Review

Aldo Clerico*, Martina Zaninotto, Alberto Aimo, Andrea Padoan, Claudio Passino, Antonio Fortunato, Claudio Galli and Mario Plebani

Advancements and challenges in high-sensitivity cardiac troponin assays: diagnostic, pathophysiological, and clinical perspectives

On behalf of the Italian Study Group on Cardiac Biomarkers

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Abstract: Although significant progress has been made in recent years, some important questions remain regarding the analytical performance, pathophysiological interpretation and clinical use of cardiac troponin I (cTnI) and T (cTnT) measurements. Several recent studies have shown that a progressive and continuous increase in circulating levels of cTnI and cTnT below the cut-off value (i.e. the 99th percentile upper reference limit) may play a relevant role in cardiovascular risk assessment both in the general population and in patients with cardiovascular or extra-cardiac disease. International guidelines recommend the use of standardized clinical algorithms based on temporal changes in circulating cTnI and cTnT levels measured by high-sensitivity (hs) methods to detect myocardial injury progressing to acute myocardial infarction. Some recent studies have shown that some point-of-care assays for cTnI with hs performance ensure a faster diagnostic turnaround time and thus significantly reduce the length of stay of patients admitted to emergency departments with chest pain. However, several confounding factors need to be considered in this setting. A novel approach may be the combined assessment of laboratory methods (including hs-cTn assay) and other clinical data, possibly using machine learning methods. In the present document of the Italian Study Group on Cardiac Biomarkers, the authors aimed to discuss these new trends regarding the analytical, pathophysiological and clinical issues related to the measurement of cardiac troponins using hs-cTnI and hs-cTnT methods.

Keywords: cardiac troponins; high-sensitivity methods; myocardial infarction; myocardial injury; point-of-care testing (POCT) methods; cardiovascular risk

Introduction

We have come a long way since September 2000, when the Joint European Society of Cardiology/American College of Cardiology Committee consensus document on the redefinition of myocardial infarction recommended for the first time that cardiac troponin I (cTnI) and T (cTnT) should be considered the preferred biomarkers for the differential diagnosis of acute coronary syndrome (ACS) [1]. Currently, all guidelines recommend that the clinical cut-off value for the diagnosis of acute myocardial infarction (AMI) should be set at the 99th percentile of the cTn distribution in a reference population (i.e. 99th percentile upper reference limit - URL) and that the analytical imprecision of cTn assays at this value (coefficient of variation, CV) should be≤10 % [2–5]. Furthermore, these recommendations require that cTn assays measure the distribution of the biomarker (including the 99th percentile URL) in a reference population with reasonable accuracy [1–3]. However, almost 15 years passed before manufacturers commercialized the first cTn immunoassays with analytical performance that met these quality specifications [2, 5, 6].

In May 2018, the expert opinion of the Academy of American Association of Clinical Chemistry (AACC) and the Task Force of the International Federation of Clinical

Aldo Clerico is the coordinator of the Italian Study Group on Cardiac Biomarkers.

***Corresponding author: Aldo Clerico**, Scuola Superiore Sant'Anna e Fondazione CNR – Regione Toscana G. Monasterio, Pisa, Italy,
E-mail: clerico@ftgm.it
Martina Zaninotto, Andrea Padoan and Mario Plebani, QI.LAB.MED, Università di Padova, Padova, Italy. https://orcid.org/0000-0003-1284-7885 (A. Padoan). https://orcid.org/0000-0002-0270-1711 (M. Plebani)
Alberto Aimo and Claudio Passino, Scuola Superiore Sant'Anna e Fondazione CNR – Regione Toscana G. Monasterio, Pisa, Italy
Antonio Fortunato, Patologia Clinica, Area Vasta 5 ASUR Marche, Ascoli-Piceno, Italy
Claudio Galli, Independent Researcher, Roma, Italy

Chemistry (IFCC) [2] stated that two criteria are needed to define high-sensitivity methods for cardiac troponin I (hs-cTnI) and T (hs-cTnT) assays: 1) the measurement error of the hs-cTn concentration, corresponding to the 99th percentile URL value, should be≤10 %; 2) measurable hs-cTn concentrations should be achievable at or above the assay's limit of detection (LoD) in≥50 % of healthy individuals of both sexes [2].

In August 2018, the Fourth Universal Definition of Myocardial Infarction [3] stated that: "The detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury". The myocardial injury is considered acute if there is a rise and/or fall in cTn values [3]. Myocardial injury can occur in several cardiac and systemic pathologies [3]. Moreover, the definition of AMI requires the preliminary detection of acute myocardial injury by means of hs-cTn assay in the setting of clinical evidence of acute myocardial ischaemia [3].

Several confounding factors must be considered when evaluating a patient presenting with chest pain to the Emergency Department (ED). Standardized clinical algorithms based on temporal changes in circulating hs-cTn levels should be used to detect myocardial injury progressing to AMI [2]. In August 2020, the European Society of Cardiology (ESC) guidelines suggested that clinical algorithms based on temporal changes of even less than 3 h may be used to diagnose ACS in patients presenting without persistent ST-segment elevation using hs-cTn methods [4].

Although significant progress has been made in recent years, some important questions remain regarding the analytical performance, pathophysiological interpretations and clinical use of hs-cTnI and hs-cTnT assays [5–8]. Some key issues relate to the analytical performance and clinical interpretation of hs-cTnI and hs-cTnT levels, in particular the implementation of new laboratory tests for hs-cTn assay in clinical practice according to the principles of precision medicine and near-patient testing methods [7–11]. In this respect, the methodology of immunoassay methods has been implemented in the last 5 years to establish some point-of-care testing (POCT) methods with analytical performances similar to those of hs-cTnI and hs-cTnT immunometric assays of analytical platforms usually used in clinical laboratories [9–21]. In particular, some POCT hs-cTnI methods have recently been commercialized and their analytical performance and clinical relevance have been validated in independent cohorts [12–14, 16–20].

From a pathophysiological perspective, the cardiomyocyte can undergo either reversible or irreversible damage, e.g. due to a brief occlusion of a coronary artery or intense physical activity [22–28]. Several recent studies have shown that reversible cardiomyocyte damage is characterized by the release into the circulation of a limited amount of cytoplasm or some blebs containing degraded sarcomeric proteins with a lower molecular weight (MW) but a higher plasma turnover rate compared to the intact sarcomeric proteins cTnI (MW=23.5 kDa) and cTnT (MW=33.5 kDa) [21–31]. Recent studies have shown that some forms of troponins I and T with reduced MW and faster plasma clearance than sarcomere-bound troponins are often measured after intense and prolonged physical exercise (e.g. marathon or cycling race) [26, 27, 29–31]. In addition, degraded forms of cTnI and cTnT can be measured in patients with end-stage renal disease [32, 33]. Unfortunately, the immunometric methods for hs-cTnI and hs-cTnT cannot directly measure and identify the circulating forms of the biomarker with lower rather than higher MW [30, 31]. Therefore, currently available hs-cTnI and hs-cTnT assays cannot differentiate between reversible and irreversible myocardial damage by a single biomarker measurement [21, 30, 31]. From a clinical point of view, some recent studies have suggested that a progressive and continuous increase in circulating levels of hs-cTnI and hs-cTnT, both in the general population and in patients with cardiovascular or extra-cardiac disease, may play a relevant role in cardiovascular risk assessment, even when the biomarker levels are still below the 99th percentile URL value [34–41]. Furthermore, a novel approach may be the use of machine learning methods to develop an algorithm for the early diagnosis of AMI in patients presenting to the emergency department, taking into account the results of laboratory methods (including hs-cTn assay) as well as other clinical data [42–44]. This review article aims to discuss these new trends in analytical, pathophysiological and clinical issues related to the measurement of cardiac troponins using hs-cTnI and hs-cTnT methods.

Analytical and methodological issues

In the last 10 years, the use of hs-cTnI and hs-cTnT has allowed the time to diagnosis of AMI to be reduced from 6-12 h to less than 3 h in most patients [4, 5, 9–11, 45, 46]. In particular, the ESC 2020 guidelines recommend the fastest clinical algorithms with blood sampling on admission and after 1 or 2 h (0–1 h or 0–2 h) for the diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) [4]. This recommendation is based on large multicentre studies reporting that these algorithms (especially the 0–1 h algorithm) allow a diagnosis to be made in the shortest possible time, in particular to rule out AMI, thus reducing the time spent in the emergency department [4, 19, 47–53]. However, faster algorithms can only be effectively implemented in

hospitals where the ED works in close collaboration with the clinical laboratory, allowing a turnaround time (TAT) of <60 min, including the time from when the sample arrives at the laboratory to when the testing is completed and the laboratory prepares and releases the results [10–12, 41, 46].

Recently, several expert documents and guidelines have suggested that POCT methods for cTnI and cTnT with high analytical sensitivity may represent a fundamental advance because these methods could further reduce the TAT of cTnI and cTnT measurement in patients with NSTEMI [9–11, 15, 54, 55]. Furthermore, these hs-cTn POCT methods may allow the diagnosis of NSTEMI at home, in the outpatient clinic or even in the ambulance, as these assays do not require sample centrifugation or other preanalytical sample processing [9–11, 15–17, 54–57]. Since 2019, some experimental studies have evaluated the analytical performance of some POCT methods for cTnI assay to test whether these methods meet the requirements for high-sensitivity assays [12–14, 57–61]. The analytical sensitivity data (i.e. limit of detection, LoD, and limit of quantitation, LoQ) and 99th percentile URL values of some POCT cTnI methods reported in these independent studies [12, 14, 57–59] are summarized in Table 1. In addition, the IFCC Committee on Clinical Applications of Cardiac Biomarkers (IFCC C-CB) regularly updates a specific and detailed document reporting the analytical characteristics and performance of all commercially available hs-cTnI and hs-cTnT methods (including POCT assays) according to the technical reports provided by the manufacturers [62]. In addition, several studies have compared the diagnostic accuracy of the POCT hs-cTnI assay with traditional hs-cTnI and hs-cTnT methods in patients with suspected NSTEMI-ACS [12–14, 54–66].

In January 2002, the IFCC C-CB published a document containing an in-depth analysis of the analytical characteristics and clinical relevance of these new POCT methods for cardiac troponins. In particular, the IFCC C-CB document provides several specific requirements for high-sensitivity imprecision criteria concerning the evaluation of several analytical parameters, including: sensitivity values (i.e., LoB, LoD, LoQ), two specific high-sensitivity criteria, linearity, imprecision, analytical specificity, examination of high-dose hook effect, comparison of sample matrix, assessment of hematocrit dependence, and comparison between methods [11]. A very common aphorism among experts in laboratory medicine is that “good, fast and cheap” laboratory testing is a mission impossible [15]. For example, a cheap test may not be cost-effective (or vice versa). However, accurate, rapid and cost-effective laboratory methods are exactly what are needed to detect acute ischaemic myocardial injury in patients presenting to the emergency department with chest pain [9–11, 15–17, 21, 67]. However, from an analytical point of view, some POCT methods are known to be more susceptible to interference from haemolysis, lipemia or sample contamination than hs-cTnI and hs-cTnT methods using automated platforms, which are more difficult to control outside a clinical laboratory [9–11]. In addition, environmental factors such as temperature fluctuations can also affect the performance of POC devices, particularly in

Table 1: Recent studies reporting an independent validation of analytic sensitivity and calculation of 99th percentile upper reference limit (URL) values of point-of-care (POC) methods for cTnI assay methods.

Immunometric system	Instrument	LoD, ng/L	LoQ 10 %, ng/L	99th percentile URL, ng/L	References
PATHFAST POC hs-cTnI	PATHFAST™ instrument	2.9	11.0	W:21.1 (13.4–25.3)[b] n=236 M:27.0 (18.5–27.7)[b] n=238 Overall: 24.2 (17.6–27.4)[b]	Sorensen NA et al. (2019) [12]
KM SPFS POC hs-cTnI method	KM SPFS POC desktop analyzer	0.54	3.9	W:10.7 (n=300) M:20.6 (n=300) Overall:12.2 ng/L (9.2–39.2)[b]	Braga F et al. (2020) [57]
Siemens POC atellica® VTLi hs-cTnI	Atellica® VTLi patient-side immunoassay analyzer	1.2	6.7	W:18.0 (9.0–78.0)[b] n=330 M:27.0 (21.0–37.0)[b] n=363	Apple FS et al. (2021) [14]
Super flex POCT hs-cTnI	SuperFlex platform	1.8	12.0	W:24.0 (n=312) M:27.0 (n=308) Overall: 25.6 (22.0–33.3)[a]	Zhang R et al. (2021) [58]
Siemens POC atellica® VTLi hs-cTnI	Atellica® VTLi patient-side immunoassay analyzer	1.24	2.1	F:18 (9–78)[a] (n=330) M: 27 (21–37)[a] (n=363) Overall: 23(20–32)[a]	Christenson RH et al. (2022) [59]

LoD, limit of detection; LoQ 10 % CV, limit of quantitation 10 % CV; W, women; M, men; overall, M+W; n, number of enrolled individuals; [a] 90 % confidence interval; [b] 95 % confidence interval.

environments without consistent climate control, potentially affecting the reliability of results. Other factors that may lead to false elevations or inaccurate results include: location of the device, allocation of collection and testing, responsibility for (non-laboratory) staff, maintenance of the device, initial and recurrent training, quality control, proficiency assessment, capture of discrepant results, troubleshooting and inventory management [11].

Although hs-cTn POCT methods significantly reduce turnaround time by providing results at the patient's bedside, they still require blood to be drawn. A possible new perspective is the development of wearable devices capable of estimating circulating cTn levels through the skin (so-called "on vivo" testing) [68, 69]. The development of wearable devices with similar analytical performance to the hs-cTn assay is a very complex task. Infrared spectroscopy is an inherently sensitive mode of detection due to its ability to interact with the material at the molecular level and has the advantage of requiring minimal or no sample preparation [67]. The same group of researchers discussed the ability of non-invasive transdermal monitoring of cTnI to provide estimates of cTn blood concentration in a first article [68], while a second article reported the clinical results obtained using the non-invasive transdermal device supported by a deep learning model [69]. In particular, the authors found a significant correlation between optically derived data obtained with the non-invasive transdermal instrument and blood-based immunoassay measurements ($r=0.777$, $p<0.001$, $n=52$ biologically independent samples) with an area under the curve (AUC) value of 0.895 (sensitivity 96 %, specificity 60 %) for predicting a clinically meaningful threshold for defining elevated circulating cTnI levels [68]. The main limitation of this study is the relatively small sample size (n=52) [68]. Sengupta et al. [69] tested the feasibility of a wrist-worn transdermal infrared spectrophotometric sensor (transdermal-ISS) and the performance of a machine learning algorithm to identify elevated hs-cTnI in 238 patients with ACS from 5 different hospitals. A deep learning model derived from the transdermal-ISS was trained and externally validated using hs-cTnI and echocardiography and angiography. The transdermal I-SS model predicted elevated hs-cTnI levels with an AUC of 0.90 [95 % CI: 0.84–0.94; sensitivity 86 %, specificity 82 %] for the internal cohorts and 0.92 (95 % CI, 0.80–0.98; sensitivity 94 %, specificity 64 %) for the validation cohorts. In addition, the model predictions were associated with regional wall motion abnormalities [odds ratio (OR), 3.37; CI, 1.02–11.15; p=0.046] and significant coronary stenosis (OR, 4.69; CI, 1.27–17.26; p=0.019).

The results of these two studies [68, 69] should be considered very preliminary due to the relatively small sample size. However, these studies represent an important first step in the long process of developing some portable devices capable of accurately measuring circulating levels of cardiac troponins [15, 17, 67]. The incorporation of machine learning (ML) and artificial intelligence (AI) capabilities into POCT could lead to compact and portable, even more miniaturized and accurate devices for hs-cTnI and/or hs-cTnT measurements.

Take-home messages

- In the last 10 years, the time to diagnosis of AMI in patients presenting to the ED with suspected ACS has been reduced from 6-12 h to less than 3 h [4, 5, 9–11, 45, 46].
- Several expert documents and guidelines have suggested that the development of POCT methods for hs-cTnI and hs-cTnT may represent a fundamental advance, as these methods could further reduce the turnaround time for cTnI and cTnT measurement in patients with NSTEMI [9–11, 15, 54, 55].
- The IFCC C-CB has published a document outlining the analytical characteristics and clinical relevance required for POCT hs-cTn methods [59].
- A very recent study reported some results on portable devices based on infrared spectroscopic detection of circulating cardiac troponin levels through the skin in hospitalized patients with ACS [69].

Pathophysiological issues

Despite dramatic improvements in assay sensitivity over the past 25 years, Kavsak et al. [70] recently reported that approximately 1/3 of devices measuring hs-cTnT do not meet the precision target at the female URL value recommended by international guidelines. Furthermore, the specific recommendation to evaluate the 99th percentile URL values of hs-cTnI and hs-cTnT methods using a reference population of >400 healthy men and women is not followed even by some studies specifically designed to evaluate the analytical performance of POCT cTnI methods (Table 1) [12, 14, 57, 58]. These data confirm that the evaluation of cut-off values (i.e. the 99th percentile URL) of hs-cTnI and hs-cTnT assays remains an open question [4–6, 11–15, 21, 45, 46, 70–73]. There are at least four main points to consider when evaluating the 99th percentile URL values of cardiac troponins in a reference population: 1) the distribution of circulating levels of hs-cTnI and hs-cTnT is highly right-skewed in healthy men and women; 2) men have significantly higher biomarker levels than women of the same age; 3) biomarker concentrations increase progressively after 55 years of age in both sexes; 4) there is no global consensus on defining health or 'normality'

in a reference population [70–75]. Collectively, these factors make the evaluation of 99th percentile URL values very challenging.

As an example, the sex-specific distributions of circulating hs-cTnI levels measured by the ARCHITECT hs-cTnI method (Abbott Laboratories, Abbott Park, IL, USA) in an Italian reference population are shown in Figure 1A for women and in Figure 1B for men. These data were obtained in a healthy Italian reference population (mean age 51 years; range 18–86 years; number of women: 648; number of men: 665) [72, 73]. In particular, considering that the LoD value of the ARCHITECT hs-cTnI method is 1.3 ng/L [72, 73, 76], more than 50 % of the healthy women enrolled in this reference population have a hs-cTnI value higher than the LoD value (Figure 1A). Although the 99th percentile values of the Italian reference population were evaluated according to all recommendations of international guidelines [2, 5, 45, 46], the sex-specific calculated 99th URL values show very large 95 % confidence intervals (CI), especially for women. In fact, the difference (i.e. 14.1 ng/L) between the high (i.e. 22.6 ng/L) and low (i.e. 8.5 ng/L) value of the 95 % CI is larger than the calculated 99th percentile value for the healthy female population (i.e. 12.4 ng/L) (Figure 1A). However, there were only two women (Figure 1A) and two men (Figure 1B) showing hs-cTnI values above the sex specific 99th URL values (i.e., clearly indicated in the Figure as outliers with an arrow). These 2 women (respectively with age of 39 and 41 years) and men (respectively with age of 22 and 48 years) should be considered true outliers because they had an age<50 years. To summarize, 99th URL values for hs-cTnI and hs-cTnT show a large variability in the reference population (i.e., including only healthy individuals), because it depends not only on the analytical performances of hs-cTnI or hs-cTnT methods, but also on age, sex and body mass of the reference population [41, 77]. Circulating hs-cTn levels of healthy adult subjects represent a reliable index of the physiological cardiomyocyte renewal, which is defined as the ability to replace loss of cardiomyocytes by new ones, as demonstrated by several experimental and clinical studies [23–25, 41, 77–79]. On average, the biological variation of cardiac troponins is similar in healthy subjects [80–85] and patients with cardiac or non-cardiac diseases [86–91]. Overall, the results of these studies [80–91] have demonstrated that both cardiac troponins have an average intra-individual biological variability of about 10 % CV as well as an individuality index of 0.3 [41, 77]. In particular, the individuality index value of cardiac troponins is comparable to that of creatinine, which is considered a reliable biomarker of skeletal muscle turnover [92]. Considering the peculiar biological and physiological characteristics of cardiac troponins, it is not surprising that the evaluation of circulating biomarker levels between two (or more) samples over a given time interval can provide more accurate pathophysiological and clinical information than the comparison of a concentration value measured in only one sample with the 99th percentile URL value of hs-cTnI and hs-cTnT, which is characterized by a high degree of statistical uncertainty because this cut-off value is calculated from a large reference population [41, 71–73, 77].

The commonly recommended statistical approach to assess the variation of a biomarker measured by the same method in two samples is to calculate the reference change

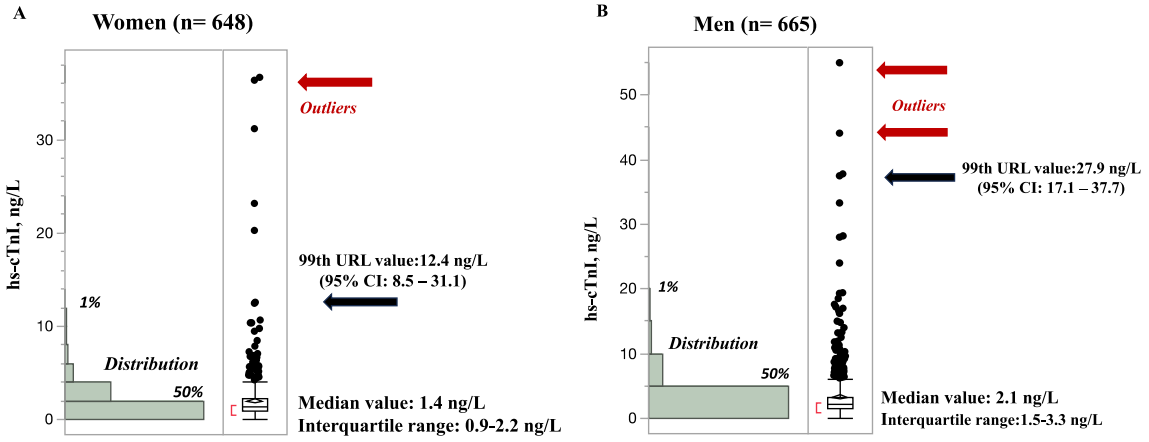

Figure 1: Sex distribution of hs-cTnI circulating levels, measured in an Italian reference population. The circulating hs-cTnI levels were measured in an Italian reference healthy population (mean age: 51.4 years; range from 18 to 86 years; number of healthy men:665, number of healthy women:648, using the ARCHITECT hs-cTnI method in the clinical laboratory of the Fondazione G. Monasterio, CNR and Regione Toscana CNR (Pisa, Italy), as previously reported in detail [72, 73]. The distribution of circulating levels and the 99th percentile URL values of the ARCHITECT hs-cTnI method (Abbott laboratories, Abbott Park, IL, USA) were calculated using the JMP-17 statistical software (SAS, statistical discovery LLC, 920 SAS camp drive cary, NC 27513) according to the harrell-davis distribution-free (non-parametric) quantile estimator [71, 72], as suggested by the International guidelines [2, 10, 11]. (A) Distribution of hs-cTnI circulating levels, measured in an Italian reference healthy population of healthy women. (B) Distribution of hs-cTnI circulating levels, measured in an Italian reference healthy population of healthy men.

value (RCV) using the following mathematical formula (1) [92, 93]:

$$RCV = 2^{½} \times Z \times \left[(CVa)^2 + (CVi)^2 \right]^{½} \quad (1)$$

Where

- CVa indicates the analytical variability of the method (i.e., the analytical imprecision expressed as a coefficient of variation, CV%);
- CVi is the intra-individual variability of the subject (expressed as %);
- Z is the Zeta score for a bidirectional probability of 95 %, equal to 1.96;
- The value $2^{½}$ (i.e., square root of 2, approximately: 1.41142) must be is used when the RCV is calculated using two consecutive samples collected from the same subject.

Considering the formula (1), the RCV related to the measurement with hs-cTnI and hs-cTnT methods of two consecutive samples from the same subject should be equal to 39 % if both CVa and CVi are equal to 10 % [41, 72, 73, 77]. In turn, CVa and CVi are considered equal to 10 % because international guidelines specifically require that all hs-cTnI and hs-cTnT methods should measure the 99th percentile URL value with an analytical error≤10 % CV (2), and the intra-individual variability is≤10 % in both healthy subjects [80–85] and patients with cardiac or non-cardiac disease [86–91].

The analytical error of a typical immunometric method, expressed as CV% values, shows a curvilinear relationship with the measured biomarker concentration [6, 15, 73]. As an example, the results shown in Figure 2A report the imprecision profile of the five most popular hs-TnI and hs-cTnT methods used by clinical laboratories in European and North American countries. The analytical error is very high for concentrations<3 ng/L, but decreases rapidly to a plateau value corresponding to approximately CV≤5 % for all measured hs-cTnI and hs-TnT values near and above the 99th percentile URL (i.e., hs-cTnI values≥10 ng/L). In addition, Figure 2 calculates the curvilinear fit, using a reciprocal function, between the data related to the imprecision profile of the five hs-TnI and hs-cTnT methods. In other words, the reciprocal function reported in Figure 2A could be considered as the "mean" imprecision profile among the five hs-cTnI and hs-TnT methods. Overall, the data presented in Figure 2A and B suggest that: 1) the imprecision profiles of the 5 hs-cTnI and cTnT methods are very similar, especially for biomarker values≥10 ng/L; 2) the analytical error of 10 CV % of these methods corresponds on average to a hs-cTn concentration of 6.3 ng/L. However, it is important to note that the differences in CV at low concentrations between the hs-cTnI and hs-cTnT methods, are relevant for the diagnosis of NSTEMI using rapid rule-out algorithms in patients presenting to the emergency department [4, 45, 46].

From a clinical point of view, several experimental studies have confirmed that biomarker variations measured by hs-cTnI and hs-cTnT methods are clinically relevant when the RCV is greater than 30 % [94–97]. This practical approach can be considered as a general rule of thumb that applies without exception to all hs-cTnI and hs-cTnT methods, as well as to any clinical condition where an increase and/or decrease in biomarker concentrations should be verified for the diagnosis of myocardial injury [3, 41].

Take-home messages

- The 99th percentile URL values for hs-cTnI and hs-cTnT show a large variability in the reference population (i.e. including only healthy adult individuals) because it depends not only on the analytical performance of the hs-cTnI or hs-cTnT method, but also on the age, sex and body mass characteristics of the reference population [41, 71, 77].
- The hs-cTnI and hs-cTnT methods have different measured concentration values and reference limits, but the RCV values are similar for the biomarker values measured around the 99th percentile URL [41, 72, 73, 77].
- Several experimental studies have shown that biomarker variations measured by hs-cTnI and hs-cTnT methods are clinically relevant when the RCV is≥30 % [94–97].

Clinical interpretation of temporal hs-cTnI and hs-cTnT variations

The Study Group on Cardiac Biomarkers of the Italian Societies of Laboratory Medicine has recently discussed the importance of evaluating hs-cTnI and hs-cTnT variations for a) the differential diagnosis of ACS in patients admitted to the emergency department [41, 98]; b) the prediction of cardiovascular risk in patients undergoing major cardiac or non-cardiac surgery [99], or c) asymptomatic subjects from the general population or athletes [31, 39, 41]; d) the assessment of cardiotoxicity caused by the administration of some chemotherapeutic drugs [100]; e) the assessment of cardiovascular risk in pregnancy [101].

For the diagnosis of ACS, both the 2020 [4] and the most recent 2023 [102] ESC guidelines recommend the most rapid algorithms (0–1 h or 0–2 h). The assessment of biomarker

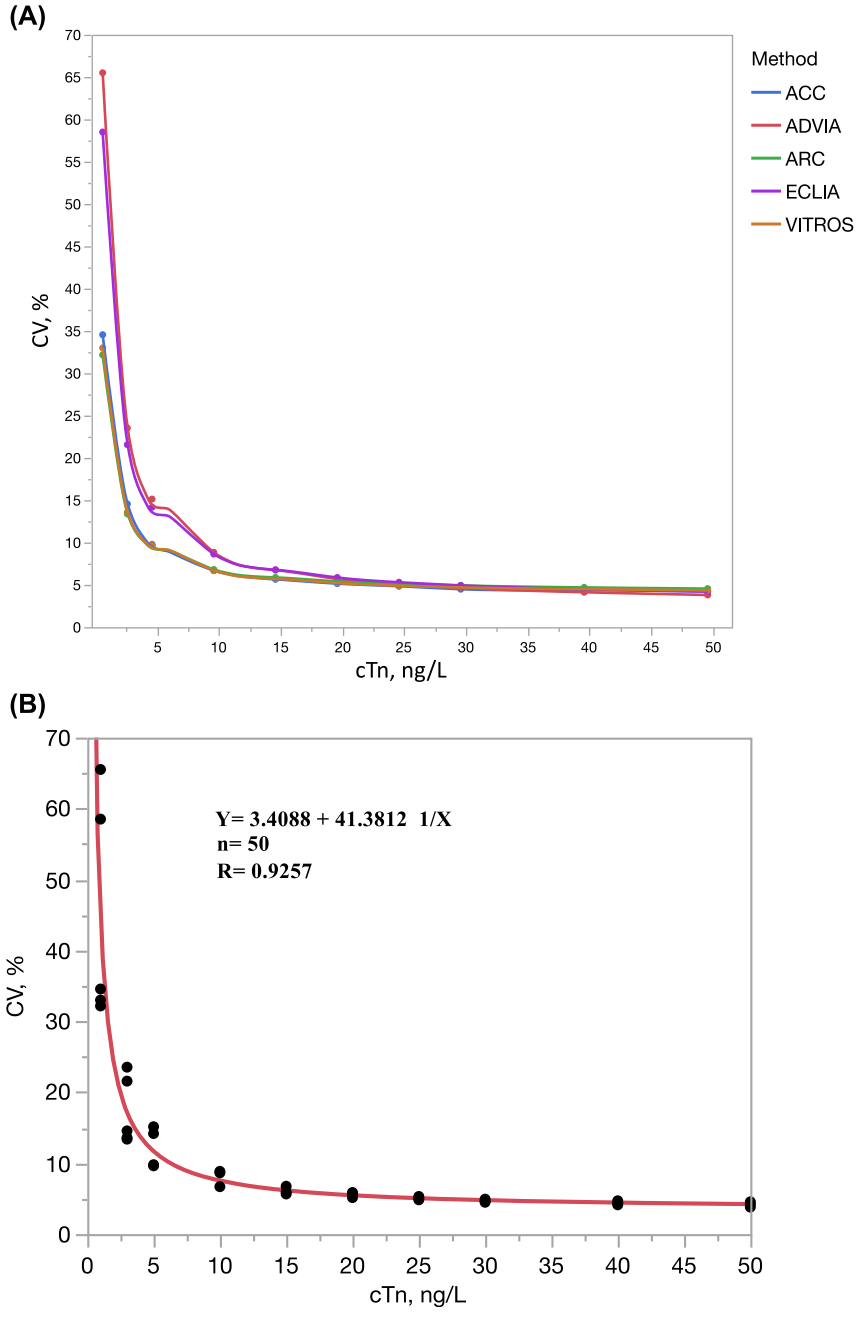

Figure 2: Imprecision profiles of hs-TnI and hs-cTnT methods. (A) The Figure shows the imprecision profile of the five most popular hs-TnI and hs-cTnT methods utilized by the clinical laboratories of European and North American countries. (B) The Figure shows the mean imprecision profile calculated from the five hs-cTnI and hs-cTnT methods reported in (A). The curvilinear fitting, using a reciprocal function, is calculated among the data related of imprecision profile of the five hs-TnI and hs-cTnT methods using the JMP-17 statistical software (SAS, statistical discovery LLC, 920 SAS Camp Drive Cary, NC 27513).

kinetics is based on cut-offs expressing the absolute difference between concentrations at baseline and at 1 or 2 h, defined as the delta (Δ) change. These cut-off values are sex independent but assay specific. In accordance with the 2023 ESC guidelines [102], these cut-off values were derived and validated in large multicentre diagnostic studies using central adjudication of the final diagnosis for all currently available hs-cTn assays [103–125]. These rapid algorithms were developed from large derivation cohorts and then validated in large independent validation cohorts [102]. The optimal rule-out thresholds were chosen to provide a negative predictive value (NPV) of at least 99 %, while the optimal rule-in threshold should be chosen to provide a positive predictive value (PPV) of at least 70 % [102]. Both the IFCC document 2021 [10] and the NICE guidelines [46] state that sex- and method-specific cut-offs are preferable, as many studies have shown that sex-based differentiation allows a more accurate diagnosis of NSTEMI-ACS, especially when hs-cTnI methods are used in female patients [125–130]. A relevant clinical finding is the time from symptom onset, which is used to evaluate the change in concentration levels measured by the hs-cTnI and hs-cTnT methods [3, 45, 98, 131].

The Fourth Universal Definition of Myocardial Infarction (3) identifies a specific group of patients who are admitted to the ED more than 12 h after the onset of symptoms of myocardial ischaemia (i.e., referred to as "late presenters"). These patients may be admitted to the ED when the peak concentration has already been reached and the circulating levels of the biomarker are therefore decreasing (i.e. the descending phase of the biomarker peak) [3, 45, 98, 131]. The decrease in cardiac troponins is usually much slower than the increase detected within the first 24 h after the onset of ischaemia. Accordingly, the late presenters may have hs-cTnI and hs-cTnT changes that are too small to be detected over a few hours (as in the 0 h/1 and 0 h/2 h algorithms), especially if the areas of myocardial necrosis due to the acute ischaemia are also small [3, 45, 98, 131]. Furthermore, late presentation is particularly prevalent in elderly patients presenting to the ED, where 36–50 % of patients aged>65–70 years who do not have AMI often present with hs-cTnI or hs-cTnT levels consistently above the 99th percentile URL value for the presence of some comorbidities, such as diabetes mellitus, chronic kidney disease and heart failure or cardiac amyloidosis [3, 45, 98, 131–135].

According to the document 2021 of the IFCC Committee on Clinical Applications of Cardiac Biomarkers [45], patients presenting late to the ED often have hs-cTnI and hs-cTnT concentrations that may not change significantly (i.e. <30 %) over 1–2 h because they are in the declining phase after the peak of the biomarker. Already in 2013, Bjurman et al. [131] suggested that 26 % of patients with a definitive diagnosis of AMI might not show dynamic changes in hs-cTnT concentrations according to the guidelines in use at that time. Specifically, these authors reported that after 6 h of observation, the relative change in hs-cTnT levels remained<20 % in 26 % and the absolute change remained<9 ng/L in 12 % of NSTEMI patients [131]. The cut-off of all hs-cTnI and hs-cTnT methods for the diagnosis of myocardial damage (i.e. the 99th percentile URL value) usually shows values≥10 ng/L [6, 15, 62, 73]. According to the data shown in Figure 2B, all hs-cTnI and hs-vcTnT methods show an approximately constant analytical error of about 5 CV% for biomarker concentrations>10 ng/L. Considering formula (1), if the CVi is 10 % and the CVa is 5 %, then the RCV for two consecutive samples is 31 %. Of course, an RCV value of 31 % is significantly higher than the<20 % increase in hs-cTnT values observed in the 26 % of some patients with a definitive diagnosis of NSTEMI included in the study by Bjurman et al. [131].

The estimated CVi values reported in the literature range from 4.2 to 63 % (mean 13.1 %) for the hs-cTnI methods and from 1.3 to 16.0 % (mean 8.2 %) for the hs-cTnT method [41, 77]. However, these values vary widely depending on the time frames used in the experimental studies to estimate RCV, which can vary from 1 h to 9 months in 10 different studies [41, 77]. As mentioned above, myocardial damage corresponds to an elevated hs-cTnI or hs-cTnT value with at least one value above the 99th URL and is considered acute if there is an increase and/or decrease in hs-cTnI or hs-cTnT values. As the 99th percentile URL values vary widely between hs-cTnI methods, cTnI should always be measured with the same hs-cTnI method and preferably in the same laboratory. Sex-specific 99th percentile URL values should be used for the pathophysiological and clinical interpretation of temporal hs-cTnI variations, as suggested by several clinical studies, expert documents and international guidelines [2, 3, 5, 11, 14, 39, 41, 45, 46, 72]. On the contrary, there is currently only one hs-cTnT assay commercially available in European and North American countries for automated platforms commonly used in clinical laboratories [6, 8, 10, 72, 73]. The manufacturer of this hs-cTnT assay indicates a cut-off for the diagnosis of myocardial injury that is not sex-specific (i.e. 14 ng/L), although several studies have reported significant sex differences between the 99th percentile URL values of hs-cTnT [6, 8, 10, 72, 73].

Evaluation of hs-cTnI and hs-cTnT kinetics is relevant in some common clinical conditions, including 1) patients undergoing major non-cardiac surgery [99, 136–144]; 2) patients undergoing cancer therapy with cardiotoxic drugs [100, 145–154]; 3) cardiovascular risk assessment in pregnant women [155–162], the general population or athletes [31, 38, 39, 99, 101]. In all these clinical conditions, the detection of myocardial damage by hs-cTnI and hs-cTnT testing is associated with a worse outcome and an increased incidence of major adverse cardiovascular events (MACE) [31, 38, 39, 99, 100]. Although there are currently no specific recommendations from international guidelines, the authors believe that it is necessary to perform a baseline measurement of hs-cTnI/hs-cTnT in every patient to evaluate any significant changes in biomarker levels following therapy or during and after surgery. Some patients may have elevated hs-cTnI and hs-cTnT prior to drug administration or surgery, particularly those over 75 years of age or with cardiovascular disease.

As recently reviewed [101], several studies have evaluated the clinical relevance of cardiac troponin assays in women with pregnancies complicated by diabetes, hypertension, eclampsia or cardiomyopathy [155–162]. In particular, some studies reported a significant association between elevated cardiac troponin levels in pregnancy and a higher risk of cardiovascular complications, dystocia and fetal distress [155, 156, 158–162].

As a general indication, given the large difference between biomarker levels measured by the different hs-cTnI and hs-cTnT methods, it is advisable to repeat biomarker measurements using the same immunoassay method and possibly in the same laboratory to reduce analytical error. In particular, this approach is necessary to accurately assess the temporal variation of hs-cTnI and hs-cTnT concentrations in the same individual or patient, whether at home or in hospital [6, 31, 41, 77, 99, 100].

Take-home messages

- Several studies have suggested that assessment of hs-cTnI and hs-cTnT kinetics is relevant in some common clinical conditions, including: 1) patients undergoing major non-cardiac surgery [99, 136–144]; 2) patients receiving cancer therapy with cardiotoxic drugs [100, 145–154]; 3) cardiovascular risk assessment in pregnant women, the general population or athletes [31, 38, 39, 99, 101].
- The European Society of Cardiology (ESC) guidelines 2020 [4] and 2023 [102] recommend the most rapid algorithms (0–1 h or 0–2 h) for the diagnosis of MI in patients presenting to the emergency department with suspected ACS.
- A relevant clinical finding is the time from the onset of ischaemic symptoms in patients admitted to the ED for the diagnosis of NSTEMI-ACS, which is used to evaluate the change in concentration levels measured by the hs-cTnI and hs-cTnT methods [3, 45, 98, 131].
- Some patients who present to the emergency department more than 12 h after symptom onset of myocardial ischaemia (i.e., referred to as “late presenters”) may be in the declining phase of biomarker levels because the peak concentration has already been reached and therefore the circulating levels of the biomarker are slowly decreasing (variations<30 %) [3, 45, 98, 131].
- Due to the systematic differences between the immunoassay methods, it is always necessary to measure the hs-cTnI and hs-cTnT levels of the same individual/patient using the same method and possibly in the same laboratory in order to reduce analytical errors as much as possible and also to more accurately estimate the variations in biomarker concentrations [6, 31, 41, 77, 99, 100].
- Although there are currently no specific recommendations from international guidelines, the authors believe that it is clinically important to perform a basal measurement of hs-cTnI/hs-cTnT before surgery or administration of cardiotoxic drugs in order to correctly assess any significant changes in biomarker levels [41, 77, 99, 100].

Artificial intelligence and hs-cTnI and hs-cTnT variants

Biological systems are extremely complex, and their analysis requires considerable clinical experience for the human brain to accurately weigh all the multiple factors when making complex decisions [163, 164], such as those related to health sciences and laboratory medicine [165–169]. In particular, laboratory medicine can now benefit from the use of some innovative technologies of network science, such as digitisation, big data, artificial intelligence (AI) and machine learning (ML) [165–169].

AI may promise to further advance the management of patients with chest pain [165]. The diagnosis of AMI is currently based on clinical presentation, ECG, hs-cTnI and hs-cTnT measurements, and cardiac imaging data [4, 10, 11, 45, 46, 165, 166]. Since 2000 [1], several clinical algorithms have been proposed for the diagnosis and management of ACS-NSTEMI in patients presenting to the ED with chest pain [4, 10, 11, 45, 46, 165, 166], but the clinical performance of these algorithms can still vary with patient age, sex and ethnicity, and the time of blood sampling from symptom onset and between samples. This heterogeneity cannot be explained solely by differences in cTnI and hs-cTnT cut-off values or clinical stratification of patient groups into two to four cardiovascular risk groups [165]. In addition, AI algorithms have been used to enhance the diagnostic accuracy of transdermal sensors, as highlighted above [69].

Network analysis can integrate data from different techniques to reveal relationships between biological and clinical factors and analyse underlying and fundamental structures [163, 164]. ML is a quantitative and reproducible way to combine and integrate a large amount of information derived from multiple variables to improve predictive accuracy, and therefore this approach may be very useful for the analysis of large data provided by clinical laboratories [163–170].

In this context, it is important to consider not only the quality of the data collected, but also the pipelines used to validate the algorithms developed [167, 171]. Furthermore, the integration of health data between laboratories and across clinical disciplines is crucial to improve the effectiveness of AI algorithms [171]. Several recent studies have demonstrated that

these innovative approaches (usually based on ML) are able to process and efficiently integrate the information produced by laboratory methods (including data on hs-cTnI and hs-cTnT assays) with those available from large datasets on socioeconomic, demographic and clinical data related to the general population and/or patients with cardiovascular disease [42–44, 172–195]. Here, we discuss only those studies that consider the combined contribution of hs-cTnI or hs-cTnT assay and ML approach, specifically for the diagnosis of AMI. Table 2 summarizes the results of some multicentre (or very large

Table 2: Clinical studies, evaluating the combined hs-cTnI and hs-cTnT assay and Machine Learning (ML) approach for the diagnosis of SCA-NSTEMI in patients admitted to ED.

Study	Study aims	Studied populations	Results
Björkelund A, et al. J Am Coll emerg physcians open 2021 [177]	Authors aimed to assess the predictive accuracy of machine learning algorithms based on paired hs-cTnT concentrations with varying sampling times, age, and sex in order to rule in or out AMI. Authors compared the performance of an artificial neural network with ESC guideline-recommended 0/1- and 0/3-h algorithms for hs-cTnT and with logistic regression without interaction.	Authors enrolled 5,695 chest pain patients at 2 hospitals in Sweden 2013–2014. Patient data on chief complaint, age, and sex and laboratory data on hs-cTnT and discharge diagnosis were extracted from the EXPECT database.	ML algorithms and logistic regression had similar (95 %) areas under the receiver operating characteristics curve. Machine learning algorithms allow for flexibility in sampling and have the potential to improve risk assessment among chest pain patients at the ED.
Liu N, et al. BMC med res methodol 2021 [178]	Authors aimed to investigate if ML dimensionality reduction methods can improve performance in deriving risk stratification models.	A retrospective analysis was conducted on the data of patients >20 years old who presented to the ED between September 2010 and July 2015. 795 chest pain patients were enrolled in this study, of which 247 (31 %) patients had MACE within 30 days of presentation to the ED.	Dimensionality reduction models showed marginal value in improving the prediction of 30-day MACE for ED chest pain patients. Moreover, they are black box models, making them difficult to explain and interpret in clinical practice.
Liu WC, et al. EuroIntervention 2021 [179]	Authors aimed to develop a deep learning model (DLM) as a diagnostic support tool based on a 12-lead electrocardiogram.	The retrospective cohort study included 1,051/697 ECGs from 737/287 coronary angiogram (CAG)-validated STEMI/NSTEMI patients and 140,336 ECGs from 76,775 non-AMI patients at the emergency department. The DLM was trained and validated in 80 and 20 % of these ECGs.	The AUC of the DLM for STEMI detection was 0.976 in the human-machine competition, which was significantly better than that of the best physicians. Furthermore, the DLM independently demonstrated sufficient diagnostic capacity for STEMI detection (AUC=0.997; sensitivity, 98.4 %; specificity, 96.9 %). Regarding NSTEMI detection, the AUC of the combined DLM and hs-cTnI increased to 0.978, which was better than that of either the DLM (0.877) or hs-cTnI (0.950).
Emakhu J, et al. Comput methods programs Biomed 2022 [183]	Authors aimed to develop an ensemble learning-driven framework as a diagnostic support tool to prevent misdiagnosis. An analytical framework equipped with many well-developed algorithms was applied to improve the data quality by addressing missing values, dimensionality reduction, and data imbalance.	This single-center study included 31,228 patients, of whom 563 (1.8 %) had ACS and 30,665 (98.2 %) had alternative diagnoses. 11 features, including systolic blood pressure, BNP, chronic heart disease, coronary artery disease, creatinine, glucose, heart attack, heart rate, nephrotic syndrome, red cell distribution width, and cTn levels, was found to be significantly contributing risk factors.	The proposed framework successfully classified the cohorts of patients with sensitivity and AUROC as high as 86.3 and 93.3 %. The evaluated model's accuracy, precision, and specificity, were: 85.7 %, 86.3%, 93%, and 80 %.
Ke J, et al. Am J emerg med 2022 [185]	The purpose of this single-center study was to identify the risk factors of in-hospital mortality in patients with ACS and to evaluate the performance of traditional regression and ML prediction models.	6,482 ACS patients were included in the study with an in-hospital mortality rate of 1.88 %. The study used univariate and multivariate logistic regression analyses to identify risk factors for in-hospital mortality of ACS patients.	The AUC ROC values of the models developed by logistic regression, gradient boosting decision tree, random forest, and support vector machine for predicting the risk of in-hospital mortality were: 0.884, 0.918, 0.913, and 0.896, respectively. Evaluation of changes in NT-proBNP, D-dimer, killip score, cTnI, and LDH values was found to improve clinical outcomes of ACS patients.

Table 2: (continued)

Study	Study aims	Studied populations	Results
Doudesis D, et al. Nat med 2023 [42]	Authors developed ML models that integrate hs-cTnI values at presentation or on serial testing with clinical features and compute the collaboration for the diagnosis and evaluation of acute coronary syndrome (CoDE-ACS) score that corresponds to an individual's probability of myocardial infarction.	The validation cohort consisted of 10,286 patients (median age 60 years, 35 % women) with possible AMI pooled from seven prospective cohort studies enrolling patients across six countries. In 8,664 and 1,622 patients with and without myocardial injury at presentation, the final adjudicated diagnosis after serial cardiac troponin measurements was AMI in 1,032 and 267 patients, respectively.	The CoDE-ACS model showed an AUC for AMI of 0.953 (95 % CI: 0.947–0.958), and identified more patients at presentation as low probability of AMI than fixed hs-cTnI assay (61 vs. 27 .) with a similar NPV and fewer as high probability of having AMI (10 vs. 16 %) with a greater PPV. Patients with a low probability of AMI had also a lower rate of cardiac death than those with intermediate or high probability at both 30 days and 1 year (P<0.001).
Neumann JT, et al. Clin res Cardiol 2023 [192]	Authors aimed to build a digital tool to directly estimate the individual probability of AMI, allowing for numerous hs-cTn assays.	In 2,575 patients presenting to the ED with suspected AMI, two ensembles of ML models using single or serial concentrations of six different hs-cTn assays were derived to estimate the individual AMI probability (ARTEMIS model). Model performance was validated in an external cohort with 1,688 patients and tested for global generalizability in 13 international cohorts with 23,411 patients.	11 routinely available variables including age, sex, cardiovascular risk factors, electrocardiography, and hs-cTn were included in the ARTEMIS models. In the validation and generalization cohorts, excellent discriminative performance was confirmed, superior to hs-cTn only. For the serial hs-cTn measurement model, AUC ranged from 0.92 to 0.98. Good calibration was observed. Using a single hs-cTn measurement, the ARTEMIS model allowed direct rule-out of MI with very high and similar safety but up to tripled efficiency compared to the guideline-recommended strategy.
Lopez-Ayala P, et al. Lancet digit health 2024 [43]	Authors validated the myocardial-ischaemic-injury-index (MI3), which is a novel machine learning algorithm for the early diagnosis of type 1 non-ST-segment elevation myocardial infarction (NSTEMI), using serial hs-cTnI measurements.	Authors enrolled 6,487 patients (median age 61.0 years [IQR 49.0–73.0]; 2,122 [33 %] female and 4,365 [67 %] male) from April 21, 2006, to Feb 27, 2019 in 12 centres from five european countries (Switzerland, Spain, Italy, Poland, and Czech republic), presenting to the ED with symptoms suggestive of AMI. 882 of these patients (13.6 %) had a definitive diagnosis of NSTEMI.	Model performance showed an AUC ROC curve of 0.961 (95 % CI 0.957 to 0.965). The model identified 4,186 (64.5 %) patients as low probability of having a type 1 NSTEMI (sensitivity 99.1 % [95 % CI 98.2 to 99.5]; NPV 99.8 % [95 % CI 99.6 to 99.9]). A model score of 49.7 or more identified 915 (14.1 %) patients as high probability of having a type 1 NSTEMI (specificity 95.0 % [94.3 to 95.5]; PPV 69.1 % [66.0–72.0]).
Boeddinghaus J, et al. Circulation 2024 [44]	The CoDE-ACS model was validated as a clinical decision-support tool that uses ML with or without serial hs-cTnI measurements at a flexible timepoint to calculate the probability of AMI.	Patients with possible AMI without ST-segment elevation were enrolled at 12 sites in five countries and underwent serial hs-cTnI measurements at 0, 1 and 2 h. In total 4,105 patients (age 61 [19, 50–73] years, 32 % women) were included where 575 (14 %) had type 1 AMI.	Overall, the CoDE-ACS model performs consistently irrespective of the timing of serial hs-cTnI assay identifying more patients as low-probability with comparable performance to international ESC 0/1 h, ESC 0/2 h and High-STEACS guidelines recommended pathways for AMI.

single-centre) studies aimed at evaluating the contribution of hs-cTnI or hs-cTnT assay and ML approach to the diagnosis of acute coronary syndrome [42–44, 175, 178, 183, 185, 187]. Other studies have used the ML approach in combination with the hs-cTnI or hs-cTnT assay to better estimate cardiovascular risk in general or heterogeneous populations [184, 186] and in patients with heart failure [189, 190] or stable coronary artery disease [186]. In particular, several studies have suggested that the ML approach in combination with hs-cTnI or hs-cTnT assay significantly improves the accuracy of diagnosis of AMI [42–44, 175, 179, 183, 185]. More specifically, the CoDE-ACS model identifies more patients as low-probability with comparable performance to the international ESC 0/1 h, ESC 0/2 h and High-STEACS guidelines recommended pathways for AMI [4, 47], with consistent performance regardless of the timing of serial hs-cTnI testing [44]. Another very recent ML approach is the

ARTEMIS model [192], which is based on heterogeneous global data and has been calibrated for European, Australian, New Zealand, North American and Japanese settings for worldwide application. This model integrates data from two POCT hs-cTnI (i.e. Pathfast and Atellica VTLi), the hs-cTnT and 3 hs-cTnI methods (i.e. Access, Archiect and Atellica) [192]. Using these POCT hs-cTnI methods, the ARTEMIS model can be applied in the outpatient setting and could improve diagnostic accuracy and speed in the outpatient setting, thereby reducing hospital admissions [192]. The results obtained with the CoDE-ACS and ARTEMIS models indicate that the innovative ML approach can overcome the drawbacks due to different cut-off values and timing related to the hs-cTnI and hs-cTnT assays, and thus may provide a faster, safer and more efficient diagnostic workup of patients with chest pain [43, 44, 192].

Several authors have recently discussed various theoretical issues, ethical challenges and other concerns regarding the application of AI in clinical and laboratory medicine [7, 167–172], [194–201]. The main ethical issues relate to the role of laboratory professionals, the automatic generation of data and the use of patient data [167–169, 195, 196]. In addition, the fundamental question of whether laboratory professionals are ready for the routine use of AI remains unanswered [167–172, 195–199]. The potential application of ML models to laboratory data could be relevant, but there is an urgent need to adapt expertise within clinical laboratories and also to improve the collaboration between laboratory medicine and AI experts [169–174, 199–202].

Take-home messages

- The integrated use of innovative strategies based on AI promises to refine the management of patients with chest pain [165].
- ML is a quantitative and reproducible way to combine and integrate large amounts of information from multiple variables to improve predictive accuracy, and so this approach may be very useful for analysing the large data provided by clinical laboratories [167–169]. However, careful consideration should be given to data collection and handling, which are of paramount importance for the effectiveness of the algorithms.
- Some recent studies have shown that the ML approach combined with hs-cTnI or hs-cTnT assay can significantly contribute to improve the accuracy of diagnosis of AMI [42–44, 175, 179, 183, 191].
- However, while the potential application of ML models to laboratory data may be relevant, there remains an urgent need to adapt expertise within clinical laboratories and improve collaboration between laboratory medicine and AI experts in order to manage the change and uncover additional benefits for patient care [167–171, 198, 199].

Conclusions

Over the past decade, hs-cTn assays have dramatically reduced the time required to diagnose AMI to less than 3 h in most cases [4]. This improvement in diagnostic speed has allowed for faster clinical decisions and interventions, especially in rule-out AMI [4, 9–11, 45, 46, 99]. In addition, new hs-cTn POCT methods [9–11, 15, 17] can further reduce laboratory turnaround times. POCT methods also have the advantage that they can be used in outpatient clinics, ambulances and even in the home [9–11, 15, 17].

Despite these advances, challenges remain in standardising hs-cTn methods and interpreting small temporal changes in biomarker levels [41, 202]. In particular, low-molecular-weight troponins, which are often released after strenuous physical activity or in patients with end-stage renal disease, present complexities in the accurate interpretation of hs-cTn results because the methods available to date are unable to distinguish between the different molecular forms of troponin circulating in the blood [26, 27, 2–33]. Furthermore, the challenge of accurately determining the 99th percentile URL for hs-cTn assays remains unresolved [71–74]. In fact, the 99th percentile URL values, which are crucial for clinical diagnosis, vary significantly not only between hs-cTnI and hs-cTnT assays, but also due to some individual conditions, in particular: age, sex and body structure [72–74]. Although the hs-cTn assay using wearable technology is not fully mature, this new technique represents an exciting frontier in continuous monitoring and early detection of myocardial injury [17, 21]. Another promising area of innovation is the integration of ML algorithms with hs-cTn assays [167–173]. Several studies have shown that these algorithms can improve the accuracy of AMI diagnosis, particularly in emergency departments [43, 189, 190, 193, 194]. In conclusion, after 25 years of continuous research and technological improvements, the task of refining and standardising analytical performance and expanding the use of hs-cTnI and hs-cTnT methods in clinical practice is not yet complete [202].

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References

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined: a consensus document of the Joint europ society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36: 959–69.
2. Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Lianos J, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American association for clinical Chemistry and the task Force on clinical applications of cardiac bio-markers of the international federation of clinical Chemistry and laboratory medicine. Clin Chem 2018;64:645–55.
3. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, ESC Scientific Document Group, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–69.
4. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289–367.
5. Januzzi JLJ, Mahler SA, Christenson RH, Rymer J, Newby LK, Body R, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing. JAAC Scientific Expert Panel. J Am Coll Cardiol 2019;73:1059–77.
6. Clerico A, Zaninotto M, Padoan A, Masotti S, Musetti V, Prontera C, et al. Evaluation of analytical performance of immunoassay methods for cardiac troponin I and T: from theory to practice. Adv Clin Chem 2019;93:239–62.
7. Lippi G, Bassi A, Bovo A. The future of laboratory medicine in the era of precision medicine. J Lab Prec Med 2016:1–5. https://doi.org/10.21037/jlpm.2016.12.01.
8. Clerico A, Lippi G. The state-of-the-art of "high-sensitivity" immunoassay for measuring cardiac troponin I and T. J Lab Prec Med 2018;3:53.
9. Collinson PO, Saenger AK, Apple FS, Ifcc C-CB. High sensitivity, contemporary and point-of-care cardiac troponin assays: educational aids developed by the IFCC Committee on Clinical Application of Cardiac Bio-Markers. Clin Chem Lab Med 2019;57:623–32.
10. Apple FS, Fantz CR, Collinson PO. On behalf of the IFCC Committee on Clinical Application of Cardiac Bio-Markers. Implementation of high-sensitivity and point-of-care cardiac troponin assays into practice: some different thoughts. Clin Chem 2021;67:70–8.
11. Collinson P, Aakre KM, Saenger A, Body R, Hammarsten O, Jaffe AS, et al. Cardiac troponin measurement at the point of care: educational recommendations on analytical and clinical aspects by the IFCC Committee on Clinical Applications of Cardiac Bio-Markers (IFCC C-CB). Clin Chem Lab Med 2023;61:989–98.
12. Sörensen NA, Neumann JT, Ojeda F, Giannitsis E, Spanuth E, Blankenberg S, et al. Diagnostic evaluation of a high-sensitivity troponin I point-of-care assay. Clin Chem 2019;65:601.
13. Boeddinghaus J, Nestelberger T, Koechlin L, Wussler D, Lopez-Ayala P, Walter JE, et al. Early diagnosis of myocardial infarction with point-of-care high-sensitivity cardiac troponin I. J Am Coll Cardiol 2020;75: 1111–24.
14. Apple FS, Schulz K, Schmidt CW, van Domburg TSY, Fonville JM, de Theije FK. Determination of sex-specific 99th percentile upper reference limits for a point of care high sensitivity cardiac troponin I assay. Clin Chem Lab Med 2021;59:1574–8.
15. Clerico A, Zaninotto M, Plebani M. High-sensitivity assay for cardiac troponins with POCT methods. The future is soon. Clin Chem Lab Med 2021;59:1477–8.
16. Apple FS, Smith SW, Greenslade JH, Sandoval Y, Parsonage W, Ranasinghe I, et al. Single high-sensitivity Point-of-Care whole-blood cardiac troponin I measurement to rule out acute myocardial infarction at low risk. Circulation 2022;146:1918–29.
17. Clerico A, Aimo A, Zaninotto M, Plebani M. Transdermal measurement of cardiac troponins: the future is now. Clin Chem Lab Med 2022;60: 1133.5.
18. Van den Bulk S, Petrus AHJ, Willemsen RTA, Boogers MJ, Meeder JG, Rahel BM, et al. Ruling out acute coronary syndrome in primary care with a clinical decision rule and a capillary, high-sensitive troponin I point of care test: study protocol of a diagnostic RCT in The Netherlands (POB HELP). BMJ Open 2023;13:e071822.
19. Stoyanov KM, Hund H, Biener M, Gandowitz J, Riedle C, Lohr J, et al. RAPID-CPU: a prospective study on implementation of the ESC 0/1-hour algorithm and safety of discharge after rule-out of myocardial infarction. Eur Heart J Acute Cardiovasc Care 2020;9:3951.
20. Pickering JW, Young JM, George PM, Watson AS, Aldous SJ, Verryt T, et al. Derivation and validation of thresholds using synthetic data methods for single-test screening of emergency department patients with possible Acute Myocardial Infarction using a Point-of-Care Troponin Assay. J Lab Med 2024;9:526–39.
21. Clerico A, Aimo A, Passino C. Point-of-care high-sensitivity troponin testing in the Emergency Department: the way of the future. J Am Coll Cardiol 2024;84:741–3.
22. Hickman PE, Potter JM, Aroney C, Koerbin G, Southcott E, Wu AH, et al. Cardiac troponin may be released by ischemia alone, without necrosis. Clin Chim Acta 2010;411:318–23.
23. Marjot J, Kaier TE, Martin ED, Reji SS, Copeland O, Iqbal M, et al. Quantifying the release of biomarkers of myocardial necrosis from cardiac myocytes and intact myocardium. Clin Chem 2017;63:990–6.
24. Hammarsten O, Mair J, Möckel M, Lindahl B, Jaffe AS. Possible mechanisms behind cardiac troponin elevations. Biomarkers 2018;23: 725–34.
25. Mair J, Lindahl B, Hammarsten O, Müller C, Giannitsis E, Huber K, et al. How is cardiac troponin released from injured myocardium? Eur Heart J Acute Cardiovasc Care 2018;7:553–60.
26. Aengevaeren VL, Baggish AL, Chung EH, George K, Kleiven Ø, Mingels AMA, et al. Exercise-induced cardiac troponin elevations: from underlying mechanisms to clinical relevance. Circulation 2021; 144:1955–72.
27. Vroemen WHM, Mezger STP, Masotti S, Clerico A, Bekers O, de Boer D, et al. Cardiac troponin T: only small molecules in recreational runners after marathon completion. J Appl Lab Med 2019;3:909–11.
28. Árnadóttir Á, Pedersen S, Bo Hasselbalch R, Goetze JP, Friis-Hansen LJ, Bloch-Münster AM, et al. Temporal release of high-sensitivity cardiac troponin T and I and copeptin after brief induced coronary artery balloon occlusion in humans. Circulation 2021;143:1095–104.
29. Aengevaeren VL, Froeling M, Hooijmans MT, Monte JR, van den Berg-Faay S, Hopman MT, et al. Myocardial injury and compromised

cardiomyocyte integrity following a marathon run. JACC Cardiovasc Imag 2020;13:1445–7.
30. Jaffe AS. Analysis of troponin fragments: of a new the start of a new era -Perhaps? Clin Chem 2024;70:1003–5.
31. Clerico A, Zaninotto M, Aimo A, Galli C, Sandri MT, Correale M, et al. Assessment of cardiovascular risk and physical activity: the role of cardiac-specific biomarkers in the general population and athletes. Clin Chem Lab Med 2024;63:71–86.
32. Mingels AM, Cardinaels EP, Broers NJ, van Sleeuwen A, Streng AS, van Dieijen-Visser MP, et al. Cardiac Troponin T: smaller molecules in pPatients with end-stage renal disease than after onset of acute myocardial infarction. Clin Chem 2017;63:683–90.
33. Airaksinen KEJ, Aalto R, Hellman T, Vasankari T, Lahtinen A, Wittfooth S. Novel troponin fragmentation assay to discriminate between troponin elevations in acute myocardial infarction and end-stage renal disease. Circulation 2022;146:1408–10.
34. Sze J, Mooney J, Barzi F, Hillis GS, Chow CK. Cardiac troponin and its relationship to cardiovascular outcomes in community populations - a systematic review and meta-analysis. Heart Lung Circ 2016;25:217–28.
35. Van der Lindel Klinkenberg LJJ, Bekers O, Loon LJCV, Dieijen-Visser MPV, Zeegers MP, et al. Prognostic value of basal high-sensitive cardiac troponin levels on mortality in the general population: a meta-analysis. Medicine 2016;95:e5703.
36. Willeit P, Welsh P, Evans JDW, Tschiderer L, Boachie C, Jukema JW, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. J Am Coll Cardiol 2017;70:558–68.
37. Lippi G, Cervellin G, Sanchis-Gomar F. Predicting mortality with cardiac troponins: recent insights from meta-analyses. Diagnosis 2019;8:37–49.
38. Farmakis D, Mueller C, Apple FS. High-sensitivity cardiac troponin assays for cardiovascular risk stratification in the general population. Eur Heart J 2020;41:4050–6.
39. Clerico A, Zaninotto M, Passino C, Aspromonte N, Piepoli MF, Migliardi M, et al. Evidence on clinical relevance of cardiovascular risk evaluation in the general population using cardio-specific biomarkers. Clin Chem Lab Med 2021;59:79–90.
40. Aimo A, Georgiopoulos G, Panichella G, Vergaro G, Passino C, Emdin M, et al. High-sensitivity troponins for outcome prediction in the general population: a systematic review and meta-analysis. Eur J Intern Med 2022;98:61–8.
41. Clerico A, Zaninotto M, Aimo A, Cardinale DM, Dittadi R, Sandri MT, et al. Variability of cardiac troponin levels in normal subjects and in patients with cardiovascular diseases: analytical considerations and clinical relevance. Clin Chem Lab Med 2023;61:1209–29.
42. Doudesis D, Lee KK, Boeddinghaus J, Bularga A, Ferry AV, Tuck C, et al. Machine learning for diagnosis of myocardial infarction using cardiac troponin concentrations. Nat Med 2023;29:1201–10.
43. Lopez-Ayala P, Boeddinghaus J, Nestelberger T, Koechlin L, Zimmermann T, Bima P, et al. External validation of the myocardial-ischaemic-injury-index machine learning algorithm for the early diagnosis of myocardial infarction: a multicentre cohort study. Lancet Digit Health 2024;6:e480–8.
44. Boeddinghaus J, Doudesis D, Lopez-Ayala P, Lee KK, Koechlin L, Wildi K, et al. Machine learning for myocardial infarction compared with guideline-recommended diagnostic pathways. Circulation 2024; 149:1090–101.
45. Apple FS, Collinson PO, Kavsak PA, Body R, Ordóñez-Llanos J, Saenger AK, et al. Getting cardiac troponin right: appraisal of the 2020 European society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on clinical applications of cardiac bio-markers. Clin Chem 2021;67:730–5.
46. NICE. High-sensitivity troponin tests for the early rule out of NSTEMI. Diagn Guid 2020. Available from: https://www.nice.org.uk/guidance/dg40.
47. Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, et al. High-STEACS investigators. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet 2018; 392:919928.
48. Wildi K, Boeddinghaus J, Nestelberger T, Twerenbold R, Badertscher P, Wussler D, et al. APACE investigators. Comparison of fourteen rule-out strategies for acute myocardial infarction. Int J Cardiol 2019;283: 4147.
49. Ambavane A, Lindahl B, Giannitsis E, Roiz J, Mendivil J, Frankenstein L, et al. TRAPID-AMI investigators. Economic evaluation of the one-hour rule-out and rule-in algorithm for acute myocardial infarction using the high-sensitivity cardiac troponin T assay in the emergency department. PLoS One 2017;12:e0187662.
50. Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Cupa J, et al. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. Circulation 2017;135:15971611.
51. Ljung L, Lindahl B, Eggers KM, Frick M, Linder R, Lofmark HB, et al. A rule-out strategy based on high-sensitivity troponin and HEART score reduces hospital admissions. Ann Emerg Med 2019;73:491499.
52. Odqvist M, Andersson PO, Tygesen H, Eggers KM, Holzmann MJ. High-sensitivity troponins and outcomes after myocardial infarction. J Am Coll Cardiol 2018;71:26162624.
53. Twerenbold R, Jaeger C, Rubini Gimenez M, Wildi K, Reichlin T, Nestelberger T, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. Eur Heart J 2016; 37:33243332.
54. Schols AMR, Stakenborg JPG, Dinant GJ, Willemsen RTA, Cals JWL. Point-of-care testing in primary care patients with acute cardiopulmonary symptoms: a systematic review. Fam Pract 2018;35:4–12.
55. Cullen L, Collinson PO, Giannitsis E. Point-of-care testing with high-sensitivity cardiac troponin assays: the challenges and opportunities. Emerg Med J 2022;39:861–6.
56. Lippi G, Pighi L, Paviati E, Demonte D, De Nitto S, Gelati M, et al. Analytical evaluation of the novel Mindray high sensitivity cardiac troponin I immunoassay on CL-1200i. Clin Chem Lab Med 2024;62: 1433–7.
57. Braga F, Aloisio E, Panzeri A, Nakagawa T, Panteghini M. Analytical validation of a highly sensitive point-of-care system for cardiac troponin I determination. Clin Chem Lab Med 2020;58:138–45.
58. Zhang R, Hong Y, Shi J, Zhao R, Song Y, Li Z, et al. Analytical characterization and clinical performance evaluation of a new point-of-care testing system for high-sensitivity cardiac troponin I assay. Ann Clin Biochem 2021;58:579–85.
59. Christenson RH, Frenk LDS, de Graaf HJ, van Domburg TSY, Wijnands FPG, Foolen HWJ, et al. Point-of-Care: roadmap for analytical characterization and validation of a high-sensitivity cardiac Troponin I Assay in plasma and whole blood matrices. J Appl Lab Med 2022;7: 971–88.
60. Fabre-Estremera B, Schulz K, Ladd A, Sexter A, Apple FS. Analytical validation of the Mindray CL1200i analyzer high sensitivity

cardiac troponin I assay: MERITnI study. Clin Chem Lab Med 2024;62: 2519–25.
61. Pittie G, Lukas P, Massart M, Cavalier E, Le Goff C. Evaluation of analytical and clinical performance of the AFIAS Tn-I plus assay – a new point-of-care. Acta Cardiol 2024;79:351–7.
62. IFCC Committee on Clinical Applications of Cardiac Bio-Markers. High-sensitivity cardiac troponin I and T assay analytical characteristics designated by manufacturer IFCC committee on clinical applications of cardiac bio-markers (C-CB) v052022. link https://ifcc.org.
63. Osredkar J, Krivic K, Fabjan T, Kumer K, Tršan J, Poljančič L, et al. Point-of-care high-sensitivity assay on PATHFAST as the backup in the emergency room. Med Access Point Care 2021;5. https://doi.org/10.1177/23992026211055095.
64. Bruinen AL, Frenk LDS, de Theije F, Kemper DWM, Janssen MJW, Rahel BM, et al. Point-of-care high-sensitivity troponin-I analysis in capillary blood for acute coronary syndrome diagnostics. Clin Chem Lab Med 2022;60:1669–74.
65. Xiong-Hang K, Schulz K, Sandoval Y, Smith SW, Saenger AK, Apple FS. Analytical performance comparing siemens whole blood point of care Atellica VTLi to the central laboratory plasma Atellica IM high-sensitivity cardiac troponin I assays. Clin Biochem 2023;114:79–85.
66. Koechlin L, Boeddinghaus J, Lopez-Ayala P, Reber C, NestelbergerT WK. Clinical and analytical performance of a novel point-of-care high-sensitivity cardiac troponin I assay. J Am Coll Cardiol 2024;84:726–40.
67. Clerico A, Passino C, Aimo A. Point-of-care high-sensitivity troponin testing in the emergency department: the way of the future? J Am Coll Cardiol 2024;84:741–3.
68. Titus J, Wu AHB, Biswal S, Burman A, Sengupta SP, Sengupta PP. Development and preliminary validation of infrared spectroscopic device for transdermal assessment of elevated cardiac troponin. Commun Med 2022;2:42.
69. Sengupta S, Biswal S, Titus J, Burman A, Reddy K, Fulwani MC, et al. A novel breakthrough in wrist-worn transdermal troponin-I-sensor assessment for acute myocardial infarction. Eur Heart J Digit Health 2023; 4:145–54.
70. Kavsak PA, Clark L, Arnoldo S, Lou A, Shea JL, Eintracht S, et al. Imprecision of high-sensitivity cardiac troponin assays at the female 99th-percentile. Clin Biochem 2024;125:110731.
71. Sandoval Y, Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. Clin Chem 2014;60: 455–62.
72. Clerico A, Zaninotto M, Ripoli M, Masotti S, Prontera C, Passino C, et al. The 99th percentile of reference population for cTnI and cTnT assay: methodology, pathophysiology, and clinical implications. Clin Chem Lab Med 2017;55:1634–51.
73. Clerico A, Ripoli A, Zaninotto M, Masotti S, Musetti V, Ciaccio M, et al. Head-to-head comparison of plasma cTnI concentration values measured with three high-sensitivity methods in a large Italian population of healthy volunteers and patients admitted to emergency department with acute coronary syndrome: a multi-center study. Clin Chim Acta 2019;496:25–34.
74. Harrell FE, Davis CE. Harrel_Davis distribution-free quantile estimator. Biometrika 1982;69:635–40.
75. Akinshin A. Trimmed Harrell-Davis quantile estimator based on the highest density interval of the given width. Commun Stat Simulat Comput 2022;53:1565–75.
76. Caselli C, Cangemi G, Masotti S, Ragusa R, Gennai I, Del Ry S, et al. Plasma cardiac troponin I concentrations in healthy neonates, children and adolescents measured with a highly sensitive immunoassay method: highly sensitive troponin I in pediatric age. Clin Chim Acta 2016;458:68–71.
77. Clerico A, Padoan A, Zaninotto M, Passino C, Plebani M. Clinical relevance of biological variation of cardiac troponins. Clin Chem Lab Med 2021;59:641–52.
78. Bergmann O, Zdunek S, Felker A, Salhpoor M, Alkass K, Bernard S, et al. Dynamics of cell generation and turnover in the human heart. Cell 2015;161:1566–75.
79. Eschenhagen T, Bolli T, Braun T, Field LJ, Fleischmann KK, Frisèn J, et al. Cardiomyocyte regeneration. A consensus statement. Circulation 2017;136:680–6.
80. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem 2009;55:52–8.
81. Wu AH, Akhigbe P, Wians F. Long-term biological variation in cardiac troponin I. Clin Biochem 2012;60:638–47.
82. Schindler EI, Szymanski JJ, Hock KG, Geltman EM, Scott MG. Short- and long-term biologic variability of Galectin-3 and other cardiac biomarkers in patients with stable heart failure and healthy adults. Clin Chem 2016;62:360–6.
83. van der Linden N, Hilderink JM, Cornelis T, Kimenai DM, Klinkenberg LJJ, van Doorn WP, et al. Twenty-four-hour biological variation profiles of cardiac troponin I in individuals with or without chronic kidney disease. Clin Chem 2017;63:1655–6.
84. Zaninotto M, Padoan A, Mion MM, Marinova M, Plebani M. Short-term biological variation and diurnal rhythm of cardiac troponin I (Access hs-TnI) in healthy subjects. Clin Chim Acta 2020;504:163–7.
85. Ceriotti F, Díaz-Garzón Marco J, Fernández-Calle P, Maregnani A, Aarsand AK, Coskun A, et al. The European Biological Variation Study (EuBIVAS): weekly biological variation of cardiac troponin I estimated by the use of two different high-sensitivity cardiac troponin I assays. Clin Chem Lab Med 2020;58:1741–7.
86. Aakre KM, Røraas T, Petersen PH, Svarstad E, Sellevoli H, Skadberg Ø, et al. Weekly and 90-minute biological variations in cardiac troponin T and cardiac troponin I in hemodialysis patients and healthy controls. Clin Chem 2014;60:838–47.
87. Corte Z, García C, Venta R. Biological variation of cardiac troponin T in patients with end-stage renal disease and in healthy individuals. Ann Clin Biochem 2015:53–60. https://doi.org/10.1177/0004563214545116.
88. Fournier S, Iten L, Marques-Vidal P, Boulat O, Bardy D, Beggah A, et al. Circadian rhythm of blood cardiac troponin T concentration. Clin Res Cardiol 2017;106:1026–32.
89. Meijers WC, van der Velde AR, Muller Kobold AC, Dijck-Brouwer J, Wu AH, Jaffe A, et al. Variability of biomarkers in patients with chronic heart failure and healthy controls. Eur J Heart Fail 2017;19:357–65.
90. Koerbin G, Potter JM, Pinto do Nascimento M, Cullen L, Scanlan S, Woods C, et al. The intra-individual variation of cardiac troponin I: the effects of sex, age, climatic season, and time between samples. Clin Chem Lab Med 2022;60:1001–9.
91. Diaz-Garzon J, Fernandez-Calle P, Sandberg S, Özcürümez M, Bartlett WA, Coskun A, et al. Biological variation of cardiac troponins in health and disease: a systematic review and meta-analysis. Clin Chem 2021;67:256–64.
92. Fraser CG. Biological variation: from principles to practice. Washington, DC: AACC Press; 2001.
93. Fraser CG. Reference change values. Clin Chem Lab Med 2012;50: 807–12.
94. Ndreu R, Musetti V, Masotti S, Zaninotto M, Prontera C, Zucchelli GC, et al. Evaluation of the cTnT immunoassay using quality control samples. Clin Chim Acta 2019;495:269–70.

95. Masotti S, Prontera C, Musetti V, Storti S, Ndreu R, Zucchelli GC, et al. Evaluation of analytical performance of a new high-sensitivity immunoassay for cardiac troponin I. Clin Chem Lab Med 2018;56: 492–501.
96. Masotti S, Musetti V, Prontera C, Storti S, Passino C, Zucchelli G, et al. Evaluation of analytical performance of a chemiluminescence enzyme immunoassay (CLEIA) for cTnI using the automated AIA-CL2400 platform. Clin Chem Lab Med 2018;56:e174–6.
97. Musetti V, Masotti S, Prontera C, Storti S, Ndreu R, Zucchelli GC, et al. Evaluation of the analytical performance of a new ADVIA immunoassay using the Centaur XPT platform system for the measurement of cardiac troponin I. Clin Chem Lab Med 2018;56:e229–31.
98. Clerico A, Zaninotto M, Aimo A, Dittadi R, Cosseddu D, Perrone M, et al. Use of high-sensitivity cardiac troponins in the emergency department for the early rule-in and rule-out of acute myocardial infarction without persistent ST-segment elevation (NSTEMI) in Italy. Clin Chem Lab Med 2022;60:169–82.
99. Clerico A, Zaninotto M, Aimo A, Musetti V, Perrone M, Padoan A, et al. Evaluation of the cardiovascular risk in patients undergoing major non-cardiac surgery: role of cardiac-specific biomarkers. Clin Chem Lab Med 2022;60:1525–42.
100. Clerico A, Cardinale DM, Zaninotto M, Aspromonte N, Sandri MT, Passino C, et al. High-sensitivity cardiac troponin I and T methods for the early detection of myocardial injury in patients on chemotherapy. Clin Chem Lab Med 2021;59:513–21.
101. Clerico A, Zaninotto M, Aimo A, Plebani M. Cardiovascular risk evaluation in pregnancy: focus on cardiac specific biomarkers. Clin Chem Lab Med 2024;62:581–92.
102. Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720–826.
103. Neumann JT, Twerenbold R, Ojeda F, Sörensen NA, Chapman AR, Shah ASV, et al. Application of high-sensitivity troponin in suspected myocardial infarction. N Engl J Med 2019;380:2529–40.
104. Boeddinghaus J, Twerenbold R, Nestelberger T, Badertscher P, Wildi K, Puelacher C, et al. Clinical validation of a novel high-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. Clin Chem 2018;64:1347–60.
105. Neumann JT, Sorensen NA, Rubsamen N, Ojeda F, Schock A, Seddighizadeh P, et al. Evaluation of a new ultra-sensitivity troponin I assay in patients with suspected myocardial infarction. Int J Cardiol 2019;283:35–40.
106. Neumann JT, Sorensen NA, Schwemer T, Ojeda F, Bourry R, Sciacca V, et al. Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. JAMA Cardiol 2016;1:397–404.
107. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172: 1211–8.
108. Boeddinghaus J, Twerenbold R, Nestelberger T, Koechlin L, Wussler D, Meier M, et al. Clinical use of a new high-sensitivity cardiac troponin I assay in patients with suspected myocardial infarction. Clin Chem 2019;65:1426–36.
109. Boeddinghaus J, Lopez-Ayala P, Nestelberger T, Koechlin L, Münch T, Miro O, et al. Prospective validation of the ESC 0/1h-algorithm using high-sensitivity cardiac troponin I. Am J Cardiol 2021;158:152–3.
110. Boeddinghaus J, Nestelberger T, Twerenbold R, Neumann JT, Lindahl B, Giannitsis E, et al. Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction. Eur Heart J 2018;39:3780–94.
111. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Puelacher C, et al. 0/1-Hour triage algorithm for myocardial infarction in patients with renal dysfunction. Circulation 2018;137:436–51.
112. Boeddinghaus J, Reichlin T, Cullen L, Greenslade JH, Parsonage WA, Hammett C, et al. Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction by use of high-sensitivity cardiac troponin I. Clin Chem 2016;62:494–504.
113. Wildi K, Cullen L, Twerenbold R, Greenslade JH, Parsonage W, Boeddinghaus J, et al. Direct comparison of 2 rule-out strategies for acute myocardial infarction: 2-h accelerated diagnostic protocol vs 2-h algorithm. Clin Chem 2017;63:1227–36.
114. Nestelberger T, Boeddinghaus J, Greenslade J, Parsonage WA, Than M, Wussler D, et al. Two-hour algorithm for rapid triage of suspected acute myocardial infarction using a high-sensitivity cardiac troponin I assay. Clin Chem 2019;65:1437–47.
115. Koechlin L, Boeddinghaus J, Nestelberger T, Lopez-Ayala P, Wussler D, Shrestha S, et al. Performance of the ESC 0/2h-algorithm using high-sensitivity cardiac troponin I in the early diagnosis of myocardial infarction. Am Heart J 2021;242:132–7.
116. Boeddinghaus J, Nestelberger T, Twerenbold R, Koechlin L, Meier M, Troester V, et al. High-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. Clin Chem 2019;65:893–904.
117. Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. JAMA 2017;318:1913–124.
118. Twerenbold R, Neumann JT, Sorensen NA, Ojeda F, Karakas M, Boeddinghaus J, et al. Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. J Am Coll Cardiol 2018;72: 620–32.
119. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.
120. Greenslade J, Cho E, Van Hise C, Hawkins T, Parsonage W, Ungerer J, et al. Evaluating rapid rule-out of acute myocardial infarction using a high-sensitivity cardiac troponin I assay at presentation. Clin Chem 2018;64:820–9.
121. Pickering JW, Than MP, Cullen L, Aldous S, Ter Avest E, Body R, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. Ann Intern Med 2017;166: 715–24.
122. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;386: 2481–8.
123. Boeddinghaus J, Nestelberger T, Lopez-Ayala P, Koechlin L, Buechi M, Miro O, et al. Diagnostic performance of the European Society of Cardiology 0/1-h algorithms in late presenters. J Am Coll Cardiol 2021; 77:1264–7.
124. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. Ann Emerg Med 2016;68:76–87.e4.
125. Lee KK, Ferry A, Anand A, Strachan FE, Chapman AR, Kimenai DM, et al. High-sensitivity troponin with sex-specific thresholds in suspected acute coronary syndrome. J Am Coll Cardiol 2019;74:2032–43.
126. Apple FS, Wu AHB, Sandoval Y, Sexter A, Love SA, Myers G, et al. Sex-specific 99th percentile upper reference limits for high sensitivity

cardiac troponin assays derived using a universal sample bank. Clin Chem 2020;66:434–44.
127. Shah A, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry A, et al. High-sensitivity cardiac troponin and the under diagnosis of myocardial infarction in women: prospective cohort study. Brit Med J 2015;350:g7873.
128. Eggers KM, Lindahl B. Impact of sex on cardiac troponin concentrations–a critical appraisal. Clin Chem 2017;63:1457–64.
129. Cullen L, Greenslade JH, Carlton EW, Than M, Pickering JW, Ho A, et al. Sex-specific versus overall cut points for a high sensitivity troponin I assay in predicting 1-year outcomes in emergency patients presenting with chest pain. Heart 2016;102:120–6.
130. Kimenai DM, Appelman Y, den Ruijter HM, Shah ASV, Mills NL, Meex SJR. Ten years of high-sensitivity troponin testing: impact on the diagnosis of myocardial infarction. Clin Chem 2021;67:324–6.
131. Bjurman C, Larsson M, Johanson P, Petzold M, Lindahl B, Fu MLX, et al. Small changes in troponin T levels are common in patients with non–ST-segment elevation myocardial infarction and are linked to higher mortality. J Am Coll Cardiol 2013;62:1231–8.
132. Hammarsten O, Fu ML, Sigurjonsdottir R, Petzold M, Said L, Landin-Wilhelmsen K, et al. Troponin T percentiles from a random population sample, emergency room patients and patients with myocardial infarction. Clin Chem 2012;58:628–37.
133. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J 2011;32:1379–89.
134. Aakre KM, Røraas T, Petersen PH, Svarstad E, Sellevoll H, Skadberg Ø, et al. Weekly and 90-minute biological variations in cardiac troponin T and cardiac troponin I in hemodialysis patients and healthy controls. Clin Chem 2014;60:838–47.
135. Roos A, Edgren G, Holzmann MJ. Temporal changes of stable high-sensitivity cardiac troponin T levels and prognosis. J Am Heart Ass 2022;11:e025082.
136. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, et al. ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383–431.
137. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety check list to reduce morbidity and mortality in a global population. N Engl J Med 2009;360:491–9.
138. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, et al. Association between post-operative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012;307:2295–304.
139. Sellers D, Srinivas C, Djaiani G. Cardiovascular complications after non-cardiac surgery. Anaesthesia 2018;73:34–42.
140. Botto F, Alonso Coello P, Chan MTV, Villar JC, Xavier D, Srinathan S, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology 2014;120:564–78.
141. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, et al, Writing committee for the VISION Study Investigators. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2017;317:1642–51.
142. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. Eur Heart J 2020;41:3083–91.
143. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. Can J Cardiol 2017;33:17–32.
144. Ruetzler K, Smilowitz NR, Berger JS, Devereaux PJ, Maron BA, Newby LK, et al. Diagnosis and management of patients with myocardial injury after noncardiac surgery: a scientific statement from the American Heart Association. Circulation 2021;144:e287–305.
145. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J Clin 2016;66:309–25.
146. Alexandre J, Cautela J, Edrhy S, Damaj GL, Salem JE, Barlesi F, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European Cardio-Oncology Guidelines. J Am Heart Assoc 2020;9:e018403.
147. Cardinale DM, Fabiani I, Cipolla CM. Cardiotoxicity of anthracyclines. Font Cardiovasc Med 2020;7:26.
148. Cardinale DM, Zaninotto M, Cipolla CM, Passino C, Plebani M, Clerico A. Cardiotoxic effects and myocardial injury: the search for a more precise definition of drug cardiotoxicity. Clin Chem Lab Med 2020;59:51–7.
149. Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J 2022;43:280–99.
150. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. ESC guidelines on cardio-oncology developed in collaboration with the European hematology association (EHA), the European society for therapeutic radiology and oncology (ESTRO) and the international cardio-oncology society (IC-OS). Eur Heart J 2022;43:4229-361
151. Semeraro GC, Cipolla CM, Cardinale DM. Role of cardiac biomarkers in cancer patients. Cancers 2021;13:5426.
152. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715–31.
153. Feola M, Garrone O, Occelli M, Francini A, Biggi A, Visconti G, et al. Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol 2011;148:194–8.
154. Demissei BG, Hubbard RA, Zhang L, Smith AM, Sheline K, McDonald C, et al. Changes in cardiovascular biomarkers with breast cancer therapy and associations with cardiac dysfunction. J Am Heart Assoc 2020;9:e014708.
155. Dockree S, Brook J, Shine B, James T, Green L, Vatish M. Cardiac specific troponins in uncomplicated pregnancy and pre-eclampsia: a systematic review. PLoS One 2021;16:e0247946.
156. Ravichandran J, Woon SY, Quek YS, Lim YC, Noor EM, Suresh K, et al. High-sensitivity Cardiac Troponin I levels in normal and hypertensive pregnancy. Am J Med 2019;132:362–6.
157. Minhas AS, Echouffo-Tcheugui JB, Zhang S, Ndumele CE, McEvoy JW, Christenson R, et al. High-sensitivity troponin T and I among pregnant women in the US-the national health and nutrition examination survey, 1999–2004. JAMA Cardiol 2023;8:406–8.
158. Pergialiotis V, Prodromidou A, Frountzas M, Perrea DN, Papantoniou N. Maternal cardiac troponin levels in pre-eclampsia: a systematic review. J Matern Fetal Neonatal Med 2016;29:3386–90.
159. Fleming SM, O'Gorman T, Finn J, Grimes H, Daly K, Morrison JJ. Cardiac Troponin I in pre-eclampsia and gestational hypertension. BJOG 2000; 107:1417–20.

160. Morton A, Morton A. High sensitivity cardiac troponin I levels in preeclampsia. Pregnancy Hypertens 2018;13:79–82.
161. Chang SA, Khakh P, Janzen M, Lee T, Kiess M, Rychel V, et al. Trending cardiac biomarkers during pregnancy in women with cardiovascular disease. Circ Heart Fail 2022;15:e009018.
162. Jacobsen DP, Røysland R, Strand H, Moe K, Sugulle M, Omland T, et al. Cardiovascular biomarkers in pregnancy with diabetes and associations to glucose control. Acta Diabetol 2022;59:1229–36.
163. Barabàsi AL. Network science, 4th printing. Cambridge: Cambridge University Press; 2019. (Printed in Singapore by Markono Print Media Pte Ltd.).
164. Newman M. Networks, 2nd ed. Oxford, United Kingdom: Oxford University Press; 2018.
165. Than MP, Pickering JW, Mair J, Mills NL, Study Group on Biomarkers of the Association for Acute CardioVascular Care of the ESC. Study Group on Biomarkers of the Association for Acute CardioVascular Care of the ESC. Clinical decision support using machine learning and cardiac troponin for the diagnosis of myocardial infarction. Eur Heart J Acute Cardiovasc Care 2024;13:634–6.
166. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720–826.
167. Padoan A, Plebani M. Artificial intelligence: is it the right time for clinical laboratories? Clin Chem Lab Med 2022;60:1859–61.
168. Çubukçu HC, Topcu Dİ, Yenice S. Machine learning-based clinical decision support using laboratory data. Clin Chem Lab Med 2024;62: 793–823.
169. Hou H, Zhang R, Li J. Artificial intelligence in the clinical laboratory. Clin Chim Acta 2024;559:119724.
170. Master SR, Badrick TC, Bietenbeck A, Haymond S. Machine learning in laboratory medicine: recommendations of the IFCC working group. Clin Chem 2023;69:690–8.
171. Lüscher TF, Wenzl FA, D'Ascenzo F, Friedman PA, Antoniades C. Artificial intelligence in cardiovascular medicine: clinical applications. Eur Heart J 2024;19:ehae465.
172. Wu AHB, Jaffe AS, Peacock WF, Kavsak P, Greene D, Christenson RH. The role of Artificial Intelligence for providing scientific content for Laboratory Medicine. J Lab Med 2024;9:386–93.
173. Wu CC, Hsu WD, Islam MM, Poly TN, Yang HC, Nguyen PA, et al. An artificial intelligence approach to early predict non-ST-elevation myocardial infarction patients with chest pain. Comput Methods Progr Biomed 2019;173:109–17.
174. Dawson LP, Smith K, Cullen L, Nehme Z, Lefkovits J, Taylor AJ, et al. Care models for acute chest pain that improve outcomes and efficiency: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;79: 2333–48.
175. Björkelund A, Ohlsson M, Lundager Forberg J, Mokhtari A, Olsson de Capretz P, Ekelund U, et al. Machine learning compared with rule-in/rule-out algorithms and logistic regression to predict acute myocardial infarction based on troponin T concentrations. et al. J Am Coll Emerg Physcians Open 2021;2:212363.
176. Hughes JW, Yuan N, He B, Ouyang J, Ebinger J, Botting P, et al. Deep learning evaluation of biomarkers from echocardiogram videos. EBioMedicine 2021;73:103613.
177. Kayvanpour E, Gi WT, Sedaghat-Hamedani F, Lehmann DH, Frese KS, Haas J, et al. microRNA neural networks improve diagnosis of acute coronary syndrome (ACS). J Mol Cell Cardiol 2021;151:155–62.
178. Liu N, Chee ML, Koh ZX, Leow SL, Ho AFW, Guo D, et al. Utilizing machine learning dimensionality reduction for risk stratification of chest pain patients in the emergency department. BMC Med Res Methodol 2021;21:74.
179. Liu WC, Lin CS, Tsai CS, Tsao TP, Cheng CC, Liou JT, et al. A deep learning algorithm for detecting acute myocardial infarction. EuroIntervention 2021;17:765–73.
180. Martínez-Sellés M, Juárez M, Marina-Breysse M, Lillo-Castellano JM, Ariza A. Rational and design of ST-segment elevation not associated with acute cardiac necrosis (LESTONNAC). A prospective registry for validation of a deep learning system assisted by artificial intelligence. J Electrocardiol 2021;69:140–4.
181. Rojas-Mendizabal V, Castillo-Olea C, Gómez-Siono A, Zuñiga C. Assessment of thoracic pain using machine learning: a case study from Baja California, Mexico. Int J Environ Res Publ Health 2021;18: 2155.
182. Doudesis D, Lee KK, Yang J, Wereski R, Shah ASV, Tsanas A, et al. Validation of the myocardial-ischaemic-injury-index machine learning algorithm to guide the diagnosis of myocardial infarction in a heterogenous population: a prespecified exploratory analysis. Lancet Digit Health 2022;4:e300–8.
183. Emakhu J, Monplaisir L, Aguwa C, Arslanturk S, Masoud S, Nassereddine H, et al. Acute coronary syndrome prediction in emergency care: a machine learning approach. Comput Methods Progr Biomed 2022;225:107080.
184. Lin MC, Tseng VS, Lin CS, Chiu SW, Pan LK, Pan LF. Quantitative prediction of SYNTAX Score for cardiovascular artery disease patients via the inverse problem algorithm technique as artificial intelligence assessment in diagnostics. Diagnostics 2022;12:3180.
185. Ke J, Chen Y, Wang X, Wu Z, Zhang Q, Lian Y, et al. Machine learning-based in-hospital mortality prediction models for patients with acute coronary syndrome. Am J Emerg Med 2022;53:127–34.
186. Kim J, Lee SY, Cha BH, Lee W, Ryu J, Chung YH, et al. Machine learning models of clinically relevant biomarkers for the prediction of stable obstructive coronary artery disease. Front Cardiovasc Med 2022;19: 933803.
187. McCord J, Gibbs J, Hudson M, Moyer M, Jacobsen G, Murtagh G, et al. Machine learning to assess for acute myocardial infarction within 30 minutes. Crit Pathw Cardiol 2022;21:67–72.
188. Chaudhari GR, Mayfield JJ, Barrios JP, Abreau S, Avram R, Olgin JE, et al. Deep learning augmented ECG analysis to identify biomarker-defined myocardial injury. Sci Rep 2023;13:3364.
189. De Michieli L, Knott JD, Attia ZI, Ola O, Mehta RA, Akula A, et al. Artificial intelligence-augmented electrocardiography for left ventricular systolic dysfunction in patients undergoing high-sensitivity cardiac troponin T. Eur Heart J Acute Cardiovasc Care 2023;12:106–14.
190. Li X, Shang C, Xu C, Wang Y, Xu J, Zhou Q. Development and comparison of machine learning-based models for predicting heart failure after acute myocardial infarction. BMC Med Inf Decis Making 2023;23:165.
191. Mohd Faizal AS, Hon WY, Thevarajah TM, Khor SM, Chang SW. A biomarker discovery of acute myocardial infarction using feature selection and machine learning. Med Biol Eng Comput 2023;61: 2527–41.
192. Neumann JT, Twerenbold R, Ojeda F, Aldous SJ, Allen BR, Apple FS, et al. Personalized diagnosis in suspected myocardial infarction. Clin Res Cardiol 2023;112:1288–301.
193. Oh AR, Park J, Shin SJ, Choi B, Lee JH, Lee SH, et al. Prediction model for myocardial injury after non-cardiac surgery using machine learning. Sci Rep 2023;13:1475.

194. Goldschmied A, Sigle M, Faller W, Heurich D, Gawaz M, Müller KAL. Preclinical identification of acute coronary syndrome without high sensitivity troponin assays using machine learning algorithms. Sci Rep 2024;14:9796.
195. McCoy LG, Banja JD, Ghassemi M, Celi LA. Ensuring machine learning for healthcare works for all. BMJ Health Care Inform 2020;27:e100237.
196. Jackson BR, Ye Y, Crawford JM, Becich MJ, Roy S, Botkin JR, et al. The ethics of Artificial Intelligence in pathology and laboratory medicine: principles and practice. Acad Pathol 2021;8. https://doi.org/10.1177/2374289521990784.
197. Pennestrì F, Banfi G. Artificial intelligence in laboratory medicine: fundamental ethical issues and normative key-points. Clin Chem Lab Med 2022;60:1867–74.
198. Carini C, Seyhan AA. Tribulations and future opportunities for artificial intelligence in precision medicine. J Transl Med 2024;22:411.
199. Youssef A, Nichol AA, Martinez-Martin N, Larson DB, Abramoff M, Wolf RM, et al. Ethical considerations in the design and conduct of clinical trials of Artificial Intelligence. JAMA Netw Open 2024;7:e2432482.
200. Cruz Rivera S, Liu X, Chan AW, Denniston AK, Calvert MJ, Ashrafian H, et al. SPIRIT-AI and CONSORT-AI Working Group. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. Lancet Digit Health 2020;2:e549–60.
201. Liu X, Cruz Rivera S, Moher D, Calvert MJ, Denniston AK, SPIRIT-AI and CONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Lancet Digit Health 2020;2:e537–48.
202. Clerico A, Zaninotto M, Passino C, Padoan A, Migliardi M, Plebani M. High-sensitivity methods for cardiac troponins: the mission is not over yet. Adv Clin Chem 2021;103:215–52.