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Predictors of long-term symptom burden and quality of life in patients hospitalised with chest pain: a prospective observational study

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ABSTRACT

Objective To describe the magnitude and predictors of symptom burden (SB) and quality of life (QoL) 3 months after hospital admission for acute chest pain.

Design Prospective observational study.

Setting Single centre, outpatient follow-up.

Participants 1506 patients.

Outcomes Scores reported for general health (RAND-12), angina-related health (Seattle Angina Questionnaire 7 (SAQ-7)) and dyspnoea (Rose Dyspnea Scale) 3 months after hospital admission for chest pain.

Methods A total of 1506 patients received questionnaires assessing general health (RAND-12), angina-related health (SAQ-7) and dyspnoea (Rose Dyspnea Scale) 3 months after discharge. Univariable and multivariable regression models identified predictors of SB and QoL scores. A mediator analysis identified factors mediating the effect of an unstable angina pectoris (UAP) diagnosis.

Results 774 (52%) responded. Discharge diagnoses were non-ST elevation myocardial infarction (NSTEMI) (14.2%), UAP (17.1%), non-coronary cardiac disease (6.6%), non-cardiac disease (6.3%) and non-cardiac chest pain (NCCP) (55.6%). NSTEMI had the most favourable, and UAP patients the least favourable SAQ-7 scores (median SAQ7-summary; 88 vs 75, p<0.001). NCCP patients reported persisting chest pain in 50% and dyspnoea in 33% of cases. After adjusting for confounders, revascularisation predicted better QoL scores, while UAP, current smoking and hypertension predicted worse outcome. NSTEMI and UAP patients who were revascularised reported higher scores (p<0.05) in SAQ-7-QL, SAQ7-PL, SAQ7-summary (NSTEMI) and all SAQ-7 domains (UAP). Revascularisation altered the unstandardised beta value (>±10%) of an UAP diagnosis for all SAQ-7 and RAND-12 outcomes.

Conclusions Patients with NSTEMI reported the most favourable outcome 3 months after hospitalisation for chest pain. Patients with other diseases, in particular UAP patients, reported lower scores. Revascularised NSTEMI and UAP patients reported higher QoL scores compared with patients receiving conservative treatment. Revascularisation mediated all outcomes in UAP patients.

Trial registration number NCT02620202.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study includes a large group of well-characterised patients admitted with chest pain, including both cardiac and non-cardiac causes of chest pain.

⇒ Both disease specific and generic quality of life data are reported, and the generic data are compared with measures from the general population.

⇒ There was a substantial proportion of missing data dominated by younger patients with overall less risk factors.

⇒ Detailed information on ethnicity, socioeconomic status and detailed angiographic data was not registered, and accordingly, these possible confounders could not be adjusted for.

⇒ Baseline scores was not available; thus, the study lacks ability to attribute the direct effect of revascularisation in improving scores between hospitalisations and 3-month phase.

INTRODUCTION

Acute chest pain is a common presenting symptom in the emergency department, accounting for approximately 10% of all non-trauma or non-surgery visits.[1 2] Implementation of the European Society of Cardiology (ESC) algorithms may lead to early discharge of up to half of patients presenting with chest pain.[2 3] As turnaround times in the hospitals decrease, two patient groups may receive less focus and consequently are at risk of undertreatment.

The first group is the large proportion suffering from non-cardiac conditions with musculoskeletal, gastrointestinal, pulmonary and other miscellaneous aetiologies.[4] Previous quality of life research have mostly focused on non-ST-elevation myocardial infarction (NSTEMI) patients, and less is known about the challenges of patients with

non-cardiac chest pain (NCCP).[5–8] These patients impose a risk of future unnecessary healthcare investigations and surplus readmissions, if symptoms persist, and no medical rationale or treatment is provided.[4]

The second group includes patients with ischaemic heart disease who are not identified as NSTEMI, commonly diagnosed as unstable angina pectoris (UAP). UAP patients may differ from NSTEMI patients and typically have ischaemic cardiac disease being less available for revascularisation.[9 10] They are typically 'ruled-out' by the ESC algorithms for non-ST segment elevation acute coronary syndrome (NSTE-ACS).[11 12] There is an ongoing debate on how this condition should be defined and what is the optimal treatment options after the implementation of high sensitivity troponin assays.[13] Data describing symptom burden or the effect of revascularisation in UAP patients as measured with validated quality of life instruments are scarce[14–18] and should be further elaborated.

The aim of this study was to describe the magnitude and predictors of symptom burden and quality of life 3 months after discharge in different groups of chest pain patients. Furthermore, we performed an in-depth analysis investigating symptom burden and quality of life in UAP patients.

METHODS
Study design
This article reports data from the *Aiming Towards Evidence Based Interpretation of Cardiac Biomarkers in Patients With Chest Pain* (WESTCOR) study, a prospective observational study recruiting patients with chest pain and suspected NSTE-ACS (Clinical Trials number NCT02620202).[19] A total of 1506 patients were included using the following criteria: ≥18 years, admission due to chest pain, an ECG excluding ST segment elevation (STEMI) and able to provide written informed consent. Patient-reported outcomes were assessed at a 3-month follow-up using self-administered disease-specific and generic questionnaires administered by postal mail.

Approximately half of the included patients (n=779 (51.7%)) responded. Five patients were excluded due to a stable angina pectoris diagnosis. Thus, this left our final analytical sample at 774 patients (figure 1).

Data collection
High sensitivity cTnT (Roche Diagnostics) and cTnI (Abbott Diagnostics), creatinine and lipid analysis were performed on admission. Details are provided in online supplemental material. The diagnosis in all patients were adjudicated by two independent cardiologists based on all available clinical data, routine laboratory results (hs-cTnT), ECG, ultrasound and imaging findings. A third adjudicator resolved disagreements. Details are described earlier[19] and provided in the online supplemental material. NSTEMI and UAP were defined according to the third universal definition for Myocardial infarction.[20] Revascularisation was defined as either percutaneous
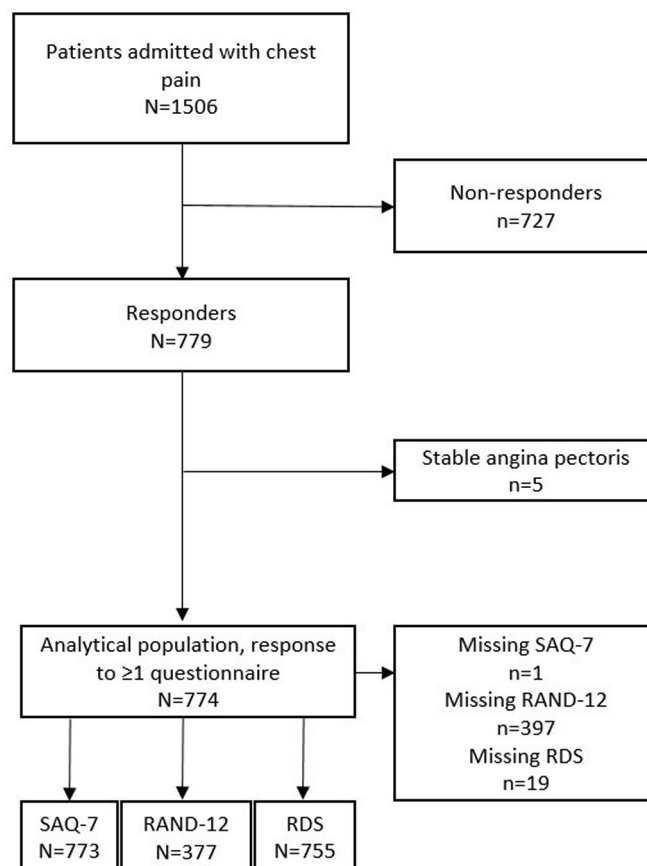

Figure 1 Flow chart of the study population. RDS, Rose Dyspnea Scale; SAQ-7, Seattle Angina Questionnaire 7.

coronary intervention (PCI) or coronary artery bypass graft (CABG) during hospitalisation or in close association with the hospitalisation (decided during hospitalisation but performed after discharge).

Quality of life instruments
Disease-specific health status related to angina was determined using a validated shortened version of the Seattle Angina Questionnaire (SAQ-7)[21] consisting of a seven-item questionnaire evaluating four key domains (angina frequency (SAQ7-AF), physical limitation (SAQ7-PL), quality of life (SAQ7-QL) and summary score (SAQ7)). The scoring ranged from 0 to 100 (best). A score of 100 on the SAQ7-AF domain was defined as angina free.[22]

The patient's level of dyspnoea with activity was assessed using the Rose Dyspnea Scale (RDS), which is a four-item questionnaire with a score range from 0 to 4, where 0 indicates no dyspnoea and 4 indicates dyspnoea with minimal activity.[23] We considered a score of 0 or 1 as 'no dyspnoea or minor dyspnoea', while a score of 2 or more was considered pronounced dyspnoea.

Generic health status was assessed using the 12-item questionnaire RAND-12, which is a truncated version of the Short Form Health Survey-36. RAND-12 ranges from 0 to 100 (best) and can be summarised in two domains: a physical component Physical Component Score (PCS-12) and a Mental Component Score (MCS-12).[24]

Missing data

SAQ-7 and RDS were distributed to all participants, while RAND-12 was included on a later time point with approximately half of the patients receiving it. Patients with complete response in at least one of the three were included in the applicable data analysis (figure 1). In the SAQ-7, missing values in one of the questions would result in taking the average of the non-missing values, as suggested by the SAQ-7 guidelines.

Normative population

The physical and mental component scores attained from the RAND-12 questionnaire were compared with scores from a normal population obtained from the Norwegian Centre for Research Data. The data stems from a large study (NorLAG) conducted in three rounds from 2002 to 2017.[25] The participants were contacted by phone, followed by questionnaires via postal mail, which they could fill in on paper or online. To match the median age in the analytical population, we excluded patients with an age below and above the 25th and 75th quartile, resulting in the inclusion of 6240 individuals.

Statistical analyses

Baseline characteristics are presented as frequencies and proportions for categorical variables and median with 25th–75th percentiles (IQR) for continuous variables. Normality was checked using the Kolmogorov-Smirnov normality test, and overall, the data were skewed. Kruskal-Wallis test was used to compare continuous variables between the five diagnostic groups, and χ^2 test or Fisher's exact test (as applicable) for comparing proportions. Mann-Whitney U test was used for comparing two groups (responders and non-responders, the patient data to the general population and revascularised vs non-revascularised).

Univariable linear regression was used to identify the association between independent explanatory variables (patient characteristics including baseline troponin concentrations, revascularisation and adjudicated diagnosis) and dependent outcome variables (the six different quality of life scores in SAQ-7 and RAND-12). Candidate predictor variables with p value ≤0.10 in univariable regression analysis were adjusted for in the multivariable linear regression models. The revascularisation variable was included in the multivariable model if p value was <0.15 because of its clinical importance. Collinearity between the predictor variables was inspected by using Spearman's rank correlation, where a limit of correlation coefficient (rho) >0.4 was set. If predictor variables had an intercorrelation exceeding this value, the variable with the most significant correlation with the outcome variable was selected. Goodness of fit was expressed as the adjusted R^2.

As the UAP patients overall had lower scores compared with others, we performed a subgroup analysis. A series of trivariable regression models were undertaken in order to evaluate which factors could mediate the effect of

quality of life in patients with UAP. Quality of life scores were assigned as the dependent variables, while UAP and potential mediators were assigned as the independent variables. The effect of the potential mediator was defined significant if it changed the unstandardised coefficient of the UAP diagnosis >±10%.

A two-tailed p value <0.05 was considered statistically significant throughout all analyses. The p value in tables 1 and 2 represents comparison across all five groups, using Kruskal-Wallis test, χ^2 test or Fisher's exact test, as applicable. Data analyses were performed using IBM SPSS software, V.25 (IBM Corp) and R software V.1.2.5001.

RESULTS

Baseline characteristics

A total of 305 women and 469 men were included in the analytical population, with a median age of 66 (57-73) years. The prevalence of NSTEMI and UAP was 14.2% and 17.1%, respectively, while non-coronary cardiac disease was 6.6%, non-cardiac disease was 6.3% and NCCP was 55.6% (table 1).

Patients with NSTEMI and UAP were more likely to be male and older compared with patients with NCCP. A subset of risk factors (hypertension, hyperlipidaemia, family history of MI and previous smoking) and prior cardiovascular disease was more frequent in patients with UAP. Patients with NSTEMI underwent revascularisation more frequently (74.5%) compared with patients with UAP (40.6%). Demographic and clinical characteristics stratified by diagnosis are provided in table 1.

When comparing patients who responded to at least one questionnaire to patients who did not respond, we found no difference as regarding sex, but the response group was older (66 years vs 58 years, p<0.001), more likely to have hypertension, known hyperlipidaemia (p<0.001 for both) and prior and currently treated with PCI (p=0.036 and p<0.001) (online supplemental table S1).

Differences in quality of life scores and symptom burden among diagnostic groups

Symptom and quality of life scores 3 months after discharge are summarised in table 2.

Patients with NSTEMI had the most favourable score in all domains except SAQ7-PL. Regarding angina frequency, patients with NSTEMI, non-cardiac disease and NCCP all had a median SAQ7-AF score of 100, whereas patients with UAP or non-coronary cardiac disease had median scores of 90 (p=0.003 across all patient groups). The latter two groups also had the lowest scores on quality of life (SAQ7-QL, p=0.009 across all patient groups), physical limitation (SAQ7-PL, p=0.001 across all patient groups) and summary SAQ7-score (p<0.001 across all patients groups). Three months after hospitalisation for chest pain, more patients with NSTEMI and non-cardiac disease were totally free of chest pain compared with remaining groups (figure 2). Patients with UAP had the highest prevalence of angina, with nearly 60% reporting

Table 1 Baseline characteristics stratified by diagnosis groups

Demographic and clinical characteristics (total=774)	NSTEMI (n=110)	UAP (n=133)	Non-coronary cardiac disease (n=51)	Non-cardiac disease (n=49)	NCCP (n=431)	P value
Age, median (25th–75th percentile)	67 (57–75)	68 (60–75)	70 (61–79)	70 (59–77)	63 (53–72)	<0.001
Gender, female, n (%)	30 (27.3)	35 (26.7)	15 (29.4)	23 (46.9)	202 (46.7)	<0.001
Risk factors, n (%)						
Hypertension	49 (44.5)	75 (56.4)	21 (41.2)	23 (46.9)	183 (42.5)	0.119
Hyperlipidaemia	34 (30.9)	88 (66.2)	26 (51.0)	18 (36.7)	176 (40.9)	<0.001
Diabetes mellitus	14 (12.7)	26 (19.5)	4 (7.8)	5 (10.2)	46 (10.6)	0.069
Insulin dependent	3 (2.7)	11 (8.4)	1 (2.0)	0 (0)	10 (2.3)	
Obesity (BMI >30)	12 (22.2)	18 (24.3)	4 (16.7)	7 (29.2)	50 (22.1)	0.876
Family history (MI)	16 (14.5)	28 (21.1)	7 (13.7)	7 (14.3)	84 (19.5)	0.501
Unknown	12 (10.9)	11 (8.4)	5 (9.8)	2 (4.1)	36 (8.3)	0.707
Current smoker	25 (22.7)	20 (15.3)	7 (13.7)	9 (18.4)	74 (17.1)	0.539
Previous smoker	44 (40.0)	64 (47.3)	24 (47.1)	21 (42.9)	202 (47.1)	0.853
Medical history, n (%)						
Prior myocardial infarction	20 (18.2)	39 (29.3)	10 (19.6)	7 (14.3)	71 (16.6)	0.019
Prior PCI	22 (20.0)	55 (41.4)	11 (21.6)	7 (14.3)	72 (16.9)	<0.001
Prior CABG	9 (8.2)	26 (19.8)	2 (3.9)	5 (10.2)	16 (3.7)	<0.001
Prior heart failure	4 (3.6)	3 (2.3)	6 (11.8)	0 (0)	13 (3.0)	0.033
Prior stroke	5 (4.5)	8 (6.1)	3 (5.9)	1 (2.0)	8 (1.8)	0.128
Peripheral vascular disease	3 (2.7)	9 (6.9)	0 (0)	0 (0)	5 (1.2)	0.006
Reduced renal function*	9 (10.7)	13 (17.8)	6 (16.2)	7 (19.4)	30 (11.3)	0.337
Vital parameters at admission, median (25th–75th percentile)						
Systolic BP, mm Hg	149 (136–176)	148 (136–160)	140 (124–155)	139 (125–158)	145 (133–161)	0.016
Diastolic BP, mm Hg	85 (75–93)	84 (76–91)	88 (76–96)	80 (73–90)	83 (75–91)	0.619
Heart rate, bpm	74 (62–82)	70 (62–80)	94 (66–130)	72 (65–87)	69 (62–80)	<0.001
BMI	26.4 (24.2–28.7)	26.1 (24.7–29.9)	27.2 (26.1–29.1)	27.3 (24.8–30.3)	26.7 (24.2–29.7)	0.879
Biomarkers, median (25th–75th percentile)						
cTnT, ng/L	50.5 (22–160.5)	9.0 (6.0–18.0)	16.0 (9.0–23.0)	8.0 (4.0–13.0)	6.0 (3.0–10.0)	<0.001
cTnI, ng/L	121.7 (26.2–462.8)	4.1 (2.6–9.4)	9.6 (4.2–24.4)	3.7 (1.8–8.3)	2.6 (1.5–4.8)	<0.001
Investigations and intervention, n (%)						
Coronary CT angiography	7 (6.4)	44 (33.1)	10 (19.6)	12 (24.5)	220 (51.0)	<0.001
Coronary angiography	100 (90.9%)	102 (76.7%)	14 (27.5%)	8 (16.3%)	84 (19.5%)	<0.001
PCI during hospitalisation	72 (65.5)	50 (37.6)	2 (3.9)	1 (2.0)	2 (0.7)	<0.001
Revascularisation	82 (74.5)	54 (40.6)	3 (5.9)	1 (2.0)	6 (1.4)	<0.001
Medications at admission, n (%)						
Statins	34 (30.9)	87 (65.4)	25 (49.0)	18 (36.7)	174 (40.4)	<0.001
Warfarin	2 (1.8)	10 (7.5)	5 (9.8)	2 (4.1)	19 (4.4)	<0.001
ASA	38 (34.5)	79 (59.4)	20 (39.2)	12 (24.5)	129 (29.9)	<0.001
Clopidogrel	5 (4.5)	15 (11.3)	2 (3.9)	1 (2.0)	16 (3.7)	0.021
Ticagrelor	3 (2.7)	10 (7.5)	2 (3.9)	0 (0.0)	11 (2.6)	0.063
ACEI	5 (4.5)	7 (5.3)	2 (3.9)	0 (0.0)	4 (0.9)	0.007
Beta blockers	11 (10.0)	5 (3.8)	8 (15.7)	0 (0.0)	3 (0.7)	<0.001
Diuretics	18 (16.4)	34 (25.6)	13 (25.5)	8 (16.3)	78 (18.1)	0.212

*eGFR < 60 mL/min/1.73m^2.
ACEI, ACE inhibitors; ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; cTnI, cardiac troponin I; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; NCCP, non-cardiac chest pain; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UAP, unstable angina pectoris.

Table 2 Quality of life indices 3 months after discharge stratified by diagnosis group

Questionnaire, median (25th–75th percentile)	NSTEMI n=110	UAP n=133	Non-coronary cardiac disease n=51	Non-cardiac disease n=49	NCCP n=431	P value
SAQ-7	n=110	n=133	n=51	n=49	n=431	
Angina frequency (SAQ7-AF)	100 (80–100)	90 (60–100)	90 (80–100)	100 (80–100)	100 (80–100)	0.003
Quality of life (SAQ7-QL)	88 (50–100)	63 (38–100)	63 (38–100)	75 (50–100)	75 (50–100)	0.009
Physical limitation (SAQ7-PL)	92 (67–100)	75 (58–100)	75 (50–100)	83 (52–100)	100 (59–100)	0.001
Summary score (SAQ7)	88 (70–100)	75 (52–100)	75 (55–94)	83 (68–100)	84 (70–100)	<0.001
RAND-12	n=42	n=77	n=21	n=22	n=215	
PCS-12 median	54 (41–60)	46 (35–55)	50 (36–55)	44 (35–57)	52 (38–57)	0.079
MCS-12 median	54 (45–60)	50 (41–56)	48 (35–60)	48 (39–57)	51 (41–58)	0.455

NCCP, non-cardiac chest pain; NSTEMI, non-ST segment elevation myocardial infarction; SAQ-7, Seattle Angina Questionnaire 7; UAP, unstable angina pectoris.

either weekly or daily episodes (figure 2). Similarly, patients with NSTEMI had the largest proportion of individuals with absence of or minor dyspnoea (71%), while patients with UAP had the largest proportion (44%) who were hindered in their daily activities by pronounced dyspnoea (figure 3).

Regarding overall health status, both components of the RAND-12 were more favourable among patients with NSTEMI, with a score of 54 (41–60) and 54 (45–60) for the physical and mental domain (PSC-12 and MCS-12), respectively (table 2). Patients with non-cardiac disease had the lowest scores, 44 (45–57) for the PSC-12 and 48 (39–57) for the MSC-12 component. However, these differences did not reach statistically significance.

Comparison between responders and the general population

The median values of the two components of RAND-12 were compared with data from a normative population with the same age in order to investigate any differences in general health between this group and responders included in the analyses. The general population showed a higher median value for MCS-12 (58 vs 51, p<0.001) but not PCS-12 (52 vs 50, p=0.383) (see online supplemental table S2).

Effect of revascularisation

A total of 74.5% of NSTEMI and 40.6% of UAP patients were revascularised. NSTEMI patients who were revascularised demonstrated better quality of life in three
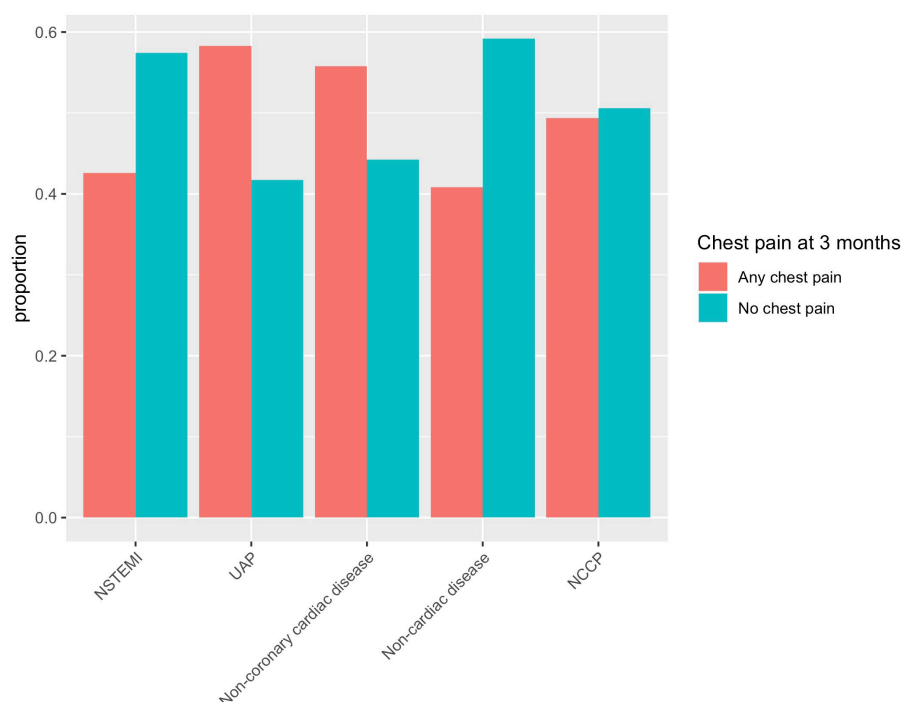

Figure 2 Proportion of patients who reported angina (chest pain) freedom at 3 months, as assessed by SAQ7-AF. NCCP, non-cardiac chest pain; NSTEMI, non-ST elevation myocardial infarction; SAQ7-AF, Seattle Angina Questionnaire 7 angina frequency; UAP, unstable angina pectoris.
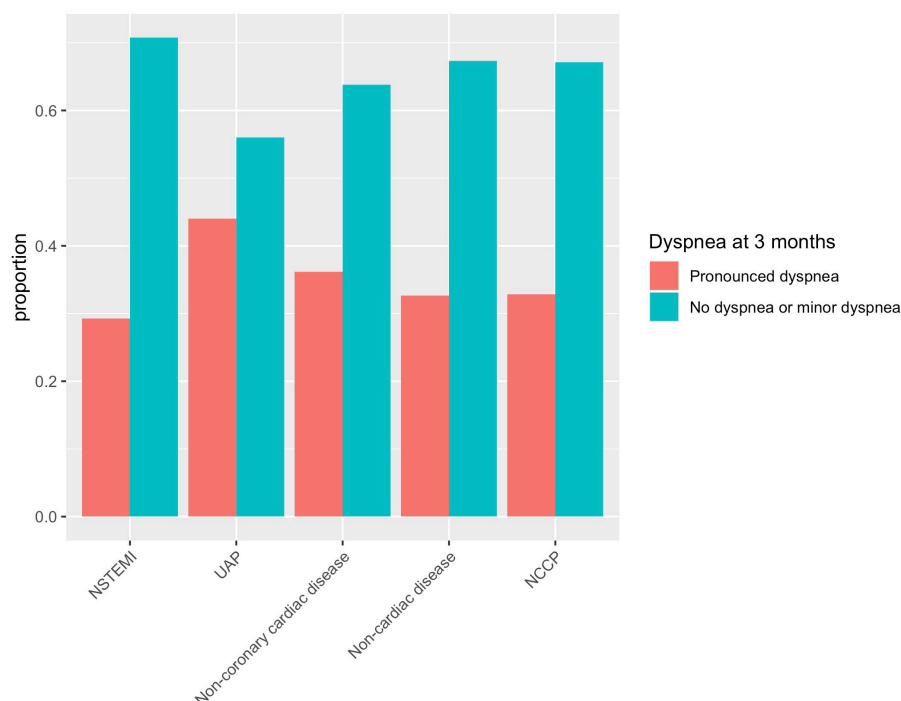
Figure 3 Proportion of patients reporting dyspnoea at 3 months, assessed by Rose Dyspnea Scale. NCCP, non-cardiac chest pain; NSTEMI, non-ST elevation myocardial infarction; UAP, unstable angina pectoris.

domains: SAQ7-QL, SAQ7-PL and SAQ7-summary (all p<0.05) compared with those treated conservatively (non-revascularised) (figure 4). Similar findings were observed in the UAP group; patients who were revascularised had significantly higher scores in all domains of the SAQ-7 questionnaire (all p<0.05).

Predictors of quality of life and symptom burden

The results of the univariable regression analyses are provided in the online supplemental table S3. Adjusted multivariable analysis demonstrated that revascularisation and a diagnosis of UAP were the most prominent predictors of angina frequency (SAQ7-AF) (table 3).

Patients who underwent revascularisation were associated with higher quality of life (SAQ7-QL) 3 months after admission (β=0.10 (95% CI 0.02 to 0.17), p=0.012), while those diagnosed with UAP (β=−0.14 (95% CI −0.21 to 0.06), p<0.001), hypertension (β=−0.10 (95% CI −0.17 to 0.02], p=0.009) and current smoking (β=−0.10 (95% CI −0.18 to 0.03), p=0.005) were associated with lower quality of life. Regarding physical limitation (SAQ7-PL), age, prior CABG, reduced renal function and current smoking were associated with a lower score (all p<0.05). Revascularisation (β=0.15 (95% CI 0.06 to 0.23), p=0.001), a diagnosis of UAP (β=−0.18 (95% CI −0.29 to 0.09], p<0.001)) or non-coronary cardiac disease (β=−0.11 (95% CI −0.19 to 0.02), p=0.013) were significant in predicting a summary score of SAQ-7.

Regarding general health, we found hypertension, current smoking, increased BMI and a diagnosis of UAP to be associated with worse general health as measured by the PCS-12 domain of the RAND-12 instrument. A history of prior MI (β=−0.11 (95% CI −0.23 to 0.01), p=0.041)

and current smoking (β=−0.13 (95% CI −0.23 to 0.03), p=0.015) were associated with worse mental health as measured by MCS-12.

Factors mediating the effect of an UAP diagnosis on quality of life and symptom burden

The mediator analysis, presented in the online supplemental table S4, showed that revascularisation was the most dominant mediator of quality of life in patients with UAP as it managed to alter the unstandardised beta coefficient of the UAP variable more than the 10% threshold in all subdomains, both in the angina-related SAQ-7 instrument and the generic RAND-12 instrument. Adding to that, prior PCI or CABG significantly mediated the effect of an UAP diagnosis on angina-related quality of life and physical limitation.

DISCUSSION

The current study has several important findings. First, NSTEMI patients report more favourable scores for angina frequency, dyspnoea and physical and mental quality of life compared with other patient groups 3 months after hospitalisation for acute chest pain. UAP patients and patients with other cardiac diseases report the lowest scores. Even though the NCCP group was heterogeneous with the upper quartile reporting excellent outcomes half of NCCP patients reported persisting chest pain and one in three reported pronounced dyspnoea. Second, patients who had been admitted for acute chest pain showed overall lower mental health indices compared with the general population. Third, the most important overall predictor for favourable scores
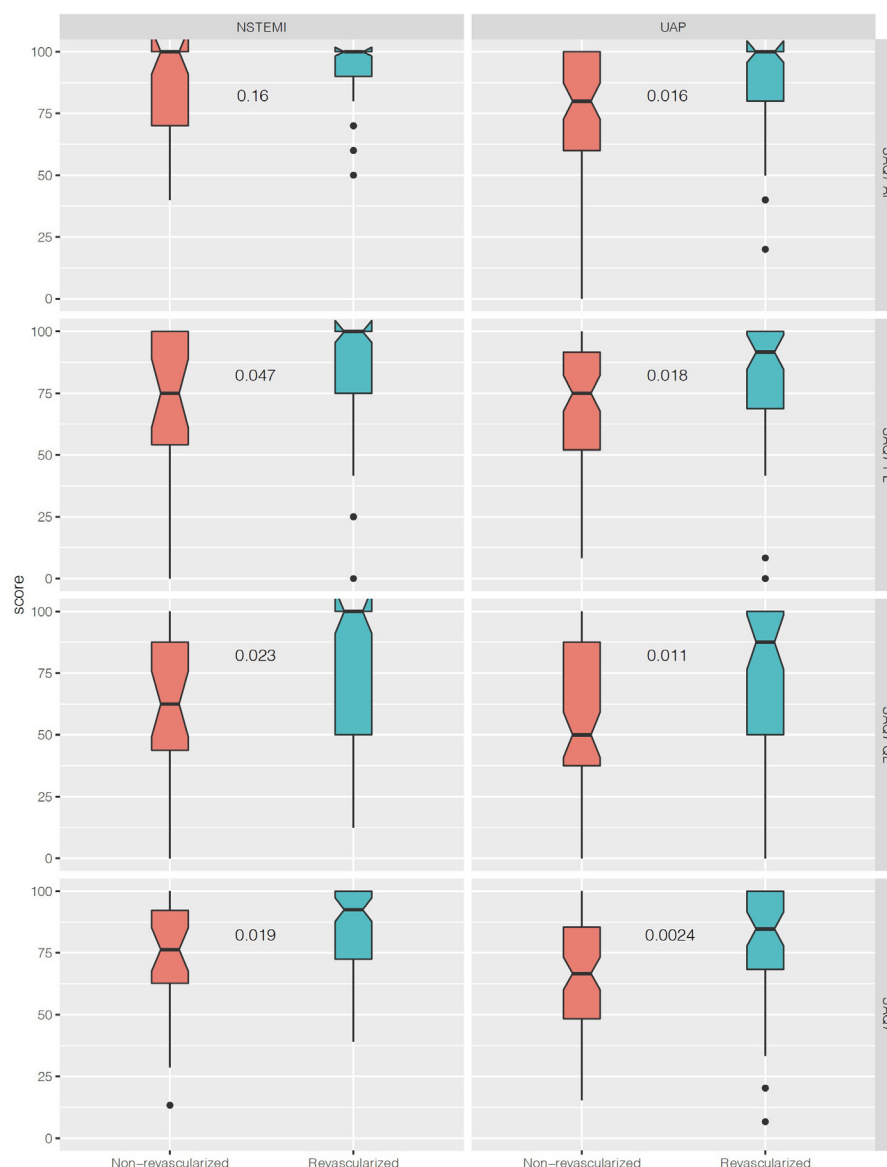
Figure 4 Boxplots of median values of four subdomain of the SAQ-7 questionnaire in revascularised and non-revascularised patients (with p values between the groups), both among NSTEMI and UAP patients. NSTEMI, non-ST elevation myocardial infarction; SAQ-7, Seattle Angina Questionnaire 7; UAP, unstable angina pectoris.

was revascularisation, while the most important predictor of unfavourable scores was a diagnosis of UAP. Finally, revascularisation appeared to mediate the unfavourable scores reported in the UAP group beneficially.

Large proportions of patients diagnosed with NCCP reported chest pain and dyspnoea 3 months after discharge. Compared with the NSTEMI population, we observed an overall higher symptom burden and lower quality of life in NCCP patients, in addition to the mental component score of RAND-12 being lower than community norms.[4] Other studies report that these patients experience a persistence of symptoms that may lead to overinvestigations if they are rehospitalised.[26 27] Wielgosz and colleagues[28] followed 821 patients with normal coronary arteries over a period of 1 year, the majority of these patients continued to suffer from chest pain, despite the observation that NCCP possessed a good prognosis. The

high symptom burden indicates that different supportive and multifaceted follow-up strategies should be investigated in NCCP patients.

The UAP patients had among the worst outcomes. This could be related to a higher prevalence of risk factors, more comorbidities[7] and treatment with revascularisation being less frequent than the NSTEMI group. One previous report by Rumsfeld *et al* also found that a discharge diagnosis of UAP was significantly associated with worse SF-36 physical component score.[17] Our study supplement the findings of Rumsfeld and colleagues by also including a disease-specific instrument (SAQ-7).

Revascularisation was an important predictor of quality of life in our data, for both NSTEMI and UAP patients. The effect on AMI have been observed earlier. The PREMIER study and TRIUMPH registry (similar PCI rate as us) reported angina at 30 days in 26.9% and 29.1%

Table 3 Multivariable regression models of the association between predictors and scores of SAQ-7 and RAND-12 instruments

	SAQ7-AF β (95% CI)	P value	SAQ7-QL β (95% CI)	P value	SAQ7-PL β (95% CI)	P value	SAQ7-summary β (95% CI)	P value	PCS-12 β (95% CI)	P value	MCS-12 β (95% CI)	P value
Age	NS		NS		−0.22 (−0.44 to 0.17)	<0.001	NS		NS		NS	
Female gender	NS		NS		NS		NS		NS		NS	
Prior MI	NS								NS		−0.11 (−0.23 to 0.01)	0.041
Prior CABG	NS		−0.08 (−0.16 to 0.01)	0.036	−0.11 (−0.20 to 0.02)	0.022	NS		NS			
Hypertension	NS		−0.10 (−0.17 to 0.02)	0.009	NS		NS		−0.24 (−0.38 to 0.11)	0.001	NS	
Current smoking			−0.10 (−0.18 to 0.03)	0.005	−0.09 (−0.18 to 0.004)	0.041	NS		−0.127 (−0.26 to 0.01)	0.060	−0.13 (−0.23 to 0.03)	0.015
Reduced renal function	NS				−0.11 (−0.21 to 0.02)	0.025	NS					
BMI									−0.18 (−0.33 to 0.04)	0.011		
Revascularisation	0.15 (0.05 to 0.23)	0.002	0.10 (0.02 to 0.17)	0.012			0.15 (0.06 to 0.23)	0.001	NS			
UAP	−0.19 (−0.31 to 0.10)	<0.001	−0.14 (−0.21 to 0.06)	<0.001	NS		−0.18 (−0.29 to 0.09)	<0.001	−0.17 (−0.29 to 0.02)	0.028		
Non-coronary cardiac disease			NS		−0.09 (−0.17 to 0.001)	0.047	−0.11 (−0.19 to 0.02)	0.013				
	R^2=0.069 p<0.001		R^2=0.061 p<0.001		R^2=0.125 p<0.001		R^2=0.070 p<0.001		R^2=0.157 p<0.001		R^2=0.037 p=0.014	

Standardised β-coefficients are provided with 95% CIs.
The empty cells denote variables that were tested in the univariable regression analysis showing no significant correlation (p value <0.10) with the applicable dependent variable and accordingly are not included in the applicable multivariable linear regression models (see Methods section).
BMI, body mass index; CABG, coronary artery bypass graft; NS, not significant; SAQ7-AF, Seattle Angina Questionnaire 7 angina frequency; SAQ7-PL, Seattle Angina Questionnaire 7 physical limitation; SAQ7-QL, Seattle Angina Questionnaire 7 quality of life; UAP, unstable angina pectoris.

of myocardial infarction patients, compared with 42.6% of NSTEMI patients in our data.[29 30] Our study adds to previous research within this field by showing that revascularisation was a strong predictor for higher SAQ7-AF score (angina freedom), SAQ7-QL and SAQ7-summary score also in patients with UAP and would clearly mediate the outcome of the scorings in this patient group. This is interesting given that the randomised CorMicA trial showed a favourable outcome in stable angina patients without significant coronary stenosis who were randomised to assessment of coronary flow reserves, microcirculation and vasoactive testing followed by targeted treatment,[31 32] as opposed to standard care. Given the lower revascularisation rate and higher symptom burden seen in UAP patients, such novel investigation and treatment protocols are highly warranted and should be further investigated in this group.[31 32]

Strengths and limitations

One of the key strengths in this study is that we include a large heterogeneous group of patients with chest pain, including both cardiac and non-cardiac causes, thereby collecting data from all relevant groups, except STEMI. Furthermore, we compare the generic quality of life data to available comparators from the general population. Another strength is the use of comprehensive measurement by use of standardised disease-specific and generic health instruments.[33] Generally, a disease-specific measure is more sensitive (in this case for cardiovascular outcomes), while a generic measure taps the patient's overall health.[34]

Our study should be viewed in the light of several limitations. First, there was a substantial proportion of missing data. These patients were younger and with overall less risk factors. This introduces a possible bias as different scores could have been reported if all patients had responded. However, we found similar physical capacity (PCS-12 score) in chest pain patients and the age-adjusted general population, strengthening the assumption that reduction in scores are due to disease-specific symptoms. Second, we did not register information on ethnicity (the western Norwegian population is mainly Caucasian) or socioeconomic status, and accordingly, could not adjust for these possible confounders. Third, the characteristics of NSTEMI and UAP groups tend to differ in both clinical and demographic components; a logistic regression model was used to compensate for this, but we could not exclude non-recognised confounders to be present. Detailed angiographic data or non-invasive ischaemia investigations were not registered so the basis for different revascularisations rates between NSTEMI and UAP patients could not be elucidated in detail.[9 10] Angiography was done on clinical indication, and patients were treated and received revascularisation in accordance with current guidelines. This means that patients received revascularisation if the operator identified a significant stenosis that was available for PCI (or CABG as applicable). A few patients (n=10) underwent revascularisation due to identification of a coronary artery stenosis during angiography, but still were not given

a final adjudicated diagnosis of acute coronary syndrome by the adjudicators who had all clinical information available including symptom development and results of investigations performed after PCI. This imposes uncertainty to our data analyses but is unlikely to impact the overall findings. Fourth, the disease-specific SAQ-7 instrument measures 'angina' but do not differentiate between chest pain of anginal aetiologies and NCCP that stem from the thorax cavity or psychogenic origins. Also, we did not measure follow-up data on intensity of medications so this could not be attributed to angina episodes and symptom burden at 3 month investigation. Finally, we did not measure baseline scores for the quality of life questionnaires and thus lack the ability to attribute the direct effect of revascularisation in improving scores between hospitalisations and 3-month phase.

Conclusion

NSTEMI patients have favourable disease-specific symptom and quality of life outcomes 3 months after the event, while the opposite may be expected in UAP and to some extent also NCCP patients. Symptom burden in UAP patients is large and should not be neglected. Revascularisation was associated with better quality of life and less symptom burden in both NSTEMI and UAP patients. Future studies should investigate if treatment (revascularisation or medical) may be expanded in UAP patients and if improved outpatient follow-up is beneficial for NCCP patients.

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REFERENCES

1 Ayerbe L, González E, Gallo V, *et al*. Clinical assessment of patients with chest pain; a systematic review of predictive tools. *BMC Cardiovasc Disord* 2016;16:18.
2 Stepinska J, Lettino M, Ahrens I, *et al*. Diagnosis and risk stratification of chest pain patients in the emergency department: focus on acute coronary syndromes. A position paper of the acute cardiovascular care association. *Eur Heart J Acute Cardiovasc Care* 2020;9:76–89.
3 Mockel M, Searle J, Muller R, *et al*. Chief complaints in medical emergencies: do they relate to underlying disease and outcome? The Charité emergency medicine study (CHARITEM). *Eur J Emerg Med* 2013;20:103–8.
4 Fass R, Achem SR. Noncardiac chest pain: epidemiology, natural course and pathogenesis. *J Neurogastroenterol Motil* 2011;17:110–23.
5 Maddox TM, Reid KJ, Rumsfeld JS, *et al*. One-year health status outcomes of unstable angina versus myocardial infarction: a prospective, observational cohort study of ACS survivors. *BMC Cardiovasc Disord* 2007;7:28.
6 Munyombwe T, Hall M, Dondo TB, *et al*. Quality of life trajectories in survivors of acute myocardial infarction: a national longitudinal study. *Heart* 2020;106:33–9.
7 Kim M-J, Jeon DS, Gwon H-C, *et al*. Health-related quality-of-life after percutaneous coronary intervention in patients with UA/NSTEMI and STEMI: the Korean multicenter registry. *J Korean Med Sci* 2013;28:848–54.
8 Brink E, Grankvist G, Karlson BW, *et al*. Health-related quality of life in women and men one year after acute myocardial infarction. *Qual Life Res* 2005;14:749–57.
9 Kvisvik B, Mørkrid L, Røsjø H, *et al*. High-sensitivity troponin T vs I in acute coronary syndrome: prediction of significant coronary lesions and long-term prognosis. *Clin Chem* 2017;63:552–62.
10 Ellis C, Gamble G, Hamer A, *et al*. Patients admitted with an acute coronary syndrome (ACS) in New Zealand in 2007: results of a second comprehensive nationwide audit and a comparison with the first audit from 2002. *N Z Med J* 2010;123:25–43.
11 Collet J-P, Thiele H, Barbato E, *et al*. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289–367.
12 Tjora HL, Steiro O-T, Langørgen J, *et al*. Diagnostic performance of novel troponin algorithms for the Rule-Out of non-ST-elevation acute coronary syndrome. *Clin Chem* 2022;68:291–302.
13 Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? *Circulation* 2013;127:2452–7.
14 Arnold SV, Smolderen KG, Kennedy KF, *et al*. Risk factors for rehospitalization for acute coronary syndromes and unplanned revascularization following acute myocardial infarction. *J Am Heart Assoc* 2015;4:1352. doi:10.1161/JAHA.114.001352
15 Fanaroff AC, Kaltenbach LA, Peterson ED, *et al*. Management of persistent angina after myocardial infarction treated with percutaneous coronary intervention: insights from the TRANSLATE-ACS study. *J Am Heart Assoc* 2017;6:e007007.
16 Cohen DJ, Van Hout B, Serruys PW, *et al*. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 2011;364:1016–26.
17 Rumsfeld JS, Magid DJ, Plomondon ME, *et al*. Predictors of quality of life following acute coronary syndromes. *Am J Cardiol* 2001;88:781–4.
18 De Smedt D, Clays E, De Bacquer D. Measuring health-related quality of life in cardiac patients. *Eur Heart J Qual Care Clin Outcomes* 2016;2:149–50.
19 Tjora HL, Steiro O-T, Langørgen J, *et al*. Aiming toWards evidence baSed inTerpretation of cardiac biOmarkers in patients pResenting with chest pain-the WESTCOR study: study design. *Scand Cardiovasc J* 2019;53:280–5.
20 Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551–67.
21 Chan PS, Jones PG, Arnold SA, *et al*. Development and validation of a short version of the Seattle angina questionnaire. *Circ Cardiovasc Qual Outcomes* 2014;7:640–7.
22 Weintraub WS, Spertus JA, Kolm P, *et al*. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 2008;359:677–87.
23 Baron SJ, Chinnakondepalli K, Magnuson EA, *et al*. Quality-of-Life After Everolimus-Eluting Stents or Bypass Surgery for Left-Main Disease: Results From the EXCEL Trial. *J Am Coll Cardiol* 2017;70:3113–22.
24 Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33.
25 Veenstra M, Herlofson K, Aartsen M, *et al*. Cohort profile: the Norwegian life course, ageing and generation study (NorLAG). *Int J Epidemiol* 2021;50:728–9.
26 Mol KA, Smoczynska A, Rahel BM, *et al*. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart* 2018;5:e000859.
27 Ruddox V, Mathisen M, Otterstad JE. Prevalence and prognosis of non-specific chest pain among patients hospitalized for suspected acute coronary syndrome - a systematic literature search. *BMC Med* 2012;10:58.
28 Wielgosz AT, Fletcher RH, McCants CB, *et al*. Unimproved chest pain in patients with minimal or no coronary disease: a behavioral phenomenon. *Am Heart J* 1984;108:67–72.
29 Longmore RB, Spertus JA, Alexander KP, *et al*. Angina frequency after myocardial infarction and quality of life in older versus younger adults: the prospective registry evaluating myocardial infarction: event and recovery study. *Am Heart J* 2011;161:631–8.
30 Doll JA, Tang F, Cresci S, *et al*. Change in angina symptom status after acute myocardial infarction and its association with readmission risk: an analysis of the translational research investigating underlying disparities in acute myocardial infarction patients' health status (triumph) registry. *J Am Heart Assoc* 2016;5:3205. doi:10.1161/JAHA.116.003205
31 Ford TJ, Stanley B, Good R, *et al*. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol* 2018;72:2841–55.
32 Ford TJ, Yii E, Sidik N, *et al*. Ischemia and NO obstructive coronary artery disease: prevalence and correlates of coronary vasomotion disorders. *Circ Cardiovasc Interv* 2019;12:e008126.
33 Kornowski R. Patient reported outcomes measures (PROMs) in cardiovascular disease. *Eur Heart J Qual Care Clin Outcomes* 2021;qcab051.
34 Brazier JE, Yang Y, Tsuchiya A, *et al*. A review of studies mapping (or cross walking) non-preference based measures of health to generic preference-based measures. *Eur J Health Econ* 2010;11:215–25.

Supplementary Material

Supplementary Methods

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Supplementary Table S4: Mediator analysis investigating which variables that could mediate the predictive value of an UAP diagnosis for the different outcomes (dependent variables). Variables that changed the unstandardized B more than 10% are marked* below.

Supplementary Methods

Adjudication

All routine clinical assessments were recorded and registered retrospectively. Demographic and clinical characteristics were obtained from electronic medical records. Two independent

1

cardiologists adjudicated the final diagnosis based on all available clinical, routine laboratory (including cTnT at admission and at 3 and 8–12 hours from admission), electrocardiogram (ECG), ultrasound, and imaging findings, including cardiac computed tomographic angiography and conventional angiography(1). A third adjudicator resolved disagreements. Specific diagnostic criteria were predefined for 22 different medical conditions based on guidelines that were available during planning of the study (see "Diagnostic definitions" below). NSTEMI was defined according to the third universal definition for MI, including a significant rise and fall of cTn with at least one value above the 99th percentile combined with symptoms of ischemia, ECG changes, and image evidence of loss of viable myocardium or intracoronary thrombus.(2) Delta values of 20% (baseline cTnT concentration >14 ng/L) or 50% (baseline cTnT concentration ≤14 ng/L) in serial cTnT measures were regarded as significant, as suggested by the ESC in 2012.(1, 2) Since 2012, several studies have found a significantly lower 99th percentile concentration of cTn for women compared with men,(3-5) but knowledge of sex-specific cutoffs for women regarding diagnosing NSTEMI is partial because of a lack of data on pathophysiology.(6) Consequently, we chose to apply a common cutoff for all patients.

Diagnostic definitions

Myocardial infarction (AMI, MI): defined according to the third universal definition of myocardial infarction (7):

2

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

1. Symptoms of ischemia

2. Development of pathologic Q waves in the electrocardiogram (ECG)

3. New or presumed new significant ST-Segment-T wave (ST-T) changes or new left bundle branch block (LBBB).

4. Identification of an intracoronary thrombus by angiography or autopsy

5. Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality

Unstable angina pectoris (UAP): defined as symptoms suggestive of an ACS without elevation in biomarkers with or without ECG changes indicative of ischemia.(8)

Stable angina was defined as typical angina symptoms lasting >1 month without an increase in magnitude, duration or frequency of the pain and a known history of coronary artery disease.(9)

Pericarditis was diagnosed if at least two of four diagnostic criteria were present, as defined in several studies: typical pleuritic chest pain, detection of a pericardial rub on auscultation, typical ECG changes, new or increased amount of pericardial effusion on echocardiography.(10)

3

Myocarditis was diagnosed according to the position statement of ESC from 2013.(11)

Takotsubo cardiomyopathy was diagnosed with the modified criteria suggested by The Mayo

Clinic in 2008.(12)

Heart failure was defined according to the ESC diagnostic criteria of 2016.(13)

Atrial fibrillation, atrial flutter and other supraventricular arrhythmias were diagnosed by

ECG findings and the lack of symptoms and biochemical results supporting another disease.

Aortic stenosis and other valvular diseases were diagnosed in accordance with

echocardiographic findings and a history supporting the valve disease as cause of the

symptoms.(14)

Myalgia was defined as chest pain provoked by palpation in lack of cardiac disease.

GERD was based on gastroscopic findings, also in the lack of cardiac disease.

Cholecystitis were defined by the Tokyo Guidelines of 2006 while other abdominal diseases

were defined according to operative, endoscopic or radiological findings.(15)

Pneumonia was defined by typical symptoms and a chest X-ray supporting the disease, while

the diagnosis of both pulmonary embolism and pneumothorax was based on radiologic

findings and the lack of concurrent cardiac disease.

COPD was defined in accordance with the criteria by Stephens MB from 2008.(16)

NCCP was defined as chest pain without any specific clinical, radiologic or biochemical

findings.

4

Biochemical analysis

Hs-cTnT was measured using the Roche Diagnostics hs-cTnT assay with limit of blank (LoB) 3 ng/L, limit of detection (LoD) 5 ng/L, 99th percentile 14 ng/L, measurement range 4 – 10 000 ng/L and 10% analytical within-series coefficient of variation (CV_A) at 4.5 ng/L; CV_A was below 5% for concentrations of 10 ng/L or higher[17]. Hs-cTnI was measured using the Abbott Diagnostics hs-cTnI assay. The assay has a LoB 0.9 ng/L, LoD 1.7 ng/L, 99th percentile 26 ng/L and measurement range 2-50 000 ng/L, with 10% CV_A at 4.6 ng/L[17].

Glucose, creatinine and lipids were measured using the Cobas 8000 from Roche Diagnostics. The glomerular filtration rate was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)[18] formula using an enzymatic isotope dilution mass spectrometry traceable creatinine assay (Roche Diagnostics) with a CV_A less than 3% for concentration > 60 µmol/L.

Supplementary Tables

Supplementary Table S1. Characteristics of responders and non-responders at 3 months. Continuous variables are reported as median values (25th percentile to 75th percentile), proportions are given as absolute numbers (percentages).

Parameter	Responder N=774 (51.9%)	Non-responder N=718 (48.3%)	P-value
Age, median (25th to 75th percentile)	66 (57-73)	58 (47-71)	<0.001
Gender, female, n (%)	305 (39.4)	284 (39.6)	0.953
Risk factors, n (%)			
Hypertension	351 (45.3)	259 (36.1)	<0.001
Hyperlipidemia (known)	342 (44.2)	237 (33.0)	<0.001
Diabetes mellitus	94 (12.1)	82 (11.4)	0.665
Insulin-dependent	25 (3.2)	25 (3.5)	0.787
Family history (MI)	142 (18.3)	127 (17.7)	0.494
Unknown	66 (8.5)	74 (10.3)	0.239
Current smoker	135 (17.4)	147 (20.5)	0.135
Previous smoker	355 (45.9)	297 (41.4)	0.080
Medical history, n (%)			
Prior MI	147 (19.0)	137 (19.1)	0.965
Prior PCI	167 (21.6)	124 (17.3)	0.036
Prior CABG	58 (7.5)	52 (7.2)	0.853
Prior Heart Failure	26 (3.4)	25 (3.5)	0.896
Prior Stroke	25 (3.2)	17 (2.4)	0.350
Peripheral vascular disease	17 (2.2)	12 (1.7)	0.463
Revascularization	146 (18.9)	72 (10.0)	<0.001
Biomarkers			
cTnT, ng/L	8.0 (4.0-18.0)	6.0 (3.0-14.0)	<0.001
cTnI, ng/L	3.8 (1.94-11.31)	2.94 (1.50-7.50)	<0.001

Supplemental material

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Supplementary Table S2: RAND-12 scores in responders and in the normative population. Data are reported as median values (25th and 75th percentile).

	Responders N= 774	General population N= 6240	P-value
PCS-12	50 (37-59)	52 (42-55)	0.383
MCS-12	51 (41-58)	58 (54-61)	<0.001

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Supplementary Table S3. Univariable linear regression analyses of candidate predictors and quality of life outcome scores.

	SAQ7-AF				SAQ7-QL		
Variable	B	95% Cl	P-value	Variable	B	95% Cl	P-value
Age	-0.02	-0.10, 0.06	0.676	Age	0.008	-0.12, 0.14	0.898
Gender	-0.14	-2.87, 2.56	0.920	Gender	-2.66	-7.10, 1.79	0.241
cTnT	0.009	-0.002, 0.02	0.116	cTnT	0.02	0.001, 0.4	0.037
cTnI	0.001	0.000, 0.001	0.115	cTnI	0.001	0.000, 0.002	0.049
Prior MI	-6.44	-9.79, -3.09	<0.001	Prior MI	-5.41	-10.82, -0.002	0.050
Prior PCI	-7.43	-10.63, -4.23	<0.001	Prior PCI	-7.40	-12.57, -2.24	0.005
Prior CABG	-4.93	-9.86, 0.012	0.051	Prior CABG	-11.02	-19.28, 2.75	0.009
Prior Stroke	-1.95	-9.37, 5.48	0.607	Prior Stroke	-1.41	-7.08, 4.25	0.624
Prior Heart failure	-0.52	-9.37, 5.48	0.607	Prior Heart failure	-11.49	-23.20, 0.22	0.054
Hypertension	-4.06	-6.716, -1.404	0.003	Hypertension	-6.11	-10.42, -1.79	0.006
Current smoker	-0.05	-3.54, 3.45	0.980	Current smoker	-8.04	-13.76, 2.32	0.006
Reduced renal function	-4.65	-9.61, 0.31	0.066	Reduced renal function	-6.71	-14.80, 1.36	0.103
Diabetes	-4.97	-9.02, -0.93	0.016	Diabetes	-5.81	-12.37, 0.74	0.082
BMI	-0.24	-0.63, 0.15	0.231	BMI	-0.19	-0.85, 0.47	0.577
eGFR	0.05	-0.04, 0.15	0.280	eGFR	0.03	-0.12, 0.19	0.667
Revascularization	2.51	-0.88, 5.89	0.146	Revascularization	5.64	0.175, 11.11	0.043
NSTEMI	3.30	-0.49, 7.09	0.088	NSTEMI	4.79	-1.31, 10.90	0.124
UAP	-9.16	-12.66, -5.65	<0.001	UAP	-9.14	-14.78, -3.50	0.002
Non-coronary cardiac disease	-2.34	-7.63, 2.95	0.386	Non-coronary cardiac disease	-8.76	-17.71, 0.19	0.055
Non-cardiac disease	2.03	-3.36, 7.42	0.460	Non-cardiac disease	2.52	-6.36, 11.40	0.578
NCCP	3.81	1.15, 6.47	0.005	NCCP	4.83	0.50, 9.16	0.029

	SAQ7-PL				SAQ7		
Variable	B	95% Cl	P-value	Variable	B	95% Cl	P-value
Age	-0.31	-0.43, -0.20	<0.001	Age	-0.11	-0.20, -0.02	0.018
Gender	-1.46	-5.37, 2.42	0.461	Gender	-1.58	-4.59, 1.43	0.304
cTnT	0.006	-0.009, 0.02	0.435	cTnT	0.01	-0.001, 0.023	0.068
cTnI	0.0008	-0.001, 0.001	0.426	cTnI	0.001	0.000, 0.001	0.076
Prior MI	-11.40	-16.19, -6.61	<0.001	Prior MI	-7.94	-11.66, -4.23	<0.001
Prior PCI	-9.74	-14.38, -5.14	<0.001	Prior PCI	-8.20	-11.74, -4.66	<0.001

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Prior CABG	-16.81	-23.99, -9.63	<0.001	Prior CABG	-9.13	-14.66, -3.60	0.001
Prior Stroke	-5.38	-10.43, -0.33	0.037	Prior Stroke	-3.13	-7.33, 0.70	0.106
Prior Heart failure	-17.15	-27.56, -6.74	0.001	Prior Heart failure	-10.14	-18.16, -2.12	0.013
Hypertension	-6.62	-10.39, -2.85	0.001	Hypertension	-5.01	-7.95, -2.07	0.001
Current smoker	-5.49	-10.50. -0.49	0.032	Current smoker	-3.54	-7.41, 0.34	0.073
Reduced renal function	-16.64	-24.02, -9.27	<0.001	Reduced renal function	-8.64	-14.11, -3.16	0.002
Diabetes	-5.27	-11.05, 0.52	0.074	Diabetes	-4.93	-9.41, -0.44	0.031
BMI	-0.08	-0.67, 0.52	0.806	BMI	-0.15	-0.59, 0.30	0.526
eGFR	0.33	0.19, 0.47	<0.001	eGFR	0.13	0.02, 0.24	0.017
Revascularization	3.48	-1.37, 8.33	0.159	Revascularization	4.10	0.29, 7.82	0.035
NSTEMI	3.34	-2.08, 8.77	0.226	NSTEMI	4.10	-0.12, 8.32	0.057
UAP	-6.86	-11.92, -1.81	0.008	UAP	-8.70	-12.59, -4.81	<0.001
Non-coronary cardiac disease	-8.02	-15.2, -0.43	0.039	Non-coronary cardiac disease	-5.86	-11.80, 0.08	0.053
Non-cardiac disease	-2.17	-9.86, 5.53	0.581	Non-cardiac disease	1.44	-4.63, 7.50	0.643
NCCP	4.93	1.14, 8.72	0.011	NCCP	4.33	1.38, 7.28	0.004

	PCS-12				MCS-12		
Variable	B	95% Cl	P-value	Variable	B	95% Cl	P-value
Age	-0.03	-0.09, 0.03	0.326	Age	0.002	-0.06, 0.06	0.988
Gender	-1.60	-4.02, 0.83	0.196	Gender	-1.79	-4.24, 0.66	0.151
cTnT	0.01	-0.002	0.103	cTnT	0.02	0.001, 0.03	0.052
cTnI	0.002	0.001, 0.005	0.070	cTnI	0.002	0.001, 0.005	0.064
Prior MI	-4.18	-7.35, -1.01	0.010	Prior MI	-2.77	-5.98, 0.45	0.092
Prior PCI	-3.57	-6.62	0.021	Prior PCI	-2.40	-5.49, 0.68	0.127
Prior CABG	-4.36	-9.51, 0.79	0.097	Prior CABG	-1.49	-6.71, 3.72	0.574
Prior Stroke	-1.586	-3.99, 0.82	0.196	Prior Stroke	-2.34	-4.76, 0.09	0.059
Prior Heart failure	-6.22	-17.77, 5.33	0.290	Prior Heart failure	-4.89	-16.56, 6.78	0.411
Hypertension	-3.86	-6.20, -1.52	0.001	Hypertension	-2.12	-4.50, 0.27	0.082
Current smoker	-2.68	-5.76, 0.49	0.098	Current smoker	-3.77	-6.91, -0.63	0.019
Reduced renal function	-3.97	-10.89, 2.96	0.259	Reduced renal function	2.15	-5.16, 9.46	0.562
Diabetes	-4.70	-8.43, -0.96	0.014	Diabetes	-2.44	-6.23, 1.36	0.207
BMI	-0.47	-0.85, -0.09	0.015	BMI	-0.30	-0.69, 0.09	0.127
eGFR	-0.002	-0.12, 0.12	0.974	eGFR	-0.10	-0.22, 0.03	0.118
Revascularization	2.71	-0.39, 5.82	0.086	Revascularization	2.77	-0.37, 5.91	0.084
NSTEMI	3.04	-0.71, 6.80	0.112	NSTEMI	3.18	-0.61, 6.97	0.100

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UAP	-3.63	-6.57, -0.69	0.016	UAP	-0.97	-3.97, 2.00	0.525
Non-coronary cardiac disease	-0.004	-5.17, 5.16	0.999	Non-coronary cardiac disease	-0.86	-6.07, 4.36	0.747
Non-cardiac disease	-1.96	-7.02, 3.09	0.445	Non-cardiac disease	-0.520	-5.63, 5.59	0.841
NCCP	1.62	-0.76, 4.00	0.182	NCCP	-0.42	-2.83, 1.96	0.734

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Supplementary Table S4: Mediator analysis investigating which variables that could mediate the predictive value of an UAP diagnosis for the different outcomes (dependent variables). Variables that changed the unstandardized B more than 10% are marked* below.

SAQ7-AF	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-10.076 to -8.244)	-9.160	1.786	-0.184	-5.129	<0.001
Revascularization*	5.077	1.742	0.107	2.914	0.004
UAP	-10.426	1.835	-0.209	-5.681	<0.001
Age	-0.006	0.041	-0.005	-0.143	0.887
UAP	-9.061	1.789	-0.182	-5.066	<0.001
Gender	-1.015	1.377	-0.027	-0.737	0.461
UAP	-9.239	1.799	-0.186	-5.136	<0.001
cTnT	0.007	0.005	0.048	1.336	0.182
UAP	-9.098	1.793	-0.182	-5.075	<0.001
Prior MI	-5.437	1.697	-0.115	-3.204	0.001
UAP	-8.353	1.788	-0.168	-4.672	<0.001
Prior CABG	-2.339	2.538	-0.034	-0.921	0.357
UAP	-8.715	1.827	-0.175	-4.770	<0.001
Hypertension	-3.450	1.339	-0.092	-2.576	0.010
UAP	-8.642	1.786	-0.174	-4.839	<0.001
Reduced renal function	-4.176	2.494	-0.075	-1.675	0.095
UAP	-8.824	2.386	-0.166	-3.698	<0.001
Diabetes	-3.933	2.042	-0.069	-1.926	0.054
UAP	-8.714	1.791	-0.175	-4.865	-1.926

SAQ7-QL	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-10.067 to -8.228)	-9.143	2.872	-0.119	-3.183	0.002
Revascularization*	8.526	2.850	0.115	2.992	0.003
UAP	-11.188	2.953	-0.145	-3.789	<0.001
Age	0.021	0.066	0.012	0.313	0.754
UAP	-9.014	2.880	-0.117	-3.130	0.002
Gender	-3.441	2.260	-0.057	-1.523	0.128
UAP	-9.428	2.887	-0.122	-3.266	0.001
cTnT	0.017	0.009	0.072	1.930	0.054
UAP	-8.962	2.880	-0.116	-3.112	0.002
Prior PCI*	-5.876	2.685	-0.084	-2.189	0.029
UAP	-7.532	2.939	-0.098	-2.563	0.011
Prior CABG*	-8.779	4.275	-0.078	-2.054	0.040
UAP	-7.780	2.924	-0.101	-2.661	0.008
Prior Heart failure	-12.017	5.928	-0.075	-2.027	0.043
UAP	-9.123	2.868	-0.118	-3.181	0.002
Hypertension	-5.548	2.196	-0.094	-2.527	0.012
UAP	-8.322	2.874	-0.108	-2.896	0.004

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Current smoking	-8.155	2.897	-0.105	-2.815	0.005
UAP	-9.061	2.860	-1.118	-3.169	0.002
Diabetes	-4.763	3.338	-0.053	-1.427	0.154
UAP	-8.520	2.888	-0.111	-2.950	0.003

SAQ7-PL	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-7.550 to -6.177)	-6.864	2.574	-0.098	-2.667	0.008
Revascularization*	5.485	2.531	0.082	2.167	0.031
UAP	-8.217	2.647	0.002	-3.104	0.002
Age*	-0.302	-0.057	-0.190	-5.271	<0.001
UAP	-5.861	2.532	-0.083	-2.315	0.021
Gender	-2.074	1.980	-0.039	-1.047	0.295
UAP	-7.102	-7.102	-0.101	-2.745	0.006
cTnT	0.005	0.008	0.024	0.650	0.516
UAP	-7.052	2.573	-0.101	-2.741	0.006
Prior MI*	-10.772	2.453	-0.160	-4.391	<0.001
UAP	-5.446	2.559	-0.077	-2.128	0.034
Prior CABG*	-15.401	3.747	-0.153	-4.110	<0.001
UAP	-4.413	2.609	-0.063	-1.691	0.091
Prior Stroke	-5.219	2.563	-0.074	-2.036	0.042
UAP	-6.669	2.566	-0.095	-2.599	0.010
Prior Heart failure	-17.492	5.282	-0.120	-3.312	0.001
UAP	-6.995	2.555	-0.100	-2.738	0.006
Hypertension*	-6.159	1.926	-0.117	-3.197	0.001
UAP	-5.949	2.569	-0.085	-2.316	0.021
Current smoking	-5.775	2.542	-0.083	-2.272	0.023
UAP	-7.031	2.566	-0.100	-2.740	0.006
Reduced renal function	-16.257	3.751	-0.196	-4.334	<0.001
UAP	-6.192	3.491	-0.080	-1.774	0.077
Diabetes	-4.466	2.954	-0.056	-1.512	0.131
UAP	-6.364	2.585	-0.091	-2.462	0.014

SAQ7 summary	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-9.570 to -7.830)	-8.700	1.981	-0.156	-4.391	<0.001
Revascularization*	6.630	1.949	0.124	3.402	0.001
UAP	-10.309	2.033	-0.184	-5.070	<0.001
Age	-0.097	0.045	-0.076	-2.147	0.032
UAP	-8.331	1.981	-0.149	-4.205	<0.001
Gender	-2.382	1.527	-0.056	-1.560	0.119
UAP	-8.945	1.994	-0.160	-4.486	<0.001
cTnT	0.010	0.006	0.058	1.623	0.105
UAP	-8.675	1.987	-0.155	-4.365	<0.001

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Prior MI*	-7.100	1.886	-0.133	-3.764	<0.001
UAP	-7.728	1.979	-0.138	-3.906	<0.001
Prior CABG*	-6.903	2.856	-0.087	-2.417	0.016
UAP	-7.562	2.020	-0.135	-3.743	<0.001
Prior Heart failure	-10.654	4.039	-0.093	-2.638	0.009
UAP	-8.731	1.975	-0.156	-4.420	<0.001
Hypertension	-4.448	1.489	-0.106	-2.987	0.003
UAP	-8.026	1.981	-0.144	-4.052	<0.001
Current smoking	-3.761	1.950	-0.068	-1.928	0.054
UAP	-8.680	1.979	-0.155	-4.385	<0.001
Reduced renal function	-8.176	2.770	-0.130	-2.952	0.003
UAP	-7.894	2.655	-0.131	-2.973	0.003
Diabetes	-3.940	2.275	-0.062	-1.732	0.084
UAP	-8.218	1.991	-0.147	-4.128	<0.001

PCS-12	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-3.994 to -3.268)	-3.631	1.497	-0.124	-2.426	0.016
Revascularization*	3.990	1.619	0.130	2.464	0.014
UAP	-4.596	1.541	-0.157	-2.982	0.003
Age	-0.028	0.031	-0.046	-0.899	0.369
UAP	-3.554	1.499	-0.121	-2.371	0.018
Gender	-1.937	1.231	-0.081	-1.574	0.116
UAP	-3.859	1.503	-0.132	-2.567	0.011
cTnT	0.011	0.007	0.078	1.521	0.129
UAP	-3.558	1.493	0.007	-2.383	0.018
Prior MI*	-3.822	1.612	-0.121	-2.371	0.018
UAP	-3.241	1.496	-0.111	-2.166	0.031
Hypertension*	-3.579	1.193	-0.153	-3.001	0.003
UAP	-3.095	1.492	-0.106	-2.075	0.039
Current smoking	-2.628	1.579	-0.085	-1.664	0.097
UAP	-3.599	1.494	-0.123	-2.409	0.016
Diabetes	-4.286	1.900	-0.115	-2.256	0.025
UAP	-3.271	1.497	-0.112	-2.185	0.029
BMI	-0.469	0.191	-0.170	-2.457	0.015
UAP	-3.298	1.956	-0.116	-1.686	0.093

MCS-12	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-1.067 to -0.873)	-0.970	1.524	-0.033	-0.636	0.525
Revascularization*	3.234	1.651	0.104	1.959	0.051
UAP	-1.797	1.572	-0.061	-1.143	0.254
Age	0.001	0.032	0.002	0.039	0.969
UAP	-0.996	1.526	-0.034	-0.653	0.514

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Gender*	-1.898	1.252	-0.078	-1.516	0.130
UAP	-1.243	1.529	-0.042	-0.813	0.417
Prior Stroke	-2.337	1.234	-0.097	-1.893	0.059
UAP	-0.992	1.518	-0.034	-0.654	0.514
Current smoking	-3.767	1.600	-0.120	-2.354	0.019
UAP	-0.985	1.514	-0.033	-0.651	0.516

References

1.   Tjora HL, Steiro OT, Langorgen J, Bjorneklett R, Nygard OK, Renstrom R, et al. Aiming toWards Evidence baSed inTerpretation of Cardiac biOmarkers in patients pResenting with chest pain-the WESTCOR study: study design. Scandinavian cardiovascular journal : SCJ. 2019:1-6.

2.   Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. European heart journal. 2012;33(20):2551-67.

3.   Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem. 2010;56(2):254-61.

4.   Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. Clin Chim Acta. 2011;412(9-10):748-54.

5.   Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. J Am Coll Cardiol. 2014;63(14):1441-8.

6.   Romiti GF, Cangemi R, Toriello F, Ruscio E, Sciomer S, Moscucci F, et al. Sex-Specific Cut-Offs for High-Sensitivity Cardiac Troponin: Is Less More? Cardiovascular therapeutics. 2019;2019:9546931.

7.   Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33(20):2551-67.

8.   Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315.

9.   Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.

10.   Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921-64.

11.   Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636-48, 48a-48d.

12.   Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J. 2008;155(3):408-17.

13.   Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.

14.   Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal. 2017;38(36):2739-91.

15.   Hirota M, Takada T, Kawarada Y, Nimura Y, Miura F, Hirata K, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):78-82.

16.   Stephens MB, Yew KS. Diagnosis of chronic obstructive pulmonary disease. Am Fam Physician. 2008;78(1):87-92.

17.   Apple F KP, Hammarsten O, Saenger A, Body R, Lam SPC, Collinson P, Jaffe A, Ordoñez-Llanos J, Omland T. Committee on Clinical Applications of Cardiac Bio-Markers (C-CB). . High-Sensitivity* Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer v072020 www.iffc.org: The International Federation of Clinical Chemistry and Laboratory Medicine; 2020 [Available from: https://www.ifcc.org/media/478592/high-sensitivity-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v072020.pdf.

18.   Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.