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Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study

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Abstract

Objective To develop and validate a symptom-based prediction rule for early recognition of acute coronary syndrome (ACS) in patients with acute chest discomfort who call out-of-hours services for primary care (OHS-PC).

Design Cross-sectional study. A diagnostic prediction rule was developed with multivariable regression analyses. All models were validated with internal-external cross validation within seven OHS-PC locations. Both age and sex were analysed as statistical interaction terms, applying for age non-linear effects.

Setting Seven OHS-PC in the Netherlands.

Participants 2,192 patients who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2017. Backed up recordings of telephone triage conversations were analysed.

Primary and secondary outcomes measures Diagnosis of ACS retrieved from the patient's medical records in general practice, including hospital specialists discharge letters. Performance of the prediction rules was calculated with the c-statistic and the final model was chosen based on net benefit analyses.

Results Among the 2,192 patients who called the OHS-PC with acute chest discomfort, 8.3% females and 15.3% males had an ACS. The final diagnostic model included seven predictors (sex, age, acute onset of chest pain lasting less than 12 hours, a pressing/heavy character of the pain, radiation of the pain, sweating, and calling at night). It had an adjusted c-statistic of 0.77 (95% CI 0.74-0.79) with good calibration.

Conclusion The final prediction model for ACS has good discrimination and calibration, and shows promise for replacing the existing telephone triage rules for patients with acute chest discomfort in general practice and OHS-PC.

Trial registration NTR7331

Key words: prediction rules, acute coronary syndrome, sex, symptoms, general practice, out-of-hours primary care

Strengths and limitations of this study

- We could analyse the original and very first telephone conversation of patients with acute chest discomfort.
- The developed prediction model is well generalizable to other OHS-PCs in the Netherlands, but also to similar OHS-PC settings in other countries or even emergency medical service settings.
- A limitation is that fully external validation of the model in another OHS-PC was impossible because no other cohort similar to ours was available.
- Another limitation is that the effects of the predictors were assumed to be similar for males and females while this is not exactly the case, but by incorporating a differential non-linear effect of age and interaction with sex in the analyses this effect is minimalized.

Introduction

Chest discomfort is among the top five reasons for telephone contact in out-of-hours services for primary care (OHS-PC) and concerns 5% of all cases at the emergency department (ED) in the USA. [1] In the Netherlands, around 80% of patients with chest discomfort first call the general practitioner (GP) or OHS-PC, while 20% directly calls the emergency medical service (EMS, or ambulance dispatch centre) or are self-referrals to the ED. [2] Adequate triage and early diagnosis in these patients is vital, because in case of an underlying acute coronary syndrome (ACS) early effective therapeutic interventions ('time is muscle') improve the patient's outcome and prognosis. [3] For the diagnosis of ACS, a 12-lead electrocardiogram (ECG) and troponin testing is needed. [3] However, before the patient is referred to an ED where these diagnostic tests can be done, patient selection is necessary based on symptom presentation retrieved by telephone triage. [4 5] Symptom-based differentiation of ACS from other causes of chest discomfort is notoriously difficult. [6] Symptom-based prediction rules for diagnosing ACS in general practice and other prehospital settings are -although highly needed- scarce. [7-9] The efficiency and safety of telephone triage in OHS-PC was poor in a population with a prior chance of ACS of 8.3% in females and 15.3% in males; almost 50% of the males and females with chest discomfort received a high priority ambulance, while 11% diagnosed with an ACS did not received a high urgency (i.e., was seen within one hour). [10]

Most prediction rules for diagnosing ACS were developed in the ED setting, and include results from ECG and troponin testing. [11] Such prediction rules cannot be straightforward implemented for telephone triage in general practice because (i) in the latter setting these diagnostic tests are not available, (ii) the prior chance of ACS is rather low, and (iii) on average disease severity is less than in those seen in the ED. [12 13] The prevalence of ACS among patients with chest discomfort who call OHS-PC or EMS is about 10-15%, and among those seen at the ED between 10 to 30%. [10 11 13 14] Only one prediction rule was developed in primary care for diagnosing ACS; the modified Grijseels prediction rule, which had moderate discriminative ability (c-statistic of 0.66) after external validation. [7 8] Five other primary care prediction rules were developed to predict CAD; e.g. the Marburg Heart Score (MHS) and INTERCHEST prediction rule (International Working Group on Chest Pain in Primary Care). [9] In these studies both patients with acute and non-acute chest discomfort were included and the prevalence of stable CAD showed to be 10.9% to 12.6%, while that of ACS was only 1.5% to 2.5%. [9] Thus, these prediction rules have limited applicability for specifically diagnosing ACS.

In most OHS-PC and about half of the EMS in the Netherlands, triage nurses use the semi-automatic 'Netherlands Triage Standard' (NTS) as a decision support tool to classify the urgency of the patient's condition. Triage nurses have to choose one out of 56 'main complaints' and based on answers linked to the triage criteria, the NTS automatically proposes one out of six levels of urgency, that is, a certain time frame in which patients should be seen (U0-U5, appendix- table 1). The NTS is a modified and shortened version of the Manchester Triage Standard which was developed in the ED setting. [15] Although the NTS was explicitly developed for telephone triage, it has not yet been validated against clinical outcomes even though it is already implemented on large scale. Recent research showed that the NTS had a poor sensitivity of 0.73 (95% CI 0.68-0.78) for telephone triage of patients with acute chest discomfort. The NTS recommended a low urgency (U3, U4 or U5) to 27% of patients who eventually showed to have an ACS or other life threatening event (LTE). [10] The NTS' specificity was also poor with 0.43 (95% CI 0.40-0.45); the NTS recommended a high urgency to 57% of the patients who eventually showed not to have an ACS or LTE. Given this poor safety and efficiency of the NTS, there is an urgent need for a better prediction model for patients with acute chest discomfort calling OHS-PC. In addition, there is a need for exploring sex-specificity of such prediction rule as there is an ongoing debate on whether females differ from males in reporting symptoms of ACS. [16 17]

The aim of this study was to develop, and internal-external cross validate a symptom-based prediction rule for diagnosing ACS which is considerate to sex categories in male and female patients who call the OHS-PC for acute chest discomfort.

Methods

We performed a cross-sectional study among 2,192 patients who called one out of seven participating OHS-PC in the Netherlands because of acute chest discomfort (pain, pressure, tightness, or discomfort) during the period 2014 to 2017. [18] These OHS-PC serve a total population of 1.5 million people and cover around 300,000 calls a year. We first selected calls based on of the International Code for Primary Care (ICPC; a WHO world-wide code system for primary care) with ICPC-codes K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98 and calls with keywords thoracic pain, chest pain, myocardial infarction, heart attack and their common abbreviations (Figure 1). We included a broad variety of symptoms to capture the entire domain of patients that could be suspected of ACS. We listed all available calls of these patients and assigned random numbers with the Random Number Generator (RAND) function in Microsoft Excel to retrieve a random sample. Calls were excluded before re-listening

when the patients' age was below 18 years or when the patient did not live in the surrounding area of the OHS-PC (in which case we could not retrieve the final diagnosis from the patient's own general practitioner). Calls were excluded during re-listening when it did not concern a triage call (e.g. inter-collegial consultation) or when the recording was of poor quality (Figure 1).

Candidate predictors

Research team members (LW, DE) and medical students listened to the call recordings, blinded for the outcome, to collect data about symptoms, medical history and urgency allocation. Patient (age, sex) and call characteristics (call time, call duration) were collected from the OHS-PC electronic medical files of the patients. As candidate predictors we included age and sex, the NTS triage criteria (see appendix-table 2), the ACS predictors from the modified Grijseels prediction model (male sex, radiation, nausea, sweating and history of CAD), the 'CAD predictors' from MHS and INTERCHEST prediction models (age, pain feels like pressure, CAD history or CV risk factors, patient assumes cardiac origin of pain), and - based on a recent own study in OHS-PC- the predictor 'calling at night between 0am and 9am'. [7-9 19]

Outcome

The primary outcome was the diagnosis ACS. The final diagnoses were retrieved from the patient's GP, and based on the GP's electronic medical files which include ED and cardiologist discharge letters and notes from the OHS-PC contact. The diagnosis ACS was nearly always made by a cardiologist (96.0%) and included information on levels of (high-sensitivity) troponin and electrocardiographic results. We used medical information up to 30-days following the contact with the OHS-PC to allow us to include diagnoses of ACS that were initially missed because the patient was not referred to the cardiologist the same day of the OHS-PC contact. However, in none of the patients in the study we had evidence of a missed diagnosis of ACS.

Sample size calculation

We relied on the minimal sample size criteria for prediction model development proposed by Riley et al, using the 'pmsampsize' package in R. [20] Based on an ACS prevalence of overall 11% and an Cox-Snell R-squared of 0.075 (a conservative value based on a model with age and sex) and a total number of 2,192 observations we were allowed to assess 19 candidate predictors. [21] Based on sample size calculations we concluded that development of separate models for males and females would require a significantly larger sample, therefore we analysed sex as a statistical interaction term. [20]

Statistical analyses

We developed three diagnostic models using multivariable logistic regression analysis. First, we developed a base model with only age and sex as predictors, where age was modelled using a restricted cubic spline function (4 knots) and an interaction with sex. This resulted in a base model with 7 predictor parameters (excluding the intercept). Second, we fitted a full model with an additional 12 pre-selected binary predictors (having chest pain, acute chest pain shorter than 12 hours, shortness of breath, sweating, retrosternal located chest pain, radiation, pressing heavy pain, stabbing pain, history of CVD, history of CAD, someone else calling, calling at night). Thirdly, we applied backward elimination, with a cut-off p-value < 0.20 for including predictors (a higher cut-off value to lower the chances of overfitting). [21]

We applied internal-external cross validation (IECV) for model validation using the seven different OHS-PC locations (Appendix-Table 3 for patient characteristics of different OHS-PC locations). [22] We evaluated the IECV performance in terms of the area under the ROC curve (c-statistic), the calibration slope and calibration in the large. The IECV estimates of performance were combined by using random-effect model (DerSimonian-Laird estimator). Based on the IECV we also constructed flexible calibration curves and decision curves. In the decision curve analyses we compared the final model with the currently used NTS triage model in OHS-PC in the Netherlands. [23] Finally, we created an illustrative table of diagnostic test accuracy for various model-based risk thresholds of the final model, following the example in Wynants et al. [23] IECV estimates for risk threshold specific sensitivity and specificity, and we applied a bivariate model commonly used for diagnostic test accuracy meta-analysis. [24]

Missing data

For missing data we carried out multiple imputation using the Multivariate Imputation via Chained Equation (MICE) package in R, with 30 imputation rounds and 30 iterations. [25] We pooled the results following Rubin's rules. [26] Predictors with over 50% missing were excluded from consideration in the models (Appendix-table 4 for details about the missing data). Characteristics were compared between patients with and without information on the medical outcome - because some GPs refused diagnosis retrieval from their files - to allow for assessment of differences in characteristics between these patient groups (Appendix-table 5). There were no clinically meaningful differences in symptoms and patient or call characteristics between the 2,192 patients with information on the outcome, and the 1,012 patients

about whom knowledge of the medical outcome related to the OHS-PC contact because of acute chest discomfort was missing.

All analyses were done in R version 4.0.3. (2020-10-10) with the Regression Modelling Strategies ('rms') package in R. [27] We reported our study in accordance to the Transparent Reporting of a multivariable prediction rules for Individual Prognosis Or Diagnosis (TRIPOD) criteria (Supplementary file). [28]

Patient and Public Involvement

No patients were involved in defining the research question or the outcome measures. Neither they were involved in developing plans for design. However, they participated in the discussion on implications and the implementation strategy. In addition, they were asked to advise on interpretation and writing up of the results. Results will be shared and discussed in more detail with representatives of the Dutch national patient community of cardiovascular diseases ('Harteraad').

Results

Among the 2,192 callers with acute chest discomfort (mean age 59.1 (SD 19.5) years and 55.3% females) 251 (11.5%) had a final diagnosis of ACS; 101 (8.3%) females and 150 (15.3%) males (Table 1). Patients with ACS were older than those without (mean age 69.7 (SD 13.4) vs. 57.7 (SD 19.8) years) and females with ACS were on average older than men with ACS (73.8 (SD 13.5) years vs. 67.0 (SD 12.6) years).

Table 1. Characteristics of 2,192 patients who called OHS PC with acute chest discomfort between 2014-2017, divided between females and males with and without ACS.

Characteristics	**1,213 females (55.3%)**		**979 males (44.7%)**	
	ACS n=101 (8.3%)	**No ACS n=1,112 (91.7%)**	**ACS n=150 (15.3%)**	**No ACS n= 829 (84.7%)**
Patient characteristics				
Mean age in years (SD)	73.8 (13.5)	58.0 (20.2)	67.0 (12.6)	57.2 (19.2)
Call characteristics				
Median call duration in min (IQR)	5:27 (3:57-8:24)	6:59 (5:06-9:47)	6:04 (4:03-8:17)	6:56 (5:10-9:23)
Mean introduction time in min (IQR)	0:13 (0:09-0:18)	0:17 (0:11-0:26)	0:14 (0:09-0:21)	0:17 (0:11-0:25)
Call during the night (0am-9am)	34 (33.7)	304 (27.3)	62 (41.3)	188 (22.7)

Triage nurse consulted the GP	43 (42.6)	580 (52.2)	75 (50.0)	449 (54.2)
Someone else called on behalf of patient	69 (68.3)	515 (46.3)	98 (65.3)	432 (52.1)
The person who calls expressed concerns	42 (95.5)	507 (90.5)	61 (96.8)	378 (87.1)
Medical history and risk factors				
Cardiovascular disease or CV risk factors	70 (81.4)	552 (61.1)	106 (78.5)	464 (64.4)
History of coronary artery disease	23 (47.9)	131 (24.2)	54 (56.3)	181 (38.8)
Diabetes	14 (42.4)	66 (14.3)	22 (39.3)	78 (22.0)
Hypertension	26 (72.2)	162 (34.0)	22 (51.2)	113 (33.3)
Hypercholesterolemia/statin use	10 (40.0)	96 (22.6)	27 (50.0)	79 (24.5)
Cardiac arrhythmia	4 (14.8)	125 (26.2)	12 (25.0)	89 (25.2)
Symptoms				
Chest pain	95 (96.9)	1007 (94.1)	139 (93.3)	758 (94.9)
Shortness of breath	57 (71.3)	559 (65.4)	63 (61.2)	415 (63.1)
Chest pain duration <12 hours	74 (86.0)	703 (72.3)	113 (82.5)	510 (71.3)
Severe pain intensity severe (NRS >7, range 1-10)	19 (61.3)	184 (39.6)	18 (25.4)	116 (33.0)
Pressing/heavy chest pain*	58 (81.7)	525 (62.5)	95 (81.2)	345 (57.7)
Stabbing chest pain*	8 (11.3)	190 (22.6)	9 (7.7)	159 (26.6)
Chest pain located retrosternal**	36 (54.5)	326 (40.0)	52 (53.1)	227 (38.7)
Chest pain located on left or right of the thorax**	19 (28.8)	318 (39.0)	28 (28.6)	262 (44.6)
Radiation of chest pain to any location	74 (86.0)	575 (67.8)	83 (65.4)	347 (56.2)
Radiation to the arm ***	37 (43.0)	218 (25.7)	54 (42.5)	143 (23.2)
Radiation to the shoulder blades ***	14 (16.3)	190 (22.4)	19 (15.0)	103 (16.7)
Radiation to the jaws ***	10 (11.6)	77 (9.1)	4 (3.1)	33 (5.3)
Sweating	36 (52.9)	279 (42.0)	54 (51.9)	190 (35.8)
Nausea or vomiting	24 (52.2)	295 (56.6)	31 (43.1)	139 (39.9)
Pallor or ashen skin	22 (59.5)	139 (44.3)	36 (64.3)	125 (46.8)
(Near) fainting	8 (9.5)	76 (7.7)	9 (6.7)	50 (6.7)
Palpitations	10 (100.0)	183 (84.7)	8 (50.0)	83 (75.5)
Patient recognizes symptoms from previous cardiac event	17 (35.4)	100 (22.0)	30 (46.9)	103 (29.5)
Urgency allocation				

High urgency (U1 or U2)	89 (88.1)	740 (66.5)	133 (88.7)	534 (64.4)
U1	75 (74.3)	443 (39.8)	106 (70.7)	350 (42.2)
U2	14 (13.9)	297 (26.7)	27 (18.0)	184 (22.2)
Low urgency (U3 or U4 or U5)	12 (11.9)	372 (33.5)	17 (11.3)	295 (35.6)

*Pain described by patient. Pressing heavy pain: pressing, heavy or tightening pain vs. other types of pain (stabbing, burning, cramping, tearing) Stabbing pain: stabbing vs. other types of pain (pressing, heavy, tightening, burning, cramping)

** Retrosternal location vs. other pain locations. Left or right side of the thorax vs. other pain locations

*** Radiation location vs. no radiation and radiation other pain

Over two thirds of all callers (68.3%) received a high urgency allocation (seen within one hour; U1 or U2) and among the 251 patients who showed to have an ACS, 88.4% received a high urgency allocation. Calls of patients who had an ACS were shorter than calls in those without ACS (median call duration 6:34 (SD 3:38) vs. 7:42 (SD 3:48) minutes).

Medical history and symptoms

Females and males with ACS had more often a history with CVD or CV risk factors than those without (females with ACS 81.4% vs. females without ACS 61.1%, males with ACS 78.5% vs. males without ACS 64.4%) (Table 2). The majority of both females and males had chest pain (94.5%) and this was similar among those with and without ACS. Overall, presented symptoms among males and females calling the OHS-PC for chest discomfort were quite similar. Symptoms associated with ACS in both sexes were pressing/heavy chest pain (females with ACS 81.7% vs. females without ACS 62.5%, males 81.2% vs. 57.7% respectively), retrosternal located chest pain (females 54.5% vs. 40.0%, males 53.1% vs. 38.7%), radiation of pain (females 86.0% vs 67.8%, males 65.4% vs 56.2%), and sweating (females 52.9% vs. 42.0%, males 51.9% vs. 35.8%).

Diagnoses

Of the 101 females with ACS, 22.8% had a ST-segment elevation myocardial infarction (STEMI), 46.5% a non ST-segment elevation myocardial infarction (NSTEMI), 19.8% unstable angina pectoris (UAP), and 10.9% non-classified ACS. In 150 males with ACS, 33.3% had a STEMI, 36.7% a NSTEMI, 26.0% UAP, and 4.0% non-classified ACS (Table 2).

Table 2. Diagnoses of 2,192 males and females who contacted the OHS-PC for acute chest discomfort between 2014-2017, by sex.

Diagnosis, n (%)	Females n= 1213	Males n= 979	p-value
Acute coronary syndrome*	101 (8.3)	150 (15.3)	<0.001
STEMI	23 (22.8)	50 (33.3)	0.071
NSTEMI	47 (46.5)	55 (36.7)	0.119
UAP	20 (19.8)	39 (26.0)	0.256
Non-classified ACS	11 (10.9)	6 (4.0)	0.033
Life threatening events (LTEs)	28 (2.3)	37 (3.8)	0.043
Pulmonary embolism	8 (28.6)	10 (27.0)	0.890
Acute abdominal aneurysm	2 (7.1)	3 (8.1)	0.885
Thoracic aortic dissection	1 (3.6)	4 (10.8)	0.278
Other**	17 (60.7)	20 (54.1)	0.591
Non-urgent cardiovascular diseases***	223 (18.4)	191 (19.5)	0.069
Musculoskeletal pain	245 (20.2)	148 (15.2)	0.039
Non-cardiac chest pain, not further specified ******	191 (15.7)	179 (18.3)	0.012
Psychogenic disorders	165 (13.6)	85 (8.7)	0.005
Gastrointestinal tract disorders	89 (7.3)	68 (6.9)	0.776
Respiratory tract disorders	61 (5.2)	56 (5.7)	0.203
Other non-urgent diagnoses*******	110 (9.1)	65 (6.6)	0.152

* Almost all patients (96.0%) were diagnosed by a cardiologist. Ten (4.0%) ACS patients were not diagnosed by a cardiologist; four died before arrival of the ambulance, one patient died after resuscitation at the ED (all these five were classified as acute cardiac death due to ACS), and in five patients the ACS diagnosis was solely based on the GP's interpretation in patients who were not referred to the hospital after shared decision because of a short life expectancy due to cancer in a palliative stage.

** Stroke, severe COPD exacerbation, acute severe heart failure, sepsis, coronary spasm caused by hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.

*** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension

**** Cardiac pathology unlikely after cardiologist's or GP's diagnostic work-up, but without differential diagnosis

***** Amongst others: anaemia, carcinoma, vasovagal collapse, side effects medication, dermatological diseases (e.g. herpes Zoster infection)

Twenty-eight (2.3%) females and 37 males (3.8%) had another life-threatening event than ACS (e.g. pulmonary embolism, thoracic aortic dissection, acute abdominal aneurysm). All other patients (85.6%) had non-urgent medical conditions such as non-urgent cardiovascular disease (18.9%), musculoskeletal pain (17.9%), non-cardiac chest pain (not further specified) (16.9%), psychogenic disorder (11.4%), gastrointestinal disorders (7.2%), respiratory disorders (5.3%), and other non-urgent diagnoses (8.0%).

Model development, performance and validation

The base model with sex and age had an apparent c-statistic of 0.72 (95% CI 0.70-0.75), and an internal-external validation based c-statistic of 0.72 (95% 0.68-0.75) (Appendix- Table 6, Figure 2). The full model including all candidate predictors had an apparent c-statistic of 0.79 (95% CI 0.76-0.81) and an internal-external validation based c-statistic of 0.77 (95% CI 0.74-0.80) (Appendix - Table 7). The full model had optimal calibration (flexible line close to the 45-degree reference line) up to a predicted probability of ACS of approximately 0.2 (Appendix-Figure 1). Risks higher than 0.2 tended to be overestimated by the model, however since any plausible risk threshold will be lower than 0.2 in the primary care setting, we find the calibration in the relevant range to be satisfactory. After backward elimination, the backward model had an apparent c-statistic of 0.79 (95% CI 0.76-0.81), and the internal-external validation c-statistic was 0.77 (95% CI 0.74-0.79). It had very similar calibration to the full model (Table 3, Figure 3).

Table 3. Final model for predicting the diagnosis ACS.

Predictors	Regression coefficients (standard error)
Intercept	-16.246 (3.527)
Age	0.293 (0.081)
Age'	-0.391 (0.125)
Age''	1.063 (0.395)
Female gender	2.504 (5.512)
Age * female gender	-0.096 (0.126)

Age' * female gender	0.189 (0.195)
Age'' * female gender	-0.556 (0.605)
Acute chest pain shorter than 12 hours	0.290 (0.198)
Sweating	0.457 (0.178)
Radiation of chest pain	0.609 (0.176)
Pressing heavy pain	0.747 (0.200)
Call during the night (0am-9am)	0.504 (0.151)
Apparent c-statistic 0.79 (95% CI 0.76-0.81) Adjusted c-statistic 0.77 (95% CI 0.74-0.79) Calibration slope 0.826 (95% CI 0.658-0.994) Calibration -0.224 (95% CI -0.604-0.157) R^2 0.106 Knots for cubic spline functions placed at 5, 35, 65 and 95	

Decision curve analyses and risk thresholds

Both the full and backward model showed a high net benefit as compared to the currently used NTS model for telephone triage in OHS-PC (Appendix - Figure 2). There was no difference in net benefit between the full model and backward model across plausible risk thresholds. Based on this analysis we decided to choose the backward as the final triage tool model because; 1) with fewer predictors the prediction of ACS remained similar accurate and 2) no valuable time is lost during telephone triage by asking the patient about symptoms that do not contribute to a better prediction. The final model included besides age and sex, the five following predictors; (i) acute onset of chest pain lasting <12 hours, (ii) a pressing/heavy character, (iii) radiation of pain, (iv) sweating, (v) calling at night between 0.00 and 9.00am. Finally, we evaluated the diagnostic performance of the final prediction model across risk thresholds that may be chosen to apply in clinical practice (Appendix- Table 8, Appendix – Figure 3).

Discussion

This is the first study that developed and internal-external validated a symptom-based prediction rule for telephone triage of ACS in male and female patients who contact OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort). ACS was present in 8.3% of the females and 15.3% of the males. The prediction rule is applicable for triage in the OHS-PC setting and consists of sex and age as

statistical interaction terms, and five other symptom-based predictors. It had a good discriminative ability (adjusted c-statistic 0.77 (95% CI 0.74-0.79)) and was well calibrated up to an ACS risk of 0.2.

Strengths and limitations

The major strength of this study is that we analysed the original and very first conversations of patients with acute chest discomfort with primary health care providers and assessed these talks without knowledge of the diagnosis; the assessment of symptoms was therefore not affected by hindsight bias caused by knowledge of the final diagnosis. [29] Furthermore, we could analyse a large sample (N=2,192) of patients which allowed us to evaluate up to nineteen candidate predictors. We assessed the risk of selection due to missing outcome data, and our data suggest that this missingness was unlikely to bias our findings. Because we used data from seven different OHS-PC our results will be well generalizable to other OHS-PC in the Netherlands, but we anticipate the model might be applicable to similar OHS-PC setting in for example the UK and Scandinavian countries. Our results may also be generalizable to some EMS settings, because the prior chance of having an ACS among those calling for acute chest discomfort is rather similar in the EMS setting as in the OHS-PC setting. [14 30]

A limitation of the study is that the final model is not yet fully externally validated. However, at the time of executing the study hardly any primary care research data were available to perform such validation. Importantly, the internal-external validation showed very good calibration up to an ACS risk of 0.2. Another limitation is that the effects of the predictors were assumed to be similar for male and female patients while that might not be optimal for the predictions. However, development of separate models for males and females would require a significantly larger sample size than was available. Importantly, a differential non-linear effect of age was incorporated using a spline function and interaction with sex was incorporated, and the final internal-external validated model did have good overall performance.

Comparison with other studies

Our prediction model had a higher discriminating ability for ACS than the NTS (c-statistic of 0.58) and modified Grijseels prediction rule (c-statistic of 0.66). [7] This may largely be explained by the addition of age, the strongest predictor of ACS. This is in line with the notion that the prevalence of ACS increases with age. [7 9 31] Importantly, in our study among people aged below 40, only one (0.4%) male patient had an ACS (UAP). Similar to the modified Grijseels prediction rule our prediction model includes sweating and radiation of pain, however, the modified Grijseels rule combined nausea and sweating to a single

predictor (i.e., nausea or sweating). [7 8] Age and sex were predictors in our model, but also in the MHS and INTERCHEST prediction models. [32 33] Also the INTERCHEST rule included pressing heavy chest pain as predictor. [32] A new predictor is calling at night (between 0.00-9.00am). [19] Previous studies in the ED setting also showed circadian variability with an early morning peak for ACS patients. [34] Finally, symptoms associated with ACS were rather similar between females and males, which is in line with recent sex-stratified studies of patients with chest discomfort who called the OHS-PC, but is in contrast with the prevailing opinion. [16 17 35]

We performed decision curve analyses to investigate what would be the optimal threshold of ACS predicted probability to initiate treatment, where 'treatment' in pre-hospital setting refers to urgent referral for hospital admission (U1, ambulance within 15 minutes). Context is needed to determine an optimal threshold, which concerns what percentage of missing ACS is considered as acceptable by health care providers, patients and policymakers. This percentage is expected to be very low because a missed ACS can result in permanent cardiac impairment, heart failure, life-threatening arrhythmias in the early phase, and death. [36] Furthermore missing an ACS is the most common reason for malpractice claims worldwide. [37] A survey performed among 1,029 ED doctors in the US, New Zealand and Australia showed that they considered an average missing rate between 0.1-1% (range 0-10%) as acceptable. [38] When we apply a maximum of 1% missing with our prediction rules, the threshold has to be set at a predicted risk of ACS of 0.05 (negative predictive value of 0.99, Table 6), which means based on our data that the majority of patients needs urgent referral. This would result in over-crowded EMS and EDs, and with the available resources being limited, this may result in exceeding target triage times, which could compromise patient safety in another way. [39] A possible alternative to consider may be applying different 'treatments' per thresholds, i.e. dispatching an ambulance (U1) for the high predicted risk patients, and GP visit within one hour (U2) for the low predicted risk patients. During GP visit more clinical parameters (blood pressure, heart rate, overall clinical impression) can be gathered to improve ACS risk prediction, and in the future, there might be room for applying point-of-care high-sensitivity troponin testing, as these are nowadays only available in the ED setting. [40] In order to determine the ideal threshold, external validation will be needed combined with clinical and management considerations.

Implications for clinical practice and future research

This symptom-based prediction model for ACS has good discrimination and calibration and could readily be applied for telephone triage of patients with acute chest discomfort in primary care, notably the OHS-PC setting. The results of the decision curve analysis showed a large net benefit over a range of plausible risk threshold as compared to the currently used NTS model in the OHS-PC in the Netherlands. For future research, full external validation in other OHS-PC or EMS populations could further optimize and update the model. Furthermore, sex-specific prediction models could be developed for ACS, but given the overlap in symptoms between men and women, this would not result in major changes in predictors.

Conclusion

The final prediction model for ACS has good discrimination and calibration, and shows promise for replacing the existing telephone triage rules for patients with acute chest discomfort in general practice and OHS-PC. However, full external validation should be considered.

Ethical approval

The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to subjects and could otherwise not be carried out logistically. Personal and research data were handled and stored according to the European General Data Protection Regulation.

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Competing interest statement All authors declare they have no conflict of interest. All authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Data sharing statement Data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DC conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript, and by MvS who was involved with the analyses. DC, EdG, LA, SP, HdR, AH and RD contributed to and approved of the final version of the manuscript.

References

1. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2017 Emergency Department Summary Tables. In: Statistics NCfH, ed., 2017.
2. Mol KA, Smoczynska A, Rahel BM, et al. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart* 2018;5(2):e000859. doi: 10.1136/openhrt-2018-000859
3. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Rev Esp Cardiol (Engl Ed)* 2021;74(6):544. doi: 10.1016/j.rec.2021.05.002
4. Burman RA, Zakariassen E, Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC family practice* 2014;15:51. doi: 10.1186/1471-2296-15-51
5. Deakin CD, Sherwood DM, Smith A, et al. Does telephone triage of emergency (999) calls using Advanced Medical Priority Dispatch (AMPDS) with Department of Health (DH) call prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42,657 emergency calls to Hampshire Ambulance Service NHS Trust. *Emergency medicine journal : EMJ* 2006;23(3):232-5. doi: 10.1136/emj.2004.022962
6. Bruyninckx R, Aertgeerts B, Bruyninckx P, et al. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2008;58(547):105-11. doi: 10.3399/bjgp08X277014
7. Bruins Slot MH, Rutten FH, van der Heijden GJ, et al. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Family practice* 2011;28(3):323-8. doi: 10.1093/fampra/cmq116
8. Grijseels EW, Deckers JW, Hoes AW, et al. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. *European heart journal* 1996;17(1):89-95.
9. Harskamp RE, Laeven SC, Himmelreich JC, et al. Chest pain in general practice: a systematic review of prediction rules. *BMJ open* 2019;9(2):e027081. doi: 10.1136/bmjopen-2018-027081
10. Wouters LT, Rutten FH, Erkelens DC, et al. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open Heart* 2020;7(2) doi: 10.1136/openhrt-2020-001376

11. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC cardiovascular disorders* 2015;15:48. doi: 10.1186/s12872-015-0049-6

12. Leeflang MM, Rutjes AW, Reitsma JB, et al. Variation of a test's sensitivity and specificity with disease prevalence. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2013;185(11):E537-44. doi: 10.1503/cmaj.121286

13. Buntinx F, Knockaert D, Bruyninckx R, et al. Chest pain in general practice or in the hospital emergency department: is it the same? *Family practice* 2001;18(6):586-9.

14. Rawshani A, Larsson A, Gelang C, et al. Characteristics and outcome among patients who dial for the EMS due to chest pain. *International journal of cardiology* 2014;176(3):859-65. doi: 10.1016/j.ijcard.2014.08.004

15. Kuriyama A, Urushidani S, Nakayama T. Five-level emergency triage systems: variation in assessment of validity. *Emergency medicine journal : EMJ* 2017;34(11):703-10. doi: 10.1136/emermed-2016-206295

16. van der Meer MG, Appelman Y, Rutten KHG, et al. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open* 2019;9(11):e031613. doi: 10.1136/bmjopen-2019-031613

17. Wouters LTCM, Zwart DLM, Erkelens DCA, et al. Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage: a cross-sectional study. *BMJ open* 2021;11 doi: 10.1136/bmjopen-2020-042406

18. Erkelens DC, Wouters LT, Zwart DL, et al. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ open* 2019;9(7):e027477. doi: 10.1136/bmjopen-2018-027477

19. Wouters LT, Zwart DL, Erkelens DC, et al. Chest discomfort at night and risk of acute coronary syndrome: cross-sectional study of telephone conversations. *Family practice* 2020 doi: 10.1093/fampra/cmaa005

20. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441. doi: 10.1136/bmj.m441

21. van Smeden M, Moons KG, de Groot JA, et al. Sample size for binary logistic prediction models: Beyond events per variable criteria. *Stat Methods Med Res* 2019;28(8):2455-74. doi: 10.1177/0962280218784726

22. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. *Journal of clinical epidemiology* 2016;69:245-7. doi: 10.1016/j.jclinepi.2015.04.005

23. Wynants L, van Smeden M, McLernon DJ, et al. Three myths about risk thresholds for prediction models. *BMC medicine* 2019;17(1):192. doi: 10.1186/s12916-019-1425-3

24. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of clinical epidemiology* 2005;58(10):982-90. doi: 10.1016/j.jclinepi.2005.02.022

25. Jolani S, Debray TP, Koffijberg H, et al. Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. *Stat Med* 2015;34(11):1841-63. doi: 10.1002/sim.6451

26. Rubin DB. Multiple imputation for non response in surveys. *John Wiley & Sons, Hoboken, NJ* 1987

27. Harrell FE, Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. . Second edition ed. Cham, Switzerland: Springer International 2015.

28. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine* 2015;162(1):W1-73. doi: 10.7326/M14-0698

29. Zwaan L, Monteiro S, Sherbino J, et al. Is bias in the eye of the beholder? A vignette study to assess recognition of cognitive biases in clinical case workups. *BMJ Qual Saf* 2017;26(2):104-10. doi: 10.1136/bmjqs-2015-005014

30. Scott G, Clawson JJ, Gardett I, et al. 9-1-1 Triage of Non-Traumatic Chest Pain: Association with Hospital Diagnosis. *Prehosp Emerg Care* 2017;21(4):525-34. doi: 10.1080/10903127.2017.1302530

31. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Jama* 2012;307(8):813-22. doi: 10.1001/jama.2012.199

32. International Working Group on Chest Pain in Primary C, Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of clinical epidemiology* 2017;81:120-28. doi: 10.1016/j.jclinepi.2016.09.011

33. Haasenritter J, Donner-Banzhoff N, Bosner S. Chest pain for coronary heart disease in general practice: clinical judgement and a clinical decision rule. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2015;65(640):e748-53. doi: 10.3399/bjgp15X687385

34. Ekelund U, Akbarzadeh M, Khoshnood A, et al. Likelihood of acute coronary syndrome in emergency department chest pain patients varies with time of presentation. *BMC Res Notes* 2012;5:420. doi: 10.1186/1756-0500-5-420

35. van Oosterhout REM, de Boer AR, Maas A, et al. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc* 2020;9(9):e014733. doi: 10.1161/JAHA.119.014733

36. Bugiardini R, Ricci B, Cenko E, et al. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc* 2017;6(8) doi: 10.1161/JAHA.117.005968 [published Online First: 2017/09/02]

37. Ernesater A, Winblad U, Engstrom M, et al. Malpractice claims regarding calls to Swedish telephone advice nursing: what went wrong and why? *J Telemed Telecare* 2012;18(7):379-83. doi: 10.1258/jtt.2012.120416

38. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *International journal of cardiology* 2013;166(3):752-4. doi: 10.1016/j.ijcard.2012.09.171

39. van der Linden MC, Meester BE, van der Linden N. Emergency department crowding affects triage processes. *Int Emerg Nurs* 2016;29:27-31. doi: 10.1016/j.ienj.2016.02.003

40. Pickering JW, Young JM, George PM, et al. Validity of a Novel Point-of-Care Troponin Assay for Single-Test Rule-Out of Acute Myocardial Infarction. *JAMA Cardiol* 2018;3(11):1108-12. doi: 10.1001/jamacardio.2018.3368

Figure legends

Figure 1. Flowchart of study population.

Figure 2. Base model with age and sex for predicting diagnosis acute coronary syndrome.

Figure 3. Callibration of final model with internal external validation.

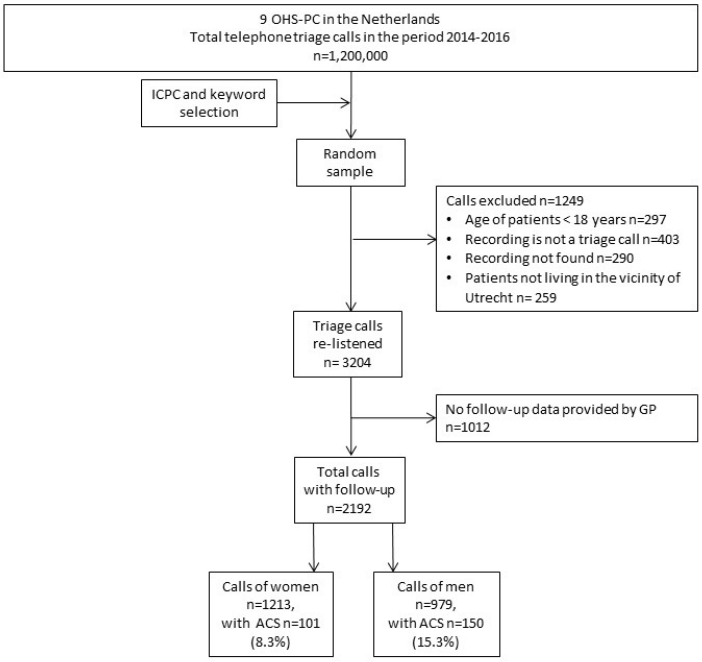

Figure 1

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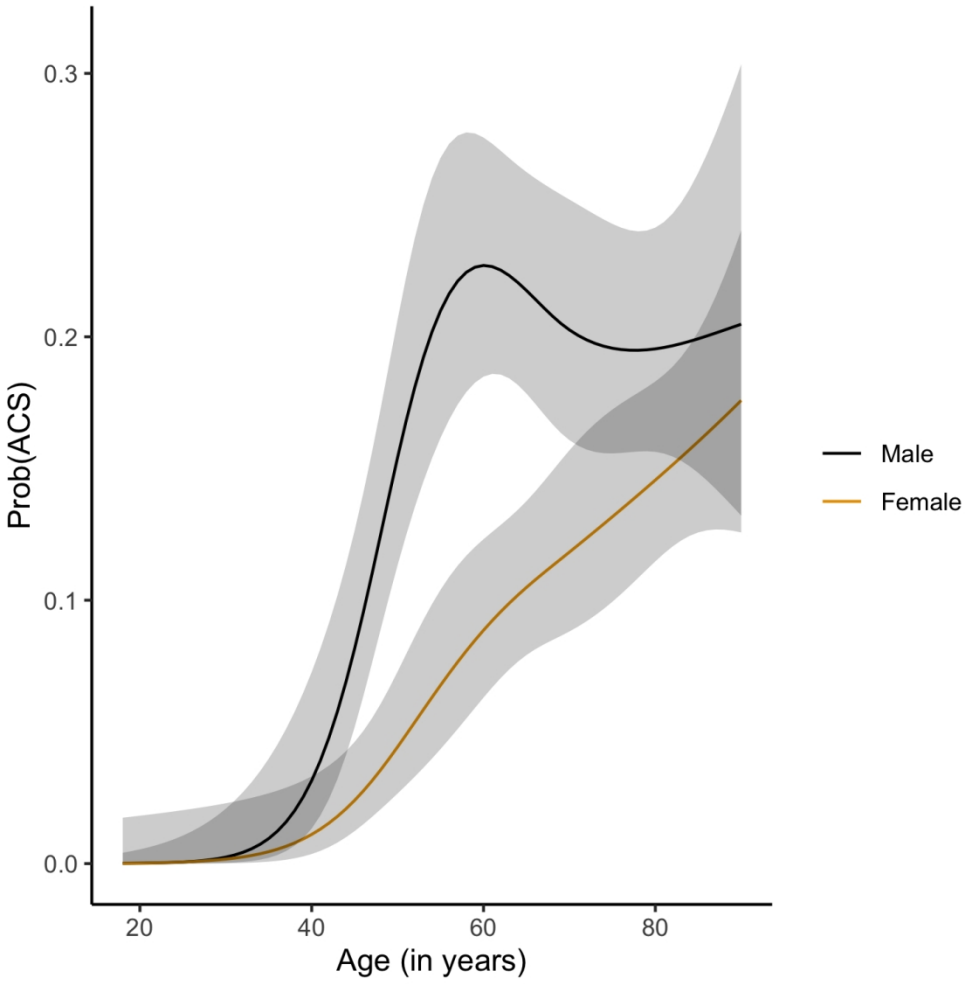
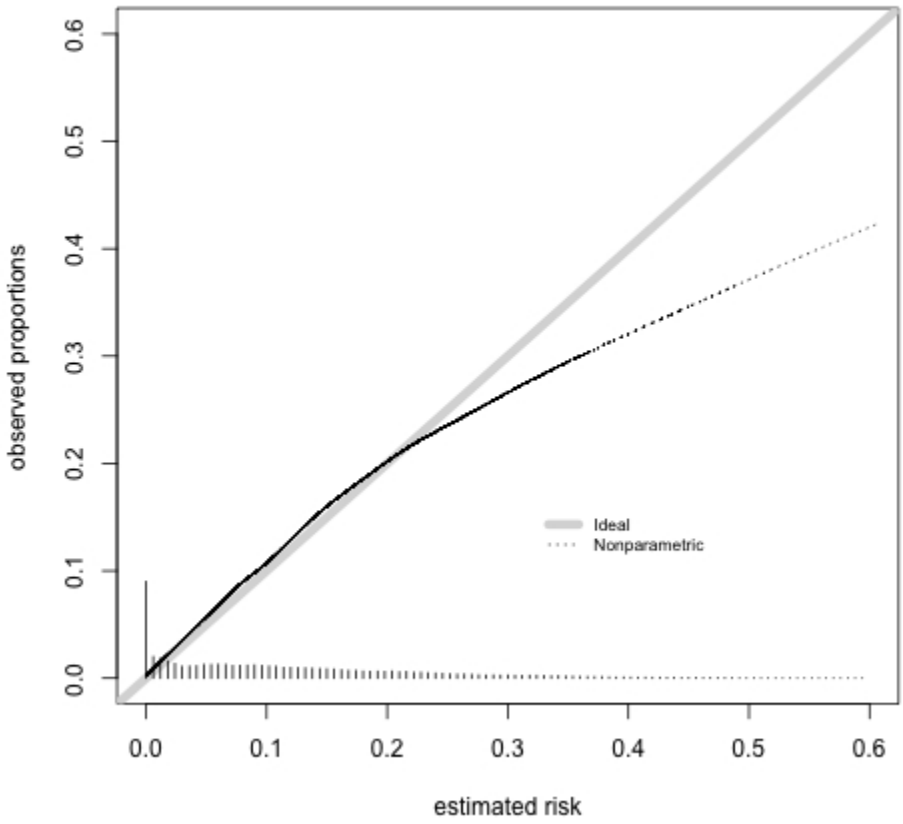


Figure 2

1360x1360mm (28 x 28 DPI)



169x169mm (72 x 72 DPI)

Appendices

Appendix - Table 1. NTS urgency levels and response times

NTS Urgency level	Definition	Response time	Medical help
U0 – Resuscitation	Loss of vital functions	Immediately	Ambulance
U1 – Life threatening	Unstable vital functions	Immediately, within 15 minutes	Ambulance
U2 – Emergent	Vital functions in danger or organ damage	As soon as possible, within 1 hour	Home visit by GP or appointment at OHS-PC
U3 – Urgent	Possible risk of damage, human reasons	A few hours (<3 hours)	Home visit by GP or appointment at OHS-PC
U4 – Non-urgent	Marginal risk of damage	24 hours	Appointment at OHS-PC or telephone advice
U5 – Advice	No risk of damage	Advice, no time related	Telephone advice

GP: general practitioner

NTS: Netherlands Triage Standard

OHS-PC: out-of-hours services in primary care

Appendix-table 2: Combinations of NTS triage criteria that generate an U1 level within the NTS main complaints that can be used for patients with chest discomfort.

→ ABCD unstable (no main complaint is selected)			**Urgency level U1: ambulance within 15 minutes**
Main complaint 'Chest pain'			
→ ABCD stable	AND severe chest pain (Numeric Rating Scale (NRS)-score ≥ 8) lasting less than 12 hours		
→ ABCD stable	AND mild (NRS ≤ 4) to moderate (NRS 5-7) chest pain lasting for less than 12 hours	AND one of the following: - retrosternal located pain - tightening or pressing - radiation to jaw, arm or upper back - progressive pain intensity in short time - past or present autonomous nervous system-related symptoms - dizziness	
Main complaint 'Collapse'			
→ ABCD stable	AND collapse	AND chest pain of any severity	
Main complaint 'Back complaints'			
→ ABCD stable	AND severe upper back pain (NRS ≥8)	AND past or present autonomous nervous system-related symptoms	

ABCD: acronym for Airway, Breathing, Circulation and Disability. When the triage nurse starts the telephone triage with the NTS, the system requires a mandatory 'ABCD-check'; i.e. the triage nurse has to ask questions to assess whether the patient has life-threatening problems concerning the Airway, Breathing, Circulation and Disability for which an ambulance should be sent immediately.

Appendix-table 3. Characteristics of patients divided among the seven OHS-PC locations.

Characteristics	Location A N=205 (9.4%)	Location B N=355 (16.2%)	Location C N=544 (24.8%)	Location D N=262 (12.0%)	Location E N=164 (7.5%)	Location F N=412 (18.8%)	Location G N=250 (11.4%)
Prevalence of ACS (n,%)	32 (15.4%)	31 (8.7%)	59 (10.8%)	35 (13.4%)	15 (9.1%)	53 (12.9%)	26 (10.4%)
Male sex (n,%)	77 (37.6%)	154 (43.4%)	256 (47.1%)	108 (41.2%)	84 (51.2%)	188 (45.6%)	112 (44.8%)
Mean age in years (SD)	62.3 (19.6)	58.6 (19.8)	58.0 (19.4)	56.6 (18.9)	61.8 (20.5)	61.6 (19.4)	56.1 (18.7)

Appendix – table 4. Overview of the percentages of missing predictors, divided into patients with and without the diagnosis ACS.

Characteristics N=2192	ACS, n=251 (11.5%) Missing (%)	No ACS, n=1941 (88.5%) Missing (%)
Mean in years age (SD)	0	0
Female sex	0	0
Median call duration in min (IQR)	0	0
Mean patient's introduction in min (IQR)	0	0
Triage nurse consulted the GP	0	0
Someone else called on behalf of patient	0	0
The person who calls expressed concerns	57.3	48.6
Cardiovascular disease or risk factor combined	12.0	16.4
History of coronary artery disease	42.6	48.1
Diabetes	64.5	58.0
Hypertension	68.5	58.0
Hypercholesterolemia/statin use	68.5	61.6
Cardiac arrhythmia	70.1	57.2
Chest pain	1.6	3.7

Shortness of breath	27.1	22.1
Chest pain duration <12 hours	11.2	13.1
Pain intensity severe (NRS >7 in range 1-10)	59.4	57.9
Pressing heavy pain*	25.1	25.9
Stabbing chest pain*	25.1	25.9
Chest pain located retrosternal**	34.7	27.7
Chest pain located left or right on thorax**	34.7	27.7
Radiation of chest pain to any location	15.1	24.5
Radiation to the arm ***	37.5	52.5
Radiation to the shoulder blades ***	37.5	52.5
Radiation to the jaws ***	37.5	52.5
Sweating	31.5	38.5
Nausea or vomiting	53.0	55.2
Pallor or ashen skin	62.9	70.1
(Near) fainting	13.1	11.2
Palpitations	89.6	83.2
Patient recognizes symptoms from previous cardiac event	55.4	58.6

*Pain described by patient. Pressing heavy pain: pressing, heavy or tightening pain vs. other types of pain (stabbing, burning, cramping, tearing) Stabbing pain: stabbing vs. other types of pain (pressing, heavy, tightening, burning, cramping)

** Retrosternal location vs. other pain locations. Left or right side thorax vs. other pain locations

*** Radiation location vs. no radiation and radiation other pain

Appendix-table 5. Patient and call characteristics of 3,204 patients with chest discomfort calling OHS-PC between 2014-2017, comparing patients with and without information on the study outcome.

Characteristics N=3204	Follow-up n= 2192 (68.4%)	No follow-up n= 1012 (31.6%)	P-value
Patient characteristics			
Median age in years (IQR)	59.1 (19.5)	57.3 (20.4)	0.020
Female sex	1213 (55.3)	565 (55.8)	0.794
Call characteristics			
Median total call duration in min (IQR)	6:51 (4:59-9:23)	6:56 (5:04-9:15)	0.836
Mean patient's introduction in min (IQR)	0:17 (0:11-0:25)	0:17 (0:11-0:26)	0.052
Triage nurse consulted the GP	1147 (52.3)	519 (51.3)	0.583
Someone else called on behalf of patient	1114 (50.8)	479 (47.3)	0.066
The person who calls expressed concerns	988 (89.7)	430 (90.1)	0.804
Medical history and risk factors			
Cardiovascular disease or risk factor combined	1192 (64.6)	515 (62.3)	0.254
History of coronary artery disease	389 (33.8)	166 (32.4)	0.573
Diabetes	180 (19.9)	68 (18.0)	0.432
Hypertension	323 (36.1)	121 (31.9)	0.150
Hypercholesterolemia/statin use	212 (25.7)	88 (25.1)	0.842
Cardiac arrhythmia	230 (25.4)	102 (24.3)	0.684
Symptoms			
Chest pain	1981 (93.6)	894 (92.8)	0.417
Shortness of breath	1094 (64.5)	520 (64.3)	0.911
Chest pain duration <12 hours	1403 (73.2)	610 (69.6)	0.052
Pain intensity severe (NRS >7 in range 1-10)	337 (36.6)	185 (43.0)	0.024
Pressing heavy pain*	1023 (62.9)	444 (61.6)	0.538
Stabbing chest pain*	366 (22.5)	177 (24.5)	0.280
Chest pain located retrosternal**	641 (40.9)	294 (40.2)	0.736
Chest pain located left or right on thorax**	627 (40.0)	294 (40.2)	0.945
Radiation of chest pain to any location	1077 (64.3)	458 (60.1)	0.047
Radiation to the arm ***	452 (42.2)	179 (39.8)	0.373

Radiation to the shoulder blades ***	326 (30.5)	136 (30.2)	0.924
Radiation to the jaws ***	124 (11.6)	41 (9.1)	0.156
Sweating	559 (40.9)	259 (42.0)	0.638
Nausea or vomiting	489 (49.5)	229 (47.1)	0.381
Pallor or ashen skin	322 (47.8)	136 (40.8)	0.038
(Near) fainting	143 (7.4)	72 (7.8)	0.678
Palpitations	284 (80.7)	125 (83.9)	0.396
Patient recognizes symptoms from previous cardiac event	250 (27.3)	102 (26.7)	0.819
Urgency allocation			
High urgency (U1 or U2)	1496 (68.2)	661 (65.3)	0.100
U1	974 (44.5)	390 (38.6)	
U2	522 (23.8)	271 (26.8)	
U3,U4,U5	696 (31.8)	351 (34.7)	

Appendix - Table 6. Base model with age and sex for predicting the diagnosis ACS.

Predictors	Regression coefficients (standard error)
Intercept	- 14.671 (3.442)
Age	0.289 (0.079)
Age’	- 0.379 (0.123)
Age’’	1.017 (0.386)
Female sex	2.155 (5.385)
Age * Female sex	- 0.084 (0.123)
Age’ * Female sex	0.175 (0.190)
Age’’ * Female sex	- 0.532 (0.589)
Apparent c-statistic 0.72 (95% CI 0.70-0.75)	
Adjusted c-statistic 0.72 (95% CI 0.68-0.75)	
Calibration slope 0.977 (95% CI 0.617-1.338)	
Calibration 0.016 (95% CI-0.702-0.734)	
R^2 0.065	
Knots for cubic spline functions placed at 5, 35, 65 and 95	

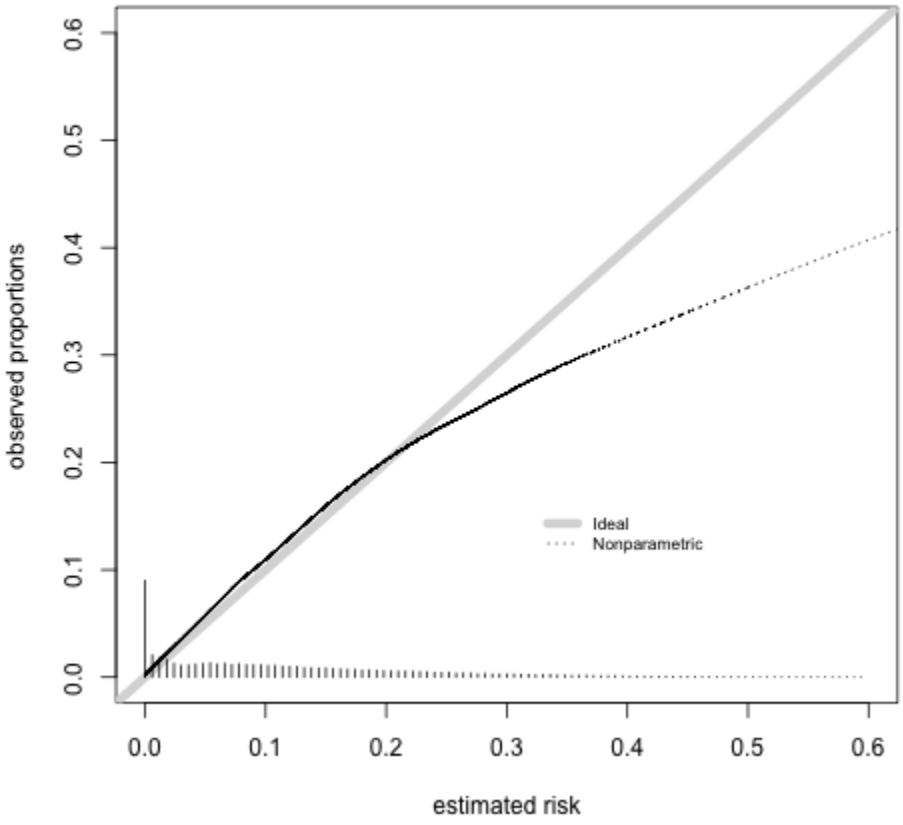
Appendix - Table 7. Full model including all candidate predictors for predicting the diagnosis ACS

Predictors	Regression coefficients (standard error)
Intercept	-15.914 (3.55)
Age	0.288 (0.081)
Age’	-0.388 (0.126)
Age’’	1.058 (0.396)
Female gender	2.459 (5.519)
Age * Female sex	-0.094 (0.126)
Age‘ * Female sex	0.187 (0.195)
Age’’ * Female sex	-0.554 (0.606)
Chest pain	-0.064 (0.365)
Acute chest pain (< 12 hours)	0.258 (0.200)
Shortness of breath	-0.141 (0.200)
Sweating	0.459 (0.183)
Retrosternal located pain	0.178 (0.177)
Radiation of chest pain	0.617 (0.180)
Pressing heavy feeling	0.619 (0.272)
Stabbing pain	-0.200 (0.353)
History of cardiovascular disease*	-0.039 (0.247)
History of coronary artery disease	0.108 (0.234)
Someone else calls instead of the patient	0.197 (0.160)
Patient calls during the night (0am-9am)	0.495 (0.152)
Apparent c-statistic 0.79 (95% CI 0.76-0.81)	
Adjusted c-statistic 0.77 (95% CI 0.74-0.80)	
Calibration slope 0.818 (95% CI 0.650-0.986)	
Calibration -0.238 (-0.621-0.145)	
R^2 0.107	
Knots for cubic spline functions placed at 5, 35, 65 and 95	

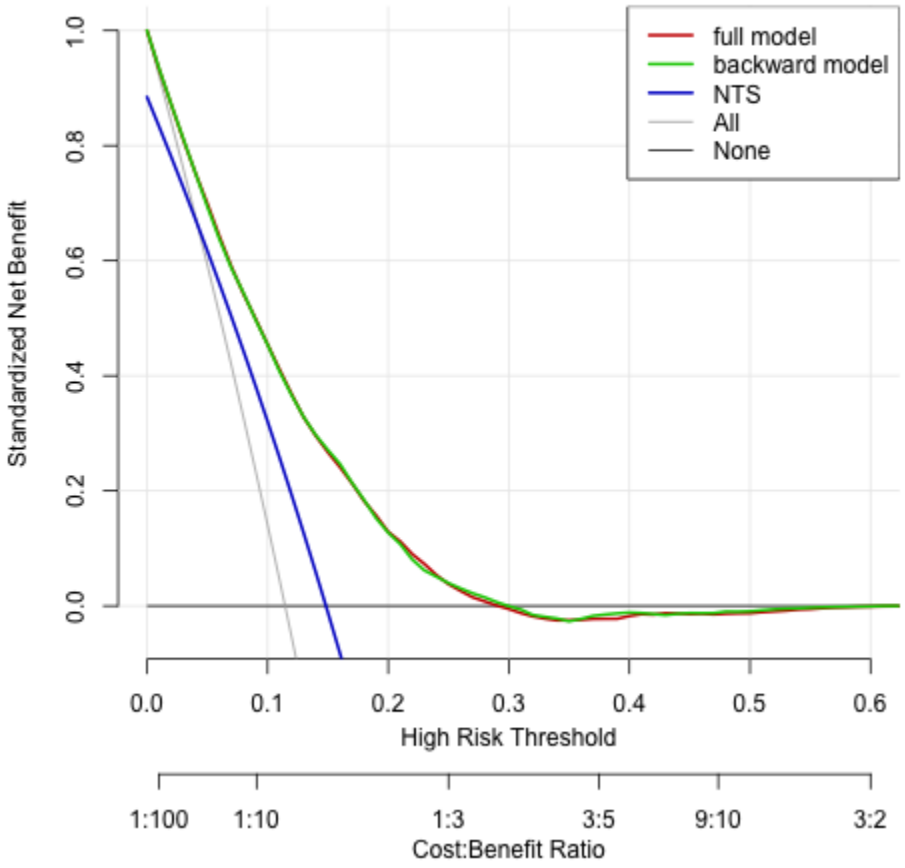
Appendix - Table 8. Diagnostic accuracy for a range of risk thresholds of the final model

Risk threshold	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
0.001	0.98 (0.95-0.99)	0.21 (0.18-0.24)	0.14	0.99
0.010	0.98 (0.95-0.99)	0.42 (0.40-0.45)	0.18	0.99
0.020	0.97 (0.94-0.99)	0.50 (0.47-0.54)	0.20	0.99
0.050	0.93 (0.87-0.96)	0.63 (0.59-0.67)	0.25	0.99
0.075	0.88 (0.81-0.92)	0.72 (0.68-0.76)	0.29	0.98
0.100	0.81 (0.7-30.87)	0.79 (0.76-0.82)	0.33	0.97
0.115 (prevalence)	0.76 (0.67-0.83)	0.82 (0.79-0.85)	0.36	0.96
0.150	0.64 (0.56-0.73)	0.88 (0.85-0.90)	0.41	0.95
0.200	0.46 (0.38-0.55)	0.93 (0.91-0.94)	0.46	0.93

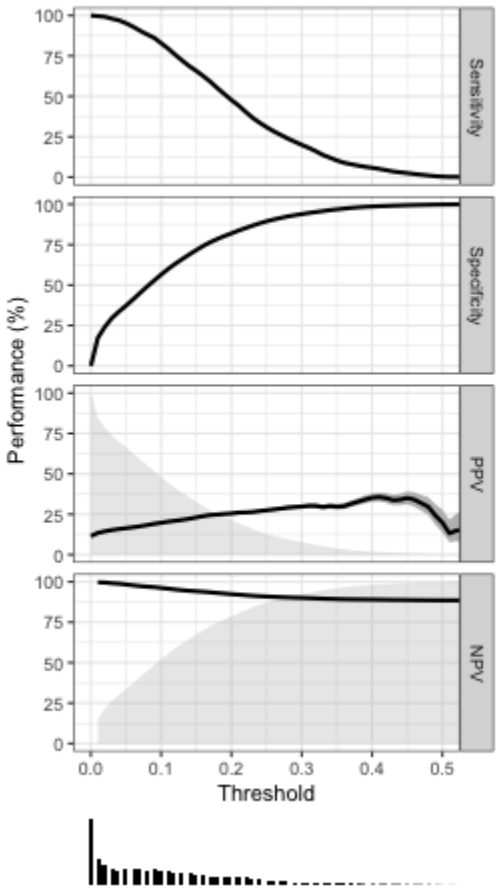
Appendix – Figure 1. Callibration of full model with internal external validation



Appendix – Figure 2. Decision curve analyses comparing the full and final models versus the currently used model and versus treat all patients.



Appendix – Figure 3. Runway plot of diagnostic accuracy measures of the final model.



TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4,5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	5,6
	5c	D;V	Give details of treatments received, if relevant.	n.a.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n.a.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	n.a.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7, suppl
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8,9,10
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	suppl
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	8
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	11,12
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	12, suppl
	15b	D	Explain how to the use the prediction model.	13
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12, 13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	12,13
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14, 15
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	17
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study

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Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study

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Abstract

Objective To develop and validate a symptom-based prediction rule for early recognition of acute coronary syndrome (ACS) in patients with acute chest discomfort who call out-of-hours services for primary care (OHS-PC).

Design Cross-sectional study. A diagnostic prediction rule was developed with multivariable regression analyses. All models were validated with internal-external cross validation within seven OHS-PC locations. Both age and sex were analysed as statistical interaction terms, applying for age non-linear effects.

Setting Seven OHS-PC in the Netherlands.

Participants 2,192 patients who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2017. Backed up recordings of telephone triage conversations were analysed.

Primary and secondary outcomes measures Diagnosis of ACS retrieved from the patient's medical records in general practice, including hospital specialists discharge letters. Performance of the prediction rules was calculated with the c-statistic and the final model was chosen based on net benefit analyses.

Results Among the 2,192 patients who called the OHS-PC with acute chest discomfort, 8.3% females and 15.3% males had an ACS. The final diagnostic model included seven predictors (sex, age, acute onset of chest pain lasting less than 12 hours, a pressing/heavy character of the pain, radiation of the pain, sweating, and calling at night). It had an adjusted c-statistic of 0.77 (95% CI 0.74-0.79) with good calibration.

Conclusion The final prediction model for ACS has good discrimination and calibration, and shows promise for replacing the existing telephone triage rules for patients with acute chest discomfort in general practice and OHS-PC.

Trial registration NTR7331

Key words: prediction rules, acute coronary syndrome, sex, symptoms, general practice, out-of-hours primary care

Strengths and limitations of this study

- We could analyse the original and very first telephone conversation of patients with acute chest discomfort.
- The developed prediction model is well generalizable to other OHS-PCs in the Netherlands, but also to similar OHS-PC settings in other countries or even emergency medical service settings.
- A limitation is that fully external validation of the model in another OHS-PC was impossible because no other cohort similar to ours was available.
- Another limitation is that the effects of the predictors were assumed to be similar for males and females while this is not exactly the case, but by incorporating a differential non-linear effect of age and interaction with sex in the analyses this effect is minimalized.

Introduction

Chest discomfort is among the top five reasons for telephone contact in out-of-hours services for primary care (OHS-PC) and concerns 5% of all cases at the emergency department (ED) in the USA. [1] In the Netherlands, around 80% of patients with chest discomfort first call the general practitioner (GP) or OHS-PC, while 20% directly calls the emergency medical service (EMS, or ambulance dispatch centre) or are self-referrals to the ED. [2] Adequate triage and early diagnosis in these patients is vital, because in case of an underlying acute coronary syndrome (ACS) early effective therapeutic interventions ('time is muscle') improve the patient's outcome and prognosis. [3] For the diagnosis of ACS, a 12-lead electrocardiogram (ECG) and troponin testing is needed. [3] However, before the patient is referred to an ED where these diagnostic tests can be done, patient selection is necessary based on symptom presentation retrieved by telephone triage. [4 5] Symptom-based differentiation of ACS from other causes of chest discomfort is notoriously difficult. [6] Symptom-based prediction rules for diagnosing ACS in general practice and other prehospital settings are -although highly needed- scarce. [7-9] The efficiency and safety of telephone triage in OHS-PC was poor in a population with a prior chance of ACS of 8.3% in females and 15.3% in males; almost 50% of the males and females with chest discomfort received a high priority ambulance, while 11% diagnosed with an ACS did not received a high urgency (i.e., was seen within one hour). [10]

Most prediction rules for diagnosing ACS were developed in the ED setting, and include results from ECG and troponin testing. [11] Such prediction rules cannot be straightforward implemented for telephone triage in general practice because (i) in the latter setting these diagnostic tests are not available, (ii) the prior chance of ACS is rather low, and (iii) on average disease severity is less than in those seen in the ED. [12 13] The prevalence of ACS among patients with chest discomfort who call OHS-PC or EMS is about 10-15%, and among those seen at the ED between 10 to 30%. [10 11 13 14] Only one prediction rule was developed in primary care for diagnosing ACS; the modified Grijseels prediction rule, which had moderate discriminative ability (c-statistic of 0.66) after external validation. [7 8] Five other primary care prediction rules were developed to predict CAD; e.g. the Marburg Heart Score (MHS) and INTERCHEST prediction rule (International Working Group on Chest Pain in Primary Care). [9] In these studies both patients with acute and non-acute chest discomfort were included and the prevalence of stable CAD showed to be 10.9% to 12.6%, while that of ACS was only 1.5% to 2.5%. [9] Thus, these prediction rules have limited applicability for specifically diagnosing ACS.

In most OHS-PC and about half of the EMS in the Netherlands, triage nurses use the semi-automatic 'Netherlands Triage Standard' (NTS) as a decision support tool to classify the urgency of the patient's condition. Triage nurses have to choose one out of 56 'main complaints' and based on answers linked to the triage criteria, the NTS automatically proposes one out of six levels of urgency, that is, a certain time frame in which patients should be seen (U0-U5, appendix- table 1). The NTS is a modified and shortened version of the Manchester Triage Standard which was developed in the ED setting. [15] Although the NTS was explicitly developed for telephone triage, it has not yet been validated against clinical outcomes even though it is already implemented on large scale. Recent research showed that the NTS had a poor sensitivity of 0.73 (95% CI 0.68-0.78) for telephone triage of patients with acute chest discomfort. The NTS recommended a low urgency (U3, U4 or U5) to 27% of patients who eventually showed to have an ACS or other life threatening event (LTE). [10] The NTS' specificity was also poor with 0.43 (95% CI 0.40-0.45); the NTS recommended a high urgency to 57% of the patients who eventually showed not to have an ACS or LTE. Given this poor safety and efficiency of the NTS, there is an urgent need for a better prediction model for patients with acute chest discomfort calling OHS-PC. In addition, there is a need for exploring sex-specificity of such prediction rule as there is an ongoing debate on whether females differ from males in reporting symptoms of ACS. [16 17]

The aim of this study was to develop, and internal-external cross validate a symptom-based prediction rule for diagnosing ACS which is considerate to sex categories in male and female patients who call the OHS-PC for acute chest discomfort.

Methods

We performed a cross-sectional study among 2,192 patients who called one out of seven participating OHS-PC in the Netherlands because of acute chest discomfort (pain, pressure, tightness, or discomfort) during the period 2014 to 2017. [18] These OHS-PC serve a total population of 1.5 million people and cover around 300,000 calls a year. We first selected calls based on of the International Code for Primary Care (ICPC; a WHO world-wide code system for primary care) with ICPC-codes K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98 and calls with keywords thoracic pain, chest pain, myocardial infarction, heart attack and their common abbreviations (Figure 1). We included a broad variety of symptoms to capture the entire domain of patients that could be suspected of ACS. We listed all available calls of these patients and assigned random numbers with the Random Number Generator (RAND) function in Microsoft Excel to retrieve a random sample. Calls were excluded before re-listening

when the patients' age was below 18 years or when the patient did not live in the surrounding area of the OHS-PC (in which case we could not retrieve the final diagnosis from the patient's own general practitioner). Calls were excluded during re-listening when it did not concern a triage call (e.g. inter-collegial consultation) or when the recording was of poor quality (Figure 1).

Candidate predictors

Research team members (LW, DE) and medical students listened to the call recordings, blinded for the outcome, to collect data about symptoms, medical history and urgency allocation. Patient (age, sex) and call characteristics (call time, call duration) were collected from the OHS-PC electronic medical files of the patients. As candidate predictors we included age and sex, the NTS triage criteria (see appendix-table 2), the ACS predictors from the modified Grijseels prediction model (male sex, radiation, nausea, sweating and history of CAD), the 'CAD predictors' from MHS and INTERCHEST prediction models (age, pain feels like pressure, CAD history or CV risk factors, patient assumes cardiac origin of pain), and - based on a recent own study in OHS-PC- the predictor 'calling at night between 0am and 9am'. [7-9 19]

Outcome

The primary outcome was the diagnosis ACS. The final diagnoses were retrieved from the patient's GP, and based on the GP's electronic medical files which include ED and cardiologist discharge letters and notes from the OHS-PC contact. The diagnosis ACS was nearly always made by a cardiologist (96.0%) and included information on levels of (high-sensitivity) troponin and electrocardiographic results. We used medical information up to 30-days following the contact with the OHS-PC to allow us to include diagnoses of ACS that were initially missed because the patient was not referred to the cardiologist the same day of the OHS-PC contact. However, in none of the patients in the study we had evidence of a missed diagnosis of ACS.

Sample size calculation

We relied on the minimal sample size criteria for prediction model development proposed by Riley et al, using the 'pmsampsize' package in R. [20] Based on an ACS prevalence of overall 11% and an Cox-Snell R-squared of 0.075 (a conservative value based on a model with age and sex) and a total number of 2,192 observations we were allowed to assess 19 candidate predictors. [21] Based on sample size calculations we concluded that development of separate models for males and females would require a significantly larger sample, therefore we analysed sex as a statistical interaction term. [20]

Statistical analyses

We developed three diagnostic models using multivariable logistic regression analysis. First, we developed a base model with only age and sex as predictors, where age was modelled using a restricted cubic spline function (4 knots) and an interaction with sex. This resulted in a base model with 7 predictor parameters (excluding the intercept). Second, we fitted a full model with an additional 12 pre-selected binary predictors (having chest pain, acute chest pain shorter than 12 hours, shortness of breath, sweating, retrosternal located chest pain, radiation, pressing heavy pain, stabbing pain, history of CVD, history of CAD, someone else calling, calling at night). Thirdly, we applied backward elimination, with a cut-off p-value < 0.20 for including predictors (a higher cut-off value to lower the chances of overfitting). [21]

We applied internal-external cross validation (IECV) for model validation using the seven different OHS-PC locations (Appendix-Table 3 for patient characteristics of different OHS-PC locations). [22] We evaluated the IECV performance in terms of the area under the ROC curve (c-statistic), the calibration slope and calibration in the large. The IECV estimates of performance were combined by using random-effect model (DerSimonian-Laird estimator). Based on the IECV we also constructed flexible calibration curves and decision curves. In the decision curve analyses we compared the final model with the currently used NTS triage model in OHS-PC in the Netherlands. [23] Finally, we created an illustrative table of diagnostic test accuracy for various model-based risk thresholds of the final model, following the example in Wynants et al. [23] IECV estimates for risk threshold specific sensitivity and specificity, and we applied a bivariate model commonly used for diagnostic test accuracy meta-analysis. [24]

Missing data

For missing data we carried out multiple imputation using the Multivariate Imputation via Chained Equation (MICE) package in R, with 30 imputation rounds and 30 iterations. [25] We pooled the results following Rubin's rules. [26] Predictors with over 50% missing were excluded from consideration in the models (Appendix-table 4 for details about the missing data). Characteristics were compared between patients with and without information on the medical outcome - because some GPs refused diagnosis retrieval from their files - to allow for assessment of differences in characteristics between these patient groups (Appendix-table 5). There were no clinically meaningful differences in symptoms and patient or call characteristics between the 2,192 patients with information on the outcome, and the 1,012 patients

about whom knowledge of the medical outcome related to the OHS-PC contact because of acute chest discomfort was missing.

All analyses were done in R version 4.0.3. (2020-10-10) with the Regression Modelling Strategies ('rms') package in R. [27] We reported our study in accordance to the Transparent Reporting of a multivariable prediction rules for Individual Prognosis Or Diagnosis (TRIPOD) criteria (Supplementary file). [28]

Patient and Public Involvement

No patients were involved in defining the research question or the outcome measures. Neither they were involved in developing plans for design. However, they participated in the discussion on implications and the implementation strategy. In addition, they were asked to advise on interpretation and writing up of the results. Results will be shared and discussed in more detail with representatives of the Dutch national patient community of cardiovascular diseases ('Harteraad').

Results

Among the 2,192 callers with acute chest discomfort (mean age 59.1 (SD 19.5) years and 55.3% females) 251 (11.5%) had a final diagnosis of ACS; 101 (8.3%) females and 150 (15.3%) males (Table 1). Patients with ACS were older than those without (mean age 69.7 (SD 13.4) vs. 57.7 (SD 19.8) years) and females with ACS were on average older than men with ACS (73.8 (SD 13.5) years vs. 67.0 (SD 12.6) years).

Table 1. Characteristics of 2,192 patients who called OHS PC with acute chest discomfort between 2014-2017, divided between females and males with and without ACS.

Characteristics	**1,213 females (55.3%)**		**979 males (44.7%)**	
	ACS n=101 (8.3%)	**No ACS n=1,112 (91.7%)**	**ACS n=150 (15.3%)**	**No ACS n= 829 (84.7%)**
Patient characteristics				
Mean age in years (SD) (n=2,192)	73.8 (13.5)	58.0 (20.2)	67.0 (12.6)	57.2 (19.2)
Call characteristics				
Median call duration in min (IQR) (n=2,192)	5:27 (3:57-8:24)	6:59 (5:06-9:47)	6:04 (4:03-8:17)	6:56 (5:10-9:23)
Mean introduction time in min (IQR) (n=2,192)	0:13 (0:09-0:18)	0:17 (0:11-0:26)	0:14 (0:09-0:21)	0:17 (0:11-0:25)
Call during the night (0am-9am) (n=2,192)	34 (33.7)	304 (27.3)	62 (41.3)	188 (22.7)

Triage nurse consulted the GP (n=2,192)	43 (42.6)	580 (52.2)	75 (50.0)	449 (54.2)
Someone else called on behalf of patient (n=2,192)	69 (68.3)	515 (46.3)	98 (65.3)	432 (52.1)
The person who calls expressed concerns (n=988)	42 (95.5)	507 (90.5)	61 (96.8)	378 (87.1)
Medical history and risk factors				
Cardiovascular disease or CV risk factors (n=1,844)	70 (81.4)	552 (61.1)	106 (78.5)	464 (64.4)
History of coronary artery disease (n=1,151)	23 (47.9)	131 (24.2)	54 (56.3)	181 (38.8)
Diabetes (n=893)	14 (42.4)	66 (14.3)	22 (39.3)	78 (22.0)
Hypertension (n=894)	26 (72.2)	162 (34.0)	22 (51.2)	113 (33.3)
Hypercholesterolemia/statin use (n=826)	10 (40.0)	96 (22.6)	27 (50.0)	79 (24.5)
Cardiac arrhythmia (n=905)	4 (14.8)	125 (26.2)	12 (25.0)	89 (25.2)
Symptoms				
Chest pain (n=2,116)	95 (96.9)	1007 (94.1)	139 (93.3)	758 (94.9)
Shortness of breath (n=1,696)	57 (71.3)	559 (65.4)	63 (61.2)	415 (63.1)
Chest pain duration <12 hours (n=1,910)	74 (86.0)	703 (72.3)	113 (82.5)	510 (71.3)
Severe pain (NRS >7, range 1-10) (n=917)	19 (61.3)	184 (39.6)	18 (25.4)	116 (33.0)
Pressing/heavy chest pain* (n=1,625)	58 (81.7)	525 (62.5)	95 (81.2)	345 (57.7)
Stabbing chest pain* (n=1,625)	8 (11.3)	190 (22.6)	9 (7.7)	159 (26.6)
Retrosternal chest pain ** (n=1,565)	36 (54.5)	326 (40.0)	52 (53.1)	227 (38.7)
Chest pain left or right of thorax** (n=1,566)	19 (28.8)	318 (39.0)	28 (28.6)	262 (44.6)
Radiation of chest pain to any location (n=1,678)	74 (86.0)	575 (67.8)	83 (65.4)	347 (56.2)
Radiation to the arm *** (n=1,677)	37 (43.0)	218 (25.7)	54 (42.5)	143 (23.2)
Radiation to the shoulder blades *** (n=1,678)	14 (16.3)	190 (22.4)	19 (15.0)	103 (16.7)
Radiation to the jaws *** (n=1,678)	10 (11.6)	77 (9.1)	4 (3.1)	33 (5.3)
Sweating (n=1,366)	36 (52.9)	279 (42.0)	54 (51.9)	190 (35.8)
Nausea or vomiting (n=987)	24 (52.2)	295 (56.6)	31 (43.1)	139 (39.9)
Pallor or ashen skin (n=673)	22 (59.5)	139 (44.3)	36 (64.3)	125 (46.8)
(Near) fainting (n=1,951)	8 (9.5)	76 (7.7)	9 (6.7)	50 (6.7)
Palpitations (n=162)	10 (100.0)	183 (84.7)	8 (50.0)	83 (75.5)
Patient recognizes symptoms from previous cardiac event (n=915)	17 (35.4)	100 (22.0)	30 (46.9)	103 (29.5)
Urgency allocation				

High urgency (U1 or U2) (n=2,192)	89 (88.1)	740 (66.5)	133 (88.7)	534 (64.4)
U1	75 (74.3)	443 (39.8)	106 (70.7)	350 (42.2)
U2	14 (13.9)	297 (26.7)	27 (18.0)	184 (22.2)
Low urgency (U3 or U4 or U5)	12 (11.9)	372 (33.5)	17 (11.3)	295 (35.6)

*Pain described by patient. Pressing heavy pain: pressing, heavy or tightening pain vs. other types of pain (stabbing, burning, cramping, tearing) Stabbing pain: stabbing vs. other types of pain (pressing, heavy, tightening, burning, cramping)

** Retrosternal location vs. other pain locations. Left or right side of the thorax vs. other pain locations

*** Radiation location vs. no radiation and radiation other pain

Over two thirds of all callers (68.3%) received a high urgency allocation (seen within one hour; U1 or U2) and among the 251 patients who showed to have an ACS, 88.4% received a high urgency allocation. Calls of patients who had an ACS were shorter than calls in those without ACS (median call duration 6:34 (SD 3:38) vs. 7:42 (SD 3:48) minutes).

Medical history and symptoms

Females and males with ACS had more often a history with CVD or CV risk factors than those without (females with ACS 81.4% vs. females without ACS 61.1%, males with ACS 78.5% vs. males without ACS 64.4%) (Table 1). The majority of both females and males had chest pain (94.5%) and this was similar among those with and without ACS. Overall, presented symptoms among males and females calling the OHS-PC for chest discomfort were quite similar. Symptoms associated with ACS in both sexes were pressing/heavy chest pain (females with ACS 81.7% vs. females without ACS 62.5%, males 81.2% vs. 57.7% respectively), retrosternal located chest pain (females 54.5% vs. 40.0%, males 53.1% vs. 38.7%), radiation of pain (females 86.0% vs 67.8%, males 65.4% vs 56.2%), and sweating (females 52.9% vs. 42.0%, males 51.9% vs. 35.8%).

Diagnoses

In total 251 patients were diagnosed with ACS and 65 with other LTEs, and of clinical relevance is that both critical events occurred significantly more in males than females (15.3% vs. 8.3%, p<0.001 for ACS, and 3.8% vs. 2.3%, p=0.04 for other LTEs, respectively). Of the 101 females with ACS, 22.8% had a ST-segment elevation myocardial infarction (STEMI), 46.5% a non ST-segment elevation myocardial infarction (NSTEMI), 19.8% unstable angina pectoris (UAP), and 10.9% non-classified ACS. In 150 males with ACS, 33.3% had a STEMI, 36.7% a NSTEMI, 26.0% UAP, and 4.0% non-classified ACS (Table 2).**Table 2. Diagnoses of 2,192 males and females who contacted the OHS-PC for acute chest discomfort between 2014-2017, by sex.**

Diagnosis, n (%)	Females n= 1213	Males n= 979	p-value
Acute coronary syndrome*	101 (8.3)	150 (15.3)	<0.001
STEMI	23 (22.8)	50 (33.3)	0.071
NSTEMI	47 (46.5)	55 (36.7)	0.119
UAP	20 (19.8)	39 (26.0)	0.256
Non-classified ACS	11 (10.9)	6 (4.0)	0.033
Life threatening events (LTEs)	28 (2.3)	37 (3.8)	0.043
Pulmonary embolism	8 (28.6)	10 (27.0)	0.890
Acute abdominal aneurysm	2 (7.1)	3 (8.1)	0.885
Thoracic aortic dissection	1 (3.6)	4 (10.8)	0.278
Other**	17 (60.7)	20 (54.1)	0.591
Non-urgent cardiovascular diseases***	223 (18.4)	191 (19.5)	0.069
Musculoskeletal pain	245 (20.2)	148 (15.2)	0.039
Non-cardiac chest pain, not further specified ******	191 (15.7)	179 (18.3)	0.012
Psychogenic disorders	165 (13.6)	85 (8.7)	0.005
Gastrointestinal tract disorders	89 (7.3)	68 (6.9)	0.776
Respiratory tract disorders	61 (5.0)	56 (5.7)	0.203
Other non-urgent diagnoses*******	110 (9.1)	65 (6.6)	0.152

* Almost all patients (96.0%) were diagnosed by a cardiologist. Ten (4.0%) ACS patients were not diagnosed by a cardiologist; four died before arrival of the ambulance, one patient died after resuscitation at the ED (all these five were classified as acute cardiac death due to ACS), and in five patients the ACS diagnosis was solely based on the GP's interpretation in patients who were not referred to the hospital after shared decision because of a short life expectancy due to cancer in a palliative stage.

** Stroke, severe COPD exacerbation, acute severe heart failure, sepsis, hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.

*** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension

**** Cardiac pathology unlikely after cardiologist's or GP's diagnostic work-up, but without differential diagnosis

***** Amongst others: anaemia, carcinoma, vasovagal collapse, side effects medication, dermatological diseases (e.g. herpes Zoster infection)

Twenty-eight (2.3%) females and 37 males (3.8%) had another life-threatening event than ACS (e.g. pulmonary embolism, thoracic aortic dissection, acute abdominal aneurysm). All other patients (85.6%) had non-urgent medical conditions such as non-urgent cardiovascular disease (18.9%), musculoskeletal pain (17.9%), non-cardiac chest pain (not further specified) (16.9%), psychogenic disorder (11.4%), gastrointestinal disorders (7.2%), respiratory disorders (5.3%), and other non-urgent diagnoses (8.0%).

Model development, performance and validation

The base model with sex and age had an apparent c-statistic of 0.72 (95% CI 0.70-0.75), and an internal-external validation based c-statistic of 0.72 (95% 0.68-0.75) (Appendix- Table 6). The basic model shows that the risk of ACS increases with age for both sexes, with a notable peak risk for men at an age near 60 years and a more gradual increase in risk of ACS for women (Figure 2). The full model including all candidate predictors had an apparent c-statistic of 0.79 (95% CI 0.76-0.81) and an internal-external validation based c-statistic of 0.77 (95% CI 0.74-0.80) (Appendix - Table 7). The full model had optimal calibration (flexible line close to the 45-degree reference line) up to a predicted probability of ACS of approximately 0.2 (Appendix-Figure 1). Risks higher than 0.2 tended to be overestimated by the model, however since any plausible risk threshold will be lower than 0.2 in the primary care setting, we find the calibration in the relevant range to be satisfactory. After backward elimination, the backward model had an apparent c-statistic of 0.79 (95% CI 0.76-0.81), and the internal-external validation c-statistic was 0.77 (95% CI 0.74-0.79). It had very similar calibration to the full model (Table 3, Figure 3).

Table 3. Final model for predicting the diagnosis ACS.

Predictors	**Regression coefficients (standard error)**
Intercept	-16.246 (3.527)
Age	0.293 (0.081)
Age’	-0.391 (0.125)
Age’’	1.063 (0.395)
Female gender	2.504 (5.512)
Age * female gender	-0.096 (0.126)
Age’ * female gender	0.189 (0.195)
Age’’ * female gender	-0.556 (0.605)
Acute chest pain shorter than 12 hours	0.290 (0.198)

Sweating	0.457 (0.178)
Radiation of chest pain	0.609 (0.176)
Pressing heavy pain	0.747 (0.200)
Call during the night (0am-9am)	0.504 (0.151)
Apparent c-statistic 0.79 (95% CI 0.76-0.81) Adjusted c-statistic 0.77 (95% CI 0.74-0.79) Calibration slope 0.826 (95% CI 0.658-0.994) Calibration -0.224 (95% CI -0.604-0.157) R^2 0.106 Knots for cubic spline functions placed at 5, 35, 65 and 95	

Decision curve analyses and risk thresholds

Both the full and backward model showed a high net benefit as compared to the currently used NTS model for telephone triage in OHS-PC (Figure 4). There was no difference in net benefit between the full model and backward model across plausible risk thresholds. Based on this analysis we decided to choose the backward as the final triage tool model because; 1) with fewer predictors the prediction of ACS remained similar accurate and 2) no valuable time is lost during telephone triage by asking the patient about symptoms that do not contribute to a better prediction. The final model included besides age and sex, the five following predictors; (i) acute onset of chest pain lasting <12 hours, (ii) a pressing/heavy character, (iii) radiation of pain, (iv) sweating, (v) calling at night between 0.00 and 9.00am. Finally, we evaluated the diagnostic performance of the final prediction model across risk thresholds that may be chosen to apply in clinical practice (Table 4, Figure 5).

Table 4. Diagnostic accuracy for a range of risk thresholds of the final model

Risk threshold	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
0.001	0.98 (0.95-0.99)	0.21 (0.18-0.24)	0.14	0.99
0.010	0.98 (0.95-0.99)	0.42 (0.40-0.45)	0.18	0.99
0.020	0.97 (0.94-0.99)	0.50 (0.47-0.54)	0.20	0.99
0.050	0.93 (0.87-0.96)	0.63 (0.59-0.67)	0.25	0.99
0.075	0.88 (0.81-0.92)	0.72 (0.68-0.76)	0.29	0.98
0.100	0.81 (0.7-30.87)	0.79 (0.76-0.82)	0.33	0.97
0.115 (prevalence)	0.76 (0.67-0.83)	0.82 (0.79-0.85)	0.36	0.96
0.150	0.64 (0.56-0.73)	0.88 (0.85-0.90)	0.41	0.95
0.200	0.46 (0.38-0.55)	0.93 (0.91-0.94)	0.46	0.93

Discussion

This is the first study that developed and internal-external validated a symptom-based prediction rule for telephone triage of ACS in male and female patients who contact OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort). ACS was present in 8.3% of the females and 15.3% of the males. The prediction rule is applicable for triage in the OHS-PC setting and consists of sex and age as statistical interaction terms, and five other symptom-based predictors. It had a good discriminative ability (adjusted c-statistic 0.77 (95% CI 0.74-0.79)) and was well calibrated up to an ACS risk of 0.2.

Strengths and limitations

The major strength of this study is that we analysed the original and very first conversations of patients with acute chest discomfort with primary health care providers and assessed these talks without knowledge of the diagnosis; the assessment of symptoms was therefore not affected by hindsight bias caused by knowledge of the final diagnosis. [29] Furthermore, we could analyse a large sample (N=2,192) of patients which allowed us to evaluate up to nineteen candidate predictors. We assessed the risk of selection due to missing outcome data, and our data suggest that this missingness was unlikely to bias our findings. Because we used data from seven different OHS-PC our results will be well generalizable to other OHS-PC in the Netherlands, but we anticipate the model might be applicable to similar OHS-PC

setting in for example the UK and Scandinavian countries. Our results may also be generalizable to some EMS settings, because the prior chance of having an ACS among those calling for acute chest discomfort is rather similar in the EMS setting as in the OHS-PC setting. [14 30]

A limitation of the study is that the final model is not yet fully externally validated. However, at the time of executing the study hardly any primary care research data were available to perform such validation. Importantly, the internal-external validation showed very good calibration up to an ACS risk of 0.2. Although, we performed extensive internal-external validation making use of the datasets of nine sites with substantial differences in case mix, we will strive for formal external validation before it can be widely applied in everyday primary care practice. Another limitation is that the effects of the predictors were assumed to be similar for male and female patients while that might not be optimal for the predictions. However, development of separate models for males and females would require a significantly larger sample size than was available. Importantly, a differential non-linear effect of age was incorporated using a spline function and interaction with sex was incorporated, and the final internal-external validated model did have good overall performance.

Comparison with other studies

Our prediction model had a higher discriminating ability for ACS than the NTS (c-statistic of 0.58) and modified Grijseels prediction rule (c-statistic of 0.66). [7] This may largely be explained by the addition of age, the strongest predictor of ACS. This is in line with the notion that the prevalence of ACS increases with age. [7 9 31] Importantly, in our study among people aged below 40, only one (0.4%) male patient had an ACS (UAP). For males to the age of 55 we found a peak risk of ACS of around 20% and remaining at this level with further age increase onwards. For females we found a gradual increase of risk with age with a maximum ACS risk of around 18% for those aged over 80 years. Similar to the modified Grijseels prediction rule our prediction model includes sweating and radiation of pain, however, the modified Grijseels rule combined nausea and sweating to a single predictor (i.e., nausea or sweating). [7 8] Age and sex were predictors in our model, but also in the MHS and INTERCHEST prediction models. [32 33] Also the INTERCHEST rule included pressing heavy chest pain as predictor. [32] A new predictor is calling at night (between 0.00-9.00am). [19] Previous studies in the ED setting also showed circadian variability with an early morning peak for ACS patients. [34] Finally, symptoms associated with ACS were rather similar between females and males, which is in line with recent sex-stratified studies of patients with chest discomfort who called the OHS-PC, but is in contrast with the prevailing opinion. [16 17 35]

We performed decision curve analyses to investigate what would be the optimal threshold of ACS predicted probability to initiate treatment, where 'treatment' in pre-hospital setting refers to urgent referral for hospital admission (U1, ambulance within 15 minutes). However, there is a principal difference between diagnostic probability and categories of urgencies. Risk prediction provides a continuous value of the probability of disease, while urgency level categorisation is based on the interpretation of how risk probability can be translated in urgency, and time within a patient should be seen and treatment delivered. Context is needed to determine optimal thresholds, which concerns what percentage of missing ACS is considered as acceptable by health care providers, patients and policymakers. This percentage is expected to be very low because a missed ACS can result in permanent cardiac impairment, heart failure, life-threatening arrhythmias in the early phase, and death. [36] Furthermore missing an ACS is the most common reason for malpractice claims worldwide. [37] A survey performed among 1,029 ED doctors in the US, New Zealand and Australia showed that they considered an average missing rate between 0.1-1% (range 0-10%) as acceptable. [38] When we apply a maximum of 1% missing with our prediction rules, the threshold has to be set at a predicted risk of ACS of 0.05 (negative predictive value of 0.99, Table 6), which means based on our data that the majority of patients needs urgent referral. This would result in over-crowded EMS and EDs, and with the available resources being limited, this may result in exceeding target triage times, which could compromise patient safety in another way. [39] A possible alternative to consider may be applying different 'treatments' per thresholds, i.e. dispatching an ambulance (U1) for the high predicted risk patients, and GP visit within one hour (U2) for the low predicted risk patients. During GP visit more clinical parameters (blood pressure, heart rate, overall clinical impression) can be gathered to improve ACS risk prediction, and in the future, there might be room for applying point-of-care high-sensitivity troponin testing, as these are nowadays only available in the ED setting. [40] In order to determine the ideal threshold, external validation will be needed combined with clinical and management considerations. The development of this diagnostic model is the necessary first step towards an implementation study in which this model is adapted to urgency levels that can be applied by triage nurses during telephone triage at the OHS-PC. The diagnostic model needs to be 'translated' in simple yes/no questions that can be incorporated in the existing NTS and a personalized risk prediction for age and gender is generated. Some older questions will then be substituted. We are aiming to do so in an implementation study applying action research.

Implications for clinical practice and future research

This symptom-based prediction model for ACS has good discrimination and calibration and could readily be applied for telephone triage of patients with acute chest discomfort in primary care, notably the OHS-PC setting. The results of the decision curve analysis showed a large net benefit over a range of plausible risk threshold as compared to the currently used NTS model in the OHS-PC in the Netherlands. For future research, full external validation in other OHS-PC or EMS populations could further optimize and update the model. Furthermore, sex-specific prediction models could be developed for ACS, but given the overlap in symptoms between men and women, this would not result in major changes in predictors.

Conclusion

The final prediction model for ACS has good discrimination and calibration, and shows promise for replacing the existing telephone triage rules for patients with acute chest discomfort in general practice and OHS-PC. However, future research with external validation needs to provide insights into how the prediction model can be applied in practice

Ethical approval

The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to subjects and could otherwise not be carried out logistically. Personal and research data were handled and stored according to the European General Data Protection Regulation.

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Data sharing statement Data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DE conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript, and by MvS who was involved with the analyses. DE, EdG, EA, HdR, AH and RD contributed to and approved of the final version of the manuscript.

References

1. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2017 Emergency Department Summary Tables. In: Statistics NCfH, ed., 2017.

2. Mol KA, Smoczynska A, Rahel BM, et al. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart* 2018;5(2):e000859. doi: 10.1136/openhrt-2018-000859

3. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Rev Esp Cardiol (Engl Ed)* 2021;74(6):544. doi: 10.1016/j.rec.2021.05.002

4. Burman RA, Zakariassen E, Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC family practice* 2014;15:51. doi: 10.1186/1471-2296-15-51

5. Deakin CD, Sherwood DM, Smith A, et al. Does telephone triage of emergency (999) calls using Advanced Medical Priority Dispatch (AMPDS) with Department of Health (DH) call prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42,657 emergency calls to Hampshire Ambulance Service NHS Trust. *Emergency medicine journal : EMJ* 2006;23(3):232-5. doi: 10.1136/emj.2004.022962

6. Bruyninckx R, Aertgeerts B, Bruyninckx P, et al. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2008;58(547):105-11. doi: 10.3399/bjgp08X277014

7. Bruins Slot MH, Rutten FH, van der Heijden GJ, et al. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Family practice* 2011;28(3):323-8. doi: 10.1093/fampra/cmq116

8. Grijseels EW, Deckers JW, Hoes AW, et al. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. *European heart journal* 1996;17(1):89-95.

9. Harskamp RE, Laeven SC, Himmelreich JC, et al. Chest pain in general practice: a systematic review of prediction rules. *BMJ open* 2019;9(2):e027081. doi: 10.1136/bmjopen-2018-027081

10. Wouters LT, Rutten FH, Erkelens DC, et al. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open Heart* 2020;7(2) doi: 10.1136/openhrt-2020-001376

11. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC cardiovascular disorders* 2015;15:48. doi: 10.1186/s12872-015-0049-6

12. Leeflang MM, Rutjes AW, Reitsma JB, et al. Variation of a test's sensitivity and specificity with disease prevalence. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2013;185(11):E537-44. doi: 10.1503/cmaj.121286

13. Buntinx F, Knockaert D, Bruyninckx R, et al. Chest pain in general practice or in the hospital emergency department: is it the same? *Family practice* 2001;18(6):586-9.

14. Rawshani A, Larsson A, Gelang C, et al. Characteristics and outcome among patients who dial for the EMS due to chest pain. *International journal of cardiology* 2014;176(3):859-65. doi: 10.1016/j.ijcard.2014.08.004

15. Kuriyama A, Urushidani S, Nakayama T. Five-level emergency triage systems: variation in assessment of validity. *Emergency medicine journal : EMJ* 2017;34(11):703-10. doi: 10.1136/emermed-2016-206295

16. van der Meer MG, Appelman Y, Rutten KHG, et al. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open* 2019;9(11):e031613. doi: 10.1136/bmjopen-2019-031613

17. Wouters LTCM, Zwart DLM, Erkelens DCA, et al. Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage: a cross-sectional study. *BMJ open* 2021;11 doi: 10.1136/bmjopen-2020-042406

18. Erkelens DC, Wouters LT, Zwart DL, et al. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ open* 2019;9(7):e027477. doi: 10.1136/bmjopen-2018-027477

19. Wouters LT, Zwart DL, Erkelens DC, et al. Chest discomfort at night and risk of acute coronary syndrome: cross-sectional study of telephone conversations. *Family practice* 2020 doi: 10.1093/fampra/cmaa005

20. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441. doi: 10.1136/bmj.m441

21. van Smeden M, Moons KG, de Groot JA, et al. Sample size for binary logistic prediction models: Beyond events per variable criteria. *Stat Methods Med Res* 2019;28(8):2455-74. doi: 10.1177/0962280218784726

22. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. *Journal of clinical epidemiology* 2016;69:245-7. doi: 10.1016/j.jclinepi.2015.04.005

23. Wynants L, van Smeden M, McLernon DJ, et al. Three myths about risk thresholds for prediction models. *BMC medicine* 2019;17(1):192. doi: 10.1186/s12916-019-1425-3

24. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of clinical epidemiology* 2005;58(10):982-90. doi: 10.1016/j.jclinepi.2005.02.022

25. Jolani S, Debray TP, Koffijberg H, et al. Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. *Stat Med* 2015;34(11):1841-63. doi: 10.1002/sim.6451

26. Rubin DB. Multiple imputation for non response in surveys. *John Wiley & Sons, Hoboken, NJ* 1987

27. Harrell FE, Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. . Second edition ed. Cham, Switzerland: Springer International 2015.

28. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine* 2015;162(1):W1-73. doi: 10.7326/M14-0698

29. Zwaan L, Monteiro S, Sherbino J, et al. Is bias in the eye of the beholder? A vignette study to assess recognition of cognitive biases in clinical case workups. *BMJ Qual Saf* 2017;26(2):104-10. doi: 10.1136/bmjqs-2015-005014

30. Scott G, Clawson JJ, Gardett I, et al. 9-1-1 Triage of Non-Traumatic Chest Pain: Association with Hospital Diagnosis. *Prehosp Emerg Care* 2017;21(4):525-34. doi: 10.1080/10903127.2017.1302530

31. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *Jama* 2012;307(8):813-22. doi: 10.1001/jama.2012.199

32. International Working Group on Chest Pain in Primary C, Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of clinical epidemiology* 2017;81:120-28. doi: 10.1016/j.jclinepi.2016.09.011

33. Haasenritter J, Donner-Banzhoff N, Bosner S. Chest pain for coronary heart disease in general practice: clinical judgement and a clinical decision rule. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2015;65(640):e748-53. doi: 10.3399/bjgp15X687385

34. Ekelund U, Akbarzadeh M, Khoshnood A, et al. Likelihood of acute coronary syndrome in emergency department chest pain patients varies with time of presentation. *BMC Res Notes* 2012;5:420. doi: 10.1186/1756-0500-5-420

35. van Oosterhout REM, de Boer AR, Maas A, et al. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc* 2020;9(9):e014733. doi: 10.1161/JAHA.119.014733

36. Bugiardini R, Ricci B, Cenko E, et al. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc* 2017;6(8) doi: 10.1161/JAHA.117.005968 [published Online First: 2017/09/02]

37. Ernesater A, Winblad U, Engstrom M, et al. Malpractice claims regarding calls to Swedish telephone advice nursing: what went wrong and why? *J Telemed Telecare* 2012;18(7):379-83. doi: 10.1258/jtt.2012.120416

38. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *International journal of cardiology* 2013;166(3):752-4. doi: 10.1016/j.ijcard.2012.09.171

39. van der Linden MC, Meester BE, van der Linden N. Emergency department crowding affects triage processes. *Int Emerg Nurs* 2016;29:27-31. doi: 10.1016/j.ienj.2016.02.003

40. Pickering JW, Young JM, George PM, et al. Validity of a Novel Point-of-Care Troponin Assay for Single-Test Rule-Out of Acute Myocardial Infarction. *JAMA Cardiol* 2018;3(11):1108-12. doi: 10.1001/jamacardio.2018.3368

Figure legends

Figure 1. Flowchart of study population.

Figure 2. Base model with age and sex for predicting diagnosis acute coronary syndrome.

Figure 3. Callibration of final model with internal external validation.

Figure 4. Decision curve analyses comparing the full and final models versus the currently used model and versus treat all patients.

Figure 5. Runway plot of diagnostic accuracy measures of the final model.

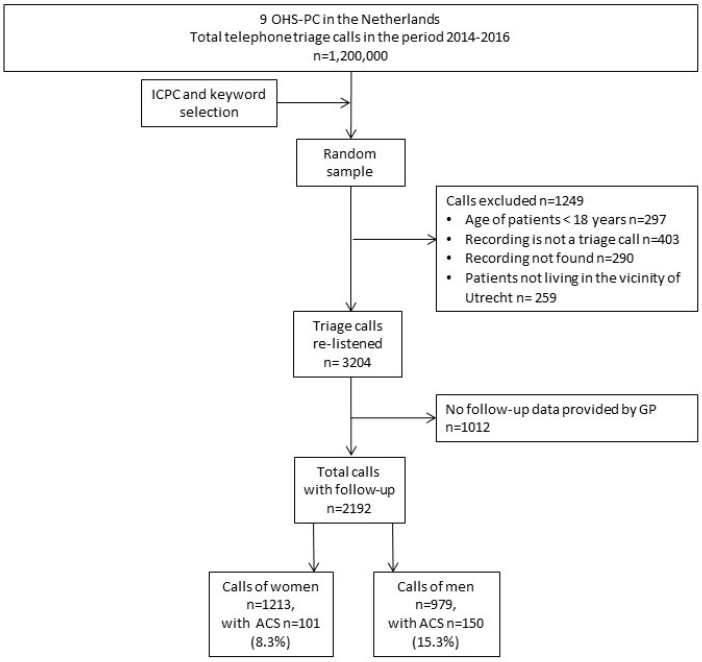

Figure 1

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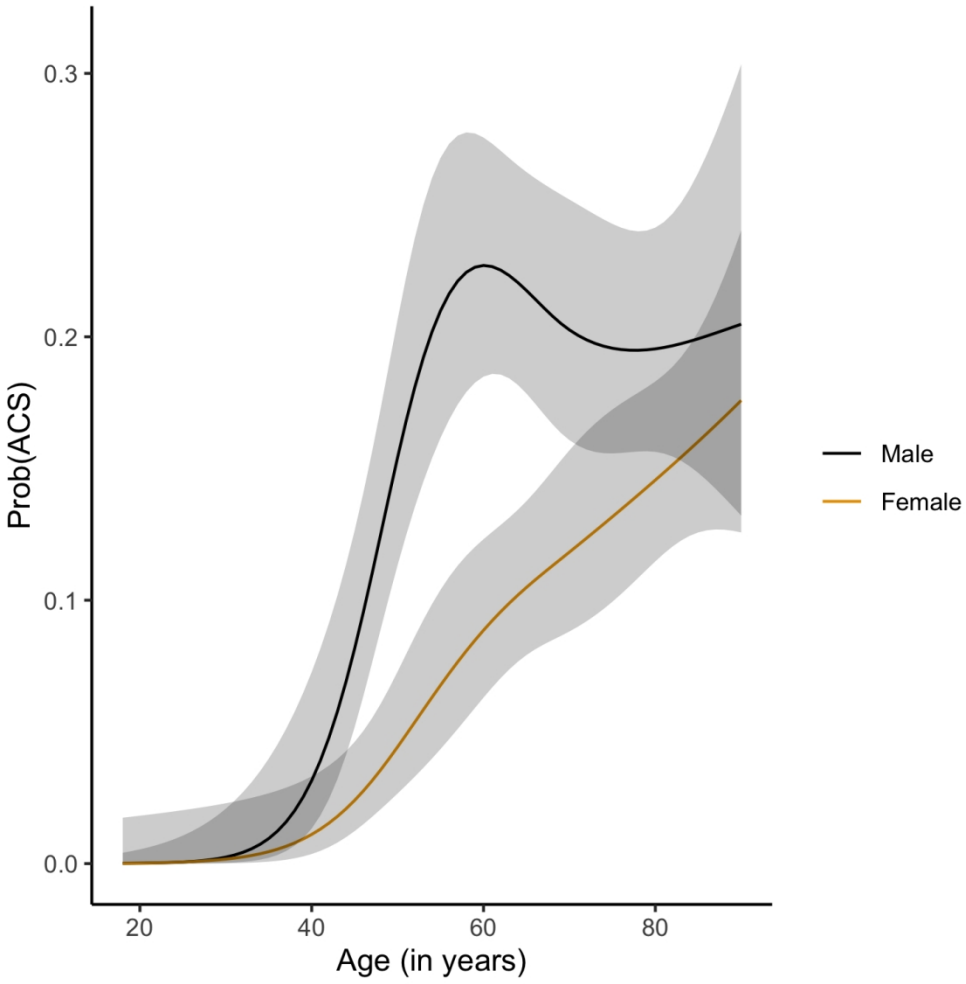

Figure 2

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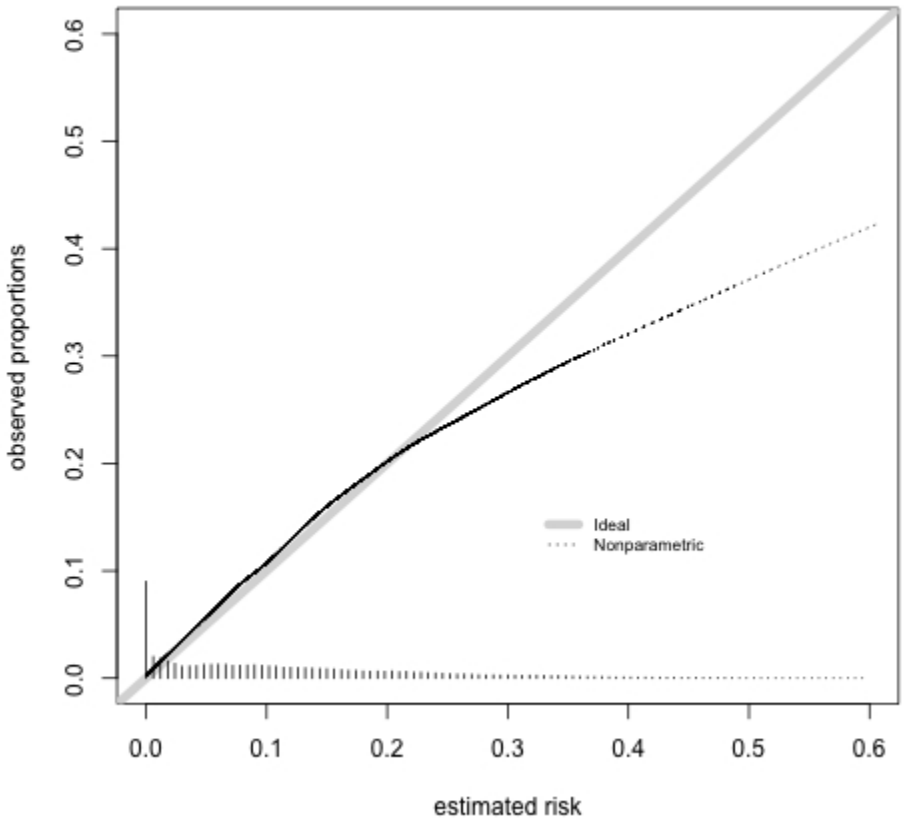

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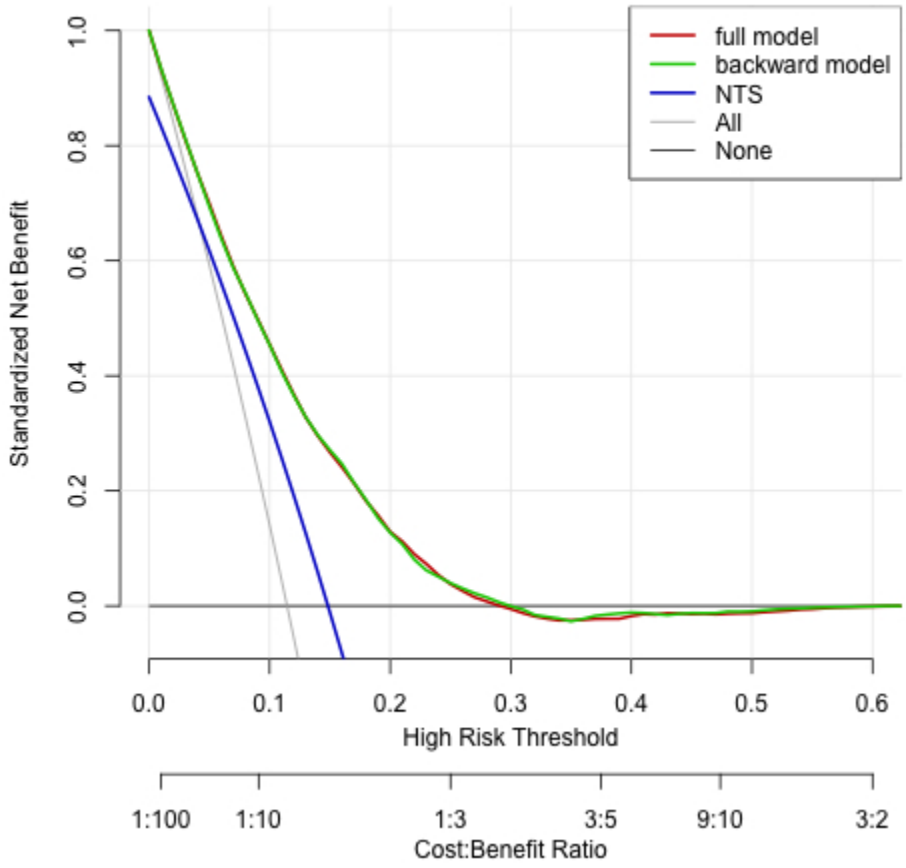

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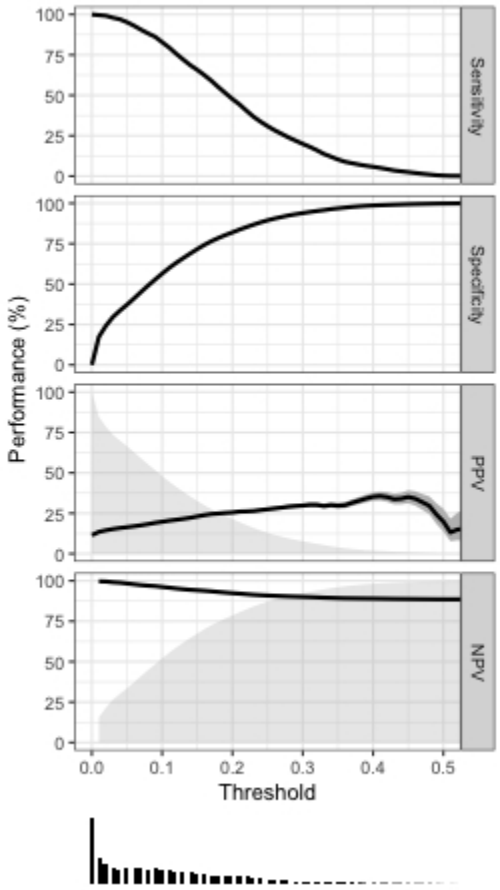

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Appendices

Appendix - Table 1. NTS urgency levels and response times

NTS Urgency level	Definition	Response time	Medical help
U0 – Resuscitation	Loss of vital functions	Immediately	Ambulance
U1 – Life threatening	Unstable vital functions	Immediately, within 15 minutes	Ambulance
U2 – Emergent	Vital functions in danger or organ damage	As soon as possible, within 1 hour	Home visit by GP or appointment at OHS-PC
U3 – Urgent	Possible risk of damage, human reasons	A few hours (<3 hours)	Home visit by GP or appointment at OHS-PC
U4 – Non-urgent	Marginal risk of damage	24 hours	Appointment at OHS-PC or telephone advice
U5 – Advice	No risk of damage	Advice, no time related	Telephone advice

GP: general practitioner

NTS: Netherlands Triage Standard

OHS-PC: out-of-hours services in primary care

Appendix-table 2: Combinations of NTS triage criteria that generate an U1 level within the NTS main complaints that can be used for patients with chest discomfort.

→ ABCD unstable (no main complaint is selected)			**Urgency level U1: ambulance within 15 minutes**
Main complaint 'Chest pain'			
→ ABCD stable	AND severe chest pain (Numeric Rating Scale (NRS)-score ≥ 8) lasting less than 12 hours		
→ ABCD stable	AND mild (NRS ≤ 4) to moderate (NRS 5-7) chest pain lasting for less than 12 hours	AND one of the following: - retrosternal located pain - tightening or pressing - radiation to jaw, arm or upper back - progressive pain intensity in short time - past or present autonomous nervous system-related symptoms - dizziness	
Main complaint 'Collapse'			
→ ABCD stable	AND collapse	AND chest pain of any severity	
Main complaint 'Back complaints'			
→ ABCD stable	AND severe upper back pain (NRS ≥8)	AND past or present autonomous nervous system-related symptoms	

ABCD: acronym for Airway, Breathing, Circulation and Disability. When the triage nurse starts the telephone triage with the NTS, the system requires a mandatory 'ABCD-check'; i.e. the triage nurse has to ask questions to assess whether the patient has life-threatening problems concerning the Airway, Breathing, Circulation and Disability for which an ambulance should be sent immediately.

Appendix-table 3. Characteristics of patients divided among the seven OHS-PC locations.

Characteristics	Location A N=205 (9.4%)	Location B N=355 (16.2%)	Location C N=544 (24.8%)	Location D N=262 (12.0%)	Location E N=164 (7.5%)	Location F N=412 (18.8%)	Location G N=250 (11.4%)
Prevalence of ACS (n,%)	32 (15.4%)	31 (8.7%)	59 (10.8%)	35 (13.4%)	15 (9.1%)	53 (12.9%)	26 (10.4%)
Male sex (n,%)	77 (37.6%)	154 (43.4%)	256 (47.1%)	108 (41.2%)	84 (51.2%)	188 (45.6%)	112 (44.8%)
Mean age in years (SD)	62.3 (19.6)	58.6 (19.8)	58.0 (19.4)	56.6 (18.9)	61.8 (20.5)	61.6 (19.4)	56.1 (18.7)

Appendix – table 4. Overview of the percentages of missing predictors, divided into patients with and without the diagnosis ACS.

Characteristics N=2192	ACS, n=251 (11.5%) Missing (%)	No ACS, n=1941 (88.5%) Missing (%)
Mean in years age (SD)	0	0
Female sex	0	0
Median call duration in min (IQR)	0	0
Mean patient's introduction in min (IQR)	0	0
Triage nurse consulted the GP	0	0
Someone else called on behalf of patient	0	0
The person who calls expressed concerns	144 (57.3)	943 (48.6)
Cardiovascular disease or risk factor combined	30 (12.0)	318 (16.4)
History of coronary artery disease	107 (42.6)	933 (48.1)
Diabetes	162 (64.5)	1126 (58.0)
Hypertension	172 (68.5)	1126 (58.0)
Hypercholesterolemia/statin use	172 (68.5)	1196 (61.6)
Cardiac arrhythmia	176 (70.1)	1110 (57.2)
Chest pain	4 (1.6)	72 (3.7)

Shortness of breath	68 (27.1)	429 (22.1)
Chest pain duration <12 hours	28 (11.2)	242 (13.1)
Pain intensity severe (NRS >7 in range 1-10)	149 (59.4)	1124 (57.9)
Pressing heavy pain*	63 (25.1)	502 (25.9)
Stabbing chest pain*	63 (25.1)	502 (25.9)
Chest pain located retrosternal**	87 (34.7)	538 (27.7)
Chest pain located left or right on thorax**	87 (34.7)	538 (27.7)
Radiation of chest pain to any location	38 (15.1)	476 (24.5)
Radiation to the arm ***	94 (37.5)	1019 (52.5)
Radiation to the shoulder blades ***	94 (37.5)	1019 (52.5)
Radiation to the jaws ***	94 (37.5)	1019 (52.5)
Sweating	79 (31.5)	747 (38.5)
Nausea or vomiting	133 (53.0)	1071 (55.2)
Pallor or ashen skin	158 (62.9)	1361 (70.1)
(Near) fainting	33 (13.1)	217 (11.2)
Palpitations	225 (89.6)	1615 (83.2)
Patient recognizes symptoms from previous cardiac event	139 (55.4)	1137 (58.6)

*Pain described by patient. Pressing heavy pain: pressing, heavy or tightening pain vs. other types of pain (stabbing, burning, cramping, tearing) Stabbing pain: stabbing vs. other types of pain (pressing, heavy, tightening, burning, cramping)

** Retrosternal location vs. other pain locations. Left or right side thorax vs. other pain locations

*** Radiation location vs. no radiation and radiation other pain

Appendix-table 5. Patient and call characteristics of 3,204 patients with chest discomfort calling OHS-PC between 2014-2017, comparing patients with and without information on the study outcome.

Characteristics N=3,204	Follow-up n= 2192 (68.4%)	No follow-up n= 1012 (31.6%)	P-value
Patient characteristics			
Median age in years (IQR) (n=3,204)	59.1 (19.5)	57.3 (20.4)	0.020
Female sex (n=3,204)	1213 (55.3)	565 (55.8)	0.794
Call characteristics			
Median total call duration in min (IQR) (n=3,204)	6:51 (4:59-9:23)	6:56 (5:04-9:15)	0.836
Mean patient's introduction in min (IQR) (n=3,204)	0:17 (0:11-0:25)	0:17 (0:11-0:26)	0.052
Triage nurse consulted the GP (n=3,204)	1147 (52.3)	519 (51.3)	0.583
Someone else called on behalf of patient (n=3,204)	1114 (50.8)	479 (47.3)	0.066
Person who calls expressed concerns (n=1,478)	988 (89.7)	430 (90.1)	0.804
Medical history and risk factors			
Cardiovascular disease or CV risk factor (n=2,672)	1192 (64.6)	515 (62.3)	0.254
History of coronary artery disease (n=1,663)	389 (33.8)	166 (32.4)	0.573
Diabetes (n=1,283)	180 (19.9)	68 (18.0)	0.432
Hypertension (n=1,274)	323 (36.1)	121 (31.9)	0.150
Hypercholesterolemia/statin use (n=1,176)	212 (25.7)	88 (25.1)	0.842
Cardiac arrhythmia (n=1,326)	230 (25.4)	102 (24.3)	0.684
Symptoms			
Chest pain (n=3,079)	1981 (93.6)	894 (92.8)	0.417
Shortness of breath (n=2,505)	1094 (64.5)	520 (64.3)	0.911
Chest pain duration <12 hours (n=2,793)	1403 (73.2)	610 (69.6)	0.052
Severe pain (NRS >7 in range 1-10) (n=1,351)	337 (36.6)	185 (43.0)	0.024
Pressing, heavy pain* (n=2,347)	1023 (62.9)	444 (61.6)	0.538
Stabbing chest pain* (n=2,349)	366 (22.5)	177 (24.5)	0.280
Chest pain located retrosternal** (n=2,298)	641 (40.9)	294 (40.2)	0.736
Chest pain located left or right on thorax** (n=2,299)	627 (40.0)	294 (40.2)	0.945
Radiation of chest pain to any location (n=2,437)	1077 (64.3)	458 (60.1)	0.047
Radiation to the arm ***(n=1,521)	452 (42.2)	179 (39.8)	0.373

Radiation to the shoulder blades *** (n=1,519)	326 (30.5)	136 (30.2)	0.924
Radiation to the jaws *** (n=1,984)	124 (11.6)	41 (9.1)	0.156
Sweating (n=1,758)	559 (40.9)	259 (42.0)	0.638
Nausea or vomiting (n=1,474)	489 (49.5)	229 (47.1)	0.381
Pallor or ashen skin (n=1,007)	322 (47.8)	136 (40.8)	0.038
(Near) fainting (n=2,855)	143 (7.4)	72 (7.8)	0.678
Palpitations (n=501)	284 (80.7)	125 (83.9)	0.396
Patient recognizes symptoms from previous cardiac event (n=1,298)	250 (27.3)	102 (26.7)	0.819
Urgency allocation			
High urgency (U1 or U2) (n=3,204)	1496 (68.2)	661 (65.3)	0.100
U1	974 (44.5)	390 (38.6)	
U2	522 (23.8)	271 (26.8)	
Low urgency (U3 or U4 or U5)	696 (31.8)	351 (34.7)	

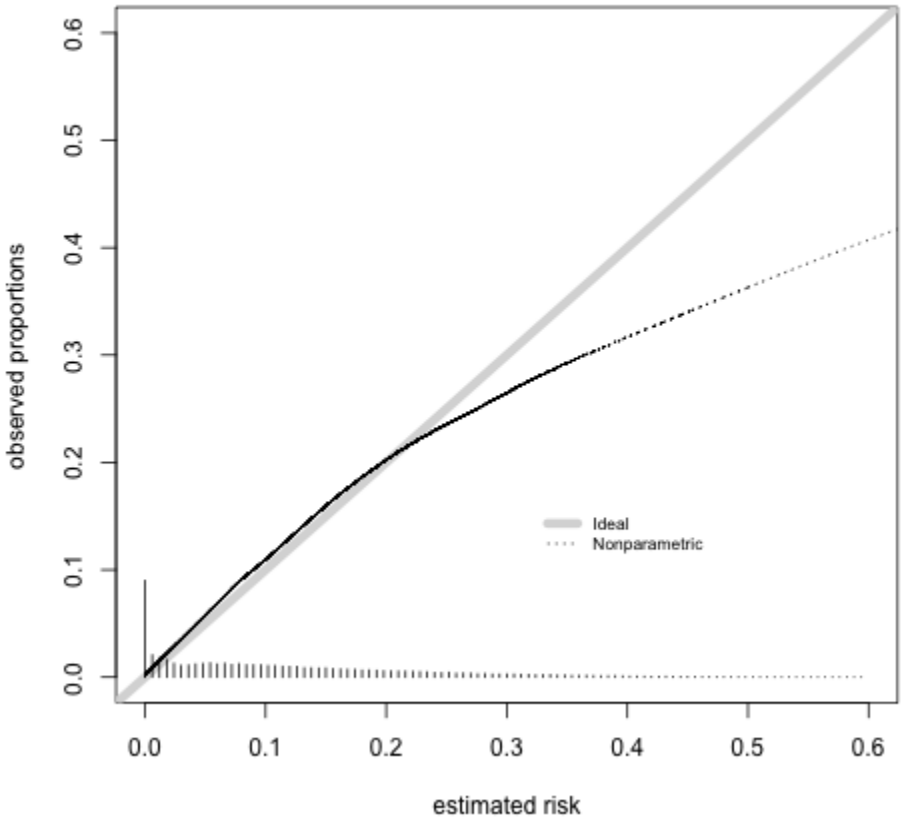
Appendix - Table 6. Base model with age and sex for predicting the diagnosis ACS.

Predictors	Regression coefficients (standard error)
Intercept	- 14.671 (3.442)
Age	0.289 (0.079)
Age’	- 0.379 (0.123)
Age’’	1.017 (0.386)
Female sex	2.155 (5.385)
Age * Female sex	- 0.084 (0.123)
Age’ * Female sex	0.175 (0.190)
Age’’ * Female sex	- 0.532 (0.589)
Apparent c-statistic 0.72 (95% CI 0.70-0.75)	
Adjusted c-statistic 0.72 (95% CI 0.68-0.75)	
Calibration slope 0.977 (95% CI 0.617-1.338)	
Calibration 0.016 (95% CI-0.702-0.734)	
R^2 0.065	
Knots for cubic spline functions placed at 5, 35, 65 and 95	

Appendix - Table 7. Full model including all candidate predictors for predicting the diagnosis ACS

Predictors	Regression coefficients (standard error)
Intercept	-15.914 (3.55)
Age	0.288 (0.081)
Age’	-0.388 (0.126)
Age’’	1.058 (0.396)
Female gender	2.459 (5.519)
Age * Female sex	-0.094 (0.126)
Age‘ * Female sex	0.187 (0.195)
Age’’ * Female sex	-0.554 (0.606)
Chest pain	-0.064 (0.365)
Acute chest pain (< 12 hours)	0.258 (0.200)
Shortness of breath	-0.141 (0.200)
Sweating	0.459 (0.183)
Retrosternal located pain	0.178 (0.177)
Radiation of chest pain	0.617 (0.180)
Pressing heavy feeling	0.619 (0.272)
Stabbing pain	-0.200 (0.353)
History of cardiovascular disease*	-0.039 (0.247)
History of coronary artery disease	0.108 (0.234)
Someone else calls instead of the patient	0.197 (0.160)
Patient calls during the night (0am-9am)	0.495 (0.152)
Apparent c-statistic 0.79 (95% CI 0.76-0.81)	
Adjusted c-statistic 0.77 (95% CI 0.74-0.80)	
Calibration slope 0.818 (95% CI 0.650-0.986)	
Calibration -0.238 (-0.621-0.145)	
R^2 0.107	
Knots for cubic spline functions placed at 5, 35, 65 and 95	

Appendix – Figure 1. Callibration of full model with internal external validation



TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4,5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	5,6
	5c	D;V	Give details of treatments received, if relevant.	n.a.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n.a.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	n.a.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7, suppl
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8,9,10
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	suppl
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	8
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	11,12
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	12, suppl
	15b	D	Explain how to the use the prediction model.	13
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12, 13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	12,13
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14, 15
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	17
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study

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Secondary Subject Heading:	Emergency medicine, Cardiovascular medicine
Keywords:	PRIMARY CARE, Myocardial infarction < CARDIOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

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Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study

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Abstract

Objective To develop and validate a symptom-based prediction rule for early recognition of acute coronary syndrome (ACS) in patients with acute chest discomfort who call out-of-hours services for primary care (OHS-PC).

Design Cross-sectional study. A diagnostic prediction rule was developed with multivariable regression analyses. All models were validated with internal-external cross validation within seven OHS-PC locations. Both age and sex were analysed as statistical interaction terms, applying for age non-linear effects.

Setting Seven OHS-PC in the Netherlands.

Participants 2,192 patients who called OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort) between 2014 and 2017. Backed up recordings of telephone triage conversations were analysed.

Primary and secondary outcomes measures Diagnosis of ACS retrieved from the patient's medical records in general practice, including hospital specialists discharge letters. Performance of the prediction rules was calculated with the c-statistic and the final model was chosen based on net benefit analyses.

Results Among the 2,192 patients who called the OHS-PC with acute chest discomfort, 8.3% females and 15.3% males had an ACS. The final diagnostic model included seven predictors (sex, age, acute onset of chest pain lasting less than 12 hours, a pressing/heavy character of the pain, radiation of the pain, sweating, and calling at night). It had an adjusted c-statistic of 0.77 (95% CI 0.74-0.79) with good calibration.

Conclusion The final prediction model for ACS has good discrimination and calibration and shows promise for replacing the existing telephone triage rules for patients with acute chest discomfort in general practice and OHS-PC.

Trial registration NTR7331

Key words: prediction rules, acute coronary syndrome, sex, symptoms, general practice, out-of-hours primary care

Strengths and limitations of this study

- We could analyse the original and very first telephone conversation of patients with acute chest discomfort.
- The developed prediction model can be well generalized to other OHS-PC locations in the Netherlands, but also to similar OHS-PC settings in other countries or even emergency medical service settings.
- A limitation is that a full external validation of the model in another OHS-PC was impossible because no other cohort similar to ours was available.
- Another limitation is that the effects of the predictors were assumed to be similar for males and females while this is not exactly the case, but by incorporating a differential non-linear effect of age and interaction with sex in the analyses this effect is minimalized.

Introduction

Chest discomfort is among the top five reasons for telephone contact in out-of-hours services for primary care (OHS-PC) and concerns 5% of all cases at the emergency department (ED) in the USA. [1] In the Netherlands, around 80% of patients with chest discomfort first call the general practitioner (GP) or OHS-PC, while 20% directly calls the emergency medical service (EMS, or ambulance dispatch centre) or are self-referrals to the ED. [2] Adequate triage and early diagnosis in these patients is vital, because in case of an underlying acute coronary syndrome (ACS) early effective therapeutic interventions ('time is muscle') improve the patient's outcome and prognosis. [3] For the diagnosis of ACS, a 12-lead electrocardiogram (ECG) and troponin testing is needed. [3] However, before the patient is referred to an ED where these diagnostic tests can be done, patient selection is necessary based on symptom presentation retrieved by telephone triage. [4 5] Symptom-based differentiation of ACS from other causes of chest discomfort is notoriously difficult. [6] Symptom-based prediction rules for diagnosing ACS in general practice and other prehospital settings are -although highly needed- scarce. [7-9] The efficiency and safety of telephone triage in OHS-PC was poor in a population with a prior chance of ACS of 8.3% in females and 15.3% in males; almost 50% of the males and females with chest discomfort received a high priority ambulance, while 11% diagnosed with an ACS did not received a high urgency (i.e., was seen within one hour). [10]

Most prediction rules for diagnosing ACS were developed in the ED setting and include results from ECG and troponin testing. [11] Such prediction rules cannot be straightforward implemented for telephone triage in general practice because (i) in the latter setting these diagnostic tests are not available, (ii) the prior chance of ACS is rather low, and (iii) on average disease severity is less than in those seen in the ED. [12 13] The prevalence of ACS among patients with chest discomfort who call OHS-PC or EMS is about 10-15%, and among those seen at the ED between 10 to 30%. [10 11 13 14] Only one prediction rule was developed in primary care for diagnosing ACS; the modified Grijseels prediction rule, which had moderate discriminative ability (c-statistic of 0.66) after external validation. [7 8] Five other primary care prediction rules were developed to predict CAD; e.g. the Marburg Heart Score (MHS) and INTERCHEST prediction rule (International Working Group on Chest Pain in Primary Care). [9] In these studies both patients with acute and non-acute chest discomfort were included and the prevalence of stable CAD showed to be 10.9% to 12.6%, while that of ACS was only 1.5% to 2.5%. [9] Thus, these prediction rules have limited applicability for specifically diagnosing ACS.

In most OHS-PC and about half of the EMS in the Netherlands, triage nurses use the semi-automatic 'Netherlands Triage Standard' (NTS) as a decision support tool to classify the urgency of the patient's condition. Triage nurses have to choose one out of 56 'main complaints' and based on answers linked to the triage criteria, the NTS automatically proposes one out of six levels of urgency, that is, a certain time frame in which patients should be seen (U0-U5, appendix- table 1). The NTS is a modified and shortened version of the Manchester Triage Standard which was developed in the ED setting. [15] Although the NTS was explicitly developed for telephone triage, it has not yet been validated against clinical outcomes even though it is already implemented on large scale. Recent research showed that the NTS had a poor sensitivity of 0.73 (95% CI 0.68-0.78) for telephone triage of patients with acute chest discomfort. The NTS recommended a low urgency (U3, U4 or U5) to 27% of patients who eventually showed to have an ACS or other life threatening event (LTE). [10] The NTS' specificity was also poor with 0.43 (95% CI 0.40-0.45); the NTS recommended a high urgency to 57% of the patients who eventually showed not to have an ACS or LTE. Given this poor safety and efficiency of the NTS, there is an urgent need for a better prediction model for patients with acute chest discomfort calling OHS-PC. In addition, there is a need for exploring sex-specificity of such a prediction rule as there is an ongoing debate on whether females differ from males in reporting symptoms of ACS. [16 17]

The aim of this study was to develop, and internal-external cross validate a symptom-based prediction rule for diagnosing ACS which is considerate to sex categories in male and female patients who call the OHS-PC for acute chest discomfort.

Methods

We performed a cross-sectional study among 2,192 patients who called one out of seven participating OHS-PC in the Netherlands because of acute chest discomfort (pain, pressure, tightness, or discomfort) during the period 2014 to 2017. [18] These OHS-PC serve a total population of 1.5 million people and cover around 300,000 calls a year. We first selected calls based on of the International Code for Primary Care (ICPC; a WHO world-wide code system for primary care) with ICPC-codes K01, K02, K03, K24, K74, K75, K76, K77, K93, L04, P74, R02, R98 and calls with keywords thoracic pain, chest pain, myocardial infarction, heart attack and their common abbreviations (Figure 1). We included a broad variety of symptoms to capture the entire domain of patients that could be suspected of ACS. We listed all available calls of these patients and assigned random numbers with the Random Number Generator (RAND) function in Microsoft Excel to retrieve a random sample. Calls were excluded before re-listening

when the patients' age was below 18 years or when the patient did not live in the surrounding area of the OHS-PC (in which case we could not retrieve the final diagnosis from the patient's own general practitioner). Calls were excluded during re-listening when it did not concern a triage call (e.g. inter-collegial consultation) or when the recording was of poor quality (Figure 1).

Candidate predictors

Research team members (LW, DE) and medical students listened to the call recordings, blinded for the outcome, to collect data about symptoms, medical history and urgency allocation. Patient (age, sex) and call characteristics (call time, call duration) were collected from the OHS-PC electronic medical files of the patients. As candidate predictors we included age and sex, the NTS triage criteria (see appendix-table 2), the ACS predictors from the modified Grijseels prediction model (male sex, radiation, nausea, sweating and history of CAD), the 'CAD predictors' from MHS and INTERCHEST prediction models (age, pain feels like pressure, CAD history or CV risk factors, patient assumes cardiac origin of pain), and - based on a recent own study in OHS-PC- the predictor 'calling at night between 0am and 9am'. [7-9 19]

Outcome

The primary outcome was the diagnosis ACS. The final diagnoses were retrieved from the patient's GP and based on the GP's electronic medical files which include ED and cardiologist discharge letters and notes from the OHS-PC contact. The diagnosis ACS was nearly always made by a cardiologist (96.0%) and included information on levels of (high-sensitivity) troponin and electrocardiographic results. We used medical information up to 30-days following the contact with the OHS-PC to allow us to include diagnoses of ACS that were initially missed because the patient was not referred to the cardiologist the same day of the OHS-PC contact. However, in none of the patients in the study we had evidence of a missed diagnosis of ACS.

Sample size calculation

We relied on the minimal sample size criteria for prediction model development proposed by Riley et al, using the 'pmsampsize' package in R. [20] Based on an ACS prevalence of overall 11% and an Cox-Snell R-squared of 0.075 (a conservative value based on a model with age and sex) and a total number of 2,192 observations we were allowed to assess 19 candidate predictors. [21] Based on sample size calculations we concluded that development of separate models for males and females would require a significantly larger sample, therefore we analysed sex as a statistical interaction term. [20]

Statistical analyses

We developed three diagnostic models using multivariable logistic regression analysis. First, we developed a base model with only age and sex as predictors, where age was modelled using a restricted cubic spline function (4 knots) and an interaction with sex. This resulted in a base model with 7 predictor parameters (excluding the intercept). Second, we fitted a full model with an additional 12 pre-selected binary predictors (having chest pain, acute chest pain shorter than 12 hours, shortness of breath, sweating, retrosternal located chest pain, radiation, pressing heavy pain, stabbing pain, history of CVD, history of CAD, someone else calling, calling at night). Thirdly, we applied backward elimination, with a cut-off p-value < 0.20 for including predictors (a higher cut-off value to lower the chances of overfitting). [21]

We applied internal-external cross validation (IECV) for model validation using the seven different OHS-PC locations (Appendix-Table 3 for patient characteristics of different OHS-PC locations). [22] We evaluated the IECV performance in terms of the area under the ROC curve (c-statistic), the calibration slope and calibration in the large. The IECV estimates of performance were combined by using random-effect model (DerSimonian-Laird estimator). Based on the IECV we also constructed flexible calibration curves and decision curves. In the decision curve analyses we compared the final model with the currently used NTS triage model in OHS-PC in the Netherlands. [23] Finally, we created an illustrative table of diagnostic test accuracy for various model-based risk thresholds of the final model, following the example in Wynants et al. [23] IECV estimates for risk threshold specific sensitivity and specificity, and we applied a bivariate model commonly used for diagnostic test accuracy meta-analysis. [24]

Missing data

For missing data we carried out multiple imputation using the Multivariate Imputation via Chained Equation (MICE) package in R, with 30 imputation rounds and 30 iterations. [25] We pooled the results following Rubin's rules. [26] Predictors with over 50% missing were excluded from consideration in the models (Appendix-table 4 for details about the missing data). Characteristics were compared between patients with and without information on the medical outcome - because some GPs refused diagnosis retrieval from their files - to allow for assessment of differences in characteristics between these patient groups (Appendix-table 5). There were no clinically meaningful differences in symptoms and patient or call characteristics between the 2,192 patients with information on the outcome, and the 1,012 patients

about whom knowledge of the medical outcome related to the OHS-PC contact because of acute chest discomfort was missing.

All analyses were done in R version 4.0.3. (2020-10-10) with the Regression Modelling Strategies ('rms') package in R. [27] We reported our study in accordance to the Transparent Reporting of a multivariable prediction rules for Individual Prognosis Or Diagnosis (TRIPOD) criteria (Supplementary file). [28]

Patient and Public Involvement

No patients were involved in defining the research question or the outcome measures. Neither they were involved in developing plans for design. However, they participated in the discussion on implications and the implementation strategy. In addition, they were asked to advise on interpretation and writing up of the results. Results will be shared and discussed in more detail with representatives of the Dutch national patient community of cardiovascular diseases ('Harteraad').

Results

Among the 2,192 callers with acute chest discomfort (mean age 59.1 (SD 19.5) years and 55.3% females) 251 (11.5%) had a final diagnosis of ACS; 101 (8.3%) females and 150 (15.3%) males (Table 1). Patients with ACS were older than those without (mean age 69.7 (SD 13.4) vs. 57.7 (SD 19.8) years) and females with ACS were on average older than men with ACS (73.8 (SD 13.5) years vs. 67.0 (SD 12.6) years).

Table 1. Characteristics of 2,192 patients who called OHS PC with acute chest discomfort between 2014-2017, divided between females and males with and without ACS.

Characteristics	**1,213 females (55.3%)**		**979 males (44.7%)**	
	ACS n=101 (8.3%)	**No ACS n=1,112 (91.7%)**	**ACS n=150 (15.3%)**	**No ACS n= 829 (84.7%)**
Patient characteristics				
Mean age in years (SD) (n=2,192)	73.8 (13.5)	58.0 (20.2)	67.0 (12.6)	57.2 (19.2)
Call characteristics				
Median call duration in min (IQR) (n=2,192)	5:27 (3:57-8:24)	6:59 (5:06-9:47)	6:04 (4:03-8:17)	6:56 (5:10-9:23)
Mean introduction time in min (IQR) (n=2,192)	0:13 (0:09-0:18)	0:17 (0:11-0:26)	0:14 (0:09-0:21)	0:17 (0:11-0:25)
Call during the night (0am-9am) (n=2,192)	34 (33.7)	304 (27.3)	62 (41.3)	188 (22.7)

Triage nurse consulted the GP (n=2,192)	43 (42.6)	580 (52.2)	75 (50.0)	449 (54.2)
Someone else called on behalf of patient (n=2,192)	69 (68.3)	515 (46.3)	98 (65.3)	432 (52.1)
The person who calls expressed concerns (n=988)	42 (95.5)	507 (90.5)	61 (96.8)	378 (87.1)
Medical history and risk factors				
Cardiovascular disease or CV risk factors (n=1,844)	70 (81.4)	552 (61.1)	106 (78.5)	464 (64.4)
History of coronary artery disease (n=1,151)	23 (47.9)	131 (24.2)	54 (56.3)	181 (38.8)
Diabetes (n=893)	14 (42.4)	66 (14.3)	22 (39.3)	78 (22.0)
Hypertension (n=894)	26 (72.2)	162 (34.0)	22 (51.2)	113 (33.3)
Hypercholesterolemia/statin use (n=826)	10 (40.0)	96 (22.6)	27 (50.0)	79 (24.5)
Cardiac arrhythmia (n=905)	4 (14.8)	125 (26.2)	12 (25.0)	89 (25.2)
Symptoms				
Chest pain (n=2,116)	95 (96.9)	1007 (94.1)	139 (93.3)	758 (94.9)
Shortness of breath (n=1,696)	57 (71.3)	559 (65.4)	63 (61.2)	415 (63.1)
Chest pain duration <12 hours (n=1,910)	74 (86.0)	703 (72.3)	113 (82.5)	510 (71.3)
Severe pain (NRS >7, range 1-10) (n=917)	19 (61.3)	184 (39.6)	18 (25.4)	116 (33.0)
Pressing/heavy chest pain* (n=1,625)	58 (81.7)	525 (62.5)	95 (81.2)	345 (57.7)
Stabbing chest pain* (n=1,625)	8 (11.3)	190 (22.6)	9 (7.7)	159 (26.6)
Retrosternal chest pain ** (n=1,565)	36 (54.5)	326 (40.0)	52 (53.1)	227 (38.7)
Chest pain left or right of thorax** (n=1,566)	19 (28.8)	318 (39.0)	28 (28.6)	262 (44.6)
Radiation of chest pain to any location (n=1,678)	74 (86.0)	575 (67.8)	83 (65.4)	347 (56.2)
Radiation to the arm *** (n=1,677)	37 (43.0)	218 (25.7)	54 (42.5)	143 (23.2)
Radiation to the shoulder blades *** (n=1,678)	14 (16.3)	190 (22.4)	19 (15.0)	103 (16.7)
Radiation to the jaws *** (n=1,678)	10 (11.6)	77 (9.1)	4 (3.1)	33 (5.3)
Sweating (n=1,366)	36 (52.9)	279 (42.0)	54 (51.9)	190 (35.8)
Nausea or vomiting (n=987)	24 (52.2)	295 (56.6)	31 (43.1)	139 (39.9)
Pallor or ashen skin (n=673)	22 (59.5)	139 (44.3)	36 (64.3)	125 (46.8)
(Near) fainting (n=1,951)	8 (9.5)	76 (7.7)	9 (6.7)	50 (6.7)
Palpitations (n=162)	10 (100.0)	183 (84.7)	8 (50.0)	83 (75.5)
Patient recognizes symptoms from previous cardiac event (n=915)	17 (35.4)	100 (22.0)	30 (46.9)	103 (29.5)
Urgency allocation				

High urgency (U1 or U2) (n=2,192)	89 (88.1)	740 (66.5)	133 (88.7)	534 (64.4)
U1	75 (74.3)	443 (39.8)	106 (70.7)	350 (42.2)
U2	14 (13.9)	297 (26.7)	27 (18.0)	184 (22.2)
Low urgency (U3 or U4 or U5)	12 (11.9)	372 (33.5)	17 (11.3)	295 (35.6)

*Pain described by patient. Pressing heavy pain: pressing, heavy or tightening pain vs. other types of pain (stabbing, burning, cramping, tearing) Stabbing pain: stabbing vs. other types of pain (pressing, heavy, tightening, burning, cramping)

** Retrosternal location vs. other pain locations. Left or right side of the thorax vs. other pain locations

*** Radiation location vs. no radiation and radiation other pain

Over two thirds of all callers (68.3%) received a high urgency allocation (seen within one hour; U1 or U2) and among the 251 patients who showed to have an ACS, 88.4% received a high urgency allocation. Calls of patients who had an ACS were shorter than calls in those without ACS (median call duration 6:34 (SD 3:38) vs. 7:42 (SD 3:48) minutes).

Medical history and symptoms

Females and males with ACS had more often a history with CVD or CV risk factors than those without (females with ACS 81.4% vs. females without ACS 61.1%, males with ACS 78.5% vs. males without ACS 64.4%) (Table 1). The majority of both females and males had chest pain (94.5%) and this was similar among those with and without ACS. Overall, presented symptoms among males and females calling the OHS-PC for chest discomfort were quite similar. Symptoms associated with ACS in both sexes were pressing/heavy chest pain (females with ACS 81.7% vs. females without ACS 62.5%, males 81.2% vs. 57.7% respectively), retrosternal located chest pain (females 54.5% vs. 40.0%, males 53.1% vs. 38.7%), radiation of pain (females 86.0% vs 67.8%, males 65.4% vs 56.2%), and sweating (females 52.9% vs. 42.0%, males 51.9% vs. 35.8%).

Diagnoses

In total 251 patients were diagnosed with ACS and 65 with other LTEs, and of clinical relevance is that both critical events occurred significantly more in males than females (15.3% vs. 8.3%, p<0.001 for ACS, and 3.8% vs. 2.3%, p=0.04 for other LTEs, respectively). Of the 101 females with ACS, 22.8% had a ST-segment elevation myocardial infarction (STEMI), 46.5% a non ST-segment elevation myocardial infarction (NSTEMI), 19.8% unstable angina pectoris (UAP), and 10.9% non-classified ACS. In 150 males with ACS, 33.3% had a STEMI, 36.7% a NSTEMI, 26.0% UAP, and 4.0% non-classified ACS (Table 2).

Table 2. Diagnoses of 2,192 males and females who contacted the OHS-PC for acute chest discomfort between 2014-2017, by sex.

Diagnosis, n (%)	Females n= 1213	Males n= 979	p-value
Acute coronary syndrome*	101 (8.3)	150 (15.3)	<0.001
STEMI	23 (22.8)	50 (33.3)	0.071
NSTEMI	47 (46.5)	55 (36.7)	0.119
UAP	20 (19.8)	39 (26.0)	0.256
Non-classified ACS	11 (10.9)	6 (4.0)	0.033
Life threatening events (LTEs)	28 (2.3)	37 (3.8)	0.043
Pulmonary embolism	8 (28.6)	10 (27.0)	0.890
Acute abdominal aneurysm	2 (7.1)	3 (8.1)	0.885
Thoracic aortic dissection	1 (3.6)	4 (10.8)	0.278
Other**	17 (60.7)	20 (54.1)	0.591
Non-urgent cardiovascular diseases***	223 (18.4)	191 (19.5)	0.069
Musculoskeletal pain	245 (20.2)	148 (15.2)	0.039
Non-cardiac chest pain, not further specified ******	191 (15.7)	179 (18.3)	0.012
Psychogenic disorders	165 (13.6)	85 (8.7)	0.005
Gastrointestinal tract disorders	89 (7.3)	68 (6.9)	0.776
Respiratory tract disorders	61 (5.0)	56 (5.7)	0.203
Other non-urgent diagnoses*******	110 (9.1)	65 (6.6)	0.152

* Almost all patients (96.0%) were diagnosed by a cardiologist. Ten (4.0%) ACS patients were not diagnosed by a cardiologist; four died before arrival of the ambulance, one patient died after resuscitation at the ED (all these five were classified as acute cardiac death due to ACS), and in five patients the ACS diagnosis was solely based on the GP's interpretation in patients who were not referred to the hospital after shared decision because of a short life expectancy due to cancer in a palliative stage.

** Stroke, severe COPD exacerbation, acute severe heart failure, sepsis, hypokalaemia, diabetic ketoacidosis, epileptic insult, bleeding from oesophageal varices, ovarian torsion, ventricular fibrillation.

*** Stable angina pectoris (including atypical chest pain), stable heart failure, arrhythmias, hypertension

**** Cardiac pathology unlikely after cardiologist's or GP's diagnostic work-up, but without differential diagnosis

***** Amongst others: anaemia, carcinoma, vasovagal collapse, side effects medication, dermatological diseases (e.g. herpes Zoster infection)

Twenty-eight (2.3%) females and 37 males (3.8%) had another life-threatening event than ACS (e.g. pulmonary embolism, thoracic aortic dissection, acute abdominal aneurysm). All other patients (85.6%) had non-urgent medical conditions such as non-urgent cardiovascular disease (18.9%), musculoskeletal pain (17.9%), non-cardiac chest pain (not further specified) (16.9%), psychogenic disorder (11.4%), gastrointestinal disorders (7.2%), respiratory disorders (5.3%), and other non-urgent diagnoses (8.0%).

Model development, performance and validation

The base model with sex and age had an apparent c-statistic of 0.72 (95% CI 0.70-0.75), and an internal-external validation based c-statistic of 0.72 (95% 0.68-0.75) (Appendix- Table 6). The basic model shows that the risk of ACS increases with age for both sexes, with a notable peak risk for men at an age near 60 years and a more gradual increase in risk of ACS for women (Figure 2). The full model including all candidate predictors had an apparent c-statistic of 0.79 (95% CI 0.76-0.81) and an internal-external validation based c-statistic of 0.77 (95% CI 0.74-0.80) (Appendix - Table 7). The full model had optimal calibration (flexible line close to the 45-degree reference line) up to a predicted probability of ACS of approximately 0.2 (Appendix-Figure 1). Risks higher than 0.2 tended to be overestimated by the model, however since any plausible risk threshold will be lower than 0.2 in the primary care setting, we find the calibration in the relevant range to be satisfactory. After backward elimination, the backward model had an apparent c-statistic of 0.79 (95% CI 0.76-0.81), and the internal-external validation c-statistic was 0.77 (95% CI 0.74-0.79). It had very similar calibration to the full model (Table 3, Figure 3).

Table 3. Final model for predicting the diagnosis ACS.

Predictors	**Regression coefficients (standard error)**
Intercept	-16.246 (3.527)
Age	0.293 (0.081)
Age’	-0.391 (0.125)
Age’’	1.063 (0.395)
Female gender	2.504 (5.512)
Age * female gender	-0.096 (0.126)

Age' * female gender	0.189 (0.195)
Age'' * female gender	-0.556 (0.605)
Acute chest pain shorter than 12 hours	0.290 (0.198)
Sweating	0.457 (0.178)
Radiation of chest pain	0.609 (0.176)
Pressing heavy pain	0.747 (0.200)
Call during the night (0am-9am)	0.504 (0.151)
Apparent c-statistic 0.79 (95% CI 0.76-0.81) Adjusted c-statistic 0.77 (95% CI 0.74-0.79) Calibration slope 0.826 (95% CI 0.658-0.994) Calibration -0.224 (95% CI -0.604-0.157) R^2 0.106 Knots for cubic spline functions placed at 5, 35, 65 and 95	

Decision curve analyses and risk thresholds

Both the full and backward model showed a high net benefit as compared to the currently used NTS model for telephone triage in OHS-PC (Figure 4). There was no difference in net benefit between the full model and backward model across plausible risk thresholds. Based on this analysis we decided to choose the backward as the final triage tool model because; 1) with fewer predictors the prediction of ACS remained similar accurate and 2) no valuable time is lost during telephone triage by asking the patient about symptoms that do not contribute to a better prediction. The final model included besides age and sex, the five following predictors; (i) acute onset of chest pain lasting <12 hours, (ii) a pressing/heavy character, (iii) radiation of pain, (iv) sweating, (v) calling at night between 0.00 and 9.00am. Finally, we evaluated the diagnostic performance of the final prediction model across risk thresholds that may be chosen to apply in clinical practice (Table 4, Figure 5).

Table 4. Diagnostic accuracy for a range of risk thresholds of the final model

Risk threshold	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
0.001	0.98 (0.95-0.99)	0.21 (0.18-0.24)	0.14	0.99
0.010	0.98 (0.95-0.99)	0.42 (0.40-0.45)	0.18	0.99
0.020	0.97 (0.94-0.99)	0.50 (0.47-0.54)	0.20	0.99
0.050	0.93 (0.87-0.96)	0.63 (0.59-0.67)	0.25	0.99
0.075	0.88 (0.81-0.92)	0.72 (0.68-0.76)	0.29	0.98
0.100	0.81 (0.7-30.87)	0.79 (0.76-0.82)	0.33	0.97
0.115 (prevalence)	0.76 (0.67-0.83)	0.82 (0.79-0.85)	0.36	0.96
0.150	0.64 (0.56-0.73)	0.88 (0.85-0.90)	0.41	0.95
0.200	0.46 (0.38-0.55)	0.93 (0.91-0.94)	0.46	0.93

Discussion

This is the first study that developed and internal-external validated a symptom-based prediction rule for telephone triage of ACS in male and female patients who contact OHS-PC for acute chest discomfort (pain, pressure, tightness, or discomfort). ACS was present in 8.3% of the females and 15.3% of the males. The prediction rule is applicable for triage in the OHS-PC setting and consists of sex and age as statistical interaction terms, and five other symptom-based predictors. It had a good discriminative ability (adjusted c-statistic 0.77 (95% CI 0.74-0.79)) and was well calibrated up to an ACS risk of 0.2.

Strengths and limitations

The major strength of this study is that we analysed the original and very first conversations of patients with acute chest discomfort with primary health care providers and assessed these talks without knowledge of the diagnosis; the assessment of symptoms was therefore not affected by hindsight bias caused by knowledge of the final diagnosis. [29] Furthermore, we could analyse a large sample (N=2,192) of patients which allowed us to evaluate up to nineteen candidate predictors. We assessed the risk of selection due to missing outcome data, and our data suggest that this missingness was unlikely to bias our findings. Because we used data from seven different OHS-PC our results will be well generalizable to other OHS-PC in the Netherlands, but we anticipate the model might be applicable to similar OHS-PC

setting in for example the UK and Scandinavian countries. Our results may also be generalizable to some EMS settings, because the prior chance of having an ACS among those calling for acute chest discomfort is rather similar in the EMS setting as in the OHS-PC setting. [14 30]

A limitation of the study is that a full external validation of the final model is not done yet. However, at the time of executing the study hardly any primary care research data were available to perform such validation. Importantly, the internal-external validation showed very good calibration up to an ACS risk of 0.2. Although we performed extensive internal-external validation making use of the datasets of nine sites with substantial differences in case mix, we will strive for formal external validation before it can be widely applied in everyday primary care practice. Another limitation is that the effects of the predictors were assumed to be similar for male and female patients while that might not be optimal for the predictions. However, development of separate models for males and females would require a significantly larger sample size than was available. Importantly, a differential non-linear effect of age was incorporated using a spline function and interaction with sex was incorporated, and the final internal-external validated model did have good overall performance.

Comparison with other studies

Our prediction model had a higher discriminating ability for ACS than the NTS (c-statistic of 0.58) and modified Grijseels prediction rule (c-statistic of 0.66). [7] This may largely be explained by the addition of age, the strongest predictor of ACS. This is in line with the notion that the prevalence of ACS increases with age. [7 9 31] Importantly, in our study among people aged below 40, only one (0.4%) male patient had an ACS (UAP). For males to the age of 55 we found a peak risk of ACS of around 20% and remaining at this level with further age increase onwards. For females we found a gradual increase of risk with age with a maximum ACS risk of around 18% for those aged over 80 years. Similar to the modified Grijseels prediction rule our prediction model includes sweating and radiation of pain, however, the modified Grijseels rule combined nausea and sweating to a single predictor (i.e., nausea or sweating). [7 8] Age and sex were predictors in our model, but also in the MHS and INTERCHEST prediction models. [32 33] Also the INTERCHEST rule included pressing heavy chest pain as predictor. [32] A new predictor is calling at night (between 0.00-9.00am). [19] Previous studies in the ED setting also showed circadian variability with an early morning peak for ACS patients. [34] Finally, symptoms associated with ACS were rather similar between females and males, which is in line with recent sex-stratified studies of patients with chest discomfort who called the OHS-PC, but is in contrast with the prevailing opinion. [16 17 35]

We performed decision curve analyses to investigate what would be the optimal threshold of ACS predicted probability to initiate treatment, where 'treatment' in pre-hospital setting refers to urgent referral for hospital admission (U1, ambulance within 15 minutes). However, there is a principal difference between diagnostic probability and categories of urgencies. Risk prediction provides a continuous value of the probability of disease, while urgency level categorisation is based on the interpretation of how risk probability can be translated in urgency, and time within a patient should be seen and treatment delivered. Context is needed to determine optimal thresholds, which concerns what percentage of missing ACS is considered as acceptable by health care providers, patients and policymakers. This percentage is expected to be very low because a missed ACS can result in permanent cardiac impairment, heart failure, life-threatening arrhythmias in the early phase, and death. [36] Furthermore missing an ACS is the most common reason for malpractice claims worldwide. [37] A survey performed among 1,029 ED doctors in the US, New Zealand and Australia showed that they considered an average missing rate between 0.1-1% (range 0-10%) as acceptable. [38] When we apply a maximum of 1% missing with our prediction rules, the threshold has to be set at a predicted risk of ACS of 0.05 (negative predictive value of 0.99, Table 6), which means based on our data that the majority of patients needs urgent referral. This would result in over-crowded EMS and EDs, and with the available resources being limited, this may result in exceeding target triage times, which could compromise patient safety in another way. [39] A possible alternative to consider may be applying different 'treatments' per thresholds, i.e. dispatching an ambulance (U1) for the high predicted risk patients, and GP visit within one hour (U2) for the low predicted risk patients. During GP visit more clinical parameters (blood pressure, heart rate, overall clinical impression) can be gathered to improve ACS risk prediction, and in the future, there might be room for applying point-of-care high-sensitivity troponin testing, as these are nowadays only available in the ED setting. [40] In order to determine the ideal threshold, external validation will be needed combined with clinical and management considerations. The development of this diagnostic model is the necessary first step towards an implementation study in which this model is adapted to urgency levels that can be applied by triage nurses during telephone triage at the OHS-PC. The diagnostic model needs to be 'translated' in simple yes/no questions that can be incorporated in the existing NTS and a personalized risk prediction for age and gender is generated. Some older questions will then be substituted. We are aiming to do so in an implementation study applying action research.

Implications for clinical practice and future research

This symptom-based prediction model for ACS has good discrimination and calibration and could readily be applied for telephone triage of patients with acute chest discomfort in primary care, notably the OHS-PC setting. The results of the decision curve analysis showed a large net benefit over a range of plausible risk threshold as compared to the currently used NTS model in the OHS-PC in the Netherlands. For future research, full external validation in other OHS-PC or EMS populations could further optimize and update the model. Furthermore, sex-specific prediction models could be developed for ACS, but given the overlap in symptoms between men and women, this would not result in major changes in predictors.

Conclusion

The final prediction model for ACS has good discrimination and calibration and shows promise for replacing the existing telephone triage rules for patients with acute chest discomfort in general practice and OHS-PC. However, future research with an external validation is needed to provide insights into how the prediction model can be applied in practice.

Ethical approval

The study (National Trial Register identification number: NTR7331) was approved by the Medical Ethics Committee Utrecht, the Netherlands (reference number WAG/mb/16/003208) and complied with the Declaration of Helsinki. A waiver of informed consent was given because our study had minimal risk to subjects and could otherwise not be carried out logistically. Personal and research data were handled and stored according to the European General Data Protection Regulation.

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Competing interest statement All authors declare they have no conflict of interest. All authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Data sharing statement Data can be made available for researchers whose proposed use of the data has been approved at request of the corresponding author, with a signed data access agreement.

Author contribution FR and DZ are the lead investigators who conceived the research idea and methodology. Funding acquisition was done by FR, DZ and RD. LW and DE conducted data acquisition. LW performed the analyses and wrote the first draft of the manuscript. She was supervised by FR and DZ, who critically revised the manuscript, and by MvS who was involved with the analyses. DE, EdG, EA, HdR, AH and RD contributed to and approved of the final version of the manuscript.

References

1. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2017 Emergency Department Summary Tables (cdc.gov).
2. Mol KA, Smoczynska A, Rahel BM, et al. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. *Open Heart* 2018;5(2):e000859. doi: 10.1136/openhrt-2018-000859
3. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Rev Esp Cardiol*2021;74(6):544. doi: 10.1016/j.rec.2021.05.002
4. Burman RA, Zakariassen E, Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC Fam Pract* 2014;15:51. doi: 10.1186/1471-2296-15-51
5. Deakin CD, Sherwood DM, Smith A, et al. Does telephone triage of emergency (999) calls using Advanced Medical Priority Dispatch (AMPDS) with Department of Health (DH) call prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42,657 emergency calls to Hampshire Ambulance Service NHS Trust. *Emerg Med J* 2006;23(3):232-5. doi: 10.1136/emj.2004.022962
6. Bruyninckx R, Aertgeerts B, Bruyninckx P, et al. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. *Br J Gen Pract* 2008;58(547):105-11. doi: 10.3399/bjgp08X277014
7. Bruins Slot MH, Rutten FH, van der Heijden GJ, et al. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Fam Pract* 2011;28(3):323-8. doi: 10.1093/fampra/cmq116
8. Grijseels EW, Deckers JW, Hoes AW, et al. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. *Eur Heart J* 1996;17(1):89-95.
9. Harskamp RE, Laeven SC, Himmelreich JC, et al. Chest pain in general practice: a systematic review of prediction rules. *BMJ open* 2019;9(2):e027081. doi: 10.1136/bmjopen-2018-027081
10. Wouters LT, Rutten FH, Erkelens DC, et al. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open Heart* 2020;7(2) doi: 10.1136/openhrt-2020-001376

11. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC Card Disorders* 2015;15:48. doi: 10.1186/s12872-015-0049-6

12. Leeflang MM, Rutjes AW, Reitsma JB, et al. Variation of a test's sensitivity and specificity with disease prevalence. *CMAJ* 2013;185(11):E537-44. doi: 10.1503/cmaj.121286

13. Buntinx F, Knockaert D, Bruyninckx R, et al. Chest pain in general practice or in the hospital emergency department: is it the same? *Fam Pract* 2001;18(6):586-9.

14. Rawshani A, Larsson A, Gelang C, et al. Characteristics and outcome among patients who dial for the EMS due to chest pain. *Int J Cardiol* 2014;176(3):859-65. doi: 10.1016/j.ijcard.2014.08.004

15. Kuriyama A, Urushidani S, Nakayama T. Five-level emergency triage systems: variation in assessment of validity. *Emerg Med J* 2017;34(11):703-10. doi: 10.1136/emermed-2016-206295

16. van der Meer MG, Appelman Y, Rutten KHG, et al. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open* 2019;9(11):e031613. doi: 10.1136/bmjopen-2019-031613

17. Wouters LTCM, Zwart DLM, Erkelens DCA, et al. Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage: a cross-sectional study. *BMJ open* 2021;11 doi: 10.1136/bmjopen-2020-042406

18. Erkelens DC, Wouters LT, Zwart DL, et al. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ open* 2019;9(7):e027477. doi: 10.1136/bmjopen-2018-027477

19. Wouters LT, Zwart DL, Erkelens DC, et al. Chest discomfort at night and risk of acute coronary syndrome: cross-sectional study of telephone conversations. *Fam Pract* 2020 doi: 10.1093/fampra/cmaa005

20. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441. doi: 10.1136/bmj.m441

21. van Smeden M, Moons KG, de Groot JA, et al. Sample size for binary logistic prediction models: Beyond events per variable criteria. *Stat Methods Med Res* 2019;28(8):2455-74. doi: 10.1177/0962280218784726

22. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016;69:245-7. doi: 10.1016/j.jclinepi.2015.04.005

23. Wynants L, van Smeden M, McLernon DJ, et al. Three myths about risk thresholds for prediction models. *BMC Med* 2019;17(1):192. doi: 10.1186/s12916-019-1425-3

24. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58(10):982-90. doi: 10.1016/j.jclinepi.2005.02.022

25. Jolani S, Debray TP, Koffijberg H, et al. Imputation of systematically missing predictors in an individual participant data meta-analysis: a generalized approach using MICE. *Stat Med* 2015;34(11):1841-63. doi: 10.1002/sim.6451

26. Rubin DB. Multiple imputation for non response in surveys. *John Wiley & Sons, Hoboken, NJ* 1987

27. Harrell FE, Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Second edition ed. Cham, Switzerland: Springer International 2015.

28. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Int Med* 2015;162(1):W1-73. doi: 10.7326/M14-0698

29. Zwaan L, Monteiro S, Sherbino J, et al. Is bias in the eye of the beholder? A vignette study to assess recognition of cognitive biases in clinical case workups. *BMJ Qual Saf* 2017;26(2):104-10. doi: 10.1136/bmjqs-2015-005014

30. Scott G, Clawson JJ, Gardett I, et al. 9-1-1 Triage of Non-Traumatic Chest Pain: Association with Hospital Diagnosis. *Prehosp Emerg Care* 2017;21(4):525-34. doi: 10.1080/10903127.2017.1302530

31. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307(8):813-22. doi: 10.1001/jama.2012.199

32. International Working Group on Chest Pain in Primary C, Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *J Clinl Epidemiol* 2017;81:120-28. doi: 10.1016/j.jclinepi.2016.09.011

33. Haasenritter J, Donner-Banzhoff N, Bosner S. Chest pain for coronary heart disease in general practice: clinical judgement and a clinical decision rule. *Br J Gen Pract* 2015;65(640):e748-53. doi: 10.3399/bjgp15X687385

34. Ekelund U, Akbarzadeh M, Khoshnood A, et al. Likelihood of acute coronary syndrome in emergency department chest pain patients varies with time of presentation. *BMC Res Notes* 2012;5:420. doi: 10.1186/1756-0500-5-420

35. van Oosterhout REM, de Boer AR, Maas A, et al. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *J Am Heart Assoc* 2020;9(9):e014733. doi: 10.1161/JAHA.119.014733

36. Bugiardini R, Ricci B, Cenko E, et al. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc* 2017;6(8) doi: 10.1161/JAHA.117.005968

37. Ernesater A, Winblad U, Engstrom M, et al. Malpractice claims regarding calls to Swedish telephone advice nursing: what went wrong and why? *J Telemed Telecare* 2012;18(7):379-83. doi: 10.1258/jtt.2012.120416

38. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *Int J Cardiol* 2013;166(3):752-4. doi: 10.1016/j.ijcard.2012.09.171

39. van der Linden MC, Meester BE, van der Linden N. Emergency department crowding affects triage processes. *Int Emerg Nurs* 2016;29:27-31. doi: 10.1016/j.ienj.2016.02.003

40. Pickering JW, Young JM, George PM, et al. Validity of a Novel Point-of-Care Troponin Assay for Single-Test Rule-Out of Acute Myocardial Infarction. *JAMA Cardiol* 2018;3(11):1108-12. doi: 10.1001/jamacardio.2018.3368

Figure legends

Figure 1. Flowchart of study population.

Figure 2. Base model with age and sex for predicting diagnosis acute coronary syndrome.

Figure 3. Callibration of the final model with internal external validation.

Figure 4. Decision curve analyses comparing the full and final models versus the currently used model and versus treat all patients.

Figure 5. Runway plot of diagnostic accuracy measures of the final model.

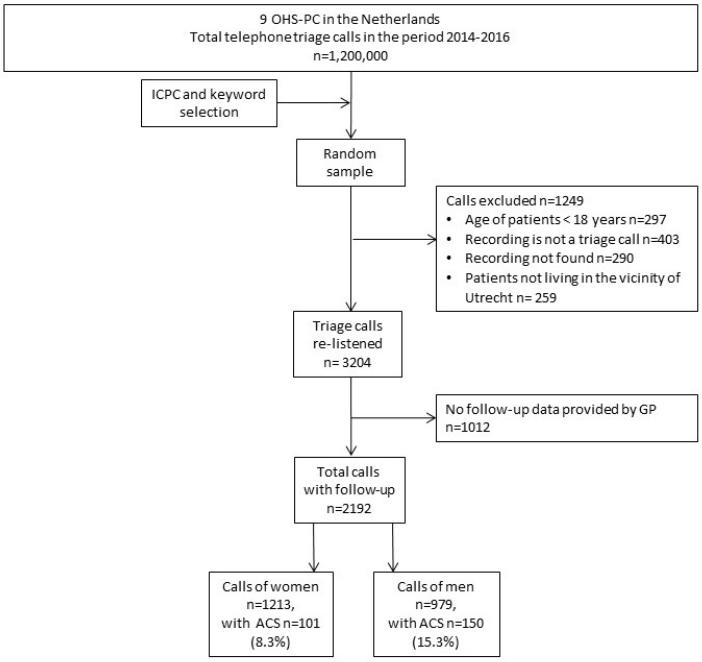

Figure 1

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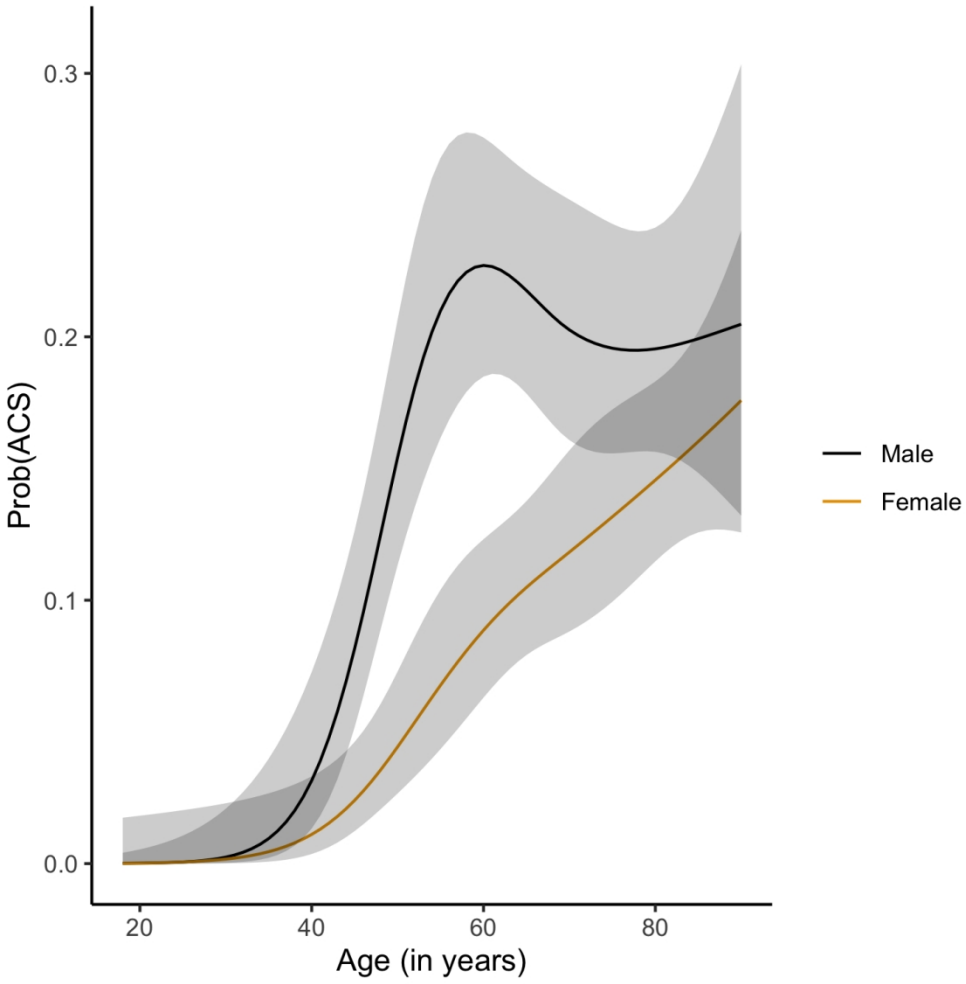

Figure 2

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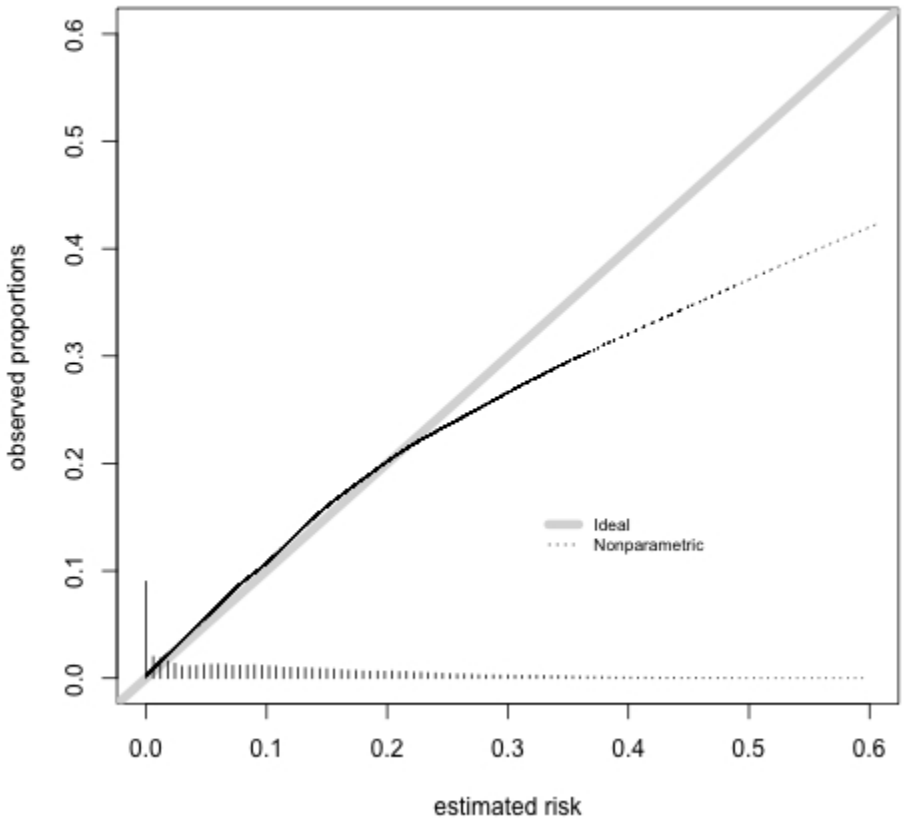

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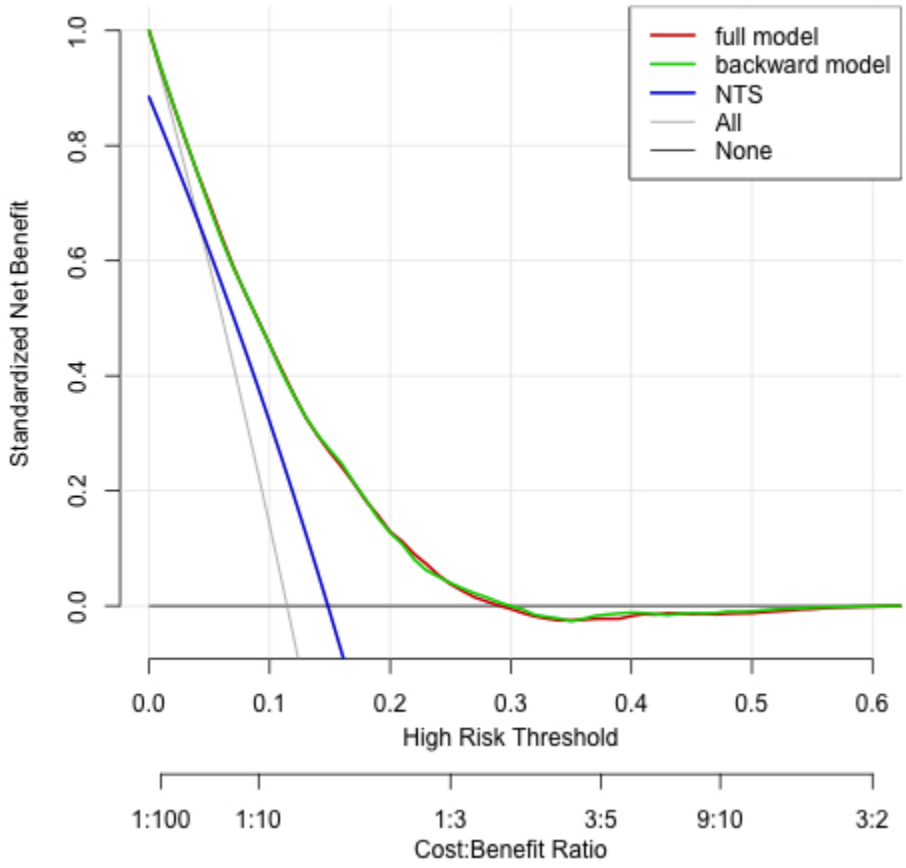

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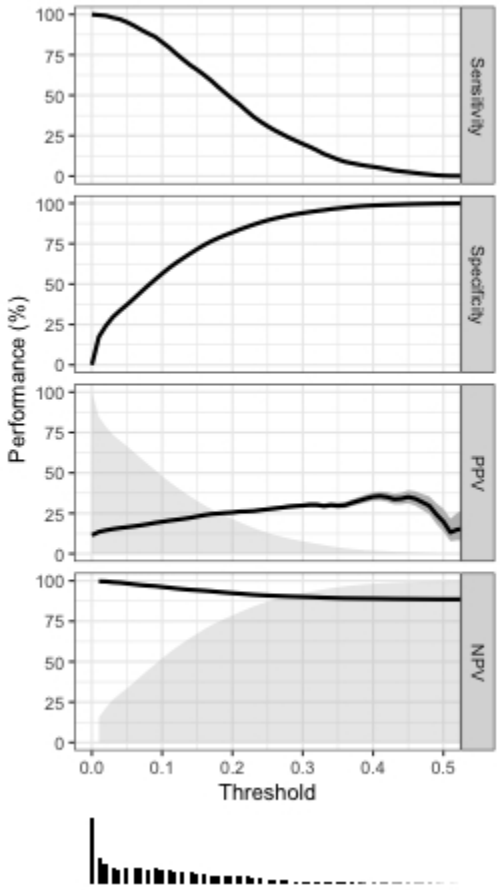

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Appendices

Appendix - Table 1. NTS urgency levels and response times

NTS Urgency level	Definition	Response time	Medical help
U0 – Resuscitation	Loss of vital functions	Immediately	Ambulance
U1 – Life threatening	Unstable vital functions	Immediately, within 15 minutes	Ambulance
U2 – Emergent	Vital functions in danger or organ damage	As soon as possible, within 1 hour	Home visit by GP or appointment at OHS-PC
U3 – Urgent	Possible risk of damage, human reasons	A few hours (<3 hours)	Home visit by GP or appointment at OHS-PC
U4 – Non-urgent	Marginal risk of damage	24 hours	Appointment at OHS-PC or telephone advice
U5 – Advice	No risk of damage	Advice, no time related	Telephone advice

GP: general practitioner

NTS: Netherlands Triage Standard

OHS-PC: out-of-hours services in primary care

Appendix-table 2: Combinations of NTS triage criteria that generate an U1 level within the NTS main complaints that can be used for patients with chest discomfort.

→ ABCD unstable (no main complaint is selected)			**Urgency level U1: ambulance within 15 minutes**
Main complaint 'Chest pain'			
→ ABCD stable	AND severe chest pain (Numeric Rating Scale (NRS)-score ≥ 8) lasting less than 12 hours		
→ ABCD stable	AND mild (NRS ≤ 4) to moderate (NRS 5-7) chest pain lasting for less than 12 hours	AND one of the following: - retrosternal located pain - tightening or pressing - radiation to jaw, arm or upper back - progressive pain intensity in short time - past or present autonomous nervous system-related symptoms - dizziness	
Main complaint 'Collapse'			
→ ABCD stable	AND collapse	AND chest pain of any severity	
Main complaint 'Back complaints'			
→ ABCD stable	AND severe upper back pain (NRS ≥8)	AND past or present autonomous nervous system-related symptoms	

ABCD: acronym for Airway, Breathing, Circulation and Disability. When the triage nurse starts the telephone triage with the NTS, the system requires a mandatory 'ABCD-check'; i.e. the triage nurse has to ask questions to assess whether the patient has life-threatening problems concerning the Airway, Breathing, Circulation and Disability for which an ambulance should be sent immediately.

Appendix-table 3. Characteristics of patients divided among the seven OHS-PC locations.

Characteristics	Location A N=205 (9.4%)	Location B N=355 (16.2%)	Location C N=544 (24.8%)	Location D N=262 (12.0%)	Location E N=164 (7.5%)	Location F N=412 (18.8%)	Location G N=250 (11.4%)
Prevalence of ACS (n,%)	32 (15.4%)	31 (8.7%)	59 (10.8%)	35 (13.4%)	15 (9.1%)	53 (12.9%)	26 (10.4%)
Male sex (n,%)	77 (37.6%)	154 (43.4%)	256 (47.1%)	108 (41.2%)	84 (51.2%)	188 (45.6%)	112 (44.8%)
Mean age in years (SD)	62.3 (19.6)	58.6 (19.8)	58.0 (19.4)	56.6 (18.9)	61.8 (20.5)	61.6 (19.4)	56.1 (18.7)

Appendix – table 4. Overview of the percentages of missing predictors, divided into patients with and without the diagnosis ACS.

Characteristics N=2192	ACS, n=251 (11.5%) Missing (%)	No ACS, n=1941 (88.5%) Missing (%)
Mean in years age (SD)	0	0
Female sex	0	0
Median call duration in min (IQR)	0	0
Mean patient's introduction in min (IQR)	0	0
Triage nurse consulted the GP	0	0
Someone else called on behalf of patient	0	0
The person who calls expressed concerns	144 (57.3)	943 (48.6)
Cardiovascular disease or risk factor combined	30 (12.0)	318 (16.4)
History of coronary artery disease	107 (42.6)	933 (48.1)
Diabetes	162 (64.5)	1126 (58.0)
Hypertension	172 (68.5)	1126 (58.0)
Hypercholesterolemia/statin use	172 (68.5)	1196 (61.6)
Cardiac arrhythmia	176 (70.1)	1110 (57.2)
Chest pain	4 (1.6)	72 (3.7)

Shortness of breath	68 (27.1)	429 (22.1)
Chest pain duration <12 hours	28 (11.2)	242 (13.1)
Pain intensity severe (NRS >7 in range 1-10)	149 (59.4)	1124 (57.9)
Pressing heavy pain*	63 (25.1)	502 (25.9)
Stabbing chest pain*	63 (25.1)	502 (25.9)
Chest pain located retrosternal**	87 (34.7)	538 (27.7)
Chest pain located left or right on thorax**	87 (34.7)	538 (27.7)
Radiation of chest pain to any location	38 (15.1)	476 (24.5)
Radiation to the arm ***	94 (37.5)	1019 (52.5)
Radiation to the shoulder blades ***	94 (37.5)	1019 (52.5)
Radiation to the jaws ***	94 (37.5)	1019 (52.5)
Sweating	79 (31.5)	747 (38.5)
Nausea or vomiting	133 (53.0)	1071 (55.2)
Pallor or ashen skin	158 (62.9)	1361 (70.1)
(Near) fainting	33 (13.1)	217 (11.2)
Palpitations	225 (89.6)	1615 (83.2)
Patient recognizes symptoms from previous cardiac event	139 (55.4)	1137 (58.6)

*Pain described by patient. Pressing heavy pain: pressing, heavy or tightening pain vs. other types of pain (stabbing, burning, cramping, tearing) Stabbing pain: stabbing vs. other types of pain (pressing, heavy, tightening, burning, cramping)

** Retrosternal location vs. other pain locations. Left or right side thorax vs. other pain locations

*** Radiation location vs. no radiation and radiation other pain

Appendix-table 5. Patient and call characteristics of 3,204 patients with chest discomfort calling OHS-PC between 2014-2017, comparing patients with and without information on the study outcome.

Characteristics N=3,204	Follow-up n= 2192 (68.4%)	No follow-up n= 1012 (31.6%)	P-value
Patient characteristics			
Median age in years (IQR) (n=3,204)	59.1 (19.5)	57.3 (20.4)	0.020
Female sex (n=3,204)	1213 (55.3)	565 (55.8)	0.794
Call characteristics			
Median total call duration in min (IQR) (n=3,204)	6:51 (4:59-9:23)	6:56 (5:04-9:15)	0.836
Mean patient's introduction in min (IQR) (n=3,204)	0:17 (0:11-0:25)	0:17 (0:11-0:26)	0.052
Triage nurse consulted the GP (n=3,204)	1147 (52.3)	519 (51.3)	0.583
Someone else called on behalf of patient (n=3,204)	1114 (50.8)	479 (47.3)	0.066
Person who calls expressed concerns (n=1,478)	988 (89.7)	430 (90.1)	0.804
Medical history and risk factors			
Cardiovascular disease or CV risk factor (n=2,672)	1192 (64.6)	515 (62.3)	0.254
History of coronary artery disease (n=1,663)	389 (33.8)	166 (32.4)	0.573
Diabetes (n=1,283)	180 (19.9)	68 (18.0)	0.432
Hypertension (n=1,274)	323 (36.1)	121 (31.9)	0.150
Hypercholesterolemia/statin use (n=1,176)	212 (25.7)	88 (25.1)	0.842
Cardiac arrhythmia (n=1,326)	230 (25.4)	102 (24.3)	0.684
Symptoms			
Chest pain (n=3,079)	1981 (93.6)	894 (92.8)	0.417
Shortness of breath (n=2,505)	1094 (64.5)	520 (64.3)	0.911
Chest pain duration <12 hours (n=2,793)	1403 (73.2)	610 (69.6)	0.052
Severe pain (NRS >7 in range 1-10) (n=1,351)	337 (36.6)	185 (43.0)	0.024
Pressing, heavy pain* (n=2,347)	1023 (62.9)	444 (61.6)	0.538
Stabbing chest pain* (n=2,349)	366 (22.5)	177 (24.5)	0.280
Chest pain located retrosternal** (n=2,298)	641 (40.9)	294 (40.2)	0.736
Chest pain located left or right on thorax** (n=2,299)	627 (40.0)	294 (40.2)	0.945
Radiation of chest pain to any location (n=2,437)	1077 (64.3)	458 (60.1)	0.047
Radiation to the arm ***(n=1,521)	452 (42.2)	179 (39.8)	0.373

Radiation to the shoulder blades *** (n=1,519)	326 (30.5)	136 (30.2)	0.924
Radiation to the jaws *** (n=1,984)	124 (11.6)	41 (9.1)	0.156
Sweating (n=1,758)	559 (40.9)	259 (42.0)	0.638
Nausea or vomiting (n=1,474)	489 (49.5)	229 (47.1)	0.381
Pallor or ashen skin (n=1,007)	322 (47.8)	136 (40.8)	0.038
(Near) fainting (n=2,855)	143 (7.4)	72 (7.8)	0.678
Palpitations (n=501)	284 (80.7)	125 (83.9)	0.396
Patient recognizes symptoms from previous cardiac event (n=1,298)	250 (27.3)	102 (26.7)	0.819
Urgency allocation			
High urgency (U1 or U2) (n=3,204)	1496 (68.2)	661 (65.3)	0.100
U1	974 (44.5)	390 (38.6)	
U2	522 (23.8)	271 (26.8)	
Low urgency (U3 or U4 or U5)	696 (31.8)	351 (34.7)	

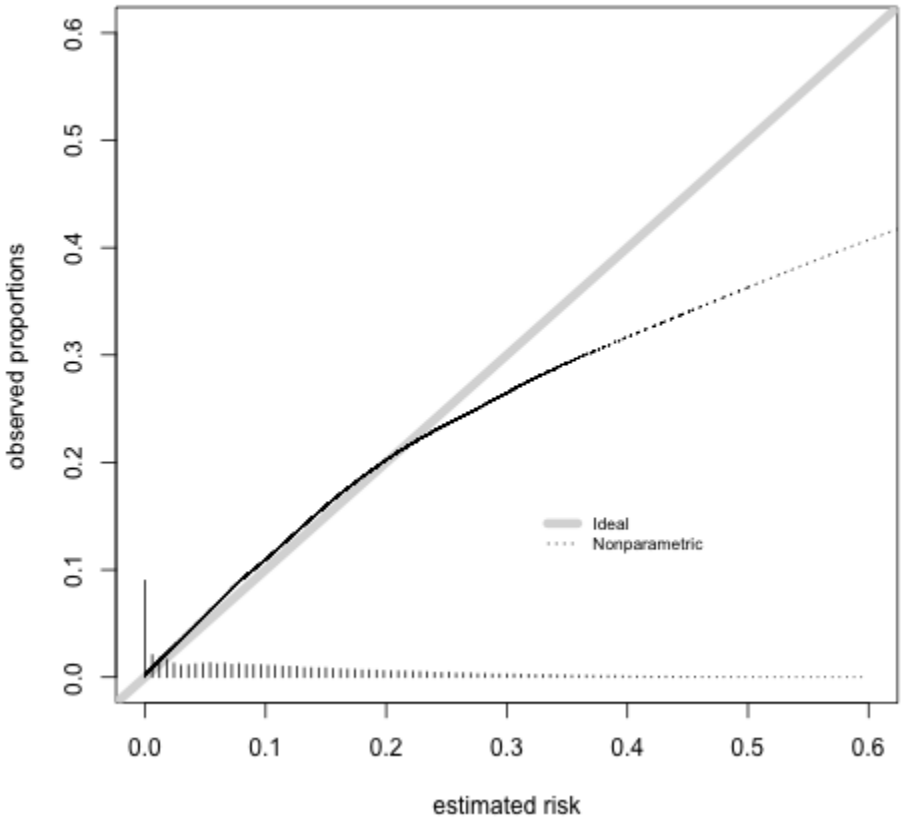
Appendix - Table 6. Base model with age and sex for predicting the diagnosis ACS.

Predictors	Regression coefficients (standard error)
Intercept	- 14.671 (3.442)
Age	0.289 (0.079)
Age’	- 0.379 (0.123)
Age’’	1.017 (0.386)
Female sex	2.155 (5.385)
Age * Female sex	- 0.084 (0.123)
Age’ * Female sex	0.175 (0.190)
Age’’ * Female sex	- 0.532 (0.589)
Apparent c-statistic 0.72 (95% CI 0.70-0.75)	
Adjusted c-statistic 0.72 (95% CI 0.68-0.75)	
Calibration slope 0.977 (95% CI 0.617-1.338)	
Calibration 0.016 (95% CI-0.702-0.734)	
R^2 0.065	
Knots for cubic spline functions placed at 5, 35, 65 and 95	

Appendix - Table 7. Full model including all candidate predictors for predicting the diagnosis ACS

Predictors	Regression coefficients (standard error)
Intercept	-15.914 (3.55)
Age	0.288 (0.081)
Age’	-0.388 (0.126)
Age’’	1.058 (0.396)
Female gender	2.459 (5.519)
Age * Female sex	-0.094 (0.126)
Age‘ * Female sex	0.187 (0.195)
Age’’ * Female sex	-0.554 (0.606)
Chest pain	-0.064 (0.365)
Acute chest pain (< 12 hours)	0.258 (0.200)
Shortness of breath	-0.141 (0.200)
Sweating	0.459 (0.183)
Retrosternal located pain	0.178 (0.177)
Radiation of chest pain	0.617 (0.180)
Pressing heavy feeling	0.619 (0.272)
Stabbing pain	-0.200 (0.353)
History of cardiovascular disease*	-0.039 (0.247)
History of coronary artery disease	0.108 (0.234)
Someone else calls instead of the patient	0.197 (0.160)
Patient calls during the night (0am-9am)	0.495 (0.152)
Apparent c-statistic 0.79 (95% CI 0.76-0.81)	
Adjusted c-statistic 0.77 (95% CI 0.74-0.80)	
Calibration slope 0.818 (95% CI 0.650-0.986)	
Calibration -0.238 (-0.621-0.145)	
R^2 0.107	
Knots for cubic spline functions placed at 5, 35, 65 and 95	

Appendix – Figure 1. Callibration of full model with internal external validation



TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4,5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	5,6
	5c	D;V	Give details of treatments received, if relevant.	n.a.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n.a.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	n.a.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7, suppl
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8,9,10
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	suppl
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	8
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	11,12
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	12, suppl
	15b	D	Explain how to the use the prediction model.	13
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12, 13
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	12,13
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14, 15
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	17
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.