspnoea and sweating cluster	Multiple symptoms cluster	p
Patient and system delays, median (IQR)							
STEMI/NC ACS							
Symptom onset – FMC (min)	85 (45-210)	135 (65-325)	0.012	90 (46-240)	90 (50-185)	83 (45-430)	0.872
Symptom onset-arterial access (min)	328 (192-1075)	414 (246-1335)	0.080	321 (194-1011)	384 (201-1440)	533 (323-1428)	0.111
NSTEACS							
Symptom onset – FMC (min)	130 (60-393)	139 (60-335)	0.633	135 (60-390)	150 (60-390)	113 (45-393)	0.795
Hospital admission- coronary angiography time (hours)	30 (18-57)	29 (20-48)	0.884	30 (18-56)	35 (18-70)	28 (20-72)	0.385
Admission variables							
Heart rate, mean (SD), bpm	77 (18)	80 (24)	0.117	78 (19)	77 (19)	78 (28)	0.923
Systolic blood pressure, mean (SD), mmHg	144 (49)	139 (30)	0.212	145 (59)	141 (30)	136 (33)	0.364
Hemodynamic instability at admission§	32 (4.6)	14 (9.7)	0.014	41 (6.4)	7 (4.2)	9 (13.4)	0.034
Risk stratification							
Calculated GRACE risk score, mean (SD)	134 (36)	147 (39)	<0.001	137 (37)	138 (35)	149 (44)	0.041
Calculated CRUSADE risk score, median (IQR)	21 (11-34)	25 (14-41)	0.012	22 (12-36)	23 (10-36)	30 (16-47)	0.019
Moderate or severe left ventricular systolic dysfunction	169 (24.9)	46 (32.9)	0.052	164 (26.4)	55 (33.3)	17 (25.4)	0.187
30-day mortality rate adjusted for the GRACE 2.0 risk score, mean (SD)	2.0 (4.0)	1.3 (1.4)	0.521	0.9 (2.0)	0.9 (2.0)	4.9 (5.5)	<0.001

IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/Non-classifiable acute coronary syndrome.
*Values are number and percentage unless otherwise indicated.
Total may not add to 100% due to missing data.
†Chest pain: retrosternal, precordial, right thoracic, or bilateral thoracic.
‡No symptom cluster: low endorsement probabilities for all items; Dyspnoea and sweating cluster: high probability for dyspnoea atrest and sweating; Multiple symptoms cluster: high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort)
§Killip class III or IV; or shock at admission.

DISCUSSION

In our study, after adjustment, no differences in the frequency and location of pain by sex were observed. Referred pain, pain radiating to typical and atypical locations, and pain of higher intensity were more likely to occur among women. Women were also more likely than men to present with symptoms other than pain. Three clusters of symptoms other than pain were identified. Women were more likely to present with the multiple symptoms cluster. Presenting with the multiple symptoms cluster was associated with a higher mean 30-day mortality rate adjusted for the GRACE 2.0 risk score.

Differences between women and men in perception of symptoms of ACS might be explained by anatomical, physiological, biological, and psychosocial differences that influence each other.[9, 21] We measured several variables of these different domains. Differences in symptom presentation by sex might be the result of differences in response to history-taking,[10] differences in neural receptors and pathways involved in pain, and subtle differences in the location and type of atherosclerotic lesions.[22, 23] Our findings of similar ACS symptoms between women and men are consistent with previous studies,[7, 24] as well as our finding that women are more likely to have atypical presentations.[9] We observed that women have a higher likelihood of atypical referred pain and of several concomitant symptoms other than pain, common to other cardiac and non-cardiac diagnoses.

In our study, chest pain was the most frequent symptom in both sexes, consistent with previous studies.[25-27] Among those with pain, typical chest pain was observed in 82% of patients, regardless of sex. The remaining patients had pain in less typical locations and were thus prone to misdiagnosis and undertreatment and, consequently, to worse outcomes.[28] Considering differences in characteristics of pain by sex, studies suggested that women, in particular older women, were less likely to have the chief complaint of chest pain associated with acute myocardial infarction; while after adjustment, among patients with 65 or less years old, female sex was no longer a significant predictor.[29] Studies reported that chest pain did not differ between women and men,[9] others that women have pain in the neck and back more often than men,[30, 31] without distinguishing between direct and referred pain. In our study, referred pain was observed in 61% of patients, was more frequent in women, and typical referred pain was only observed in 33%. Notably, a study on diagnostic acuity of ACS symptoms showed that shoulder and arm pain was predictive of the diagnosis of ACS for women only.[24] Another study on sex differences in ACS symptom presentation in patients with 55 years old or younger showed that being a woman was independently associated with ACS presentation without chest pain.[27] Differences in age distribution, in

clinical presentation measuring, in selection and definition of confounder variables limit conclusive comparisons of studies evaluating differences in frequency and location of pain between women and men. According to previous studies, with regard to other symptoms, a higher proportion of women have less typical symptoms than men.[8, 31] Women have also reported other symptoms, such as indigestion, palpitations, nausea, numbness in the hands, and unusual fatigue, more frequently than men.[9] In our cohort, three symptom clusters were identified. Women had the multiple symptoms cluster more frequently than did men, characterized by high probabilities for all symptoms. According to Rosenfeld et al. women are more likely to cluster in a similar class, called the heavy symptom burden class.[32] With regard to ACS symptom clustering, there are contradictory findings on identified clusters, the proportion of patients per cluster, and differences between clusters regarding demographic factors. In our study, cluster 1 and 3 (low and high probabilities for all symptoms, respectively) are in line with observations of other settings.[18, 33] A recent systematic review of symptom clusters in cardiovascular disease[34] identified clusters with the most symptoms and clusters with the lowest number of symptoms. Our dyspnoea and sweating cluster has two common symptoms with the Riegel et al.[26] stress symptoms cluster, which includes shortness of breath, sweating, nausea, indigestion, dread, and anxiety.

Methodological differences related to sampling and measuring might explain these different results. Strengths of our study include consecutive sampling, a questionnaire with detailed clinical information was systematically applied, and we adjusted for several confounding variables.

The value of symptoms for diagnosis of ACS varies across studies.[14, 35, 36] Overall, the diagnostic performance of chest pain characteristics for diagnosis is limited, with likelihood ratios close to 1.[37] Sensitivity for individual symptoms of ACS, using the 13-Item Acute Coronary Syndrome Checklist, ranges from 27% to 67% for women and 14% to 72% for men. Additionally, specificity ranges from 33% to 78% for women and 34% to 78% for men, with different associations between some symptoms and diagnosis of ACS by sex.[24] However, physicians still base the likelihood of ACS mainly on symptoms and use the electrocardiogram to rule in the diagnosis.[38] Evaluation of these patients is mostly unchanged, without implementation of evidence-based assessment tools in clinical practice to improve diagnostic accuracy. Public health messages should take into account the complexity of presenting symptoms of ACS, particularly the significant proportion of women and men with ACS without typical chest pain. Additionally, there is a higher likelihood of atypical referred pain and multiple concomitant symptoms in

women. These factors should be accounted for to encourage timely and appropriate care of patients with ACS.

Presenting without chest pain and with the multiple symptoms cluster was associated with several markers of higher ACS severity and longer time delays, particularly significant among patients with STEMI/NC ACS. In our study, presenting with the multiple symptoms cluster, but not with atypical or mixture location of pain, was associated with a higher mean 30-day mortality adjusted for GRACE risk score. These results are consistent with data from the GRACE registry, that showed that patients with symptoms other than pain experienced greater morbidity and higher in-hospital mortality across the spectrum of ACS.[28] Other registry showed that the higher in-hospital mortality observed among women and men without chest pain, decreased or even reversed with advanced age.[39] Mortality is adjusted for GRACE risk score, however we cannot conclude that the difference in outcome observed is explained by symptoms other than pain per se. Previous studies showed that the higher in-hospital mortality of ACS patients who presented without chest pain was mostly due to late hospital arrival, comorbidities and underuse of medications and invasive procedures. [6, 39, 40] These studies focused mainly on presence of chest pain to define atypical presentation and used medical record reviews to characterize clinical presentation. More studies are needed to further explore the association between symptoms other than pain and outcomes.

Limitations

Participants were interviewed as soon as possible after admission, but this does not obviate the retrospective nature of data collection and the possibility of recall bias. Furthermore preceding interviews by physicians may have influenced answers to the questionnaire, however different consequences in women and men are not expected. The results of this study are valid for stable patients, who were admitted to the hospital and were able to answer the questionnaire in the acute phase of ACS. This type of study misses patients who die before reaching the hospital, patients who do not seek medical care, patients who are mistakenly discharged or misdiagnosed and admitted to non-cardiology departments. This sample selection process may contribute to underestimate the true prevalence of ACS atypical presentation in women and men.[27] For patients who were eligible but not enrolled only information on

sex, age and type of ACS was available. Patients who died before the interview were older (81.5±11.8 vs 64.6±13.1 years, p<0.001), were more often women (66.7% vs 26.0%, p<0.001), and more frequently had a diagnosis of STEMI (81.3% vs 43.4%, p=0.003) than did participants. Patients who were discharged or transferred to another hospital before the interview had STEMI less often (25.0% vs 43.4%, p=0.005) and patients who were not enrolled because of clinical instability or inability to understand the questionnaire were older. Patients who refused to participate were older (72.7±11.0 vs 64.0±13.0 years, p<0.001), were less often partnered (65.7% vs 76.8%, p=0.036), and had little formal education (43.1% vs 19.7%, p<0.001) compared with participants. Except for deceased patients, no difference in sex proportion was observed between participants and non-participants. We cannot exclude that some of the sex differences were caused by selection bias because of a higher risk of non-inclusion of women due to death in the early hours of admission, or due to a possible higher probability of misdiagnosis in women, particularly those with unstable angina.[41] Considering that atypical presentation is associated with a worse prognosis and with a higher probability of misdiagnosis, the proportion of patients with ACS presenting without typical chest pain or that of women with an atypical presentation could be even higher.[28]

CONCLUSION

This study shows no significant differences in the frequency and location of pain by sex, but approximately 20% of patients do not present with chest pain, regardless of sex. Women are more likely to report referred pain and multiple symptoms simultaneously. Presentation with the multiple symptoms cluster pain is associated with higher 30-day mortality adjusted for GRACE score. Health education messages should take into account the complexity of presentation of ACS and emphasize the possible non-chest location of pain in both sexes and the higher probability of concomitant symptoms other than pain in women. Further sex-stratified analysis of ACS presentation is required to determine the diagnostic accuracy of symptoms by sex.

Figure 1. Flow chart of the study population

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Contributors

Carla Araújo and Ana Azevedo had the original idea to develop the EPIHeart cohort study and were responsible for acquiring the study grant. Carla Araújo raised the hypotheses, participated in data collection and field work, analysed and interpreted the data, and drafted the first version of the manuscript. Olga Laszczyńska analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. Marta Viana and Andreia Borges participated in data collection, field work and interpretation of the data. Filipa Melão and Ana Henriques interpreted data. Milton Severo analysed and interpreted the data. Maria Júlia Maciel and Ilídio Moreira were involved in the conception of the study and in field work. Ana Azevedo was the responsible for the conception and development of the study, analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. All authors were involved in writing the paper, in revising it critically and approved the final version of the submitted manuscript.

Data sharing

Data are available by email the corresponding author at carla-r-araujo@hotmail.com.

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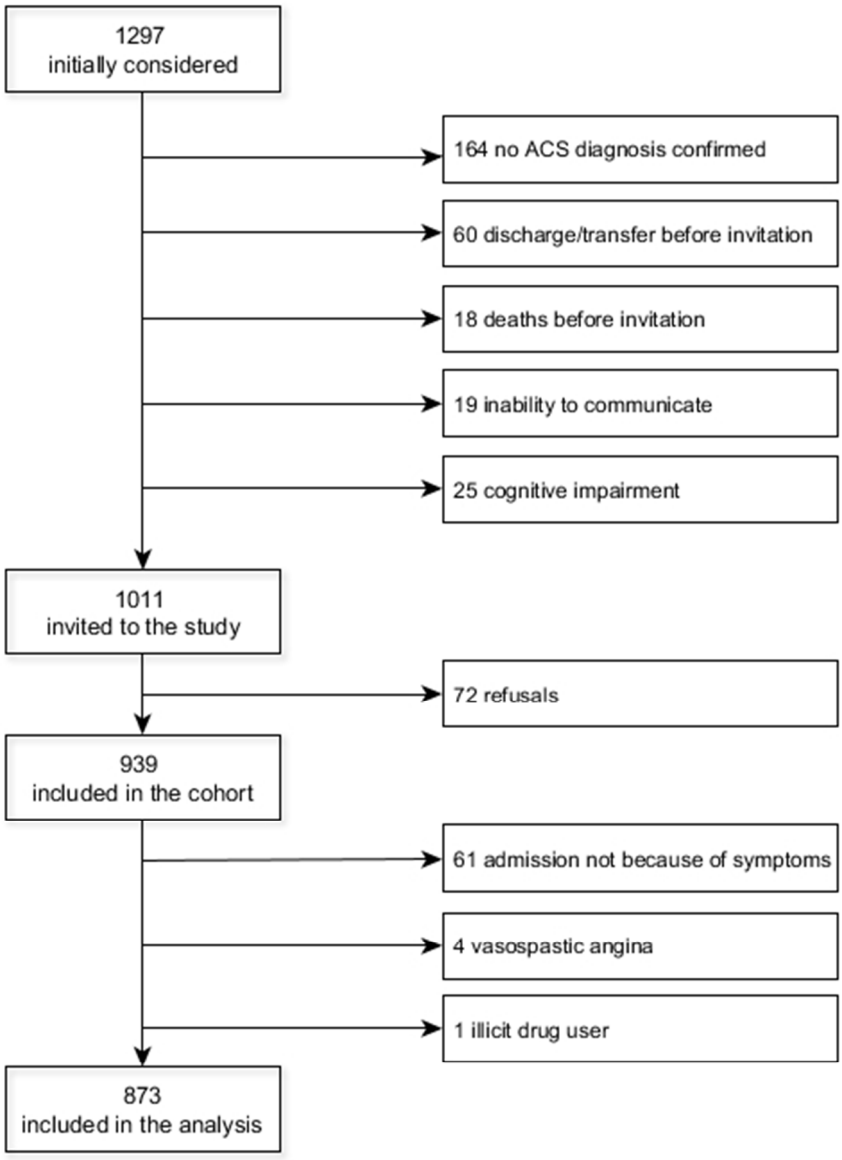

Figure 1. Flow chart of the study population

41x56mm (300 x 300 DPI)

Supplementary Table 1. Clinical presentation of patients with ST elevation myocardial infarction/non-classifiable acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	6 (5.9)	22 (21.8)	53 (52.5)	20 (19.8)	101 (100.0)		37 (13.3)	144 (51.8)	77 (27.7)	20 (7.2)	278 (100)		
Pain	6 (100.0)	21 (95.5)	52 (98.1)	16 (80.0)	95 (94.1)	0.039	36 (97.3)	142 (98.6)	73 (94.8)	20 (100.0)	271 (97.5)	0.338	0.106
Pain location†													
Typical	5 (83.3)	17 (81.0)	44 (84.6)	9 (56.3)	75 (78.9)		31 (88.6)	120 (85.1)	55 (76.4)	13 (65.0)	219 (81.7)		
Atypical	1 (16.7)	4 (19.0)	2 (3.8)	5 (31.3)	12 (12.6)		1 (2.9)	17 (12.1)	14 (19.4)	5 (25.0)	37 (13.8)		
Mixture	0 (0.0)	0 (0.0)	6 (11.5)	2 (12.5)	8 (8.4)	0.021	3 (8.6)	4 (2.8)	3 (4.2)	2 (10.2)	12 (4.5)	0.032	0.347
Referred pain	4 (66.7)	18 (85.7)	38 (73.1)	8 (50.0)	68 (71.6)	0.114	24 (66.7)	90 (63.4)	51 (69.9)	7 (35.0)	172 (63.5)	0.038	0.152
Radiation type‡													
Typical	3 (75.0)	8 (44.4)	17 (44.7)	1 (12.5)	29 (42.6)		19 (79.2)	53 (59.6)	26 (51.0)	3 (42.9)	101 (59.1)		
Atypical	0 (0.0)	5 (27.8)	10 (26.3)	4 (50.0)	19 (27.9)		5 (20.8)	21 (23.6)	9 (17.6)	3 (42.9)	38 (22.2)		
Mixture	1 (25.0)	5 (27.8)	11 (28.9)	3 (37.5)	20 (29.4)	0.504	0 (0.0)	15 (16.9)	16 (31.4)	1 (14.3)	32 (18.7)	0.018	0.060
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-10)	8.5 (8-9)	9 (8-10)	0.784	9 (7.5-10)	8 (7-10)	8 (6.5-9)	7.5 (6.5-9)	8 (7-10)	0.064	<0.001
Symptom	5 (83.3)	20 (90.9)	47 (88.7)	17 (85.0)	89 (88.1)	0.794	23 (62.2)	105 (72.9)	61 (79.2)	14 (70.0)	203 (73.0)	0.283	0.002
Symptom clusters‖													
Cluster 1	2 (33.3)	18 (81.8)	27 (50.9)	11 (55.0)	58 (57.4)		26 (70.3)	102 (70.8)	54 (70.1)	16 (80.0)	198 (71.2)		
Cluster 2	3 (50.0)	2 (9.1)	16 (30.2)	4 (20.0)	25 (24.8)		9 (24.3)	36 (25.0)	19 (24.7)	3 (15.0)	67 (24.1)		
Cluster 3	1 (16.7)	2 (9.1)	10 (18.9)	5 (25.0)	18 (17.8)	0.132	2 (5.4)	6 (4.2)	4 (5.2)	1 (5.0)	13 (4.7)	0.967	<0.001
Activity													
Sleep	1 (16.7)	3 (14.3)	4 (7.8)	3 (15.8)	11 (11.3)		5 (13.5)	29 (20.1)	10 (13.0)	4 (20.0)	48 (17.3)		
Rest	3 (50.0)	9 (42.9)	22 (43.1)	14 (73.7)	48 (49.5)		19 (51.4)	65 (45.1)	43 (55.8)	13 (65.0)	140 (50.4)		
Exertion	2 (33.3)	9 (42.9)	25 (49.0)	2 (10.5)	38 (39.2)	0.069	13 (35.1)	50 (34.7)	24 (31.2)	3 (15.0)	90 (32.4)	0.393	0.274
Stress trigger	1 (16.7)	2 (9.1)	4 (7.5)	3 (15.8)	10 (10.0)	0.519	5 (13.5)	11 (7.7)	6 (7.9)	2 (10.0)	24 (8.7)	0.669	0.697

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 2. Clinical presentation of patients with non-ST elevation acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	8 (6.3)	32 (25.4)	56 (44.4)	30 (23.8)	126 (100)		24 (6.5)	159 (43.2)	143 (38.9)	42 (11.4)	368 (100)		
Pain	8 (100.0)	31 (96.9)	52 (92.9)	28 (93.3)	119 (94.4)	0.864	24 (100.0)	155 (97.5)	141 (98.6)	38 (90.5)	358 (97.3)	0.073	0.131
Pain location†													
Typical	7 (87.5)	26 (83.9)	44 (86.3)	23 (82.1)	100 (84.7)		22 (91.7)	126 (82.4)	120 (85.1)	31 (81.6)	299 (84.0)		
Atypical	0 (0.0)	5 (16.1)	3 (5.9)	1 (3.6)	9 (7.6)		2 (8.3)	16 (10.5)	16 (11.3)	5 (13.2)	39 (11.0)		
Mixture	1 (12.5)	0 (0.0)	4 (7.8)	4 (14.3)	9 (7.6)	0.172	0 (0.0)	11 (7.2)	5 (3.5)	2 (5.3)	18 (5.1)	0.778	0.367
Referred pain	5 (62.5)	23 (74.2)	34 (65.4)	17 (60.7)	79 (66.4)	0.728	14 (58.3)	89 (57.4)	75 (53.2)	16 (42.1)	194 (54.2)	0.350	0.020
Radiation type‡													
Typical	5 (100.0)	12 (52.2)	11 (32.4)	6 (35.3)	34 (43.0)		9 (64.3)	61 (69.3)	41 (54.7)	7 (43.8)	118 (61.1)		
Atypical	0 (0.0)	8 (34.8)	8 (23.5)	9 (52.9)	25 (31.6)		2 (14.3)	16 (18.2)	30 (40.0)	5 (31.3)	53 (27.5)		
Mixture	0 (0.0)	3 (13.0)	15 (44.1)	2 (11.8)	20 (25.3)	0.008	3 (21.4)	11 (12.5)	4 (5.3)	4 (25.0)	22 (11.4)	0.007	0.005
Pain intensity§	9.5 (8.5-10)	9.5 (8-10)	8 (8-10)	8 (7-9)	9 (8-10)	0.224	8 (6-9)	8 (6-9)	8 (6-9)	8 (7.5-9)	8 (6-9)	0.200	<0.001
Symptom	6 (75.0)	25 (78.1)	44 (78.6)	24 (80.0)	99 (78.6)	0.992	20 (83.3)	104 (65.4)	90 (62.9)	28 (66.7)	242 (65.8)	0.278	0.007
Symptom clusters‖													
Cluster 1	5 (62.5)	23 (71.9)	35 (62.5)	21 (70.0)	84 (66.7)		17 (70.8)	130 (81.8)	116 (81.1)	36 (85.7)	299 (81.3)		
Cluster 2	2 (25.0)	6 (18.8)	12 (21.4)	4 (13.3)	24 (19.1)		6 (25.0)	23 (14.5)	16 (11.2)	6 (14.3)	51 (13.9)		
Cluster 3	1 (12.5)	3 (9.4)	9 (16.1)	5 (16.7)	18 (14.3)	0.919	1 (4.2)	6 (3.8)	11 (7.7)	0 (0.0)	18 (4.9)	0.231	<0.001
Activity													
Sleep	1 (14.3)	13 (44.8)	7 (12.7)	4 (14.3)	25 (21.0)		1 (4.2)	36 (23.1)	25 (17.7)	9 (22.0)	71 (19.6)		
Rest	2 (28.6)	9 (31.0)	28 (50.9)	15 (53.6)	54 (45.4)		15 (62.5)	59 (37.8)	62 (44.0)	20 (48.8)	156 (43.1)		
Exertion	4 (57.1)	7 (24.1)	20 (36.4)	9 (32.1)	40 (33.6)	0.032	8 (33.3)	61 (39.1)	54 (38.3)	12 (29.3)	135 (37.3)	0.180	0.768
Stress trigger	1 (12.5)	4 (12.5)	7 (12.7)	0 (0.0)	12 (9.6)	0.140	6 (25.0)	12 (7.7)	9 (6.4)	4 (9.8)	31 (8.6)	0.044	0.731

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 3. Marginal percentage of subjects with each symptom in each assigned cluster*

	Symptom clusters		
	Cluster 1* n=639	**Cluster 2†** n=167	**Cluster 3‡** n=67
Dyspnoea at rest	17.4	34.2	37.3
Exertional dyspnoea	6.0	2.1	14.5
Sweating	22.2	89.6	71.7
Nausea and vomiting	6.5	9.7	41.4
Dizziness	2.6	18.0	74.1
Blurry vision	0.6	4.4	27.5
Presyncope	1.3	11.4	42.7
Syncope	1.6	3.6	10.5
Palpitations	0.3	5.4	19.5
Weakness	7.5	17.8	64.4
"Other symptoms"	4.5	5.5	12.8
Other digestive symptoms	1.0	1.0	1.4
Discomfort	1.3	1.1	4.2

*Values are percentages.

* Cluster 1: no symptom cluster; † Cluster 2: dyspnoea and sweating cluster; ‡Cluster 3: multiple symptoms cluster.

STROBE Statement—checklist of items : ***Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **page 1 (title) and page 2 (abstract)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **page 4**
Objectives	3	State specific objectives, including any prespecified hypotheses - **page 4**
Methods		
Study design	4	Present key elements of study design early in the paper – **pages 4 and 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **pages 4-6**
Participants	6	*Cohort study:* Give the eligibility criteria, and the sources and methods of selection of participants – **pages 4 and 5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **pages 6 and 7**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **pages 5, 6 and 7**
Bias	9	Describe any efforts to address potential sources of bias - **page 7**
Study size	10	Explain how the study size was arrived at – **page 5 and figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why –**page 6 and 7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - **page7**
		(*b*) Describe any methods used to examine subgroups and interactions – **page 7**
		(*c*) Explain how missing data were addressed –**Patients who were unable to answer the questionnaire (with missing data on clinical presentation) were not included.**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed –**Data were collected within a cohort study, but clinical presentation was collected through a questionnaire.**
		(*e*) Describe any sensitivity analyses –**We analysed clinical presentation separately by type of acute coronary syndrome (Supplementary tables 1 and 2), but as results were similar by sex and age both types of acute coronary syndrome were analysed together.**

Continued on next page

Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed –**pages 4 and 5**
		(b) Give reasons for non-participation at each stage –**page 5**
		(c) Consider use of a flow diagram – **Figure 1.**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **pages 8-9**
		(b) Indicate number of participants with missing data for each variable of interest –**page 9**
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time –**pages 10-12**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **pages 13-16**
		(*b*) Report category boundaries when continuous variables were categorized – **pages 10-14**
Other analyses	17	Report other analyses done— eg analyses of subgroups and interactions, and sensitivity analyses – **page 10**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **page 17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias –**pages 19 and 20**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - **pages 17-19**
Generalisability	21	Discuss the generalisability (external validity) of the study results –**page 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based –**page 22**

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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ABSTRACT

Objectives: Prompt diagnosis of acute coronary syndrome (ACS) remains a challenge, with presenting symptoms affecting the diagnosis algorithm and, consequently, management and outcomes. This study aimed to identify sex differences in presenting symptoms of ACS.

Design: Data were collected within a prospective cohort study (EPIHeart).

Setting: Patients with confirmed diagnosis of type 1 (primary spontaneous) ACS who were consecutively admitted to the Cardiology Department of two tertiary hospitals in Portugal between August 2013 and December 2014.

Participants: Presenting symptoms of 873 patients (227 women) were obtained through a face-to-face interview.

Outcome measures: Typical pain was defined according to the definition of cardiology societies. Clusters of symptoms other than pain were identified by latent class analysis. Logistic regression was used to quantify differences in presentation of ACS symptoms by sex.

Results: Chest pain was reported by 82% of patients, with no differences in frequency or location between sexes. Women were more likely to feel pain with an intensity higher than 8/10 and this association was stronger for patients under 65 years old (interaction p=0.028). Referred pain was also more likely in women, particularly pain referred to typical and atypical locations simultaneously. The multiple symptoms cluster, which was characterized by a high probability of presenting with all symptoms, was almost 4-fold more prevalent in women (3.92, 2.21–6.98). Presentation with this cluster was associated with a higher 30-day mortality rate adjusted for the GRACE 2.0 risk score (4.9% vs 0.9% for the two other clusters, p<0.001).

Conclusions: While there are no significant differences in the frequency or location of pain between sexes, women are more likely to feel pain of higher intensity and to present with referred pain and symptoms other than pain. Knowledge of these ACS presentation profiles is important for health policy decisions and clinical practice.

Keywords: Sex; acute coronary syndrome; women; diagnosis.

Strengths and limitations

Within a prospective cohort study, presenting symptoms of acute coronary syndrome were obtained through a structured questionnaire applied within the first 48 hours after admission.

Consecutive sampling, the detailed clinical information obtained through the questionnaire and adjustment for several confounding variables strengthens our results.

The results of this study are valid for stable patients admitted to the hospital and who were able to answer the questionnaire in the acute phase of the acute coronary syndrome.

Some of the sex differences in presenting symptoms may be influenced by selection bias because of a higher risk of non-inclusion of women due to misdiagnosis or death in the early hours of admission.

INTRODUCTION

Acute coronary syndrome (ACS) is still one of the main causes of death worldwide and in Europe.[1, 2] Coronary heart disease mortality has decreased in the last decades in developed countries because of primary prevention and improvement in treatment of patients with ACS.[2] Attainment of the maximal benefit of treatment of these patients is threatened by delayed diagnosis, partly dependent on clinical suspicion of ACS. The subjective experience of symptoms influences patients' attitudes in seeking help and professionals' interpretation of clinical presentations.[3] Early recognition of ACS may be challenging because while patients with presumed ACS have contact with healthcare providers,[4] many patients do not have an electrocardiogram before hospitalization.[5] Therefore, physicians frequently have to make decisions that are only clinically based.

The population of patients with atypical ACS presentation is still not well characterized.[6] Women and men generally have the same type of symptoms during an ACS episode, although the proportion presenting with different combinations of symptoms varies.[7] This conflicting evidence can be partly explained by the diverse methodology used, with few prospective studies, usually without a specific questionnaire. In prospective studies, small convenience samples were used and confounding was not always adequately addressed.[8, 9] Therefore, sex-specific research on ACS presentation is a challenge and priority.[10]

This study aimed to analyse sex differences in presenting symptoms of ACS within a prospective cohort study, taking into account the contribution of age, socioeconomic data, previous history of coronary heart disease, risk factors, comorbidities, type of ACS and coronary anatomy to the presenting symptoms.

METHODS

Study Design and Sample Selection

The EPIHeart cohort study was designed to identify inequalities in management and outcomes of patients with ACS. This study included all consecutive patients who were admitted between August 2013 and December 2014 to the Cardiology Department of two tertiary hospitals in two regions in northern Portugal (Hospital de São João, Porto, covering the metropolitan area of Porto in the coast; and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). Eligible patients were 18 years old or older who lived in the catchment area of these hospitals (districts: Porto, Vila Real, Bragança, and Viseu),

with confirmed diagnosis of type 1 (primary spontaneous) ACS. The diagnosis of type 1 ACS and the classification in different subtypes was determined by the treating cardiologist, based on symptoms and signs at presentation, electrocardiogram findings and the increase in cardiac enzyme levels (high-sensitivity troponin I or T were used), according to the third universal definition of myocardial infarction.[11] The patients were also expected to be hospitalized for at least 48 hours and not institutionalized before the event. Of 1297 patients initially considered, in 164 the diagnosis of type 1 ACS was not confirmed, 60 were excluded due to discharge or transfer before the interview, 18 died before being invited, and 44 were unable to answer the questionnaire because of clinical instability, no understanding of Portuguese, hearing problems, or cognitive impairment. Seventy-two patients refused to participate. For this analysis, we excluded 61 patients who were not admitted because of a symptom (patients referred by a doctor, after a scheduled appointment or diagnostic exam), four with vasospastic angina, and one illicit drug user. A total of 873 patients were included (Figure 1). The study protocol was in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of both hospitals (*Comissão de Ética para a Saúde do Centro Hospitalar de S. João* and *Comissão de Ética do Centro Hospitalar de Trás-os-Montes e Alto Douro*, reference numbers of the approvals: 82/13 and 1286, respectively). All patients gave written informed consent.

Procedures and data collection

Presenting symptoms were obtained face-to-face using a structured questionnaire applied by trained interviewers, within the first 48 hours after admission, whenever possible. Over the following days, a second interview was conducted to collect data on sociodemographic characteristics and risk factors. Medical records were reviewed to extract data regarding previous medical history, admission information, and clinical data during hospitalization.

Pain, referred pain, and symptoms other than pain were measured dichotomously (yes/no). For the location of pain (direct and referred) patients were asked to point out where pain was occurring. To measure the intensity of pain, a 10-point scale (0, no pain; 10, pain of maximal intensity) was used. Symptoms other than pain included dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, and an open-ended question of "other" (12 items). Answers to the last item enabled identification of two other relatively frequent symptoms, other digestive symptoms and discomfort. Activity at the onset of the episode was measured

dichotomously, including sleeping, rest, and any exertion. A stress trigger was assigned if the patient answered "yes" for at least one of following events within 24 hours preceding the episode: accident, recent diagnosis of disease, financial problems, and news of death/disease of a relative/friend.

Marital status was considered partnered for married patients or living in civil union. Education was recorded as completed years of schooling and classified into four categories: less than 4 (little formal education), 4 (elementary school), less than 12 (high school), and 12 or more years (secondary education or more). Occupations were classified into major professional groups, according to the Portuguese Classification of Occupations 2010,[12] integrated in the International Standard Classification of Occupations (ISCO/2008).

Definition of Variables

Although symptoms of ACS have been widely described, their value for diagnosis of ACS is not unanimously recognized.[13-15] After discussion with clinical cardiologists of our team, we opted to use Cardiology Societies' position papers to define direct and referred pain locations and to select symptoms to evaluate.[16, 17] Direct pain location was classified as follows: 1) typical for retrosternal, precordial, right thoracic, or bilateral thoracic pain (chest pain); 2) atypical for epigastric pain or located in the back, left arm or shoulder, right arm or shoulder, neck, or jaw; and 3) a mixture when both typical and atypical locations were present. Referred pain location was considered as follows: 1) typical if pain referred to the left arm or shoulder, right arm or shoulder, neck, or jaw; 2) atypical if pain referred to retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; and 3) a mixture for referred pain in typical and atypical locations.

Patients rarely present with a single symptom during an episode of ACS, and present with multiple symptoms instead that do not occur in isolation and may cluster.[18] There has been increasing interest in symptom cluster analysis in cardiovascular disease because it aids in assessment by enhancing recognition of patients with similar symptom profiles.[19] Groups of symptoms other than pain were obtained by latent class analysis.

The small group of non-classified (NC) patients with ACS (patients with left bundle branch block) was grouped with patients with ST elevation myocardial infarction (STEMI) (STEMI/NC ACS group). Non-ST elevation ACS (NSTEACS) included unstable angina and non-ST elevation acute myocardial infarction or subacute myocardial infarction.

Considering the possible association between coronary anatomy and clinical presentation, we grouped patients according to coronary angiography into five groups: managed conservatively; non-obstructive coronary artery disease; lesions exclusively in the anterior descending artery; lesions in the right and/or circumflex artery; and lesions in the left main coronary artery, three-vessel disease or disease both in the anterior descending artery and the right or circumflex artery.

Data Analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). Categorical variables are shown as number and percentage. To compare differences between women and men, and by age-groups, the chi-square or Fisher's test was used for categorical variables and the t-test, Mann-Whitney or Kruskal-Wallis tests for continuous variables. Latent class analysis was used to identify distinct groups of individuals from a sample (clusters) who were homogeneous within the group. This was based on the fact that performance of an individual in a set of items is explained by a categorical latent variable with K classes (clusters), commonly called latent classes. The number of latent clusters was defined according to the Akaike information criterion (AIC). Starting from one single cluster and increasing one cluster at each step, the best solution was identified when an increase in the number of clusters did not lead to a decrease in the AIC.

Patient and system delays, severity indicators, risk stratification using calculated GRACE and CRUSADE risk scores, left ventricular systolic dysfunction and 30-day mortality rate adjusted for the GRACE 2.0 risk score,[20] were assessed according to presence of typical (chest) pain and cluster of symptoms other pain. The 30-day mortality adjusted for the GRACE 2.0 risk score was estimated based on predicted probabilities derived from logistic regression. Logistic regression was used to identify variables associated with clinical presentation. Variables with $p<0.15$ for a crude association with the endpoint were entered in the initial model and a backward strategy was used to exclude the least significant variables, based on Wald tests. We were then able to obtain the most parsimonious model with all the important determinants. Previous data support significant interaction between age and sex with clinical presentation, attenuated with advancing age, mainly in those 65 years old or older.[3] We assessed for effect measure modification by stratifying adjusted analyses based on two age groups (under 65 and 65 years old or older). Considering the relevance of analysing sex differences in ACS clinical presentation in younger

patients, we also performed the age stratified multivariate models using 55 years old as cut-off. Sex, age (continuous), and type of ACS were forced to remain in the models.

All analyses were performed using STATA version 11.1 for Windows (Stata Corp LP, College Station, TX) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Women (n=227, 26.0%) were older (69.1 vs 62.2 years, p<0.001) and more frequently lived in the interior region (52.4% vs 38.7%, p<0.001) than men. Women were more often treated conservatively and had non-obstructive coronary artery disease more frequently than men. In this sample, no difference by sex was observed in the type of ACS, where 56.6% of the patients had a discharge diagnosis of NSTEACS (Table 1).

Women more frequently had hypertension (81.5% vs 62.7%, p<0.001) and diabetes (38.8% vs 29.9%, p=0.014), and were more frequently obese (25.5% vs 18.5%, p=0.020) and never smokers compared with men (p<0.001, Table 1). Men were submitted to percutaneous coronary intervention more often than women. There were no significant differences in a previous history of renal failure, prior myocardial infarction, prior coronary artery bypass surgery, prior heart failure, and dementia by sex (Table 1).

Women were more likely to be unpartnered, disabled, less educated, and had a lower income compared with men. The median time that elapsed between admission and application of the symptom questionnaire was slightly longer in women than in men (Table 1).

Table 1. Baseline demographic, socioeconomic and clinical characteristics in the whole sample and by sex*

	Total (n = 873)	Women (n = 227)	Men (n = 646)	p
Age (years), mean (SD)	64.0 (13.0)	69.1 (12.7)	62.2 (12.7)	<0.001
Socioeconomic				
Marital status				
Partnered	667 (76.8)	133 (58.9)	534 (83.2)	<0.001
Education				
Little formal education	172 (19.9)	95 (42.4)	77 (12.0)	
Elementary school	337 (39.1)	73 (32.6)	264 (41.3)	
High school	213 (24.7)	32 (14.3)	181 (28.3)	
Secondary education or more	141 (16.3)	24 (10.7)	117 (18.3)	<0.001
Employment status				
Employed/looking after home	282 (32.6)	64 (28.3)	218 (34.1)	
Unemployed	107 (12.4)	16 (7.1)	91 (14.2)	
Retired	334 (38.6)	93 (41.2)	241 (37.7)	
Disabled	143 (16.5)	53 (23.5)	90 (14.1)	<0.001
Subjective social class				
Low	281 (32.2)	81 (35.7)	200 (31.0)	
Lower-middle	281 (32.2)	58 (25.6)	223 (34.5)	
Higher-middle/High	60 (6.9)	16 (7.1)	44 (6.8)	
No response	251 (28.8)	72 (31.7)	179 (27.7)	0.097
Household income (euros)				
<500	204 (23.4)	77 (33.9)	127 (19.7)	
501-1000	276 (31.6)	60 (26.4)	216 (33.4)	
1001 – 2000	146 (16.7)	22 (9.7)	124 (19.2)	
>2000	88 (10.1)	14 (6.2)	74 (11.5)	
No response	159 (18.2)	54 (23.8)	105 (16.3)	<0.001
Region				
Metropolitan area of Porto	504 (57.7)	108 (47.6)	396 (61.3)	
North-eastern region of Portugal	369 (42.3)	119 (52.4)	250 (38.7)	<0.001
Cardiovascular risk factors				
Smoking habit				
Never	369 (42.3)	184 (81.0)	185 (28.6)	
Current	283 (32.4)	34 (15.0)	249 (38.5)	
Former	221 (25.3)	9 (4.0)	212 (32.8)	<0.001
Hypertension	590 (67.6)	185 (81.5)	405 (62.7)	<0.001
Diabetes mellitus	281 (32.2)	88 (38.8)	193 (29.9)	0.014
Dyslipidaemia	535 (61.4)	144 (63.4)	391 (60.6)	0.454
BMI (kg/m^2)				
Median (IQR)	26.5 (18.0-44.6)	26.7 (19.5-37.9)	26.4 (18.2-39.2)	0.531
Underweight	11 (1.4)	2 (0.9)	9 (1.5)	
Normal weight	272 (33.4)	80 (37.0)	192 (32.1)	
Overweight	366 (44.9)	79 (36.6)	287 (47.9)	
Obese	166 (20.4)	55 (25.5)	111 (18.5)	0.020
Family history of CVD	303 (34.7)	73 (32.2)	230 (35.6)	0.105
Previous medical history				
Renal failure	64 (7.3)	14 (6.1)	50 (7.7)	0.434
Myocardial infarction	156 (17.9)	34 (15.0)	122 (18.9)	0.186
PCI	100 (12.4)	18 (8.4)	82 (13.8)	0.041
CABG	34 (4.2)	5 (2.3)	29 (4.9)	0.111
Heart failure	63 (7.5)	21 (9.6)	42 (6.8)	0.172
Dementia	7 (0.8)	4 (1.8)	3 (0.5)	0.060
ACS type				
STEMI/NC ACS	379 (43.4)	101 (44.5)	278 (43.0)	
NSTEACS	494 (56.6)	126 (55.5)	368 (57.0)	0.703
Coronary anatomy				
Non-obstructive disease	57 (6.9)	22 (10.6)	35 (5.61)	
Left anterior descending artery only	162 (19.5)	38 (18.3)	124 (19.9)	
Right and/or circumflex artery only	196 (23.6)	46 (22.1)	150 (24.0)	
Mixture	417 (50.1)	102 (49.0)	315 (50.5)	
Not submitted to coronary angiography	41 (4.7)	19 (8.4)	22 (3.4)	0.004
Symptom questionnaire application				
Time from admission (hours), median (IQR)	42.1 (25.0-68.0)	45.4 (28.5-72.3)	40.0 (24.0-67.4)	0.052

*Values are number and percentage unless otherwise indicated.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; CVD, cardiovascular diseases; IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/non-classifiable acute coronary syndrome.

Symptom characteristics by sex and age

Because differences in symptoms by sex and age were similar in direction and magnitude in STEMI/NC ACS and NSTEACS (Supplementary Tables 1 and 2), both types of ACS were analysed together.

Although pain was present in most patients, men presented with pain more frequently than did women (97.4% vs 94.3%, p=0.028), with a higher sex difference among patients with 80 or more years old (88.0% vs 93.5%). Older patients presented less often pain, but the difference by age group in both sexes was not significant (Table 2). No difference was found in the location of pain by sex. Approximately 80% of patients felt chest pain (typical pain). Older women presented less frequently with chest pain and had chest pain and pain in other locations (mixture group) more often than did younger women (p=0.014). Referred pain was observed more frequently in women and in younger patients (only significant for men, p=0.024); again in the older age group, the difference between women and men was notorious (56.8% vs 39.7%, respectively). Atypical and mixture referred pain were more frequent in women than in men (p<0.001), mainly in women aged ≥65 years (p=0.009). Women felt pain with higher intensity than did men (median [IQR]: 9 [8–10] vs 8 [6–9], p<0.001), without a difference by age (Table 2). Women presented with symptoms other than pain more frequently than did men (82.8% vs 68.9%, p<0.001), with no difference by age group in both sexes (Table 2).

Considering symptoms other than pain, the AIC optimum value supported a preference for a three-cluster solution (AIC 7207.508, 6869.390, 6862.476, and 6870.372 for one, two, three, and four clusters, respectively). Cluster 1 had low endorsement probabilities for all items (no symptoms cluster). Cluster 2 had a high probability for dyspnoea at rest and sweating, and a low probability for the remaining items (dyspnoea and sweating cluster). Cluster 3 had high probabilities for all items (multiple symptoms cluster). This three-cluster model made sense conceptually to cardiologists of our team. Clusters counts and probabilities of occurrence of symptoms in established clusters are shown in Supplementary Table 3. Differences in proportions of women and men in the three clusters were observed (p<0.001, Table 2). Cluster 1 was the most prevalent, in which men presented with the no symptoms cluster more frequently (76.9% vs 62.6%) and the multiple symptoms cluster less frequently (4.8% vs 15.9%) than did women. Higher differences of multiple symptoms cluster proportions between women and men were observed among patients in the older age group. The proportion of dyspnoea and sweating cluster was similar in men and women (Table 2).

Approximately 45% of patients were at rest and 35% were under physical effort at the beginning of the episode. Older women were more frequently at rest at the beginning of the episode and younger women were more frequently under effort (p=0.011). Less than 10% of patients identified a stressful event in the previous 24 hours, with no difference by sex, but among men, a younger age was slightly associated with this trigger (p=0.045, Table 2).

Table 2. Clinical presentation of patients with acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	14 (6.2)	54 (23.8)	109 (48.0)	50 (22.0)	227 (100.0)		61 (9.4)	303 (46.9)	220 (34.1)	62 (9.6)	646 (100)		
Pain	14 (100.0)	52 (96.3)	104 (95.4)	44 (88.0)	214 (94.3)	0.229	60 (98.4)	297 (98.0)	214 (97.3)	58 (93.5)	629 (97.4)	0.228	0.028
Pain location†													
Typical	12 (85.7)	43 (82.7)	88 (85.4)	32 (72.7)	175 (82.2)		53 (89.8)	246 (83.7)	175 (82.2)	44 (75.9)	518 (83.0)		
Atypical	1 (7.1)	9 (17.3)	5 (4.9)	6 (13.6)	175 (9.9)		3 (5.1)	33 (11.2)	30 (14.1)	10 (17.2)	76 (12.2)		
Mixture	1 (7.1)	0 (0.0)	10 (9.7)	6 (13.6)	17 (8.0)	0.014	3 (5.1)	15 (5.1)	8 (3.8)	4 (6.9)	30 (4.8)	0.327	0.165
Referred pain	9 (64.3)	41 (78.8)	72 (69.2)	25 (56.8)	147 (68.7)	0.129	38 (63.3)	179 (60.3)	126 (58.9)	23 (39.7)	366 (58.2)	0.024	0.007
Radiation type‡													
Typical	8 (88.9)	20 (48.8)	28 (38.9)	7 (28.0)	63 (42.9)		28 (73.7)	114 (64.4)	67 (53.2)	10 (43.5)	219 (60.2)		
Atypical	0 (0.0)	13 (31.7)	18 (25.0)	13 (52.0)	44 (29.9)		7 (18.4)	37 (20.9)	39 (31.0)	8 (34.8)	91 (25.0)		
Mixture	1 (11.1)	8 (19.5)	26 (36.1)	5 (20.0)	40 (27.2)	0.009	3 (7.9)	26 (14.7)	20 (15.9)	5 (21.7)	54 (14.8)	0.104	<0.001
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-9)	8 (8-9)	9 (8-10)	0.170	8 (7-10)	8 (6-9)	8 (6-9)	8 (7-9)	8 (6-9)	0.095	<0.001
Symptom	11 (78.6)	45 (83.3)	91 (83.5)	41 (82.0)	188 (82.8)	0.947	43 (70.5)	209 (69.0)	151 (68.6)	42 (67.7)	445 (68.9)	0.989	<0.001
Symptom clusters‖													
Cluster 1	7 (50.0)	41 (75.9)	62 (56.9)	32 (64.0)	142 (62.6)		43 (70.5)	232 (76.6)	170 (77.3)	52 (83.9)	497 (76.9)		
Cluster 2	5 (35.7)	8 (14.8)	28 (25.7)	8 (16.0)	49 (21.6)		15 (25.6)	59 (19.5)	35 (15.9)	9 (14.5)	118 (18.3)		
Cluster 3	2 (14.3)	5 (9.3)	19 (17.4)	10 (20.0)	36 (15.9)	0.183	3 (4.9)	12 (4.0)	15 (6.8)	1 (1.61)	31 (4.80)	0.345	<0.001
Activity													
Sleep	2 (15.4)	16 (32.0)	11 (10.4)	7 (14.9)	36 (16.7)		6 (9.8)	65 (21.7)	35 (16.1)	13 (21.3)	119 (18.6)		
Rest	5 (38.5)	18 (36.0)	50 (47.2)	29 (61.7)	102 (47.2)		34 (55.7)	124 (41.3)	105 (48.2)	33 (54.1)	296 (46.3)		
Exertion	6 (46.2)	16 (32.0)	45 (42.5)	11 (23.4)	78 (36.1)	0.011	21 (34.4)	111 (37.0)	78 (35.8)	15 (24.6)	225 (35.2)	0.087	0.816
Stress trigger	2 (14.3)	6 (11.1)	11 (10.2)	3 (6.1)	22 (9.8)	0.700	11 (18.0)	23 (7.7)	15 (6.9)	6 (9.8)	55 (8.6)	0.045	0.605

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ||Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Multivariate models

Despite the higher probability of women below or above 65 years old to present without pain than men, no differences were observed in the adjusted pain frequency and location between men and women. Referred pain was more likely to be experienced by women (<65 years old: adjusted odds ratio [OR] 2.90, 95% confidence interval [95% CI] 1.47-5.72; >=65 years old: 1.60 (0.99-2.60), p for interaction=0.528)). Moreover, women below or above 65 years old had a higher probability of having pain radiating to typical and atypical locations and of feeling pain with an intensity higher than 8 (Table 3). The association between intensity of pain and female sex was stronger for patients below 65 years old (interaction p=0.028) (Table 3).

The presence of at least one symptom other than pain occurred almost two times more often in women than in men. With cluster 1 as the reference, cluster 2 and 3 were positively associated with female sex, with the latter being statistically significant. The multiple symptoms cluster was almost 4-fold more likely in women than in men (3.92, 2.21-6.98 in the whole sample, interaction p=0.501) (Table 3).

No difference in the type of patients' activities at the beginning of the episode by sex was observed (Table 3).

Performance of age stratified multivariate models using the 55 years old cut-off revealed similar results to the observed using the 65 years old cut-off, with some differences mainly in the strength of association of some clinical presentation variables with sex among the younger age group (Supplementary Table 4), Although still not significant, among patients below 55 years old, women were less likely to present with typical chest pain (0.65, 0.23-1.86). A stronger association between female sex and referred pain, and intensity of pain higher than 8/10, among patients in the younger age groups was observed using the 55 instead of the 65 years cut-off. The remaining results were similar in direction and strength of association (Table 3 and Supplementary Table 4). The precision of the estimates is lower using the 55 cut-off, due to the small sample of patients below 55 years old.

Table 3. Differences between women and men in clinical presentation of acute coronary syndrome, by age group
(men are the reference class).

	<65 years		>=65 years			
Symptoms	**OR**	**95% CI**	**OR**	**95% CI**	**Interaction p-value**	**Adjusted for**
Pain	0.76	0.14-4.0	0.52	0.19-1.47	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)*	0.97	0.44-2.14	1.71	0.90-3.23	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	2.90	1.47-5.72	1.60	0.99-2.60	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type†						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.49	0.70-3.20	1.38	0.72-2.66	0.415	
Mixture	1.77	0.73-4.29	2.75	1.36-5.57	0.606	
Pain intensity (higher than 8/10)	3.81	2.04-7.13	2.03	1.22-3.37	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.98	1.00.3.91	1.85	1.10-3.12	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters‡						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	1.07	0.53-2.15	1.67	0.97-2.87	0.246	
Cluster 3	3.14	1.15-8.62	4.23	2.03-8.81	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.68	0.33-1.38	1.38	0.74-2.57	0.284	
Exertion	0.77	0.37-1.59	1.70	0.89-3.25	0.408	

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG: coronary artery bypass surgery; CI, confidence interval; OR, odds ratio.
*Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.
†Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.
‡Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

Clinical presentation and outcomes

Patients with a diagnosis of STEMI/NC ACS who presented with atypical or mixture pain took longer to seek medical care (135 vs 85 min., p=0.012) and had longer total ischemic times (414 vs 328 min., p=0.080) than patients with chest pain (Table 4). Among patients with NSTEACS, differences in time delays according to pain location were not significant. Patients with atypical or mixture pain presented more frequently with hemodynamic instability at admission (9.7% vs 4.6%, p=0.014) and had also more often moderate to severe left ventricular systolic dysfunction (32.9 vs 24.9%, p=0.052) than patients with chest pain. The 30-day mortality adjusted for GRACE 2.0 was not significantly different between patients with chest pain and those with atypical or mixture pain (Table 4).

Among patients with STEMI/NC ACS, the total ischemic time was longer for patients with the multiple symptoms cluster compared with patients who presented with the two other symptoms clusters (533 minutes vs 321 and 384, p=0.111). Patients with the multiple symptom cluster presented more often with hemodynamic instability at admission than patients with the other symptoms clusters (13.4% vs 6.4% and 4.2%, p=0.034). The mean 30-day mortality rate adjusted for the GRACE 2.0 risk score was significantly higher for patients presenting with the multiple symptom cluster (4.9% vs 0.9% for the two other clusters, p<0.001) (Table 4).

Patients with atypical or mixture chest pain and patients with the multiple symptom cluster had higher mean GRACE and median CRUSADE risk scores (Table 4).

Table 4. Patient and system delays, severity indicators, risk stratification and 30-day mortality according to clinical presentation*

	Typical (chest) pain†	Atypical or mixture pain	p	No symptom cluster ‡	Dyspnoea and sweating cluster	Multiple symptoms cluster	p
Patient and system delays, median (IQR)							
STEMI/NC ACS							
Symptom onset – FMC (min)	85 (45-210)	135 (65-325)	0.012	90 (46-240)	90 (50-185)	83 (45-430)	0.872
Symptom onset-arterial access (min)	328 (192-1075)	414 (246-1335)	0.080	321 (194-1011)	384 (201-1440)	533 (323-1428)	0.111
NSTEACS							
Symptom onset – FMC (min)	130 (60-393)	139 (60-335)	0.633	135 (60-390)	150 (60-390)	113 (45-393)	0.795
Hospital admission- coronary angiography time (hours)	30 (18-57)	29 (20-48)	0.884	30 (18-56)	35 (18-70)	28 (20-72)	0.385
Admission variables							
Heart rate, mean (SD), bpm	77 (18)	80 (24)	0.117	78 (19)	77 (19)	78 (28)	0.923
Systolic blood pressure, mean (SD), mmHg	144 (49)	139 (30)	0.212	145 (59)	141 (30)	136 (33)	0.364
Hemodynamic instability at admission§	32 (4.6)	14 (9.7)	0.014	41 (6.4)	7 (4.2)	9 (13.4)	0.034
Risk stratification							
Calculated GRACE risk score, mean (SD)	134 (36)	147 (39)	<0.001	137 (37)	138 (35)	149 (44)	0.041
Calculated CRUSADE risk score, median (IQR)	21 (11-34)	25 (14-41)	0.012	22 (12-36)	23 (10-36)	30 (16-47)	0.019
Moderate or severe left ventricular systolic dysfunction	169 (24.9)	46 (32.9)	0.052	164 (26.4)	55 (33.3)	17 (25.4)	0.187
30-day mortality rate adjusted for the GRACE 2.0 risk score, mean (SD)	2.0 (4.0)	1.3 (1.4)	0.521	0.9 (2.0)	0.9 (2.0)	4.9 (5.5)	<0.001

IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/Non-classifiable acute coronary syndrome.
*Values are number and percentage unless otherwise indicated.
Total may not add to 100% due to missing data.
†Chest pain: retrosternal, precordial, right thoracic, or bilateral thoracic.
‡No symptom cluster: low endorsement probabilities for all items; Dyspnoea and sweating cluster: high probability for dyspnoea atrest and sweating; Multiple symptoms cluster: high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort)
§Killip class III or IV; or shock at admission.

DISCUSSION

In our study, after adjustment, no differences in the frequency and location of pain by sex were observed. Referred pain, pain radiating to typical and atypical locations, and pain of higher intensity were more likely to occur among women. Women were also more likely than men to present with symptoms other than pain. Three clusters of symptoms other than pain were identified. Women were more likely to present with the multiple symptoms cluster. Presenting with the multiple symptoms cluster was associated with a higher mean 30-day mortality rate adjusted for the GRACE 2.0 risk score.

Differences between women and men in perception of symptoms of ACS might be explained by anatomical, physiological, biological, and psychosocial differences that influence each other.[9, 21] We measured several variables of these different domains. Differences in symptom presentation by sex might be the result of differences in response to history-taking,[10] differences in neural receptors and pathways involved in pain, and subtle differences in the location and type of atherosclerotic lesions.[22, 23] Our findings of similar ACS symptoms between women and men are consistent with previous studies,[7, 24] as well as our finding that women are more likely to have atypical presentations.[9] We observed that women have a higher likelihood of atypical referred pain and of several concomitant symptoms other than pain, common to other cardiac and non-cardiac diagnoses.

In our study, chest pain was the most frequent symptom in both sexes, consistent with previous studies.[25-27] Among those with pain, typical chest pain was observed in 82% of patients, regardless of sex. The remaining patients had pain in less typical locations and were thus prone to misdiagnosis and undertreatment and, consequently, to worse outcomes.[28] Considering differences in characteristics of pain by sex, studies suggested that women, in particular older women, were less likely to have the chief complaint of chest pain associated with acute myocardial infarction; while after adjustment, among patients with 65 or less years old, female sex was no longer a significant predictor.[29] Studies reported that chest pain did not differ between women and men,[9] others that women have pain in the neck and back more often than men,[30, 31] without distinguishing between direct and referred pain. In our study, referred pain was observed in 61% of patients, was more frequent in women, and typical referred pain was only observed in 33%. Notably, a study on diagnostic acuity of ACS symptoms showed that shoulder and arm pain was predictive of the diagnosis of ACS for women only.[24] Another study (GENESIS PRAXY) on sex differences in ACS symptom presentation in patients with 55 years old or younger showed that being a woman was independently associated with ACS presentation without chest pain.[27] Although the

association was not significant, and relied on a small sample of patients, our finding that women with 55 years old or younger were less likely to present with typical chest pain is in line with the GENESIS PRAXY study result.[27] Furthermore it stresses the relevance of taking into account age for studying the association between sex and clinical presentation. Differences in age distribution, in clinical presentation measuring, in selection and definition of confounder variables limit conclusive comparisons of studies evaluating differences in frequency and location of pain between women and men.

According to previous studies, with regard to other symptoms, a higher proportion of women have less typical symptoms than men.[8, 31] Women have also reported other symptoms, such as indigestion, palpitations, nausea, numbness in the hands, and unusual fatigue, more frequently than men.[9] In our cohort, three symptom clusters were identified. Women had the multiple symptoms cluster more frequently than did men, characterized by high probabilities for all symptoms. According to Rosenfeld et al. women are more likely to cluster in a similar class, called the heavy symptom burden class.[32] With regard to ACS symptom clustering, there are contradictory findings on identified clusters, the proportion of patients per cluster, and differences between clusters regarding demographic factors. In our study, cluster 1 and 3 (low and high probabilities for all symptoms, respectively) are in line with observations of other settings.[18, 33] A recent systematic review of symptom clusters in cardiovascular disease[34] identified clusters with the most symptoms and clusters with the lowest number of symptoms. Our dyspnoea and sweating cluster has two common symptoms with the Riegel et al.[26] stress symptoms cluster, which includes shortness of breath, sweating, nausea, indigestion, dread, and anxiety.

Methodological differences related to sampling and measuring might explain these different results. Strengths of our study include consecutive sampling, a questionnaire with detailed clinical information was systematically applied, and we adjusted for several confounding variables.

The value of symptoms for diagnosis of ACS varies across studies.[14, 35, 36] Overall, the diagnostic performance of chest pain characteristics for diagnosis is limited, with likelihood ratios close to 1.[37] Sensitivity for individual symptoms of ACS, using the 13-Item Acute Coronary Syndrome Checklist, ranges from 27% to 67% for women and 14% to 72% for men. Additionally, specificity ranges from 33% to 78% for women and 34% to 78% for men, with different associations between some symptoms and diagnosis of ACS by sex.[24] However, physicians still base the likelihood of ACS mainly on symptoms and use the electrocardiogram to rule in the diagnosis.[38] Evaluation of these patients is mostly unchanged, without implementation of evidence-based assessment tools in clinical practice to improve diagnostic

accuracy. Public health messages should take into account the complexity of presenting symptoms of ACS, particularly the significant proportion of women and men with ACS without typical chest pain. Additionally, there is a higher likelihood of atypical referred pain and multiple concomitant symptoms in women. These factors should be accounted for to encourage timely and appropriate care of patients with ACS.

Presenting without chest pain and with the multiple symptoms cluster was associated with several markers of higher ACS severity and longer time delays, particularly significant among patients with STEMI/NC ACS. In our study, presenting with the multiple symptoms cluster, but not with atypical or mixture location of pain, was associated with a higher mean 30-day mortality adjusted for GRACE risk score. These results are consistent with data from the GRACE registry, that showed that patients with symptoms other than pain experienced greater morbidity and higher in-hospital mortality across the spectrum of ACS.[28] Other registry showed that the higher in-hospital mortality observed among women and men without chest pain, decreased or even reversed with advanced age.[39] Mortality is adjusted for GRACE risk score, however we cannot conclude that the difference in outcome observed is explained by symptoms other than pain per se. Previous studies showed that the higher in-hospital mortality of ACS patients who presented without chest pain was mostly due to late hospital arrival, comorbidities and underuse of medications and invasive procedures. [6, 39, 40] These studies focused mainly on presence of chest pain to define atypical presentation and used medical record reviews to characterize clinical presentation. More studies are needed to further explore the association between symptoms other than pain and outcomes.

Limitations

Participants were interviewed as soon as possible after admission, but this does not obviate the retrospective nature of data collection and the possibility of recall bias. Furthermore preceding interviews by physicians may have influenced answers to the questionnaire, however different consequences in women and men are not expected. The results of this study are valid for stable patients, who were admitted to the hospital and were able to answer the questionnaire in the acute phase of ACS. This type of study misses patients who die before reaching the hospital, patients who do not seek medical care, patients who are mistakenly discharged or misdiagnosed and admitted to non-cardiology departments.

This sample selection process may contribute to underestimate the true prevalence of ACS atypical presentation in women and men.[27] For patients who were eligible but not enrolled only information on sex, age and type of ACS was available. Patients who died before the interview were older (81.5±11.8 vs 64.6±13.1 years, p<0.001), were more often women (66.7% vs 26.0%, p<0.001), and more frequently had a diagnosis of STEMI (81.3% vs 43.4%, p=0.003) than did participants. Patients who were discharged or transferred to another hospital before the interview had STEMI less often (25.0% vs 43.4%, p=0.005) and patients who were not enrolled because of clinical instability or inability to understand the questionnaire were older. Patients who refused to participate were older (72.7±11.0 vs 64.0±13.0 years, p<0.001), were less often partnered (65.7% vs 76.8%, p=0.036), and had little formal education (43.1% vs 19.7%, p<0.001) compared with participants. Except for deceased patients, no difference in sex proportion was observed between participants and non-participants. We cannot exclude that some of the sex differences were caused by selection bias because of a higher risk of non-inclusion of women due to death in the early hours of admission, or due to a possible higher probability of misdiagnosis in women, particularly those with unstable angina.[41] Considering that atypical presentation is associated with a worse prognosis and with a higher probability of misdiagnosis, the proportion of patients with ACS presenting without typical chest pain or that of women with an atypical presentation could be even higher.[28]

CONCLUSION

This study shows no significant differences in the frequency and location of pain by sex, but approximately 20% of patients do not present with chest pain, regardless of sex. Women are more likely to report referred pain and multiple symptoms simultaneously. Presentation with the multiple symptoms cluster pain is associated with higher 30-day mortality adjusted for GRACE score. Health education messages should take into account the complexity of presentation of ACS and emphasize the possible non-chest location of pain in both sexes and the higher probability of concomitant symptoms other than pain in women. Further sex-stratified analysis of ACS presentation, also addressing the role of age for the relation between sex and clinical presentation, is required to determine the diagnostic accuracy of symptoms by sex.

Figure 1. Flow chart of the study population

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Contributors

Carla Araújo and Ana Azevedo had the original idea to develop the EPIHeart cohort study and were responsible for acquiring the study grant. Carla Araújo raised the hypotheses, participated in data collection and field work, analysed and interpreted the data, and drafted the first version of the manuscript. Olga Laszczyńska analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. Marta Viana and Andreia Borges participated in data collection, field work and interpretation of the data. Filipa Melão and Ana Henriques interpreted data. Milton Severo analysed and interpreted the data. Maria Júlia Maciel and Ilídio Moreira were involved in the conception of the study and in field work. Ana Azevedo was the responsible for the conception and development of the study, analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. All authors were involved in writing the paper, in revising it critically and approved the final version of the submitted manuscript.

Data sharing

Data are available by email the corresponding author at carla-r-araujo@hotmail.com.

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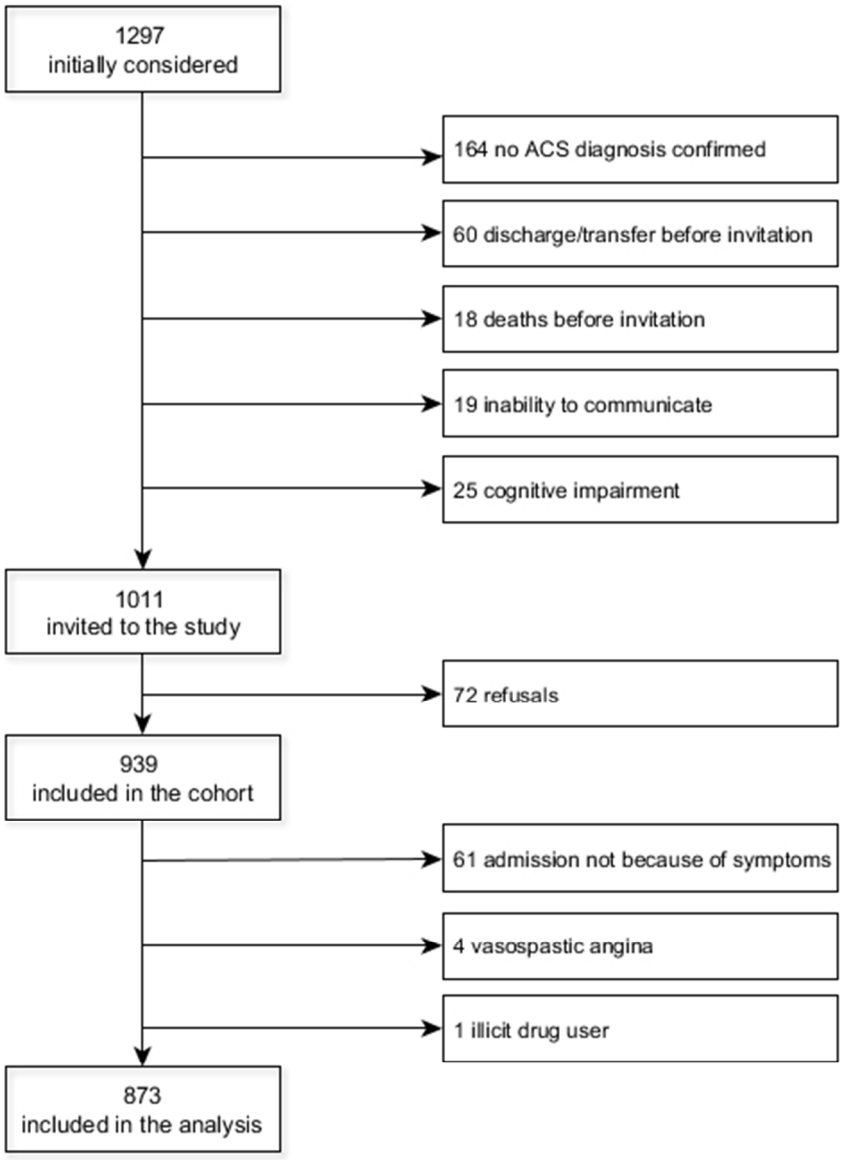

Figure 1. Flow chart of the study population

41x56mm (300 x 300 DPI)

Supplementary Table 1. Clinical presentation of patients with ST elevation myocardial infarction/non-classifiable acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	6 (5.9)	22 (21.8)	53 (52.5)	20 (19.8)	101 (100.0)		37 (13.3)	144 (51.8)	77 (27.7)	20 (7.2)	278 (100)		
Pain	6 (100.0)	21 (95.5)	52 (98.1)	16 (80.0)	95 (94.1)	0.039	36 (97.3)	142 (98.6)	73 (94.8)	20 (100.0)	271 (97.5)	0.338	0.106
Pain location†													
Typical	5 (83.3)	17 (81.0)	44 (84.6)	9 (56.3)	75 (78.9)		31 (88.6)	120 (85.1)	55 (76.4)	13 (65.0)	219 (81.7)		
Atypical	1 (16.7)	4 (19.0)	2 (3.8)	5 (31.3)	12 (12.6)		1 (2.9)	17 (12.1)	14 (19.4)	5 (25.0)	37 (13.8)		
Mixture	0 (0.0)	0 (0.0)	6 (11.5)	2 (12.5)	8 (8.4)	0.021	3 (8.6)	4 (2.8)	3 (4.2)	2 (10.2)	12 (4.5)	0.032	0.347
Referred pain	4 (66.7)	18 (85.7)	38 (73.1)	8 (50.0)	68 (71.6)	0.114	24 (66.7)	90 (63.4)	51 (69.9)	7 (35.0)	172 (63.5)	0.038	0.152
Radiation type‡													
Typical	3 (75.0)	8 (44.4)	17 (44.7)	1 (12.5)	29 (42.6)		19 (79.2)	53 (59.6)	26 (51.0)	3 (42.9)	101 (59.1)		
Atypical	0 (0.0)	5 (27.8)	10 (26.3)	4 (50.0)	19 (27.9)		5 (20.8)	21 (23.6)	9 (17.6)	3 (42.9)	38 (22.2)		
Mixture	1 (25.0)	5 (27.8)	11 (28.9)	3 (37.5)	20 (29.4)	0.504	0 (0.0)	15 (16.9)	16 (31.4)	1 (14.3)	32 (18.7)	0.018	0.060
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-10)	8.5 (8-9)	9 (8-10)	0.784	9 (7.5-10)	8 (7-10)	8 (6.5-9)	7.5 (6.5-9)	8 (7-10)	0.064	<0.001
Symptom	5 (83.3)	20 (90.9)	47 (88.7)	17 (85.0)	89 (88.1)	0.794	23 (62.2)	105 (72.9)	61 (79.2)	14 (70.0)	203 (73.0)	0.283	0.002
Symptom clusters‖													
Cluster 1	2 (33.3)	18 (81.8)	27 (50.9)	11 (55.0)	58 (57.4)		26 (70.3)	102 (70.8)	54 (70.1)	16 (80.0)	198 (71.2)		
Cluster 2	3 (50.0)	2 (9.1)	16 (30.2)	4 (20.0)	25 (24.8)		9 (24.3)	36 (25.0)	19 (24.7)	3 (15.0)	67 (24.1)		
Cluster 3	1 (16.7)	2 (9.1)	10 (18.9)	5 (25.0)	18 (17.8)	0.132	2 (5.4)	6 (4.2)	4 (5.2)	1 (5.0)	13 (4.7)	0.967	<0.001
Activity													
Sleep	1 (16.7)	3 (14.3)	4 (7.8)	3 (15.8)	11 (11.3)		5 (13.5)	29 (20.1)	10 (13.0)	4 (20.0)	48 (17.3)		
Rest	3 (50.0)	9 (42.9)	22 (43.1)	14 (73.7)	48 (49.5)		19 (51.4)	65 (45.1)	43 (55.8)	13 (65.0)	140 (50.4)		
Exertion	2 (33.3)	9 (42.9)	25 (49.0)	2 (10.5)	38 (39.2)	0.069	13 (35.1)	50 (34.7)	24 (31.2)	3 (15.0)	90 (32.4)	0.393	0.274
Stress trigger	1 (16.7)	2 (9.1)	4 (7.5)	3 (15.8)	10 (10.0)	0.519	5 (13.5)	11 (7.7)	6 (7.9)	2 (10.0)	24 (8.7)	0.669	0.697

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 2. Clinical presentation of patients with non-ST elevation acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	8 (6.3)	32 (25.4)	56 (44.4)	30 (23.8)	126 (100)		24 (6.5)	159 (43.2)	143 (38.9)	42 (11.4)	368 (100)		
Pain	8 (100.0)	31 (96.9)	52 (92.9)	28 (93.3)	119 (94.4)	0.864	24 (100.0)	155 (97.5)	141 (98.6)	38 (90.5)	358 (97.3)	0.073	0.131
Pain location†													
Typical	7 (87.5)	26 (83.9)	44 (86.3)	23 (82.1)	100 (84.7)		22 (91.7)	126 (82.4)	120 (85.1)	31 (81.6)	299 (84.0)		
Atypical	0 (0.0)	5 (16.1)	3 (5.9)	1 (3.6)	9 (7.6)		2 (8.3)	16 (10.5)	16 (11.3)	5 (13.2)	39 (11.0)		
Mixture	1 (12.5)	0 (0.0)	4 (7.8)	4 (14.3)	9 (7.6)	0.172	0 (0.0)	11 (7.2)	5 (3.5)	2 (5.3)	18 (5.1)	0.778	0.367
Referred pain	5 (62.5)	23 (74.2)	34 (65.4)	17 (60.7)	79 (66.4)	0.728	14 (58.3)	89 (57.4)	75 (53.2)	16 (42.1)	194 (54.2)	0.350	0.020
Radiation type‡													
Typical	5 (100.0)	12 (52.2)	11 (32.4)	6 (35.3)	34 (43.0)		9 (64.3)	61 (69.3)	41 (54.7)	7 (43.8)	118 (61.1)		
Atypical	0 (0.0)	8 (34.8)	8 (23.5)	9 (52.9)	25 (31.6)		2 (14.3)	16 (18.2)	30 (40.0)	5 (31.3)	53 (27.5)		
Mixture	0 (0.0)	3 (13.0)	15 (44.1)	2 (11.8)	20 (25.3)	0.008	3 (21.4)	11 (12.5)	4 (5.3)	4 (25.0)	22 (11.4)	0.007	0.005
Pain intensity§	9.5 (8.5-10)	9.5 (8-10)	8 (8-10)	8 (7-9)	9 (8-10)	0.224	8 (6-9)	8 (6-9)	8 (6-9)	8 (7.5-9)	8 (6-9)	0.200	<0.001
Symptom	6 (75.0)	25 (78.1)	44 (78.6)	24 (80.0)	99 (78.6)	0.992	20 (83.3)	104 (65.4)	90 (62.9)	28 (66.7)	242 (65.8)	0.278	0.007
Symptom clusters‖													
Cluster 1	5 (62.5)	23 (71.9)	35 (62.5)	21 (70.0)	84 (66.7)		17 (70.8)	130 (81.8)	116 (81.1)	36 (85.7)	299 (81.3)		
Cluster 2	2 (25.0)	6 (18.8)	12 (21.4)	4 (13.3)	24 (19.1)		6 (25.0)	23 (14.5)	16 (11.2)	6 (14.3)	51 (13.9)		
Cluster 3	1 (12.5)	3 (9.4)	9 (16.1)	5 (16.7)	18 (14.3)	0.919	1 (4.2)	6 (3.8)	11 (7.7)	0 (0.0)	18 (4.9)	0.231	<0.001
Activity													
Sleep	1 (14.3)	13 (44.8)	7 (12.7)	4 (14.3)	25 (21.0)		1 (4.2)	36 (23.1)	25 (17.7)	9 (22.0)	71 (19.6)		
Rest	2 (28.6)	9 (31.0)	28 (50.9)	15 (53.6)	54 (45.4)		15 (62.5)	59 (37.8)	62 (44.0)	20 (48.8)	156 (43.1)		
Exertion	4 (57.1)	7 (24.1)	20 (36.4)	9 (32.1)	40 (33.6)	0.032	8 (33.3)	61 (39.1)	54 (38.3)	12 (29.3)	135 (37.3)	0.180	0.768
Stress trigger	1 (12.5)	4 (12.5)	7 (12.7)	0 (0.0)	12 (9.6)	0.140	6 (25.0)	12 (7.7)	9 (6.4)	4 (9.8)	31 (8.6)	0.044	0.731

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 3. Marginal percentage of subjects with each symptom in each assigned cluster*

	Symptom clusters		
	Cluster 1* n=639	**Cluster 2†** n=167	**Cluster 3‡** n=67
Dyspnoea at rest	17.4	34.2	37.3
Exertional dyspnoea	6.0	2.1	14.5
Sweating	22.2	89.6	71.7
Nausea and vomiting	6.5	9.7	41.4
Dizziness	2.6	18.0	74.1
Blurry vision	0.6	4.4	27.5
Presyncope	1.3	11.4	42.7
Syncope	1.6	3.6	10.5
Palpitations	0.3	5.4	19.5
Weakness	7.5	17.8	64.4
"Other symptoms"	4.5	5.5	12.8
Other digestive symptoms	1.0	1.0	1.4
Discomfort	1.3	1.1	4.2

*Values are percentages.
* Cluster 1: no symptom cluster; † Cluster 2: dyspnoea and sweating cluster; ‡Cluster 3: multiple symptoms cluster.

Supplementary Table 4. Differences between women and men in clinical presentation of acute coronary syndrome, by age group (< 55 vs ≥55 years old)
(men are the reference class).

	<55 years		>=55 years			
Symptoms	**OR**	**95% CI**	**OR**	**95% CI**	**Interaction p-value**	**Adjusted for**
Pain	--*	--*	0.46	0.18-1.18	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)†	0.65	0.23-1.86	1.55	0.88-2.71	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	3.81	1.41-10.3	1.73	1.14-2.61	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type‡						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.19	0.41-3.45	1.34	0.77-2.35	0.415	
Mixture	1.43	0.40-5.16	2.56	1.39-4.71	0.606	
Pain intensity (higher than 8/10)	5.23	2.17-12.60	2.09	1.35-3.24	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.88	0.76-.4.66	1.91	1.21-3.04	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters§						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	0.88	0.31-2.50	1.49	0.93-2.38	0.246	
Cluster 3	3.30	0.99-10.97	4.08	2.07-8.05	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.74	0.25-2.19	1.08	0.64-1.81	0.284	
Exertion	0.89	0.29-2.67	1.27	0.74-2.16	0.408	

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG: coronary artery bypass surgery; CI, confidence interval; OR, odds ratio.
*All women below 55 years old presented with pain.
†Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.
‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.
§Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

STROBE Statement—checklist of items : ***Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **page 1 (title) and page 2 (abstract)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **page 4**
Objectives	3	State specific objectives, including any prespecified hypotheses - **page 4**
Methods		
Study design	4	Present key elements of study design early in the paper – **pages 4 and 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **pages 4-6**
Participants	6	*Cohort study:* Give the eligibility criteria, and the sources and methods of selection of participants – **pages 4 and 5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **pages 6 and 7**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **pages 5, 6 and 7**
Bias	9	Describe any efforts to address potential sources of bias - **page 7**
Study size	10	Explain how the study size was arrived at – **page 5 and figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why –**page 6 and 7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - **page7**
		(*b*) Describe any methods used to examine subgroups and interactions – **page 7**
		(*c*) Explain how missing data were addressed –**Patients who were unable to answer the questionnaire (with missing data on clinical presentation) were not included.**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed –**Data were collected within a cohort study, but clinical presentation was collected through a questionnaire.**
		(*e*) Describe any sensitivity analyses –**We analysed clinical presentation separately by type of acute coronary syndrome (Supplementary tables 1 and 2), but as results were similar by sex and age both types of acute coronary syndrome were analysed together.**

Continued on next page

Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed –**pages 4 and 5**
		(b) Give reasons for non-participation at each stage –**page 5**
		(c) Consider use of a flow diagram – **Figure 1.**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **pages 8-9**
		(b) Indicate number of participants with missing data for each variable of interest –**page 9**
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time –**pages 10-12**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **pages 13-16**
		(*b*) Report category boundaries when continuous variables were categorized – **pages 10-14**
Other analyses	17	Report other analyses done— eg analyses of subgroups and interactions, and sensitivity analyses – **page 10**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **page 17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias –**pages 19 and 20**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - **pages 17-19**
Generalisability	21	Discuss the generalisability (external validity) of the study results –**page 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based –**page 22**

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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ABSTRACT

Objectives: Prompt diagnosis of acute coronary syndrome (ACS) remains a challenge, with presenting symptoms affecting the diagnosis algorithm and, consequently, management and outcomes. This study aimed to identify sex differences in presenting symptoms of ACS.

Design: Data were collected within a prospective cohort study (EPIHeart).

Setting: Patients with confirmed diagnosis of type 1 (primary spontaneous) ACS who were consecutively admitted to the Cardiology Department of two tertiary hospitals in Portugal between August 2013 and December 2014.

Participants: Presenting symptoms of 873 patients (227 women) were obtained through a face-to-face interview.

Outcome measures: Typical pain was defined according to the definition of cardiology societies. Clusters of symptoms other than pain were identified by latent class analysis. Logistic regression was used to quantify differences in presentation of ACS symptoms by sex.

Results: Chest pain was reported by 82% of patients, with no differences in frequency or location between sexes. Women were more likely to feel pain with an intensity higher than 8/10 and this association was stronger for patients under 65 years old (interaction p=0.028). Referred pain was also more likely in women, particularly pain referred to typical and atypical locations simultaneously. The multiple symptoms cluster, which was characterized by a high probability of presenting with all symptoms, was almost 4-fold more prevalent in women (3.92, 2.21–6.98). Presentation with this cluster was associated with a higher 30-day mortality rate adjusted for the GRACE 2.0 risk score (4.9% vs 0.9% for the two other clusters, p<0.001).

Conclusions: While there are no significant differences in the frequency or location of pain between sexes, women are more likely to feel pain of higher intensity and to present with referred pain and symptoms other than pain. Knowledge of these ACS presentation profiles is important for health policy decisions and clinical practice.

Keywords: Sex; acute coronary syndrome; women; diagnosis.

Strengths and limitations

Within a prospective cohort study, presenting symptoms of acute coronary syndrome were obtained through a structured questionnaire applied within the first 48 hours after admission.

Consecutive sampling, the detailed clinical information obtained through the questionnaire and adjustment for several confounding variables strengthens our results.

The results of this study are valid for stable patients admitted to the hospital and who were able to answer the questionnaire in the acute phase of the acute coronary syndrome.

Some of the sex differences in presenting symptoms may be influenced by selection bias because of a higher risk of non-inclusion of women due to misdiagnosis or death in the early hours of admission.

INTRODUCTION

Acute coronary syndrome (ACS) is still one of the main causes of death worldwide and in Europe.[1, 2] Coronary heart disease mortality has decreased in the last decades in developed countries because of primary prevention and improvement in treatment of patients with ACS.[2] Attainment of the maximal benefit of treatment of these patients is threatened by delayed diagnosis, partly dependent on clinical suspicion of ACS. The subjective experience of symptoms influences patients' attitudes in seeking help and professionals' interpretation of clinical presentations.[3] Early recognition of ACS may be challenging because while patients with presumed ACS have contact with healthcare providers,[4] many patients do not have an electrocardiogram before hospitalization.[5] Therefore, physicians frequently have to make decisions that are only clinically based.

The population of patients with atypical ACS presentation is still not well characterized.[6] Women and men generally have the same type of symptoms during an ACS episode, although the proportion presenting with different combinations of symptoms varies.[7] This conflicting evidence can be partly explained by the diverse methodology used, with few prospective studies, usually without a specific questionnaire. In prospective studies, small convenience samples were used and confounding was not always adequately addressed.[8, 9] Therefore, sex-specific research on ACS presentation is a challenge and priority.[10]

This study aimed to analyse sex differences in presenting symptoms of ACS within a prospective cohort study, taking into account the contribution of age, socioeconomic data, previous history of coronary heart disease, risk factors, comorbidities, type of ACS and coronary anatomy to the presenting symptoms.

METHODS

Study Design and Sample Selection

The EPIHeart cohort study was designed to identify inequalities in management and outcomes of patients with ACS. This study included all consecutive patients who were admitted between August 2013 and December 2014 to the Cardiology Department of two tertiary hospitals in two regions in northern Portugal (Hospital de São João, Porto, covering the metropolitan area of Porto in the coast; and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). Eligible patients were 18 years old or older who lived in the catchment area of these hospitals (districts: Porto, Vila Real, Bragança, and Viseu),

with confirmed diagnosis of type 1 (primary spontaneous) ACS. The diagnosis of type 1 ACS and the classification in different subtypes was determined by the treating cardiologist, based on symptoms and signs at presentation, electrocardiogram findings and the increase in cardiac enzyme levels (high-sensitivity troponin I or T were used), according to the third universal definition of myocardial infarction.[11] The patients were also expected to be hospitalized for at least 48 hours and not institutionalized before the event. Of 1297 patients initially considered, in 164 the diagnosis of type 1 ACS was not confirmed, 60 were excluded due to discharge or transfer before the interview, 18 died before being invited, and 44 were unable to answer the questionnaire because of clinical instability, no understanding of Portuguese, hearing problems, or cognitive impairment. Seventy-two patients refused to participate. For this analysis, we excluded 61 patients who were not admitted because of a symptom (patients referred by a doctor, after a scheduled appointment or diagnostic exam), four with vasospastic angina, and one illicit drug user. A total of 873 patients were included (Figure 1). The study protocol was in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of both hospitals (*Comissão de Ética para a Saúde do Centro Hospitalar de S. João* and *Comissão de Ética do Centro Hospitalar de Trás-os-Montes e Alto Douro*, reference numbers of the approvals: 82/13 and 1286, respectively). All patients gave written informed consent.

Procedures and data collection

Presenting symptoms were obtained face-to-face using a structured questionnaire applied by trained interviewers, within the first 48 hours after admission, whenever possible. Over the following days, a second interview was conducted to collect data on sociodemographic characteristics and risk factors. Medical records were reviewed to extract data regarding previous medical history, admission information, and clinical data during hospitalization.

Pain, referred pain, and symptoms other than pain were measured dichotomously (yes/no). For the location of pain (direct and referred) patients were asked to point out where pain was occurring. To measure the intensity of pain, a 10-point scale (0, no pain; 10, pain of maximal intensity) was used. Symptoms other than pain included dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, and an open-ended question of "other" (12 items). Answers to the last item enabled identification of two other relatively frequent symptoms, other digestive symptoms and discomfort. Activity at the onset of the episode was measured

dichotomously, including sleeping, rest, and any exertion. A stress trigger was assigned if the patient answered "yes" for at least one of following events within 24 hours preceding the episode: accident, recent diagnosis of disease, financial problems, and news of death/disease of a relative/friend.

Marital status was considered partnered for married patients or living in civil union. Education was recorded as completed years of schooling and classified into four categories: less than 4 (little formal education), 4 (elementary school), less than 12 (high school), and 12 or more years (secondary education or more). Occupations were classified into major professional groups, according to the Portuguese Classification of Occupations 2010,[12] integrated in the International Standard Classification of Occupations (ISCO/2008).

Definition of Variables

Although symptoms of ACS have been widely described, their value for diagnosis of ACS is not unanimously recognized.[13-15] After discussion with clinical cardiologists of our team, we opted to use Cardiology Societies' position papers to define direct and referred pain locations and to select symptoms to evaluate.[16, 17] Direct pain location was classified as follows: 1) typical for retrosternal, precordial, right thoracic, or bilateral thoracic pain (chest pain); 2) atypical for epigastric pain or located in the back, left arm or shoulder, right arm or shoulder, neck, or jaw; and 3) a mixture when both typical and atypical locations were present. Referred pain location was considered as follows: 1) typical if pain referred to the left arm or shoulder, right arm or shoulder, neck, or jaw; 2) atypical if pain referred to retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; and 3) a mixture for referred pain in typical and atypical locations.

Patients rarely present with a single symptom during an episode of ACS, and present with multiple symptoms instead that do not occur in isolation and may cluster.[18] There has been increasing interest in symptom cluster analysis in cardiovascular disease because it aids in assessment by enhancing recognition of patients with similar symptom profiles.[19] Groups of symptoms other than pain were obtained by latent class analysis.

The small group of non-classified (NC) patients with ACS (patients with left bundle branch block) was grouped with patients with ST elevation myocardial infarction (STEMI) (STEMI/NC ACS group). Non-ST elevation ACS (NSTEACS) included unstable angina and non-ST elevation acute myocardial infarction or subacute myocardial infarction.

Considering the possible association between coronary anatomy and clinical presentation, we grouped patients according to coronary angiography into five groups: managed conservatively; non-obstructive coronary artery disease; lesions exclusively in the anterior descending artery; lesions in the right and/or circumflex artery; and lesions in the left main coronary artery, three-vessel disease or disease both in the anterior descending artery and the right or circumflex artery.

Data Analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). Categorical variables are shown as number and percentage. To compare differences between women and men, and by age-groups, the chi-square or Fisher's test was used for categorical variables and the t-test, Mann-Whitney or Kruskal-Wallis tests for continuous variables. Latent class analysis was used to identify distinct groups of individuals from a sample (clusters) who were homogeneous within the group. This was based on the fact that performance of an individual in a set of items is explained by a categorical latent variable with K classes (clusters), commonly called latent classes. The number of latent clusters was defined according to the Akaike information criterion (AIC). Starting from one single cluster and increasing one cluster at each step, the best solution was identified when an increase in the number of clusters did not lead to a decrease in the AIC.

Patient and system delays, severity indicators, risk stratification using calculated GRACE and CRUSADE risk scores, left ventricular systolic dysfunction and 30-day mortality rate adjusted for the GRACE 2.0 risk score,[20] were assessed according to presence of typical (chest) pain and cluster of symptoms other pain. The 30-day mortality adjusted for the GRACE 2.0 risk score was estimated based on predicted probabilities derived from logistic regression. Logistic regression was used to identify variables associated with clinical presentation. Variables with $p<0.15$ for a crude association with the endpoint were entered in the initial model and a backward strategy was used to exclude the least significant variables, based on Wald tests. We were then able to obtain the most parsimonious model with all the important determinants. Previous data support significant interaction between age and sex with clinical presentation, attenuated with advancing age, mainly in those 65 years old or older.[3] We assessed for effect measure modification by stratifying adjusted analyses based on two age groups (under 65 and 65 years old or older). Considering the relevance of analysing sex differences in ACS clinical presentation in younger

patients, we also performed the age stratified multivariate models using 55 years old as cut-off. Sex, age (continuous), and type of ACS were forced to remain in the models.

All analyses were performed using STATA version 11.1 for Windows (Stata Corp LP, College Station, TX) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Women (n=227, 26.0%) were older (69.1 vs 62.2 years, p<0.001) and more frequently lived in the interior region (52.4% vs 38.7%, p<0.001) than men. Women were more often treated conservatively and had non-obstructive coronary artery disease more frequently than men. In this sample, no difference by sex was observed in the type of ACS, where 56.6% of the patients had a discharge diagnosis of NSTEACS (Table 1).

Women more frequently had hypertension (81.5% vs 62.7%, p<0.001) and diabetes (38.8% vs 29.9%, p=0.014), and were more frequently obese (25.5% vs 18.5%, p=0.020) and never smokers compared with men (p<0.001, Table 1). Men were submitted to percutaneous coronary intervention more often than women. There were no significant differences in a previous history of renal failure, prior myocardial infarction, prior coronary artery bypass surgery, prior heart failure, and dementia by sex (Table 1).

Women were more likely to be unpartnered, disabled, less educated, and had a lower income compared with men. The median time that elapsed between admission and application of the symptom questionnaire was slightly longer in women than in men (Table 1).

Table 1. Baseline demographic, socioeconomic and clinical characteristics in the whole sample and by sex*

	Total (n = 873)	Women (n = 227)	Men (n = 646)	p
Age (years), mean (SD)	64.0 (13.0)	69.1 (12.7)	62.2 (12.7)	<0.001
Socioeconomic				
Marital status				
Partnered	667 (76.8)	133 (58.9)	534 (83.2)	<0.001
Education				
Little formal education	172 (19.9)	95 (42.4)	77 (12.0)	
Elementary school	337 (39.1)	73 (32.6)	264 (41.3)	
High school	213 (24.7)	32 (14.3)	181 (28.3)	
Secondary education or more	141 (16.3)	24 (10.7)	117 (18.3)	<0.001
Employment status				
Employed/looking after home	282 (32.6)	64 (28.3)	218 (34.1)	
Unemployed	107 (12.4)	16 (7.1)	91 (14.2)	
Retired	334 (38.6)	93 (41.2)	241 (37.7)	
Disabled	143 (16.5)	53 (23.5)	90 (14.1)	<0.001
Subjective social class				
Low	281 (32.2)	81 (35.7)	200 (31.0)	
Lower-middle	281 (32.2)	58 (25.6)	223 (34.5)	
Higher-middle/High	60 (6.9)	16 (7.1)	44 (6.8)	
No response	251 (28.8)	72 (31.7)	179 (27.7)	0.097
Household income (euros)				
<500	204 (23.4)	77 (33.9)	127 (19.7)	
501-1000	276 (31.6)	60 (26.4)	216 (33.4)	
1001 – 2000	146 (16.7)	22 (9.7)	124 (19.2)	
>2000	88 (10.1)	14 (6.2)	74 (11.5)	
No response	159 (18.2)	54 (23.8)	105 (16.3)	<0.001
Region				
Metropolitan area of Porto	504 (57.7)	108 (47.6)	396 (61.3)	
North-eastern region of Portugal	369 (42.3)	119 (52.4)	250 (38.7)	<0.001
Cardiovascular risk factors				
Smoking habit				
Never	369 (42.3)	184 (81.0)	185 (28.6)	
Current	283 (32.4)	34 (15.0)	249 (38.5)	
Former	221 (25.3)	9 (4.0)	212 (32.8)	<0.001
Hypertension	590 (67.6)	185 (81.5)	405 (62.7)	<0.001
Diabetes mellitus	281 (32.2)	88 (38.8)	193 (29.9)	0.014
Dyslipidaemia	535 (61.4)	144 (63.4)	391 (60.6)	0.454
BMI (kg/m^2)				
Median (IQR)	26.5 (18.0-44.6)	26.7 (19.5-37.9)	26.4 (18.2-39.2)	0.531
Underweight	11 (1.4)	2 (0.9)	9 (1.5)	
Normal weight	272 (33.4)	80 (37.0)	192 (32.1)	
Overweight	366 (44.9)	79 (36.6)	287 (47.9)	
Obese	166 (20.4)	55 (25.5)	111 (18.5)	0.020
Family history of CVD	303 (34.7)	73 (32.2)	230 (35.6)	0.105
Previous medical history				
Renal failure	64 (7.3)	14 (6.1)	50 (7.7)	0.434
Myocardial infarction	156 (17.9)	34 (15.0)	122 (18.9)	0.186
PCI	100 (12.4)	18 (8.4)	82 (13.8)	0.041
CABG	34 (4.2)	5 (2.3)	29 (4.9)	0.111
Heart failure	63 (7.5)	21 (9.6)	42 (6.8)	0.172
Dementia	7 (0.8)	4 (1.8)	3 (0.5)	0.060
ACS type				
STEMI/NC ACS	379 (43.4)	101 (44.5)	278 (43.0)	
NSTEACS	494 (56.6)	126 (55.5)	368 (57.0)	0.703
Coronary anatomy				
Non-obstructive disease	57 (6.9)	22 (10.6)	35 (5.61)	
Left anterior descending artery only	162 (19.5)	38 (18.3)	124 (19.9)	
Right and/or circumflex artery only	196 (23.6)	46 (22.1)	150 (24.0)	
Mixture	417 (50.1)	102 (49.0)	315 (50.5)	
Not submitted to coronary angiography	41 (4.7)	19 (8.4)	22 (3.4)	0.004
Symptom questionnaire application				
Time from admission (hours), median (IQR)	42.1 (25.0-68.0)	45.4 (28.5-72.3)	40.0 (24.0-67.4)	0.052

*Values are number and percentage unless otherwise indicated.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; CVD, cardiovascular diseases; IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/non-classifiable acute coronary syndrome.

Symptom characteristics by sex and age

Because differences in symptoms by sex and age were similar in direction and magnitude in STEMI/NC ACS and NSTEACS (Supplementary Tables 1 and 2), both types of ACS were analysed together.

Although pain was present in most patients, men presented with pain more frequently than did women (97.4% vs 94.3%, p=0.028), with a higher sex difference among patients with 80 or more years old (88.0% vs 93.5%). Older patients presented less often pain, but the difference by age group in both sexes was not significant (Table 2). No difference was found in the location of pain by sex. Approximately 80% of patients felt chest pain (typical pain). Older women presented less frequently with chest pain and had chest pain and pain in other locations (mixture group) more often than did younger women (p=0.014). Referred pain was observed more frequently in women and in younger patients (only significant for men, p=0.024); again in the older age group, the difference between women and men was notorious (56.8% vs 39.7%, respectively). Atypical and mixture referred pain were more frequent in women than in men (p<0.001), mainly in women aged ≥65 years (p=0.009). Women felt pain with higher intensity than did men (median [IQR]: 9 [8–10] vs 8 [6–9], p<0.001), without a difference by age (Table 2). Women presented with symptoms other than pain more frequently than did men (82.8% vs 68.9%, p<0.001), with no difference by age group in both sexes (Table 2).

Considering symptoms other than pain, the AIC optimum value supported a preference for a three-cluster solution (AIC 7207.508, 6869.390, 6862.476, and 6870.372 for one, two, three, and four clusters, respectively). Cluster 1 had low endorsement probabilities for all items (no symptoms cluster). Cluster 2 had a high probability for dyspnoea at rest and sweating, and a low probability for the remaining items (dyspnoea and sweating cluster). Cluster 3 had high probabilities for all items (multiple symptoms cluster). This three-cluster model made sense conceptually to cardiologists of our team. Clusters counts and probabilities of occurrence of symptoms in established clusters are shown in Supplementary Table 3. Differences in proportions of women and men in the three clusters were observed (p<0.001, Table 2). Cluster 1 was the most prevalent, in which men presented with the no symptoms cluster more frequently (76.9% vs 62.6%) and the multiple symptoms cluster less frequently (4.8% vs 15.9%) than did women. Higher differences of multiple symptoms cluster proportions between women and men were observed among patients in the older age group. The proportion of dyspnoea and sweating cluster was similar in men and women (Table 2).

Approximately 45% of patients were at rest and 35% were under physical effort at the beginning of the episode. Older women were more frequently at rest at the beginning of the episode and younger women were more frequently under effort (p=0.011). Less than 10% of patients identified a stressful event in the previous 24 hours, with no difference by sex, but among men, a younger age was slightly associated with this trigger (p=0.045, Table 2).

Table 2. Clinical presentation of patients with acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	14 (6.2)	54 (23.8)	109 (48.0)	50 (22.0)	227 (100.0)		61 (9.4)	303 (46.9)	220 (34.1)	62 (9.6)	646 (100)		
Pain	14 (100.0)	52 (96.3)	104 (95.4)	44 (88.0)	214 (94.3)	0.229	60 (98.4)	297 (98.0)	214 (97.3)	58 (93.5)	629 (97.4)	0.228	0.028
Pain location†													
Typical	12 (85.7)	43 (82.7)	88 (85.4)	32 (72.7)	175 (82.2)		53 (89.8)	246 (83.7)	175 (82.2)	44 (75.9)	518 (83.0)		
Atypical	1 (7.1)	9 (17.3)	5 (4.9)	6 (13.6)	175 (9.9)		3 (5.1)	33 (11.2)	30 (14.1)	10 (17.2)	76 (12.2)		
Mixture	1 (7.1)	0 (0.0)	10 (9.7)	6 (13.6)	17 (8.0)	0.014	3 (5.1)	15 (5.1)	8 (3.8)	4 (6.9)	30 (4.8)	0.327	0.165
Referred pain	9 (64.3)	41 (78.8)	72 (69.2)	25 (56.8)	147 (68.7)	0.129	38 (63.3)	179 (60.3)	126 (58.9)	23 (39.7)	366 (58.2)	0.024	0.007
Radiation type‡													
Typical	8 (88.9)	20 (48.8)	28 (38.9)	7 (28.0)	63 (42.9)		28 (73.7)	114 (64.4)	67 (53.2)	10 (43.5)	219 (60.2)		
Atypical	0 (0.0)	13 (31.7)	18 (25.0)	13 (52.0)	44 (29.9)		7 (18.4)	37 (20.9)	39 (31.0)	8 (34.8)	91 (25.0)		
Mixture	1 (11.1)	8 (19.5)	26 (36.1)	5 (20.0)	40 (27.2)	0.009	3 (7.9)	26 (14.7)	20 (15.9)	5 (21.7)	54 (14.8)	0.104	<0.001
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-9)	8 (8-9)	9 (8-10)	0.170	8 (7-10)	8 (6-9)	8 (6-9)	8 (7-9)	8 (6-9)	0.095	<0.001
Symptom	11 (78.6)	45 (83.3)	91 (83.5)	41 (82.0)	188 (82.8)	0.947	43 (70.5)	209 (69.0)	151 (68.6)	42 (67.7)	445 (68.9)	0.989	<0.001
Symptom clusters‖													
Cluster 1	7 (50.0)	41 (75.9)	62 (56.9)	32 (64.0)	142 (62.6)		43 (70.5)	232 (76.6)	170 (77.3)	52 (83.9)	497 (76.9)		
Cluster 2	5 (35.7)	8 (14.8)	28 (25.7)	8 (16.0)	49 (21.6)		15 (25.6)	59 (19.5)	35 (15.9)	9 (14.5)	118 (18.3)		
Cluster 3	2 (14.3)	5 (9.3)	19 (17.4)	10 (20.0)	36 (15.9)	0.183	3 (4.9)	12 (4.0)	15 (6.8)	1 (1.61)	31 (4.80)	0.345	<0.001
Activity													
Sleep	2 (15.4)	16 (32.0)	11 (10.4)	7 (14.9)	36 (16.7)		6 (9.8)	65 (21.7)	35 (16.1)	13 (21.3)	119 (18.6)		
Rest	5 (38.5)	18 (36.0)	50 (47.2)	29 (61.7)	102 (47.2)		34 (55.7)	124 (41.3)	105 (48.2)	33 (54.1)	296 (46.3)		
Exertion	6 (46.2)	16 (32.0)	45 (42.5)	11 (23.4)	78 (36.1)	0.011	21 (34.4)	111 (37.0)	78 (35.8)	15 (24.6)	225 (35.2)	0.087	0.816
Stress trigger	2 (14.3)	6 (11.1)	11 (10.2)	3 (6.1)	22 (9.8)	0.700	11 (18.0)	23 (7.7)	15 (6.9)	6 (9.8)	55 (8.6)	0.045	0.605

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ||Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Multivariate models

Despite the higher probability of women below or above 65 years old to present without pain than men, no differences were observed in the adjusted pain frequency and location between men and women. Referred pain was more likely to be experienced by women (<65 years old: adjusted odds ratio [OR] 2.90, 95% confidence interval [95% CI] 1.47-5.72; >=65 years old: 1.60 (0.99-2.60), p for interaction=0.528)). Moreover, women below or above 65 years old had a higher probability of having pain radiating to typical and atypical locations and of feeling pain with an intensity higher than 8 (Table 3). The association between intensity of pain and female sex was stronger for patients below 65 years old (interaction p=0.028) (Table 3).

The presence of at least one symptom other than pain occurred almost two times more often in women than in men. With cluster 1 as the reference, cluster 2 and 3 were positively associated with female sex, with the latter being statistically significant. The multiple symptoms cluster was almost 4-fold more likely in women than in men (3.92, 2.21-6.98 in the whole sample, interaction p=0.501) (Table 3).

No difference in the type of patients' activities at the beginning of the episode by sex was observed (Table 3).

Performance of age stratified multivariate models using the 55 years old cut-off revealed similar results to the observed using the 65 years old cut-off, with some differences mainly in the strength of association of some clinical presentation variables with sex among the younger age group (Supplementary Table 4), Although still not significant, among patients below 55 years old, women were less likely to present with typical chest pain (0.65, 0.23-1.86). A stronger association between female sex and referred pain, and intensity of pain higher than 8/10, among patients in the younger age groups was observed using the 55 instead of the 65 years cut-off. The remaining results were similar in direction and strength of association (Table 3 and Supplementary Table 4). The precision of the estimates is lower using the 55 cut-off, due to the small sample of patients below 55 years old.

Table 3. Differences between women and men in clinical presentation of acute coronary syndrome, by age group
(men are the reference class).

	<65 years		>=65 years			
Symptoms	**OR**	**95% CI**	**OR**	**95% CI**	**Interaction p-value**	**Adjusted for**
Pain	0.76	0.14-4.0	0.52	0.19-1.47	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)*	0.97	0.44-2.14	1.71	0.90-3.23	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	2.90	1.47-5.72	1.60	0.99-2.60	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type†						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.49	0.70-3.20	1.38	0.72-2.66	0.415	
Mixture	1.77	0.73-4.29	2.75	1.36-5.57	0.606	
Pain intensity (higher than 8/10)	3.81	2.04-7.13	2.03	1.22-3.37	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.98	1.00.3.91	1.85	1.10-3.12	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters‡						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	1.07	0.53-2.15	1.67	0.97-2.87	0.246	
Cluster 3	3.14	1.15-8.62	4.23	2.03-8.81	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.68	0.33-1.38	1.38	0.74-2.57	0.284	
Exertion	0.77	0.37-1.59	1.70	0.89-3.25	0.408	

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG: coronary artery bypass surgery; CI, confidence interval; OR, odds ratio.
*Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.
†Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.
‡Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

Clinical presentation and outcomes

Patients with a diagnosis of STEMI/NC ACS who presented with atypical or mixture pain took longer to seek medical care (135 vs 85 min., p=0.012) and had longer total ischemic times (414 vs 328 min., p=0.080) than patients with chest pain (Table 4). Among patients with NSTEACS, differences in time delays according to pain location were not significant. Patients with atypical or mixture pain presented more frequently with hemodynamic instability at admission (9.7% vs 4.6%, p=0.014) and had also more often moderate to severe left ventricular systolic dysfunction (32.9 vs 24.9%, p=0.052) than patients with chest pain. The 30-day mortality adjusted for GRACE 2.0 was not significantly different between patients with chest pain and those with atypical or mixture pain (Table 4).

Among patients with STEMI/NC ACS, the total ischemic time was longer for patients with the multiple symptoms cluster compared with patients who presented with the two other symptoms clusters (533 minutes vs 321 and 384, p=0.111). Patients with the multiple symptom cluster presented more often with hemodynamic instability at admission than patients with the other symptoms clusters (13.4% vs 6.4% and 4.2%, p=0.034). The mean 30-day mortality rate adjusted for the GRACE 2.0 risk score was significantly higher for patients presenting with the multiple symptom cluster (4.9% vs 0.9% for the two other clusters, p<0.001) (Table 4).

Patients with atypical or mixture chest pain and patients with the multiple symptom cluster had higher mean GRACE and median CRUSADE risk scores (Table 4).

Table 4. Patient and system delays, severity indicators, risk stratification and 30-day mortality according to clinical presentation*

	Typical (chest) pain†	Atypical or mixture pain	p	No symptom cluster ‡	Dyspnoea and sweating cluster	Multiple symptoms cluster	p
Patient and system delays, median (IQR)							
STEMI/NC ACS							
Symptom onset – FMC (min)	85 (45-210)	135 (65-325)	0.012	90 (46-240)	90 (50-185)	83 (45-430)	0.872
Symptom onset-arterial access (min)	328 (192-1075)	414 (246-1335)	0.080	321 (194-1011)	384 (201-1440)	533 (323-1428)	0.111
NSTEACS							
Symptom onset – FMC (min)	130 (60-393)	139 (60-335)	0.633	135 (60-390)	150 (60-390)	113 (45-393)	0.795
Hospital admission- coronary angiography time (hours)	30 (18-57)	29 (20-48)	0.884	30 (18-56)	35 (18-70)	28 (20-72)	0.385
Admission variables							
Heart rate, mean (SD), bpm	77 (18)	80 (24)	0.117	78 (19)	77 (19)	78 (28)	0.923
Systolic blood pressure, mean (SD), mmHg	144 (49)	139 (30)	0.212	145 (59)	141 (30)	136 (33)	0.364
Hemodynamic instability at admission§	32 (4.6)	14 (9.7)	0.014	41 (6.4)	7 (4.2)	9 (13.4)	0.034
Risk stratification							
Calculated GRACE risk score, mean (SD)	134 (36)	147 (39)	<0.001	137 (37)	138 (35)	149 (44)	0.041
Calculated CRUSADE risk score, median (IQR)	21 (11-34)	25 (14-41)	0.012	22 (12-36)	23 (10-36)	30 (16-47)	0.019
Moderate or severe left ventricular systolic dysfunction	169 (24.9)	46 (32.9)	0.052	164 (26.4)	55 (33.3)	17 (25.4)	0.187
30-day mortality rate adjusted for the GRACE 2.0 risk score, mean (SD)	2.0 (4.0)	1.3 (1.4)	0.521	0.9 (2.0)	0.9 (2.0)	4.9 (5.5)	<0.001

IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; SD, standard deviation; STEMI/NC ACS, ST elevation myocardial infarction/Non-classifiable acute coronary syndrome.
*Values are number and percentage unless otherwise indicated.
Total may not add to 100% due to missing data.
†Chest pain: retrosternal, precordial, right thoracic, or bilateral thoracic.
‡No symptom cluster: low endorsement probabilities for all items; Dyspnoea and sweating cluster: high probability for dyspnoea atrest and sweating; Multiple symptoms cluster: high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort)
§Killip class III or IV; or shock at admission.

DISCUSSION

In our study, after adjustment, no differences in the frequency and location of pain by sex were observed. Referred pain, pain radiating to typical and atypical locations, and pain of higher intensity were more likely to occur among women. Women were also more likely than men to present with symptoms other than pain. Three clusters of symptoms other than pain were identified. Women were more likely to present with the multiple symptoms cluster. Presenting with the multiple symptoms cluster was associated with a higher mean 30-day mortality rate adjusted for the GRACE 2.0 risk score.

Differences between women and men in perception of symptoms of ACS might be explained by anatomical, physiological, biological, and psychosocial differences that influence each other.[9, 21] We measured several variables of these different domains. Differences in symptom presentation by sex might be the result of differences in response to history-taking,[10] differences in neural receptors and pathways involved in pain, and subtle differences in the location and type of atherosclerotic lesions.[22, 23] Our findings of similar ACS symptoms between women and men are consistent with previous studies,[7, 24] as well as our finding that women are more likely to have atypical presentations.[9] We observed that women have a higher likelihood of atypical referred pain and of several concomitant symptoms other than pain, common to other cardiac and non-cardiac diagnoses.

In our study, chest pain was the most frequent symptom in both sexes, consistent with previous studies.[25-27] Among those with pain, typical chest pain was observed in 82% of patients, regardless of sex. The remaining patients had pain in less typical locations and were thus prone to misdiagnosis and undertreatment and, consequently, to worse outcomes.[28] Considering differences in characteristics of pain by sex, studies suggested that women, in particular older women, were less likely to have the chief complaint of chest pain associated with acute myocardial infarction; while after adjustment, among patients with 65 or less years old, female sex was no longer a significant predictor.[29] Studies reported that chest pain did not differ between women and men,[9] others that women have pain in the neck and back more often than men,[30, 31] without distinguishing between direct and referred pain. In our study, referred pain was observed in 61% of patients, was more frequent in women, and typical referred pain was only observed in 33%. Notably, a study on diagnostic acuity of ACS symptoms showed that shoulder and arm pain was predictive of the diagnosis of ACS for women only.[24] Another study (GENESIS PRAXY) on sex differences in ACS symptom presentation in patients with 55 years old or younger showed that being a woman was independently associated with ACS presentation without chest pain.[27] Although the

association was not significant, and relied on a small sample of patients, our finding that women with 55 years old or younger were less likely to present with typical chest pain is in line with the GENESIS PRAXY study result.[27] We were also able to find a stronger association between female sex and presence of referred pain, and of pain with intensity higher than 8 among the younger subgroups of patients (below 55 and 65 years old). These findings stress the relevance of taking into account age for studying the association between sex and clinical presentation. However, further conclusions on the role of age to this relation are limited by the small number of women below 55 included in our study. Differences in age distribution, in clinical presentation measuring, in selection and definition of confounder variables limit conclusive comparisons of studies evaluating differences in frequency and location of pain between women and men.

According to previous studies, with regard to other symptoms, a higher proportion of women have less typical symptoms than men.[8, 31] Women have also reported other symptoms, such as indigestion, palpitations, nausea, numbness in the hands, and unusual fatigue, more frequently than men.[9] In our cohort, three symptom clusters were identified. Women had the multiple symptoms cluster more frequently than did men, characterized by high probabilities for all symptoms. Age did not change the association between female sex and presentation with symptoms other than pain and with the multiple symptoms cluster. According to Rosenfeld et al. women are more likely to cluster in a similar class, called the heavy symptom burden class.[32] With regard to ACS symptom clustering, there are contradictory findings on identified clusters, the proportion of patients per cluster, and differences between clusters regarding demographic factors. In our study, cluster 1 and 3 (low and high probabilities for all symptoms, respectively) are in line with observations of other settings.[18, 33] A recent systematic review of symptom clusters in cardiovascular disease[34] identified clusters with the most symptoms and clusters with the lowest number of symptoms. Our dyspnoea and sweating cluster has two common symptoms with the Riegel et al.[26] stress symptoms cluster, which includes shortness of breath, sweating, nausea, indigestion, dread, and anxiety.

Methodological differences related to sampling and measuring might explain these different results. Strengths of our study include consecutive sampling, a questionnaire with detailed clinical information was systematically applied, and we adjusted for several confounding variables.

The value of symptoms for diagnosis of ACS varies across studies.[14, 35, 36] Overall, the diagnostic performance of chest pain characteristics for diagnosis is limited, with likelihood ratios close to 1.[37]

Sensitivity for individual symptoms of ACS, using the 13-Item Acute Coronary Syndrome Checklist, ranges from 27% to 67% for women and 14% to 72% for men. Additionally, specificity ranges from 33% to 78% for women and 34% to 78% for men, with different associations between some symptoms and diagnosis of ACS by sex.[24] However, physicians still base the likelihood of ACS mainly on symptoms and use the electrocardiogram to rule in the diagnosis.[38] Evaluation of these patients is mostly unchanged, without implementation of evidence-based assessment tools in clinical practice to improve diagnostic accuracy. Public health messages should take into account the complexity of presenting symptoms of ACS, particularly the significant proportion of women and men with ACS without typical chest pain. Additionally, there is a higher likelihood of atypical referred pain and multiple concomitant symptoms in women. These factors should be accounted for to encourage timely and appropriate care of patients with ACS.

Presenting without chest pain and with the multiple symptoms cluster was associated with several markers of higher ACS severity and longer time delays, particularly significant among patients with STEMI/NC ACS. In our study, presenting with the multiple symptoms cluster, but not with atypical or mixture location of pain, was associated with a higher mean 30-day mortality adjusted for GRACE risk score. These results are consistent with data from the GRACE registry, that showed that patients with symptoms other than pain experienced greater morbidity and higher in-hospital mortality across the spectrum of ACS.[28] Other registry showed that the higher in-hospital mortality observed among women and men without chest pain, decreased or even reversed with advanced age.[39] Mortality is adjusted for GRACE risk score, however we cannot conclude that the difference in outcome observed is explained by symptoms other than pain per se. Previous studies showed that the higher in-hospital mortality of ACS patients who presented without chest pain was mostly due to late hospital arrival, comorbidities and underuse of medications and invasive procedures. [6, 39, 40] These studies focused mainly on presence of chest pain to define atypical presentation and used medical record reviews to characterize clinical presentation. More studies are needed to further explore the association between symptoms other than pain and outcomes.

Limitations

Participants were interviewed as soon as possible after admission, but this does not obviate the retrospective nature of data collection and the possibility of recall bias. Furthermore preceding interviews by physicians may have influenced answers to the questionnaire, however different consequences in women and men are not expected. The results of this study are valid for stable patients, who were admitted to the hospital and were able to answer the questionnaire in the acute phase of ACS. This type of study misses patients who die before reaching the hospital, patients who do not seek medical care, patients who are mistakenly discharged or misdiagnosed and admitted to non-cardiology departments. This sample selection process may contribute to underestimate the true prevalence of ACS atypical presentation in women and men.[27] For patients who were eligible but not enrolled only information on sex, age and type of ACS was available. Patients who died before the interview were older (81.5±11.8 vs 64.6±13.1 years, p<0.001), were more often women (66.7% vs 26.0%, p<0.001), and more frequently had a diagnosis of STEMI (81.3% vs 43.4%, p=0.003) than did participants. Patients who were discharged or transferred to another hospital before the interview had STEMI less often (25.0% vs 43.4%, p=0.005) and patients who were not enrolled because of clinical instability or inability to understand the questionnaire were older. Patients who refused to participate were older (72.7±11.0 vs 64.0±13.0 years, p<0.001), were less often partnered (65.7% vs 76.8%, p=0.036), and had little formal education (43.1% vs 19.7%, p<0.001) compared with participants. Except for deceased patients, no difference in sex proportion was observed between participants and non-participants. We cannot exclude that some of the sex differences were caused by selection bias because of a higher risk of non-inclusion of women due to death in the early hours of admission, or due to a possible higher probability of misdiagnosis in women, particularly those with unstable angina.[41] Considering that atypical presentation is associated with a worse prognosis and with a higher probability of misdiagnosis, the proportion of patients with ACS presenting without typical chest pain or that of women with an atypical presentation could be even higher.[28]

CONCLUSION

This study shows no significant differences in the frequency and location of pain by sex, but approximately 20% of patients do not present with chest pain, regardless of sex. Women are more likely to report referred pain and multiple symptoms simultaneously. Presentation with the multiple symptoms cluster pain is associated with higher 30-day mortality adjusted for GRACE score. Health education

messages should take into account the complexity of presentation of ACS and emphasize the possible non-chest location of pain in both sexes and the higher probability of concomitant symptoms other than pain in women. Further sex-stratified analysis of ACS presentation, also addressing the role of age for the relation between sex and clinical presentation, is required to determine the diagnostic accuracy of symptoms by sex.

Figure 1. Flow chart of the study population

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Contributors

Carla Araújo and Ana Azevedo had the original idea to develop the EPIHeart cohort study and were responsible for acquiring the study grant. Carla Araújo raised the hypotheses, participated in data collection and field work, analysed and interpreted the data, and drafted the first version of the manuscript. Olga Laszczyńska analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. Marta Viana and Andreia Borges participated in data collection, field work and interpretation of the data. Filipa Melão and Ana Henriques interpreted data. Milton Severo analysed and interpreted the data. Maria Júlia Maciel and Ilídio Moreira were involved in the conception of the study and in field work. Ana Azevedo was the responsible for the conception and development of the study, analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. All authors were involved in writing the paper, in revising it critically and approved the final version of the submitted manuscript.

Data sharing

Data are available by email the corresponding author at carla-r-araujo@hotmail.com.

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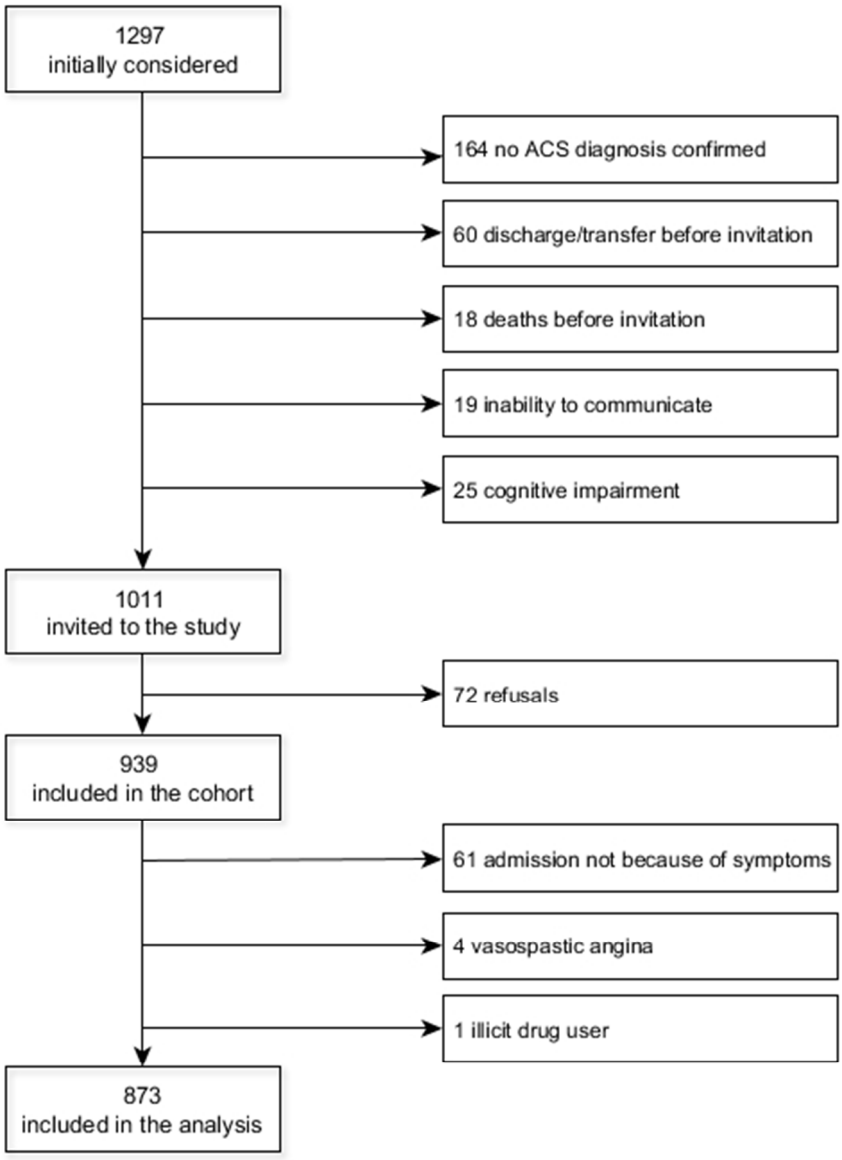

Figure 1. Flow chart of the study population

41x56mm (300 x 300 DPI)

Supplementary Table 1. Clinical presentation of patients with ST elevation myocardial infarction/non-classifiable acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	6 (5.9)	22 (21.8)	53 (52.5)	20 (19.8)	101 (100.0)		37 (13.3)	144 (51.8)	77 (27.7)	20 (7.2)	278 (100)		
Pain	6 (100.0)	21 (95.5)	52 (98.1)	16 (80.0)	95 (94.1)	0.039	36 (97.3)	142 (98.6)	73 (94.8)	20 (100.0)	271 (97.5)	0.338	0.106
Pain location†													
Typical	5 (83.3)	17 (81.0)	44 (84.6)	9 (56.3)	75 (78.9)		31 (88.6)	120 (85.1)	55 (76.4)	13 (65.0)	219 (81.7)		
Atypical	1 (16.7)	4 (19.0)	2 (3.8)	5 (31.3)	12 (12.6)		1 (2.9)	17 (12.1)	14 (19.4)	5 (25.0)	37 (13.8)		
Mixture	0 (0.0)	0 (0.0)	6 (11.5)	2 (12.5)	8 (8.4)	0.021	3 (8.6)	4 (2.8)	3 (4.2)	2 (10.2)	12 (4.5)	0.032	0.347
Referred pain	4 (66.7)	18 (85.7)	38 (73.1)	8 (50.0)	68 (71.6)	0.114	24 (66.7)	90 (63.4)	51 (69.9)	7 (35.0)	172 (63.5)	0.038	0.152
Radiation type‡													
Typical	3 (75.0)	8 (44.4)	17 (44.7)	1 (12.5)	29 (42.6)		19 (79.2)	53 (59.6)	26 (51.0)	3 (42.9)	101 (59.1)		
Atypical	0 (0.0)	5 (27.8)	10 (26.3)	4 (50.0)	19 (27.9)		5 (20.8)	21 (23.6)	9 (17.6)	3 (42.9)	38 (22.2)		
Mixture	1 (25.0)	5 (27.8)	11 (28.9)	3 (37.5)	20 (29.4)	0.504	0 (0.0)	15 (16.9)	16 (31.4)	1 (14.3)	32 (18.7)	0.018	0.060
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-10)	8.5 (8-9)	9 (8-10)	0.784	9 (7.5-10)	8 (7-10)	8 (6.5-9)	7.5 (6.5-9)	8 (7-10)	0.064	<0.001
Symptom	5 (83.3)	20 (90.9)	47 (88.7)	17 (85.0)	89 (88.1)	0.794	23 (62.2)	105 (72.9)	61 (79.2)	14 (70.0)	203 (73.0)	0.283	0.002
Symptom clusters‖													
Cluster 1	2 (33.3)	18 (81.8)	27 (50.9)	11 (55.0)	58 (57.4)		26 (70.3)	102 (70.8)	54 (70.1)	16 (80.0)	198 (71.2)		
Cluster 2	3 (50.0)	2 (9.1)	16 (30.2)	4 (20.0)	25 (24.8)		9 (24.3)	36 (25.0)	19 (24.7)	3 (15.0)	67 (24.1)		
Cluster 3	1 (16.7)	2 (9.1)	10 (18.9)	5 (25.0)	18 (17.8)	0.132	2 (5.4)	6 (4.2)	4 (5.2)	1 (5.0)	13 (4.7)	0.967	<0.001
Activity													
Sleep	1 (16.7)	3 (14.3)	4 (7.8)	3 (15.8)	11 (11.3)		5 (13.5)	29 (20.1)	10 (13.0)	4 (20.0)	48 (17.3)		
Rest	3 (50.0)	9 (42.9)	22 (43.1)	14 (73.7)	48 (49.5)		19 (51.4)	65 (45.1)	43 (55.8)	13 (65.0)	140 (50.4)		
Exertion	2 (33.3)	9 (42.9)	25 (49.0)	2 (10.5)	38 (39.2)	0.069	13 (35.1)	50 (34.7)	24 (31.2)	3 (15.0)	90 (32.4)	0.393	0.274
Stress trigger	1 (16.7)	2 (9.1)	4 (7.5)	3 (15.8)	10 (10.0)	0.519	5 (13.5)	11 (7.7)	6 (7.9)	2 (10.0)	24 (8.7)	0.669	0.697

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 2. Clinical presentation of patients with non-ST elevation acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	8 (6.3)	32 (25.4)	56 (44.4)	30 (23.8)	126 (100)		24 (6.5)	159 (43.2)	143 (38.9)	42 (11.4)	368 (100)		
Pain	8 (100.0)	31 (96.9)	52 (92.9)	28 (93.3)	119 (94.4)	0.864	24 (100.0)	155 (97.5)	141 (98.6)	38 (90.5)	358 (97.3)	0.073	0.131
Pain location†													
Typical	7 (87.5)	26 (83.9)	44 (86.3)	23 (82.1)	100 (84.7)		22 (91.7)	126 (82.4)	120 (85.1)	31 (81.6)	299 (84.0)		
Atypical	0 (0.0)	5 (16.1)	3 (5.9)	1 (3.6)	9 (7.6)		2 (8.3)	16 (10.5)	16 (11.3)	5 (13.2)	39 (11.0)		
Mixture	1 (12.5)	0 (0.0)	4 (7.8)	4 (14.3)	9 (7.6)	0.172	0 (0.0)	11 (7.2)	5 (3.5)	2 (5.3)	18 (5.1)	0.778	0.367
Referred pain	5 (62.5)	23 (74.2)	34 (65.4)	17 (60.7)	79 (66.4)	0.728	14 (58.3)	89 (57.4)	75 (53.2)	16 (42.1)	194 (54.2)	0.350	0.020
Radiation type‡													
Typical	5 (100.0)	12 (52.2)	11 (32.4)	6 (35.3)	34 (43.0)		9 (64.3)	61 (69.3)	41 (54.7)	7 (43.8)	118 (61.1)		
Atypical	0 (0.0)	8 (34.8)	8 (23.5)	9 (52.9)	25 (31.6)		2 (14.3)	16 (18.2)	30 (40.0)	5 (31.3)	53 (27.5)		
Mixture	0 (0.0)	3 (13.0)	15 (44.1)	2 (11.8)	20 (25.3)	0.008	3 (21.4)	11 (12.5)	4 (5.3)	4 (25.0)	22 (11.4)	0.007	0.005
Pain intensity§	9.5 (8.5-10)	9.5 (8-10)	8 (8-10)	8 (7-9)	9 (8-10)	0.224	8 (6-9)	8 (6-9)	8 (6-9)	8 (7.5-9)	8 (6-9)	0.200	<0.001
Symptom	6 (75.0)	25 (78.1)	44 (78.6)	24 (80.0)	99 (78.6)	0.992	20 (83.3)	104 (65.4)	90 (62.9)	28 (66.7)	242 (65.8)	0.278	0.007
Symptom clusters‖													
Cluster 1	5 (62.5)	23 (71.9)	35 (62.5)	21 (70.0)	84 (66.7)		17 (70.8)	130 (81.8)	116 (81.1)	36 (85.7)	299 (81.3)		
Cluster 2	2 (25.0)	6 (18.8)	12 (21.4)	4 (13.3)	24 (19.1)		6 (25.0)	23 (14.5)	16 (11.2)	6 (14.3)	51 (13.9)		
Cluster 3	1 (12.5)	3 (9.4)	9 (16.1)	5 (16.7)	18 (14.3)	0.919	1 (4.2)	6 (3.8)	11 (7.7)	0 (0.0)	18 (4.9)	0.231	<0.001
Activity													
Sleep	1 (14.3)	13 (44.8)	7 (12.7)	4 (14.3)	25 (21.0)		1 (4.2)	36 (23.1)	25 (17.7)	9 (22.0)	71 (19.6)		
Rest	2 (28.6)	9 (31.0)	28 (50.9)	15 (53.6)	54 (45.4)		15 (62.5)	59 (37.8)	62 (44.0)	20 (48.8)	156 (43.1)		
Exertion	4 (57.1)	7 (24.1)	20 (36.4)	9 (32.1)	40 (33.6)	0.032	8 (33.3)	61 (39.1)	54 (38.3)	12 (29.3)	135 (37.3)	0.180	0.768
Stress trigger	1 (12.5)	4 (12.5)	7 (12.7)	0 (0.0)	12 (9.6)	0.140	6 (25.0)	12 (7.7)	9 (6.4)	4 (9.8)	31 (8.6)	0.044	0.731

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 3. Marginal percentage of subjects with each symptom in each assigned cluster*

	Symptom clusters		
	Cluster 1* n=639	**Cluster 2†** n=167	**Cluster 3‡** n=67
Dyspnoea at rest	17.4	34.2	37.3
Exertional dyspnoea	6.0	2.1	14.5
Sweating	22.2	89.6	71.7
Nausea and vomiting	6.5	9.7	41.4
Dizziness	2.6	18.0	74.1
Blurry vision	0.6	4.4	27.5
Presyncope	1.3	11.4	42.7
Syncope	1.6	3.6	10.5
Palpitations	0.3	5.4	19.5
Weakness	7.5	17.8	64.4
"Other symptoms"	4.5	5.5	12.8
Other digestive symptoms	1.0	1.0	1.4
Discomfort	1.3	1.1	4.2

*Values are percentages.

* Cluster 1: no symptom cluster; † Cluster 2: dyspnoea and sweating cluster; ‡Cluster 3: multiple symptoms cluster.

Supplementary Table 4. Differences between women and men in clinical presentation of acute coronary syndrome, by age group (< 55 vs ≥55 years old)
(men are the reference class).

	<55 years		>=55 years			
Symptoms	**OR**	**95% CI**	**OR**	**95% CI**	**Interaction p-value**	**Adjusted for**
Pain	--*	--*	0.46	0.18-1.18	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)†	0.65	0.23-1.86	1.55	0.88-2.71	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	3.81	1.41-10.3	1.73	1.14-2.61	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type‡						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.19	0.41-3.45	1.34	0.77-2.35	0.415	
Mixture	1.43	0.40-5.16	2.56	1.39-4.71	0.606	
Pain intensity (higher than 8/10)	5.23	2.17-12.60	2.09	1.35-3.24	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.88	0.76-.4.66	1.91	1.21-3.04	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters§						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	0.88	0.31-2.50	1.49	0.93-2.38	0.246	
Cluster 3	3.30	0.99-10.97	4.08	2.07-8.05	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.74	0.25-2.19	1.08	0.64-1.81	0.284	
Exertion	0.89	0.29-2.67	1.27	0.74-2.16	0.408	

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG: coronary artery bypass surgery; CI, confidence interval; OR, odds ratio.
*All women below 55 years old presented with pain.
†Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.
‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.
§Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

STROBE Statement—checklist of items : ***Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – **page 1 (title) and page 2 (abstract)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – **page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – **page 4**
Objectives	3	State specific objectives, including any prespecified hypotheses - **page 4**
Methods		
Study design	4	Present key elements of study design early in the paper – **pages 4 and 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – **pages 4-6**
Participants	6	*Cohort study:* Give the eligibility criteria, and the sources and methods of selection of participants – **pages 4 and 5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – **pages 6 and 7**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – **pages 5, 6 and 7**
Bias	9	Describe any efforts to address potential sources of bias - **page 7**
Study size	10	Explain how the study size was arrived at – **page 5 and figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why –**page 6 and 7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - **page7**
		(*b*) Describe any methods used to examine subgroups and interactions – **page 7**
		(*c*) Explain how missing data were addressed –**Patients who were unable to answer the questionnaire (with missing data on clinical presentation) were not included.**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed –**Data were collected within a cohort study, but clinical presentation was collected through a questionnaire.**
		(*e*) Describe any sensitivity analyses –**We analysed clinical presentation separately by type of acute coronary syndrome (Supplementary tables 1 and 2), but as results were similar by sex and age both types of acute coronary syndrome were analysed together.**

Continued on next page

Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed –**pages 4 and 5**
		(b) Give reasons for non-participation at each stage –**page 5**
		(c) Consider use of a flow diagram – **Figure 1.**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – **pages 8-9**
		(b) Indicate number of participants with missing data for each variable of interest –**page 9**
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time –**pages 10-12**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – **pages 13-16**
		(*b*) Report category boundaries when continuous variables were categorized – **pages 10-14**
Other analyses	17	Report other analyses done— eg analyses of subgroups and interactions, and sensitivity analyses – **page 10**
Discussion		
Key results	18	Summarise key results with reference to study objectives – **page 17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias –**pages 19 and 20**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - **pages 17-19**
Generalisability	21	Discuss the generalisability (external validity) of the study results –**page 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based –**page 22**