The importance of evaluating measurement uncertainty for troponin I

Measurement uncertainty of troponin I

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Abstract

Aim: Myocardial infarction can be life threatening and the early diagnosis of acute myocardial infarction is highly important. The measurement of cardiac troponin is the preferred way to establish the diagnosis of acute myocardial infarction. Measurement uncertainty provides quantitative estimates of the level of confidence that a laboratory has in its analytical precision of test results. The aim of this study is to present the importance of reporting hs-troponin I analysis results with measurement uncertainty estimation. Material and Method: The results of 16679 patients (8060 males and 8619 females) whose hs-troponin I results were analyzed in our laboratory in 2016 were retrospectively reviewed. The uncertainty of measurement was calculated according to Eurachem/CITAC Guide CG. The hs-troponin I analysis results were re-evaluated by estimation of measurement uncertainty. Results: Measurement uncertainty for hs-troponin I is estimated to be ± 19.60 %. In this study, 346 hs-troponin I analysis results (206 females and 140 males) which are above manufacturer recommended cutoff values might be below cutoff values if they were assessed based on measurement uncertainty. Also, 260 Troponin I analysis results (155 females and 105 males) which are below manufacturer recommended cutoff values cutoff values might be above cutoff values if they were assessed based on measurement uncertainty. The results of 606 out of 16679 patients (3.63%) were affected by uncertainty values. Discussion: Medical laboratories should calculate uncertainty of troponin tests and report this in conjunction with troponin results to help clinicians. A test result is not powerful enough without an assessment of its reliability. Therefore, hs-troponin I results which are close to cutoff values should be evaluated with uncertainty of measurement.

Keywords

Measurement Uncertainty; High-Sensitivity Troponin I; Myocardial Infarction

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Introduction

Heart disease is an important cause of death all over the world. Myocardial infarction can be life threatening and the early diagnosis of acute myocardial infarction (AMI) is highly important. Early diagnosis and treatment is important for people who are suspected of having an AMI and prevents complications that can be caused by AMI.

The measurement of cardiac troponin (cTn) is the preferred way to establish the diagnosis of acute myocardial infarction (AMI) [1]. European Society of Cardiology (ESC) guidelines recommend serial measurement of troponin after 1 or 3 hours, when using high-sensitivity assays [2]. High-sensitivity troponin (hs-troponin) assays have been developed for detection of extremely low troponin concentrations [3]. Such hs-troponin assays are recommended in early rule-out protocols for AMI [4]. Hs-troponin assays are now being used more frequently worldwide [5]. The recommended diagnostic cutoff value for AMI is a cardiac troponin value that exceeds the 99th percentile of a healthy population, as determined by an assay with acceptable precision [1].

Uncertainty of measurement is a quality parameter of measurement results, which is used to represent a dispersing level of test results [6]. ISO 17025 and 15189 accreditation standards recommend that laboratories provide the measurement uncertainty of the results and the calculation of total allowable error (TAE) [7]. Hs-troponin levels, on which clinical decisions are based, should be standardized and reliable. So laboratories should study imprecision, method validation, reference change value and uncertainty. The aim of this study is to present the importance of reporting hs-troponin I analysis results with measurement uncertainty estimation.

Material and Method

The study was conducted in Ankara Polatlı Public Hospital. We retrospectively reviewed the records of 16679 patients (8060 males and 8619 females) who hs-troponin I results were analyzed from January 2016 to December 2016.

Hs-troponin I method

The CMIA (Chemiluminescent Microparticle ImmunoAssay) method in i2000 Architect Abbott auto analyzer (Rungis, France) was used to determine hs-troponin I values in human serum samples per the manufacturer's instructions. The samples were analyzed per manufacturer's instructions using original commercial kits.

Imprecision

The normal and abnormal level samples were used to determine the assay imprecision (Table 1) by estimating within-run and total standard deviations and by calculation of coefficient of variation (% CV), according to the CLSI (formerly NCCLS) EP5A protocol [8].

For the normal level sample (mean value 25.7, hs-Troponin I), the within-run precision was 3.85% CV (SD=0.992), between-run precision was 5.71% CV (SD=1.47), between-day precision was 1.61% CV (SD=0.415), and total precision was 7.08% CV (SD=1.82). For the abnormal level sample (mean value 60.3, hs-Troponin I), the within-run precision was 4.84% CV (SD=2.88), between-run precision was 1.85% (SD=1.10), between-day precision was 2.86% CV (SD=1.71), and total precision was 5.92% CV (SD=3.53).

Estimation of measurement uncertainty

The hs-troponin I analysis results were re-evaluated by estimation of measurement uncertainty (MU). We used internal and external quality control results to calculate MU according to Eurachem/CITAC Guide CG 4(Table 2) [6].

The formulation of uncertainty is explained below.

uRW: √ ((CV1 (internal quality control (level1))² + CV2 (internal quality control (level2)²)/2))

To calculate uncertainty of within-laboratory reproducibility (uRW), we used Architect Stat Troponin I control level 1 coefficient of variation (CV %) and level 2 %CV for a month.

RMS bias :√[(∑bias (external quality control) ²/n] (n: number of external quality control).

Table 1. Precision study's data of the hs-Troponin I assay

	Normal sample	Abnormal sample
A.Within run precision		
Number of data points	80	80
Total mean	25.7	60.3
Within run SD	0.992	2.889
Within run CV%	3.85	4.84
B.Between run precision		
Number of data points	80	80
Total mean	25.7	60.3
Between run SD	1.473	1.10
Between run CV%	5.71	1.85
C.Between day precision		
Number of data points	80	80
Total mean	25.7	60.3
Between day SD	0.415	1.71
Between day CV%	1.61	2.86
D. Total Precision		
Number of data points	80	80
Total mean	25.7	60.3
Total SD	1.82	3.53
Total precision CV%	7.08	5.92

Table 2. Values used for calculation of measurement uncertainty of hs-troponin I

Internal quality control, CV% and uRw values.	Internal quality control level 1 (mean and CV%)	24.73- 8.94%
	Internal quality control level 2 (mean and CV%)	59.85- 5.99%
	uRW	7.61
External quality control, RMS bias, CV%, n and u(cref) values.	RMSbias	6.04
	CV%	8.27
	n	40
	Ucref	1.29
Standard, combined and expanded uncertainty values	Standard uncertainty(ubias)	6.17
	Combined uncertainty(u)	9.80
	Expanded uncertainty	19.60

For calculation bias, we used RIQAs external quality control results for eight months. Root Mean Squares of Biases (RMS bias) and uncertainty component from the certified or nominal value (ucref) were calculated. External quality control bias results were used to calculate RMS bias.

ucref: (sR / √n)

External quality control result's mean CV% (sR) and number of laboratory were used to calculate ucref.

Standard uncertainty (ubias):√((RMSbias)^2 + (ucref)^2)

Combined uncertainty (u) = √(((uRW)^2 + (ubias)^2) / 2)

Expanded uncertainty (U) = k * u

k: coverage factor (for 95% level of confidence k=2)

Expanded uncertainty results were compared to total allowable error of hs-troponin I test.

Results

Values of Troponin I cut off were recommended by manufacturer as 34.2 pg/mL for male and 15.6 pg/mL for female in data sheets of the commercial kits. Values used for calculation of measurement uncertainty of hs-troponin I are given in Table 1. Measurement uncertainty (95% confidence interval) for hs-troponin I is estimated to be ± 19.60 %. In this study, 346 hs-troponin I analysis results (206 females and 140 males) which are above cutoff values might be below cutoff values if they were assessed based on measurement uncertainty. Also, 260 hs-troponin I analysis results (155 females and 105 males) which are below cutoff values might be above cutoff values if they were assessed based on measurement uncertainty. It was observed that the results of 606 out of 16679 patients (3.63%) were affected by uncertainty values.

TAE was ± 27.91 % to Desirable Biological Variation Database. Estimated Measurement uncertainty of hs-troponin I is (±19.60 %) lower than TAE in our study.

Discussion

Measurement uncertainty provides quantitative estimates of the level of confidence that a laboratory has in its analytical precision of test results. According to ISO 15189, MU should be made available by the laboratory on request [9]. The laboratory should determine the uncertainty of results where relevant and possible. Since the evaluation of MU was determined essential and important, several studies have investigated measurement uncertainties of different parameters [10,11].

Cardiac markers play a major role in the diagnosis and treatment of patients suspected of having AMI. Standardization of hs-troponin I is important for laboratories but standardization is difficult for heterogeneous molecules such as troponin I [12]. The ESC and ACC recommend a single decision cutoff point for cTn based on the 99th percentile of a reference population for the diagnosis of patients presenting with AMI and an imprecision of 10% coefficient of variation (CV) at the 99th percentile [13].

We calculated %CV of hs-troponin I assay according to EP5A protocol. For clinical use, acceptable %CV for cardiac troponin assays is %10 at the 99th percentile [14]. The hs-assays have less analytical error and reach the highest precision of clinical-practice guideline precision recommendations (% CV <10%) at the 99th percentile [15]. In our laboratory, total %CV of both two levels were 7.08% and 5.92% for hs-troponin I, and they were within acceptable range.

Measurement uncertainty estimates an interval of values within which the 'true' value of a measured analyte lies, with a stated level of confidence [16]. Troponin measurement should be made with standardized methods to achieve comparable results regardless of the assay system or laboratory where the measurement is performed [17]. Laboratories should calculate uncertainty of troponin tests and report these in conjunction with troponin results to help clinicians. For standardization of troponin results, uncertainty of measurement becomes important.

Medical laboratories should calculate uncertainty of troponin tests and report these with troponin results to help clinicians. A test result is not powerful enough without an assessment of its reliability. Therefore, hs-troponin I results which are close to cut off should be evaluated with uncertainty of measurement. Reporting hs-troponin I results with measurement uncertainty is important to show measurements that are contained within the true limits and the level of confidence.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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