Clinica Chimica Acta 487 (2018) 66–74

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Evaluation of sex-specific cut-off values of high-sensitivity cardiac troponin I and T assays in an emergency department setting – Results from the Linz Troponin (LITROP) study

Thomas Mueller[a,*], Margot Egger[b], Evi Peer[a], Erika Jani[a], Benjamin Dieplinger[b]

[a] Department of Clinical Pathology, Hospital of Bolzano, Bolzano, Italy
[b] Department of Laboratory Medicine, Konventhospital Barmherzige Brueder Linz, Linz, Austria

ARTICLE INFO

Keywords:
Cardiac troponin
Diagnosis
Emergency department
Method comparison
Myocardial injury

ABSTRACT

Background: The aim of the present analysis was to evaluate sex-specific cut-off values of a high-sensitivity cardiac troponin T (hs-cTnT) assay and a high-sensitivity cardiac troponin I (hs-cTnI) assay in an emergency department setting.

Methods: We retrospectively studied 1945 male and 1643 female emergency department patients in whom we had measured both Roche hs-cTnT and Abbott hs-cTnI routinely upon every troponin measurement request. We performed reclassification analyses of sex-specific thresholds versus sex-neutral thresholds of both assays. In addition, we performed sensitivity analyses to find those sex-specific cut-off values for the Roche hs-cTnT and the Abbott hs-cTnI assays with the lowest possible rate of discordant classifications by both assays.

Results: Compared with the classification by the sex-neutral thresholds (i.e., 14 ng/L for hs-cTnT and 26 ng/L for hs-cTnI), using sex-specific thresholds (i.e., 16 ng/L in males and 9 ng/L in females for hs-cTnT; and in 34 ng/L males and 16 ng/L in females for hs-cTnI) resulted in a total reclassification rate of 4% for hs-cTnT and 3% for hs-cTnI in male individuals, and of 11% and 6%, respectively, in female individuals. In our cohort, the sex-specific hs-cTnT cut-off values currently in use (i.e., 16 ng/L in males and 9 ng/L in females) were best matched to a hs-cTnI cut-off value of 11 ng/L in male and 5 ng/L in female individuals. Conversely, the sex-specific hs-cTnI cut-off values currently in use (i.e., 34 ng/L in males and 16 ng/L in females) were best matched to a hs-cTnT cut-off value of 49 ng/L in male and 24 ng/L in female individuals. These "harmonised" cut-off values reduced discordant classifications between both assays by 43–68% compared to using cut-off values currently in use.

Conclusion: Especially in women, reclassification rates were high, when using sex specific versus sex-neutral thresholds. Best matching cut-off values for hs-cTnT and hs-cTnI were markedly different to those currently in use. These "harmonised" cut-off values minimised discordant classifications between both assays.

1. Introduction

Cardiac troponins T and I are well established as the biomarkers of choice to detect acute myocardial infarction and any other myocardial injury [1,2]. Assays for measuring plasma concentrations of cardiac troponins started to develop in the early 1990s but have been progressively improved over the past decade. These developments have improved analytical precision at very low concentrations [2]. Guidelines claimed that the analytical coefficient of variation (CV) of cardiac troponin assays should be < 10% at the 99th percentile upper reference limit (URL) of a normal reference population and that cardiac troponin assays need to measure analyte concentrations above their limit of detection (LOD) in ≥50% of a normal reference population [2]. The assays fulfilling these requirements are currently termed high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI) assays [2].

In the emergency department, cardiac troponin values are used 1) to detect myocardial injury and 2) to distinguish acute cardiac presentations from chronic cardiac diseases [3]. Notably, acute myocardial infarction is only one reason for acute myocardial injury [1,3]. Clinicians

Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; LITROP study, Linz Troponin study; LOD, limit of detection; ROC, receiver operating characteristic; URL, upper reference limit

* Corresponding author at: Department of Clinical Pathology, Hospital of Bolzano, Via Lorenz Boehler 5, 39100 Bolzano, Italy.
E-mail address: thomas.mueller@sabes.it (T. Mueller).

https://doi.org/10.1016/j.cca.2018.09.026
Received 9 July 2018; Received in revised form 24 August 2018; Accepted 13 September 2018
Available online 15 September 2018
0009-8981/

try to exclude, e.g., acute myocardial infarction rapidly in the emergency department [3]. Studies have demonstrated, that using hs-cTnT and hs-cTnI assays can decrease the time for ruling out acute myocardial infarction in low-risk patients compared to using the older "contemporary" assays [3]. Acute myocardial infarction is diagnosed with a combination of clinical presentation, electrocardiogram, imaging studies, and cardiac troponin measures [1]. Besides an increased cardiac troponin concentration above the 99th percentile URL, changing cardiac troponin concentrations over time by serial measurements in a distinct patient is a key criterion for diagnosing acute myocardial infarction [1–3].

Currently, there are one hs-cTnT assay (Roche) and six hs-cTnI assays (Abbott, Beckman Coulter, BioMerieux, Pathfast, Siemens and Singulex) commercially available. In Europe (and other parts of the world), physicians have used hs-cTnT and hs-cTnI assays for several years in clinical practice [2]. In the Unites States of America (USA), however, there are currently only two high-sensitivity assays cleared by the Food and Drug Administration (FDA) and, thus, approved for the use in clinical practice. Only in January 2017 the FDA cleared the first high-sensitivity cardiac troponin assay, namely the Roche hs-cTnT assay [7]. The second high-sensitivity cardiac troponin assay, the Beckman Coulter hs-cTnI assay, was cleared by the FDA in June 2018. Most probably, other hs-cTnI assays will follow soon.

In the Linz Troponin (LITROP) study, which evaluated cardiac troponin testing in "real-life use" in a European setting, we recently identified different characteristics of the Roche hs-cTnT and Abbott hs-cTnI assays [4]. Clinically, these different characteristics were related to discordant results in the diagnosis and prognosis of patients presenting to an emergency department when the European sex-neutral assay specific 99th percentile URLs were applied [4]. With the present work, we now intended to go further into the matter and aimed to evaluate sex-specific 99th percentile URLs of both assays in the LITROP study.

According to the European package insert, the Roche hs-cTnT assay has a sex-neutral 99th percentile URL of 14 ng/L, which is in accordance to the information provided by the original papers evaluating the Roche hs-cTnT assay [5,6]. In the European package insert, no sex-specific reference values are provided. However, in the original multicenter study evaluating the Roche hs-cTnT assay [6], sex-specific 99th percentile URLs were found to be 16 ng/L for male individuals and 9 ng/L for female individuals – these sex-specific hs-cTnT thresholds are generally accepted in Europe. In January 2017, the FDA cleared the Roche hs-cTnT assay for the USA and included different sex-specific 99th URLs in the US package insert (i.e., 22 ng/L for male individuals and 14 ng/L for female individuals) [7]. According to the European package insert, the Abbott hs-cTnI assay has a sex-neutral 99th percentile URL of 26 ng/L and sex-specific 99th percentile URLs of 34 ng/L for male individuals and 16 ng/L for female individuals [8]. In contrast to the Roche hs-cTnT assay, the Abbott hs-cTnI assay has not yet been cleared by the FDA. Thus, there are no FDA approved 99th percentile URLs for the Abbott hs-cTnI assay. In general, in different normal reference populations a substantial heterogeneity of the 99th percentile URLs for both, the Roche hs-cTnT assay and the Abbott hs-cTnI assay has been reported [8].

Published studies provide evidence that the 99th percentile URLs of a normal reference population as measured by both hs-cTnT and hs-cTnI assays are substantial higher for men than for women [2,8], and this is explained by the larger heart mass of men over that of women. Therefore, guidelines have endorsed sex-specific 99th percentile URLs [1,2]. Relative to sex-neutral 99th percentile URLs, a lower sex-specific 99th percentile URLs for women will theoretically increase clinical sensitivity for myocardial injury and the reverse will be true for men. However, the clinical superiority of using sex-specific 99th percentile URLs compared to sex-neutral 99th percentile URLs has not been proven yet [2,8] because controversy exists about the clinical utility of sex-specific 99th percentile URLs [9,10]. Furthermore, the thresholds for the Roche hs-cTnT and the Abbott hs-cTnI assays are not harmonised to each other. As a consequence, the previously described 99th percentile URLs of both assays are considered clinically not equivalent [8,11–18] and might therefore contribute to inconsistencies in the diagnosis of acute myocardial infarction or myocardial injury.

In this context, two open research questions remain: 1) we are not sure whether applying sex-specific hs-cTnT and hs-cTnI thresholds outperform sex-neutral hs-cTnT and hs-cTnI thresholds for the diagnosis of acute myocardial infarction, and reduce under-diagnosis of acute myocardial infarction particularly in women; and 2) we are not sure whether the sex-specific hs-cTnI and hs-cTnT 99th percentile URLs are numerically correct and thus interchangeable for the diagnosis of acute myocardial infarction. Thus, the aims of the present explorative analysis of the LITROP study were twofold: 1) to evaluate the reclassification rate of women and men using sex-specific hs-cTnT and hs-cTnI thresholds as compared with the use of (European) sex-neutral hs-cTnT and hs-cTnI thresholds in an emergency department setting; and 2) to find those sex-specific cut-off values for the Roche hs-cTnT and the Abbott hs-cTnI assays in emergency department patients with the lowest possible rate of discordant classifications by both assays.

2. Methods

2.1. Design of the LITROP study

The LITROP study, which evaluated cardiac troponin testing in "real-life use", was a retrospective study [4]. We measured both Abbott hs-cTnI and Roche hs-cTnT routinely upon every troponin measurement request in the Department of Laboratory Medicine of the Krankenhaus Barmherzige Brueder Linz, Austria and the Krankenhaus Barmherzige Schwestern, Linz, Austria from February 19, 2013 to May 21, 2013. Thus, eligible for the LITROP study were all blood samples drawn in clinical routines with the request to measure cardiac troponin. Exclusion criteria were (1) haemolysed blood samples (i.e., free haemoglobin in plasma > 100 mg/dL); (2) not enough plasma available for measurement of both hs-cTnI and hs-cTnT; and (3) blood samples from patients < 18 years of age. The detailed study design and a study flow chart have been published previously [4]. In brief, we evaluated 3588 consecutive patients presenting in the emergency department with blood samples drawn in clinical routines with the request to measure cardiac troponin. The LITROP study was approved by the ethics committees of the Krankenhaus Barmherzige Brueder Linz, Austria and the Krankenhaus Barmherzige Schwestern, Linz, Austria [4].

2.2. Design of the present work

The present work is an explorative study, and the design of this work is based on pragmatic considerations. The definition of "myocardial injury" was primarily based on hs-cTnI and hs-cTnT. During the study period in 2013, all hs-cTnT and hs-cTnI patient results obtained in our laboratory in clinical practice were reported to the attending physicians immediately after finishing the respective measurements along with the European sex-neutral clinical cut-offs of 14 ng/L for hs-cTnT and 26 ng/L for hs-cTnI. Thus, in the present work, we decided for pragmatic reasons to use these clinical cut-off values as the thresholds for defining "myocardial injury" in our reclassification analyses. Thus, based on the European sex-neutral clinical cut-offs of 14 ng/L for hs-cTnT and 26 ng/L for hs-cTnI, we performed reclassification analyses in men and women separately using sex-specific hs-cTnT and hs-cTnI thresholds as described in the introduction.

In order to find those sex-specific cut-off values for the Roche hs-cTnT and the Abbott hs-cTnI assays with the lowest possible rate of discordant classifications by both assays, we performed sensitivity analyses in men and women separately. For this purpose, we used 1) Roche hs-cTnT with the European sex specific cut-offs (i.e., 16 ng/L for male individuals and 9 ng/L for female individuals) as "reference