International Journal of Cardiology 187 (2015) 246–251

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Sex differences of troponin test performance in chest pain patients

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ARTICLE INFO

Article history:
Received 28 March 2014
Received in revised form 4 March 2015
Accepted 19 March 2015
Available online 19 March 2015

Keywords:
Acute myocardial infarction
Chest pain diagnosis
Gender
Sex
Troponin

ABSTRACT

Background: Current guidelines recommend troponin as the preferred biomarker to diagnose acute myocardial infarction (AMI) irrespective of the patient's sex. Recent reports have shown that sex-specific cut-offs should be considered but studies investigating sex-differences in the diagnostic accuracy of cardiac troponins are sparse.
Objective: To evaluate whether the diagnostic performance of cardiac troponin at admission (cTn) under routine conditions is influenced by patient's sex.
Methods: Between 15th of February 2009 and 15th of February 2010, women (n = 1648) and men (n = 2305) who presented to the emergency department with chest pain (n = 3954) were enrolled.
The diagnostic performance of the routine, contemporary sensitive cTn assays (TnI; Stratus® CS, Siemens and TnT; Roche Diagnostics) at baseline for the diagnosis of non-ST-elevation myocardial infarction (NSTEMI) was analyzed.
Results: NSTEMI was diagnosed in 7.3% (n = 287) of all patients. Men were more likely to be diagnosed with NSTEMI (8.8%; n = 202) as compared to women (5.2%; n = 85; $p < 0.001$). Sensitivity was 56.1% (95% CI: 44.7–67.0%) in women and 70.1% (95% CI: 63.1–76.4%) in men. Specificity was 96.8% (95% CI: 95.6–97.7%) in women and 94.5% (95% CI: 93.3–95.6%) in men. This resulted in a lower positive predictive value (PPV) for women (53.5%; 95% CI: 42.4–64.3) as compared to men (60.8%; 95% CI: 54.1–67.2) and a slightly higher negative predictive value (NPV) for women: 97.1% (95% CI: 96.0–97.9) vs. 96.3% (95% CI: 95.2–97.2) in men.
Conclusions: The findings of this study underline that the performance of cTn for the diagnosis of NSTEMI depends on a patient's sex, with a lower sensitivity and NPV in women. The definition and implementation of sex-specific cut-off values for cTn into clinical routine seems to be highly recommendable.

1. Introduction

Cardiovascular diseases accounted for 30% of all deaths globally in 2008 [1], with the majority of cardiovascular deaths occurring in women (51%) [2].

Even though cardiovascular mortality has decreased in the general population from 1997 to 2008, the decrease was more pronounced in men as compared to women [3]. Mortality after acute myocardial infarction (AMI) is higher in women as compared to men [4–6]. This is especially true for "short-term" mortality in young female patients with AMI [6–9]. Some reports show that crude differences in mortality were reduced by adjustment for age and other risk factors [10]. Regarding the pathophysiology of acute myocardial infarction, several differences between men and women have been reported [4,11–16]. In general, women are underrepresented in clinical studies investigating risk factors, risk-stratification, diagnosis and treatment of AMI [6,12,17,18] and stratified analyses are sparse.

For the diagnosis of acute myocardial infarction, cardiac troponin is one of the key components in the clinical evaluation of patients with suspected ACS. The recommended cut-off value for troponin and thus the diagnosis of AMI is the 99th percentile of a healthy reference population [19]. Several studies have shown that the 99th percentile value is dependent on patient sex as well as on the reference population under study [20,21]. The implementation of sex-dependent troponin cut-offs into clinical practice has been suggested recently [22], but until now no consensus has been achieved.

In the present secondary data analysis, the diagnostic performance of cardiac troponins T and I at admission was evaluated under routine

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http://dx.doi.org/10.1016/j.ijcard.2015.03.261
0167-5273/

conditions in an unselected population of men and women who attended the emergency department with a chief complaint of chest pain.

2. Materials and methods

2.1. Population

The study was originally designed to assess the association between chief complaint at admission and final diagnosis [23]. All internal emergency patients who attended one of the emergency departments (EDs) of the Charité CBF and CVK between 15th of February 2009 and 2010 were included (n = 34,333). Of these, patients with a chief complaint of acute chest pain (n = 3954) were included into this analysis. No exclusion criteria were applied.

2.2. Data collection

The data collection of this study has been described in detail elsewhere [23]. In brief, routine data of all patients were retrieved retrospectively from the hospital information system (HIS) in an automated way. Prospectively, a mandatory property field was implemented in the ED-documentation to assess the patient's chief complaint at admission. Additional information about symptoms, diagnostic procedures, medication and medical history were retrieved from the free text fields of the ED-documentation and entered in an electronic case report form (eCRF). Laboratory test results were retrieved from the first blood draw directly after admission. No serial troponin measurements were analyzed, but were performed in clinical routine and contributed to the final diagnosis.

2.3. Sex and gender

Patient's sex was assessed from the health insurance identity card. In patients without health insurance, it was assessed by patient interrogation during the administrative admission process. Sex was categorized in three categories: “female”, “male” and “unknown”. Sex was unknown in one person only. This person was excluded from sex-stratified analyses. Gender in this article is used as a term for social and cultural influences. Gender was not explicitly operationalized in this study.

2.4. Cardiac troponin assays

Two different routine troponin-assays were used during the study period in the participating EDs. The first was a point-of care cardiac troponin I assay (Stratus® CS, Siemens) with a recommended cut-off value of 100 ng/L (based on 10% CV at this threshold). Second, a contemporary sensitive cardiac troponin T assay (Roche Diagnostics) was used in the central laboratory of the Charité with a cut-off value of 30 ng/L. For statistical analysis, the troponin test results of both assays in the initial blood draw were combined. In patients, who had only one initial troponin-test, the result of this test was used for statistical analysis. In patients where both assays were used, the combined troponin was suggested to be positive if at least one troponin assay revealed a positive test result.

2.5. Diagnoses

The diagnoses of all patients were retrieved from the HIS as described above. As a final diagnosis for in-patients the main hospital diagnosis was used. This diagnosis is a very well defined and validated diagnosis, which is closely monitored by insurance companies as DRG classification and reimbursement is based upon it. For out-patients, the discharge diagnoses as assigned by the treating physician were analyzed. All diagnoses were retrieved as ICD-10 codes (international classification of disease; Version 10) and as free-texts. For the diagnosis “acute myocardial infarction” (AMI), the first three digits of ICD-10 code “I21” were used. The diagnosis of unstable angina pectoris (UAP) is coded by I20.0. All other diagnoses were summarized by the first three digits of the ICD-10 code. In patients with ST-segment elevations in the ECG at admission and an ICD-10 code confirming a transmural MI (I21.0–I21.3) a final diagnosis of ST-elevation myocardial infarction (STEMI) was defined (n = 112; women: n = 31 and men: n = 81). In these patients, the further clinical course and the diagnosis of an AMI is not dependent on troponin-testing, thus these patients as well as patients without an initial troponin value were excluded from the evaluation of the diagnostic performance of troponin. In all patients with inconclusive ECG at admission, diagnostic accuracy was evaluated. All diagnoses were based on serial troponin measurements, a clinical evaluation of the patient, ECG-findings and results of diagnostic procedures such as coronary angiography.

2.6. In-hospital course

Only in-patients are assigned a main hospital diagnosis. Out-patients received acute care in the ED and where then discharged into ambulant care. Some of these patients stayed on the chest pain unit (CPU) for several hours in order to exclude AMI by serial troponin measurements or to perform additional diagnostic procedures.

2.7. Statistical analysis

All analyses were performed with SPSS (Statistical Package for Social Science; Version 20; IBM). In order to assess sex-related differences, a stratified analysis was performed and results were compared between men and women. Frequencies are shown as relative and absolute frequencies for categorial variables, and as median and interquartile ranges (IQR) for numeric variables. This is a secondary data analysis of routinely documented clinical data. Thus data of some variables were not complete for every patient and relative frequencies generally are shown as a proportion of valid values of the respective variable. Statistical testing was performed using Chi-square test for categorial variables and Mann–Whitney-U-test for numeric variables. The test results were reported to be statistically significant when the p-value was below 0.05. Due to the exploratory character of this analysis, no corrections for multiple testing were done.

The diagnostic performance of cardiac troponin was calculated using the established formulas for sensitivity, specificity and predictive values and corresponding exact binomial 95% confidence intervals. The accuracy was defined as the proportion of patients with correct prediction.

2.8. Ethical considerations

The ethics committee of Charité confirmed that the analysis was acceptable in relation to standard ethical rules in science and research.

2.9. Trial registration

The study was registered on 16th of November 2009 in the German Clinical Trials Register linked to the webpage of the World Health Organization (Universal Trial Number: U1111-1112-5093).

3. Results

Overall, 34,333 internal emergency patients were included in the study. Of these, 3954 patients presented with chest pain, 58.3% of them male (n = 2305) and 41.7% female (n = 1648). Patient characteristics of men and women with chest pain are shown in Table 1.