Estimation of Values below the Limit of Detection of a Contemporary Sensitive Troponin I Assay Improves Diagnosis of Acute Myocardial Infarction

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BACKGROUND: The limit of detection (LoD) is the minimal amount of a substance that can be consistently detected. In the diagnosis of acute myocardial infarction (AMI) many patients present with troponin concentrations below the LoD of contemporary sensitive cardiac troponin I (cs-cTnI) assays. These censored values below the LoD influence the diagnostic performance of these assays compared to highly sensitive cTnI (hs-cTnI) assays. Therefore we assessed the impact of a new approach for interpolation of the left-censored data of a cs-cTnI assay in the evaluation of patients with suspected AMI.

METHODS: Our posthoc analysis used a real world cohort of 1818 patients with suspected MI. Data on cs-cTnI was available in 1786 patients. As a comparator the hs-cTnI version of the assay was used. To reconstruct quantities below the LoD of the cs-cTnI assay, a γ regression approach incorporating the GRACE (Global Registry of Acute Coronary Events) score variables was used.

RESULTS: Censoring of cs-cTnI data below the LoD yielded weaker diagnostic information [area under the curve (AUC), 0.781; 95% CI, 0.731–0.831] regarding AMI compared to the hs-cTnI assay (AUC, 0.949; CI, 0.936–0.961). Use of our model to estimate cs-cTnI values below the LoD showed an AUC improvement to 0.921 (CI, 0.902–0.940). The cs-cTnI LoD concentration had a negative predictive value (NPV) of 0.950. An estimated concentration that was to be undercut by 25% of patients presenting with suspected AMI was associated with an improvement of the NPV to 0.979.

CONCLUSIONS: Estimation of values below the LoD of a cs-cTnI assay with this new approach improves the diagnostic performance in evaluation of patients with suspected AMI.

The term limit of detection (LoD) is used to define the minimal amount of a substance that can be consistently detected in a biomedical analytical procedure (1). In relation to this definition, the minimum concentration that can be reliably quantified with stated acceptable imprecision and bias (i.e., measurement uncertainty) is defined as the limit of quantification (LoQ) (1). Although the LoD is determined by the substance and method of detection, the LoQ strongly depends upon consensus of the acceptable measurement uncertainty. Accordingly, the LoQ is usually higher than the LoD (2).

In most cases only 1 of the 2 definitions is provided by the manufacturer, e.g., in a package insert. In clinical practice quantification of very small analyte concentrations near the LoD is often not necessary because expected concentration ranges of common biomarkers are likely far above the LoD in current analytical procedures (2).

In a clinical context some exceptions exist. One important setting concerns cardiac troponin I/cardiac tro-
ponin T (cTnI/T), the goldstandard biomarker in the discrimination of an acute myocardial infarction (AMI), a setting in which timely diagnosis is crucial. Concentrations of cTnI/T are usually below the LoD under physiologic or nondisease conditions in the majority of individuals if a contemporary-sensitive cardiac troponin (cs-cTn) assay is used (3). Significant increases are observed mainly in disease states associated with relevant myocardial injury (4). On the basis of the recommendations on test precision at a concentration representing the 99th percentile of a reference population used as diagnostic cutoff (5), assays with improved analytical sensitivity have been developed and introduced into clinical practice. These high-sensitivity cardiac troponin (hs-cTn) assays with their high precision in low analyte concentrations have brought the LoD itself into focus regarding the diagnostic use of the biomarker (6) [see also (7) for cardiac troponin assay characteristics]. Such an improved sensitivity of troponin determination has been shown to the speed up diagnosis and facilitate treatment (8–10), including lower individual assay LoDs with its clinical implications compared to cs-cTn assays currently in use in many laboratories.

Beyond cardiac troponins, another setting in which reliable detection of very low analyte concentrations is important is clinical toxicology. Here, detectability of a substance such as methamphetamine after ingestion is dependent on the lowest concentration that can be reliably quantified by the assay, underlining the importance of how to deal with measurement of very low concentrations (11).

Missing biomarker data in a clinical setting, such as not recorded or not reported measurements below the LoD, which are therefore censored from the standpoint of the treating physician, can have a large impact on diagnostic ability of a biomarker, especially if the amount of censored data is high. Simple substitution of values below the LoD with a constant value related to the respective LoD, as often done, can lead to a significant variance of the measured parameter in the whole cohort (12). Therefore, in cohorts in which the total percentage of values measured below the LoD is >15%, simple substitution is not advised (13). Several more advanced approaches have been proposed regarding how to handle data below the LoD (14, 15). In this context, parametric and nonparametric methods, as well as regression modeling and the mentioned simple substitution method, have been discussed (12).

Therefore, the aim of the present study was to assess the impact of different approaches for interpolation of censored data on the discriminatory value of cs-cTn compared to hs-cTn using patient variables available in the evaluation of patients with suspected AMI.

Methods

STUDY COHORT

For the present posthoc analyses a cohort of 1818 patients with suspected AMI was used. This study population has been described earlier (16). In brief, patients with symptoms suggestive of an acute coronary syndrome (ACS) presenting to the chest pain unit of 1 of 3 participating hospitals were enrolled in this multicenter observational study in an unselected manner. Participation was voluntary and each patient gave written informed consent. The study was approved by the local ethics committees. The original final study diagnosis was based on all available clinical, imaging, and laboratory findings, including serially determined cardiac troponin using conventional in-house cTn-I/T assays, with the respective lowest concentrations with a 10% CV as the diagnostic threshold as suggested before the design of the study (17). All of this information was reviewed by 2 independent cardiologists, which led to the final diagnosis. A third cardiologist refereed in situations of disagreement. Furthermore, a reclassification of the final diagnosis was made using the same clinical and imaging results and additionally applying a cs-cTn assay, fulfilling the assay imprecision recommendations (5) and using the same serial samples. Selection of patients included in this study was based on data availability. To exclude a bias, only patients with a complete dataset regarding the variables used in the different statistical models were used. The study design is shown as a flow scheme in Fig. 1. Based on a total number of 1876 patients admitted, after exclusion of 58 patients because of predefined criteria or withdrawal of consent, an overall patient number of 1818 remained. Data on the cs-cTn assay was available for 1786 on the hs-cTn assay for 1606 patients.

As additional variables used in the statistical estimation models the parameters of the Global Registry of Acute Coronary Events (GRACE) (18) were taken, and therefore only complete cases in respect to these parameters comprised the final patient cohort of 1549 individuals.

In the original study cohort, the final diagnosis was made on the basis of clinical evaluation and serial troponin testing using conventional troponin assays as described earlier (8). To account for the current universal definition of MI (5), with its recommendation regarding the use of the 99th percentile diagnostic threshold (rise or fall of at least 30%) as suggested in a comparable setting with a different cTn assay (19) all patients were reclassified on the basis of clinical information and this troponin criterion using the investigational cs-cTn assay, leading to 314 patients with AMI and 227 with unstable angina. Suffering an AMI or unstable angina was defined as diagnosis ACS in this context. All analyses are presented using this reclassified cohort.
LABORATORY ANALYSES
Blood was drawn for routine workup and sample storage at presentation and after 3 and 6 h, including EDTA plasma, citrate plasma, and serum samples, centrifuged, aliquoted, and stored at −80 °C. An investigational troponin a cs-cTnI assay was used (Architect STAT troponin I assay, Abbott Diagnostics). According to manufacturer, this assay has an LoD of 10 pg/mL, with a measurement range of 0–50000 pg/mL. The lowest concentration with CV of 10% as well as the 99th percentile cutoff concentration is 32 pg/mL.

As comparator and gold standard regarding available diagnostic information below the LoD of the cs-cTnI assay, the recently available version of the respective cTnI assay with substantially improved analytically sensitivity was used (hs-cTnI). This assay (Architect STAT high sensitive troponin, Abbott Diagnostics) has an LoD of 1.9 ng/L, with measurement range of 0–50000 pg/mL and lowest concentration with CV ≤10% at 5.2 ng/L.

Both described cTnI assays were performed by experienced technical assistants blinded to patient characteristics. cs-cTnI and hs-cTnI were assayed each as 1 batch using new aliquots without additional freeze/thaw cycles in 2009 (cs-cTnI) and 2010 (hs-cTnI). Because these 2 assays were applied to frozen samples, research staff involved in enrollment as well as treating physicians were unaware of theses troponin measurements at time of treatment.

STATISTICAL METHODS
For descriptive statistics, data are presented as mean with SD or median with interquartile range (IQR), as appropriate. Accordingly, groups were compared using the Fisher exact test, t-test or Mann–Whitney rank–sum test. Correlations between continuous variables were assessed by Spearman rank correlation coefficients. To describe the diagnostic value of the 2 cTnI assays, including different models to estimate values below the LoD of cs-
cTnI, assay ROC curves based on the continuous biomarker concentrations were calculated. To test for differences in the area under the curve (AUC) 95% CIs were computed (21). Diagnostic sensitivity, diagnostic specificity, and negative predictive value (NPsVs) of all possible thresholds were computed by applying the specific cutoff values and calculating the corresponding numbers based on a 2 × 2 table.

To estimate/reconstruct quantities below the LoD (< L), different models were applied. As the comparator, only individuals with cs-cTnI values above the LoD were used (model 1).

As model 2, values below the LoD were replaced by a constant (LoD/2). Additionally, other available clinical parameters were taken into account to serve as predictors in a model. Here we used a model using sex and age (model 3) as well as a model incorporating the variables of the GRACE score, a well-established clinical score to define high-risk individuals in patients with suspected ACS (model 4).

The following considerations were used for the estimation model 3 and 4: the distribution of troponin I, parameters were taken into account to serve as predictors in a model. Here we used a model using sex and age (model 3) as well as a model incorporating the variables of the GRACE score, a well-established clinical score to define high-risk individuals in patients with suspected ACS (model 4).

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Results

Determination of cs-cTnI assay results in the cohort of 1549 patients with suspected ACS led to measurable values above the LoD in 462 (30%) individuals and levels above the LoD but below the 99th percentile in 105 (7%) patients, whereas 357 (23%) patients showed increased levels above the 99th percentile at presentation. Forty-seven (5%) of the patients with very low (below LoD) and 41 (39%) of those with intermediate (between LoD and 99th percentile) cs-cTnI values developed an AMI. Table 1 provides the baseline characteristics of the study cohort classified according to cs-cTnI concentration. Because the comparator hs-cTnI was measured in the same individuals, the number of patients with undetectable values (below LoD) was reduced, with values above the LoD in 1164 (75%) individuals and levels above the LoD but below the 99th percentile in 767 (50%) patients, whereas 397 (26%) patients showed increased levels above the 99th percentile at presentation. Two (< 1%) of the patients with hs-cTnI levels below the LoD as well as 68 (9%) patients with levels between LoD and 99th percentile on admission developed an AMI.

DIAGNOSTIC VALUE BELOW THE LOD OF A cs-cTnI ASSAY

First, to depict the effect of low cTnI values on a diagnostic rule-in approach, the association of troponin I, determined highly sensitive, and the extent of the coronary artery disease quantified by the angiographical severity between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) score is depicted in Fig. 2A [r = 0.471 (CI, 0.399–0.538), p_corr < 0.001]. Fig. 2B shows the loss in information when artificially limiting the LoD of the hs-cTnI assay to the LoD of the cs-cTnI assay. Such a substitution of hs-cTnI measurements below the LoD of the cs-cTnI assay with a constant value, in this case the LoD concentration, tended to decrease the association, with a lower correlation with the SYNTAX score (r = 0.457, CI, 0.384–0.525), (p_corr < 0.001) (P = 0.78 for comparison).
Second, in respect to a diagnostic rule-out approach of an ACS (Fig. 2C) or an MI (Fig. 2D), the NPV of different hs-cTnI concentrations is provided, showing the loss in diagnostic information when applying the LoD of the cs-cTnI assay, especially to exclude ACS.

**ESTIMATION OF VALUES BELOW THE LOD OF A cs-cTnI ASSAY**

To estimate cTnI values determined with a cs-cTnI assay below the respective LoD, 4 models were tested. To reflect the clinical relevance, the impact on the diagnostic performance with respect to the diagnosis of ACS or AMI of the different methods with the substitution of low cTnI values was quantified using the AUC in ROC analyses of the 4 models. To avoid random effects on the ROC curves, all patients in models 3 and 4 have been put into the order of their estimated conditional expected values.

As a first model, a simple depletion of cs-cTnI data measured below the LoD was used, which demonstrated a rather extensive loss of information for the diagnosis of AMI, with AUC of 0.781 (CI, 0.731–0.831), as well as ACS, with AUC of 0.801 (CI, 0.766–0.836) using the cs-cTnI assay compared to the hs-cTnI assay [AUC for AMI, 0.949 (CI, 0.936–0.961); for ACS, 0.862 (CI, 0.842–0.882)] (Fig. 3A and E).

As a second model, the commonly used substitution of data measured below the LoD with a constant value was used. This led to an improved diagnostic ability of the cs-cTnI assay, with AUC of 0.895 (CI, 0.873–0.917) for diagnosis of AMI compared to model 1, but still below the discriminatory information of the hs-cTnI assay (Fig. 3B). Of interest, the AUC for diagnosis of ACS for cs-cTnI did not improve, with a comparable AUC of 0.790 (CI, 0.767–0.813) (Fig. 3E).

As a third model, patient data easily available in clinical routine, namely age and sex, were used in a modified y regression model. This estimation approach led to a slightly further improved cs-cTnI AUC for diagnosis for AMI of 0.906 (CI, 0.884–0.927) and an improved AUC for the diagnosis of ACS of 0.834 (CI, 0.812–0.856) (Fig. 3D and 3H).

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**Table 1. Baseline characteristics of the study cohort of patients with suspected acute coronary syndrome.**

<table>
<thead>
<tr>
<th></th>
<th>cTnIbelowLoD(n = 935)</th>
<th>cTnIbetweenLoDand99th percentile(n = 85)</th>
<th>cTnIabove99th percentile(n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>59 (14)</td>
<td>67 (13)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Sex, males</td>
<td>629/935 (67%)</td>
<td>49/85 (58%)</td>
<td>211/323 (65%)</td>
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<tr>
<td>Classical risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index &gt;30</td>
<td>248/867 (29%)</td>
<td>19/77 (25%)</td>
<td>79/298 (27%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>645/935 (69%)</td>
<td>68/85 (80%)</td>
<td>253/323 (78%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>153/935 (16%)</td>
<td>21/85 (20%)</td>
<td>72/323 (22%)</td>
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<tr>
<td>Current smoking</td>
<td>230/934 (25%)</td>
<td>20/85 (24%)</td>
<td>93/323 (29%)</td>
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<tr>
<td>Dyslipidemia</td>
<td>665/935 (71%)</td>
<td>62/85 (73%)</td>
<td>247/323 (76%)</td>
</tr>
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<td>Parental CAD</td>
<td>334/934 (36%)</td>
<td>20/85 (24%)</td>
<td>109/322 (34%)</td>
</tr>
<tr>
<td>Known CAD</td>
<td>303/934 (32%)</td>
<td>40/85 (47%)</td>
<td>123/323 (38%)</td>
</tr>
<tr>
<td>GRACE score variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>59 (14)</td>
<td>67 (13)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Heart rate, mean (SD)</td>
<td>73 (15)</td>
<td>73 (17)</td>
<td>77 (17)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD)</td>
<td>142 (23)</td>
<td>149 (28)</td>
<td>144 (25)</td>
</tr>
<tr>
<td>Creatinine, median (IQR)</td>
<td>0.93 (0.81–1.06)</td>
<td>1.00 (0.88–1.22)</td>
<td>0.99 (0.87–1.21)</td>
</tr>
<tr>
<td>Killip class, 3-tuple</td>
<td>(81%, 8%, 10%)</td>
<td>(75%, 15%, 9%)</td>
<td>(73%, 16%, 11%)</td>
</tr>
<tr>
<td>ST elevation</td>
<td>72/935 (8%)</td>
<td>14/85 (16%)</td>
<td>51/323 (16%)</td>
</tr>
<tr>
<td>ST depression</td>
<td>60/935 (6%)</td>
<td>15/85 (18%)</td>
<td>77/323 (24%)</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>47/938 (5%)</td>
<td>41/105 (39%)</td>
<td>226/279 (81%)</td>
</tr>
<tr>
<td>ACS</td>
<td>191/1087 (18%)</td>
<td>46/105 (44%)</td>
<td>304/357 (85%)</td>
</tr>
</tbody>
</table>

* Patient characteristics are given according to cTnI concentrations if determined using a contemporary sensitive assay. Data are presented as number with percentage, mean with SD, or median with IQR as appropriate.
* LoD denotes level of detection and 99th percentile of the diagnostic threshold concentration of the used cs-cTnI with 10 ng/L and 32 ng/L, respectively. CAD, coronary artery disease.
Our fourth model incorporated data of the GRACE score variables, usually used in the setting of ACS risk classification. Here, the same modified regression approach as in model 3 was used. Application of this model to estimate troponin I values below the LoD using the cs-cTnI assay further enhanced the discriminatory information with AUC of 0.921 (CI, 0.902–0.940) for AMI and of 0.838 (CI, 0.816–0.860) for ACS in close approximation to the AUC of 0.949 (CI, 0.936–0.961) and 0.862 (CI, 0.842–0.882) for AMI and ACS respectively if using the hs-cTnI assay (Fig. 3, D and H).

**Fig. 2. Additional diagnostic value of troponin I levels below the LoD.**

Troponin I measured using an hs-cTnI assay in patients with suspected ACS. The blue line depicts the LoD concentration of the cs-cTnI assay. (A) and (B) present the association of cTnI and extent of coronary artery disease quantified by the SYNTAX score. (C) and (D) show the NPV of troponin I to exclude the diagnosis of ACS or AMI (D).

**IMPROVEMENT OF RULEOUT BY USE OF ESTIMATED cs-cTnI VALUES BELOW THE LOD**

The fourth model, which showed greatest improvement of the AUC in the setting of ACS and AMI, was then applied to the clinical approach to rule out these unfavorable diagnoses. The NPV was used to quantify the diagnostic rule-out ability.

The LoD of the cs-cTnI assay as cutoff was associated with an NPV of 0.950 and of 0.826 regarding exclusion of AMI and ACS, respectively. Using the estimated values below the LoD (averaged from random samples of cardinality


\[ \kappa = 5 \text{ for each patient}, \] a cs-cTnI concentration that turned out to be undercut by 25% of patients was associated with an NPV of 0.979 for AMI and of 0.907 for ACS, constituting a clinically relevant improvement of the NPV for rule-out of these diagnoses (Fig. 4). As a comparator hs-cTnI was measured in the same individuals, providing an NPV using the respective LoD as threshold of 0.994 to ruleout AMI and of 0.925 to rule out ACS.

**Fig. 3.** Diagnostic ability of cTnI determined with a cs-cTnI assay and estimated values below the LoD. Area under the ROC of cs-TnI to identify AMI (A–D) or ACS (E–H). hs-TnI assays are presented as comparator. Values of cs-cTnI below the LoD were classified as missing in model 1 (A, E), substituted with constant value LoD/2 in model 2 (B, F), or estimated on the basis of a 2-parameter (model 3; C, G) and 7-parameter model (model 4; D, H).

**Discussion**

Cardiac troponin assays as diagnostic tools are subject to continuous evolution toward increasing the analytical sensitivity of the assay for the respective analyte. The higher analytical sensitivity of hs-cTnI assays in comparison to cs-cTnI assays amended the diagnosis of AMI, especially in regard to early ruleout (16). This improved

**Fig. 4.** Improvement of ruleout of AMI (A) or ACS (B) by use of estimated cTnI values below the LoD. cs-cTnI measurements (right of most right line) and estimated values (5 repetitions). The NPV of estimated cTnI concentrations to be expected in at least 25% and 50% of patients are given.
Given that more sensitive troponin assays provide additional diagnostic information in evaluation of suspected AMI compared to less sensitive assays(16), one could question the real world use of such a statistical models to artificially improve contemporary assay data.

In the setting of prospective patient evaluation, both in a clinical and a scientific context, it will be difficult to argue for not using the most sensitive assay available. Even in cases of less sensitive assays it might be of use to report all determined values as recommended by the IUPAC or ISO guidelines instead of censoring data. Use of very low cardiac troponin concentrations at the LoD or even below the LoD irrespective of the CV at this concentration, instead of censoring such data, is supported by our data showing an additional diagnostic rule-out potential even of statistically estimated values below the LoD. Contrarily, according to the US Food and Drug Administration, in patient care only values measured on US instruments with acceptable imprecision, usually at the lowest concentration with CV ≤20%, should currently be reported.

Moreover, application of our estimation model could be beneficial in other biomarkers with available assays in earlier developmental stages compared to modern hs-cTnI assays. With respect to posthoc analyses of large data sets, e.g., of clinical studies, such an information gain using estimation of nonreported values could be an alternative to remeasurement using more sensitive assays. Here, economic considerations, sample availability, and needed volume must be considered. Finally, for point-of-care measurement, application of our model might overcome the limited sensitivity compared to measurements in a centralized laboratory (27).

It would be interesting to posthoc compare our estimated troponin values with the actually measured uncensored raw data of the used analyzer. Unfortunately, these data on cs-cTnI values below the LoD were not stored at the time of measurement and were not available at the time of the present analyses. We believe that this does not compromise the finding that cs-cTnI values below the LoD, even with potential imprecision because of a statistical estimation, provided valid diagnostic information.

We applied our estimation approach in the setting of ACS, whereas it is unclear if this is applicable in other clinical settings. Our analyses were all carried out using the R statistical software package; we additionally provide a Microsoft Excel Version (see online Supplemental File) as proposed by others (15). We encourage all readers to test our approach with their own datasets.

In conclusion, estimation of values below the CV-based LoD of a cs-cTnI assay with a statistical approach incorporating additional information of relevant clinical parameters improved the diagnostic performance of the cs-cTnI assay in evaluation of patients with suspected AMI.
Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References


