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Establishment of gender related 99th percentile values for cardiac Troponin-T among young and middle-aged adult Egyptians.

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ABSTRACT:

Background: Cardiac troponins are the preferred biomarkers for the diagnosis of acute myocardial infarction (AMI). The stable nature of cardiac troponin T (cTnT) in the circulation and the worldwide available single standardized assay make it a more precise biomarker of AMI. In practice, the upper reference limit (URL) for the High-sensitivity cardiac troponin T (hs-cTnT) assay does not take into consideration patients' gender, age or race.

Method: A descriptive cross-sectional study was done aiming at deriving gender-specific upper reference limit (URL) for hs-cTnT in healthy young and middle-aged adult Egyptians, with validation of assay precision at proposed URLs. Serum hs-cTnT was determined among 240 adult Egyptians (120 males and 120 females) aged (18-45y), using a commercially available hs-cTnT electrochemiluminescent immunoassay. The participants were recruited from Mustafa Kamel Military Hospital during their general health check-up as a prerequisite for applying to various governmental jobs in the period from May to October 2019. According to the CLSI approved guidelines (document EP15-A2) (Chesher, 2008), two precision studies were done to verify imprecision at claimed assay's LOQ at 13 ng/L, and to validate imprecision at 10ng/L. The gender related 99th percentile (p99) values and Age specific p99 at cutoff 36years, were then calculated to represent the URLs for hs-cTnT according to the CLSI and IFCC approved guidelines.

Results: Serum hs-cTnT was significantly higher in males compared to females ($p<0.001$). The p99 URL for hs-cTnT in females (12.6 ng/L) was lower than that of males (19.6 ng/L)**.** Applying an age cutoff value of 36 years to all, serum hs-cTnT level was significantly lower among those aged <36 years (n=119) compared to those aged ≥36 years (n=121) ($p<0.001$), with a p99 URL 10.0 ng/L for the younger and 12.6 ng/L for the older subgroup.

Conclusion: The use of locally driven age and gender specific p99 value as an URL of hs-cTnT assay could reduce over-diagnosis in males and improve assay's sensitivity among adult females by decreasing under-diagnosis of myocardial injury in ischemic as well as other non-ischemic cardiac conditions. The Cobas e601 module is more precis than Cobas e411 and a lower LOQ of 10.0 ng/L (than that assigned for both in package insert 13ng/L) can be adopted for Cobas e601 module and still guarantee a (%CV) of <10% as recommended.

Keywords: 99th percentile URL, p99, Age, Gender, myocardial damage, High-sensitivity Cardiac Troponin T, hs-cTnT.

1. INTRODUCTION

A nationwide cross-sectional study conducted from November 2015 to August 2018 highlighted the treatment of 3224 patients with acute coronary syndromes (ACS) across 30 coronary care centres in Egypt. The study showed a high incidence of ACS, with 51% of patients presenting with premature ACS, including 45% of males and 69.6% of females under the age of 55, indicating a high prevalence of premature ACS. Generally, the most common age group for ACS was 56-65 years, accounting for 37% of the population. Men constituted most ACS patients (74%). Among female patients, 92% were post-menopausal. There were noticeable gender disparities in the prevalence of risk factors, with abdominal obesity being the most common (66%). Traditional risk factors, excluding smoking, were more prevalent among women than men (Reda et al., 2020). The rising incidence of ACS among younger women in recent decades goes hand in hand with the rising incidence of diabetes mellitus, metabolic syndrome, polycystic ovaries and non-traditional risk factors such as anxiety, depression, stress, and the use of oral contraceptives pills (Chandrasekhar et al., 2018).

Circulating levels of cardiac troponins (cTn) considered the preferred biomarkers in the diagnosis of ACS. According to the Fourth Universal Definition of Myocardial Infarction

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published in August 2018; detection of an elevated cTn value above the 99th percentile (p99) upper reference limit (URL) defines myocardial injury, where injury is considered acute if there is a rise and/or fall of cTn values (Thygesen et al., 2018).

Two types of assays exist for cardiac troponins, cardiac troponin-I (cTnI) and cardiac troponin-T (cTnT) immunoassays. Different cTnI immunoassays use various capture and detection antibodies that recognize different epitopes of cTnI with varying affinities for its forms in the circulation, whether resulting from post-translational modifications [proteolytic degradation, phosphorylation, oxidation, and reduction] or complexing with other molecules [Troponin-C, heparin, heterophile or human anti-mouse antibodies, and cTnI specific autoantibodies circulating in blood] (Giannitsis et al., 2010; Herman et al., 2017). Moreover, the lack of a commutable reference material to standardize cTnI results makes absolute concentrations of cTnI determined by different immunoassays very inconsistent even for different assays and instruments marketed by the same manufacturer (Giannitsis et al., 2010).

On the other hand, the more stable nature of cTnT molecule in circulation and the worldwide availability of a single standardized hs-cTnT assay, make it a more precise biomarker of ACS (Apple et al., 2012). The cTnT electrochemiluminescent immunoassay developed by Roche Diagnostics, which holds the patent and antibodies, underwent many modifications through five generations that ended with Roche becoming the first in vitro diagnostics company to receive the United States Food and Drug Administration clearance for a truly high-sensitivity cardiac troponin T assay hs-cTnT (5th generation) (Apple et al., 2012; Apple et al., 2017).

The clinical use of the manufacturer's declared upper reference limit (URL) for the hs-cTnT assay still does not consider patients' gender, age or race (de Lemos, 2013). Gender differences in the URL for hs-cTn assays have been reported in a number of small non-specific studies with a trend for higher values in males compared to females especially among young adults (Kimenai et al., 2018; Shah et al., 2017). The establishment and adoption of a more racial, gender and age-specific URL particularly for hs-cTnT assay would be expected to decrease both over-diagnosis and under diagnosis of ACS (de Lemos, 2013; Romiti et al., 2019). particularly in adult males and females respectively. The aim of this work was to establish and compare a locally driven gender-specific URL for hs-cTnT among adult Egyptians and to evaluate assay's precision at those URL

2. Method

The current study is a descriptive cross-sectional study aiming at deriving gender-specific upper reference limit (URL) for hs-cTnT in healthy young and middle-aged adult Egyptians, with validation of assay precision at proposed URLs. Serum hs-cTnT was determined among 240 adult Egyptians (120 males and 120 females) aged (18-45y), using a commercially available hs-cTnT electrochemiluminescent immunoassay. The design aligns with standardized guidelines for defining, establishing, and verifying reference intervals in the clinical laboratory [document E28–A3, published in 2008 by Clinical Laboratory Standard Institute (CLSI) and International Federation of Clinical Chemistry (IFCC)] (Horowitz, 2008; Horowitz et al., 2008).

A written consent was obtained from every participant included in this study that was approved by the Ethics Committee of Medical Research Institute. The participants were recruited from Mustafa Kamel Military Hospital during their general health check-up as a prerequisite for applying to various governmental jobs in the period from May to October 2019.

Population selection was based on the most stringent criteria for selection of reference group (normal) as published in 2012 by Collinson et al, as those individuals who gave no history of cardiovascular / vascular disease, hypertension, diabetes mellitus, or heavy alcohol intake (defined as > 29.4 grams of pure alcohol per day for males and > 15.4 grams of pure alcohol per day for females), and whom had blood pressure ≤140/90 mmHg, fasting serum glucose up to 5.55 mmol/L (100 mg/dL), estimated glomerular filtration rate (eGFR) more than 60 mL/min /1.73 m^2, receiving no cardiac medication and their echocardiography showing left ventricular ejection fraction (LVEF) exceeding 55 % with no significant left ventricular hypertrophy, diastolic heart failure, valvular heart disease or regional wall-motion abnormalities (Apple et al., 2012). Furthermore, subjects with normal lung function and no liver affection (free of viral hepatitis B and C affection and with activities of aminotransferases within permissible reference limits for both genders) as well as absent history of pulmonary embolism, sepsis, rhabdomyolysis, burns, drug toxicity, stroke and recent hospitalization within the last six months prior to recruitment in this study were included (Tanindi & Cemri, 2011).

To all participants, detailed history taking, and thorough physical examination were done, along with echocardiography using the General Electric (GE)-Vivid T8 cardiovascular ultrasound machine to measure left ventricular ejection fraction, to exclude all subclinical cases of cardiovascular disease. (Details for methodology are provided in **Supplementary appendix A**)

Laboratory investigations were done on a fasting serum sample obtained from every participant following an overnight (8–10 hours) fasting period with venous blood collected aseptically according to the standardized protocol of sampling developed by the CLSI for cTnT. Portion of the serum was used for the determination of serum levels of glucose and creatinine as well as activities of alanine and aspartate. Estimated glomerular filtration rate (eGFR) was calculated using the corrected modification of diet in renal disease (MDRD) equation (McKie et al., 2013). The rest of the serum sample was used in the determination of hs-cTnT using the 5^{th} generation hs-cTnT electro-chemiluminescent (ECL) immunoassay on the Cobas e601 module (immunoassay unit) of the Cobas 6000 modular analytical system platform (Roche Diagnostics, GmbH, D-68305 Mannheim, Germany). (Details are provided in **Supplementary appendixes A and B**).

According to the manufacturer claims, the assay had a dynamic range of 5.0–10000 ng/L, where 5.0 ng/L

corresponded to limit of detection (LOD), whereas limit of blank (LOB) was claimed at 3.0 ng/L. The reported limit of quantitation (LOQ) was 13.0 ng/L (guaranteed percent coefficient of variation (%CV) of <10%).

In order to verify such claims concerning the precision at 13.0 ng/L (LOQ), three replicates daily over five days (3× 5 days design) precision verification protocol was applied according to the CLSI approved guidelines (document EP15-A2) (Chesher, 2008) describing protocols undertaken by the user to verify manufacturer's precision claims.

A precision validation protocol twice daily over the 20 days period (2 × 20 days design) was also carried out according to the CLSI approved guidelines (document EP15-A2) (Chesher, 2008) to validate the imprecision of the assay at the proposed level of 10.0 ng/L.

Statistical analysis

Statistical analysis was done using SPSS program version 22 (Puri, 2002) and MedCalc for Windows, version 15.0 (Daly & Bourke, 2008). Data were entered as numerical or categorical, as appropriate. Shapiro test for normality was applied. For non-parametric variables, median and interquartile range (IQR) were calculated. All participants with serum hs-cTnT below LOD were given a 5.0 ng/L value for sake of proper ranking of all distribution independent non-parametric ranking analyses that follows. Mann Whiteny test was used to compare non-parametric variables across groups. The p99 URL of serum hs-cTnT was calculated as the absolute single upper p99 value (1–sided 99% reference interval) using the non-parametrical percentile method for the p99 according to the approved guidelines for defining, establishing, and verifying reference intervals in the clinical laboratory document E28–A3, published in 2008 by Clinical Laboratory Standard Institute (CLSI) and International Federation of Clinical Chemistry (IFCC) (Horowitz, 2008). Testing for presence of outliers was done using the method described by Reed et al. (1971) (Reed et al., 1971).

3. Results

Although all participants had an age range from 18–45 years, yet male participants had significantly higher median age value than females. Regarding blood pressure measurements, despite the statistically significant difference noted in systolic, diastolic and mean arterial blood pressure median values, yet all did not exceed the 140/90, which is the cut off value for defining hypertension. The left ventricular ejection fraction value was significantly higher in males compared to females, yet all had an ejection fraction above 55% which is considered normal according to the guidelines issued by several cardiology societies. (Detailed tables of results is provided in **supplementary appendix C**).

Verification of imprecision of the hs-cTnT assay using a 13.0 ng/L (claimed by the manufacturer as LOQ) sample revealed an overall mean value of 12.9 ng/L, a SD of 0.864 ng/L, a %CV of 6.7%, a minimum value of 11.8 ng/L and a maximum value of 14.0 ng/L, with no outliers detected. (table 1)

In order to validate the assay's imprecision at 10.0 ng/L which is below the assay's claimed LOQ of 13.0 ng/L, revealed a calculated mean value of 10.0 ng/L and an overall measured mean value of 10.0 ng/L, a SD of 0.761 ng/L, and a %CV of 7.7%, with a minimum value of 9.0 ng/L and a maximum value of 11.0 ng/L, with no outliers detected. (table 1)

Table 1: Comparing manufacturer precision assessment to that of the current study.

Sample	Mean ng/L	Intermediate precision SD ng/L	Intermediate precision CV %
Results of our current study's Intermediate precision Studies (on Cobas e 601)			
Human serum 1	10	0.76	**7.7**
Human serum 2	12.9	0.86	6.7
Elecsys ROCHE hs-cTnT, package insert (for Cobas e 601, and Cobas e 602 analysers			
Human serum 1	6.5	0.6	**8.6**
Human serum 2	11	0.6	**5.2**
Elecsys ROCHE hs-cTnT, package insert (for Cobas e 411 analysers)			
Human serum 1	7.5	1.1	**15**
Human serum 2	13.5	0.7	**5.2**

Using the non-parametric Mann Whiteny test, after ranking all our subjects in ascending order according to their serum hs-cTnT, comparing serum hs-cTnT ranks among the two genders (120 males vs 120 females) revealed a significantly higher level among male subjects (median = 5.5 ng/L and average of their ranks (mean rank) =135.7) compared to female subjects (median = 5 ng/L and mean rank =105.3) p<0.001. Table 2 While, comparing serum hs-cTnT among the two age groups (119 subjects with age <36y vs 121 subjects with age ≥36) a revealed a significantly higher level among older subjects with Age ≥36 (median = 6 ng/L and mean rank =150.6) compared to younger subjects with age <36y (median = 5 ng/L and mean rank =89.9) p<0.001. (Table 2)

Table 2: Comparing serum hs-cTnT among participants according to gender or age at cutoff 36y

Comparison	Number of participants	Median (IQR)	Mean rank	MWp value
Gender (in All)				
Males	120	5.5 (1.7)	135.7	<0.001
Females	120	5 (0.5)	105.3	
Age (in All) at cutoff 36Y				
Age <36	119	5 (0)	89.9	<0.001
Age ≥36	121	6 (2)	150.6	

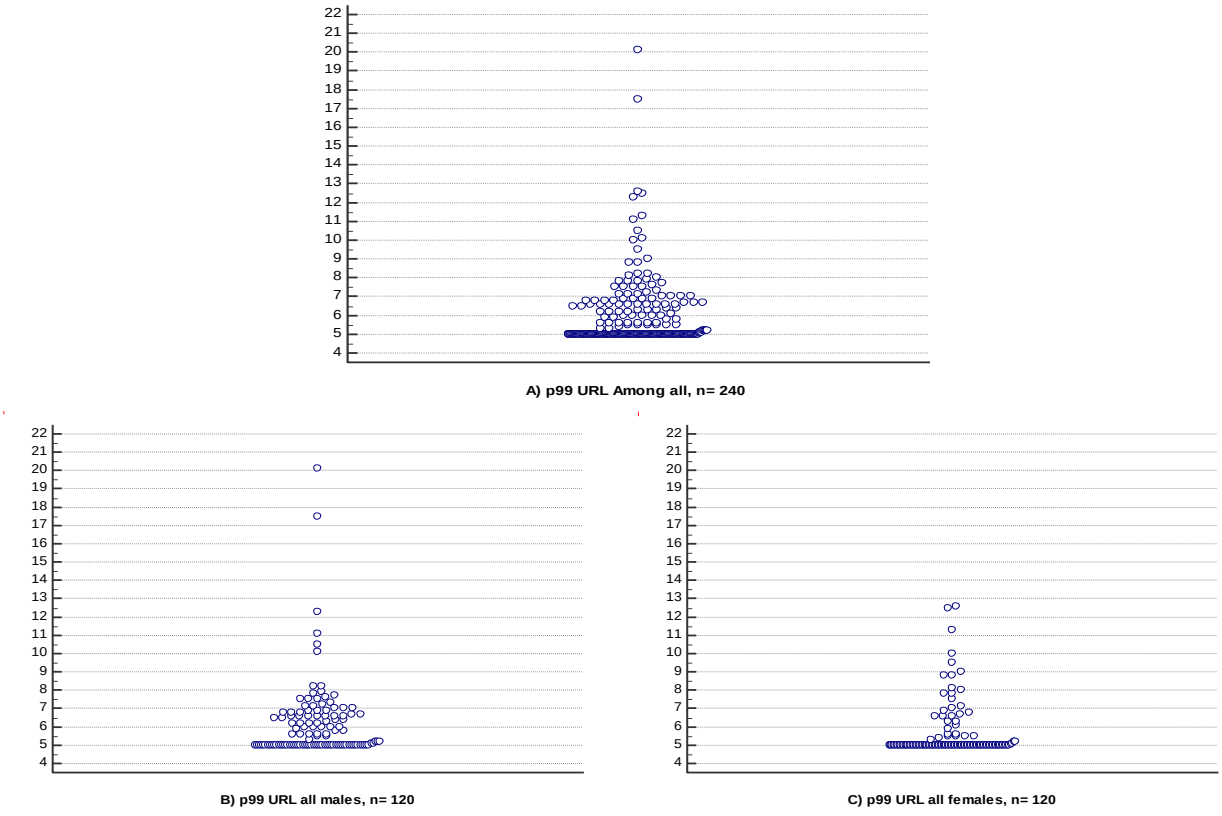
MWp: Mann Whiteny test p value, IQR: Inter-quartile range; significance level at p<0.05; Mean rank: is the average of the ranks for all observations within each stratum

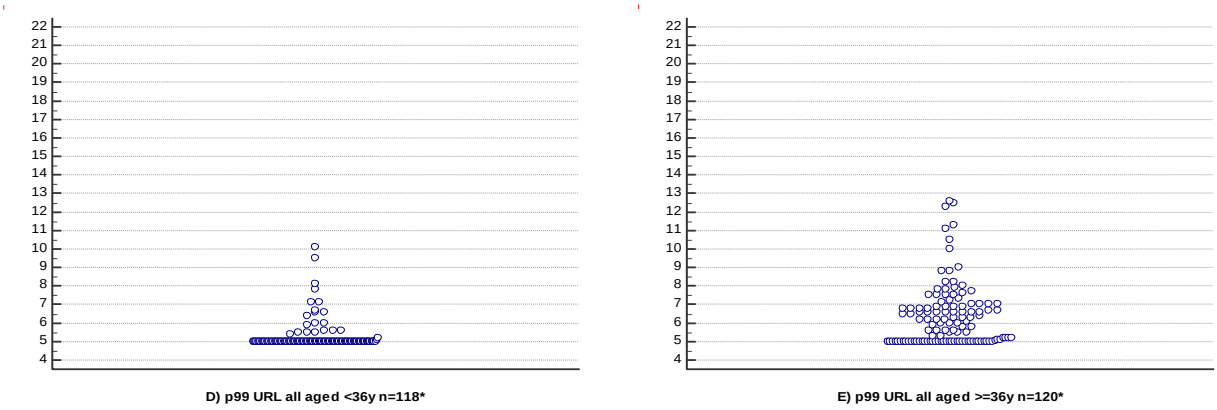
Determining p99 URL of serum hs-cTnT using the non-parametric percentile method for the p99 according to the guidelines E28–A3, published in 2008 by CLSI and IFCC, (Horowitz, 2008) revealed the following results summarized in **table 3** and displayed in **figure 1 (A,B,C,D&E)** including detailed serum hs-cTnT results and the p99 URL across all 240 participants, and when stratified according to gender or age at cutoff 36y.

Table 3: Established p99 URL of serum hs-cTnT serum hs-cTnT among participants

Group (Stratum)	Total n	Count (%) hs-cTnT ≥LOD (5ng/L)	Final n	hs-cTnT p99 URL (ng/L)
All participants	240	154 (64.2%)	240	15.5
Males	120	69 (42.5%)	120	19.6
Females	120	37 (30.8%)	120	12.6
All < 36	119	23 (19.3%)	118*	10
All ≥ 36 years	121	83 (68.6%)	120*	12.6

n: Number of participants per stratum; hs-cTnT p99 URL: 99th *percentile Upper reference limit of High-sensitivity Cardiac Troponin T all calculated after Outliers exclusion; LOD: Limit of detection; * Outliers excluded (detection done using method developed by (Reed et al., 1971)Reed et al. (1971).*





**Outliers excluded (detection done using Reed's et al, method)*

Fig.1: (A/B/C/D/E): p99 URL for serum hs-cTnT among all subjects (A), and when divided according to gender (B, C) and according to age (cutoff 36y) (D, E)

4. Discussion

In this study, we carried out a descriptive cross-sectional study aiming at deriving gender-specific upper reference limit (URL) for hs-cTnT in healthy young and middle-aged adult Egyptians, with validation of assay precision at proposed URL. Our result established a locally driven 99th percentile URL for serum hs-cTnT among adult male and female subjects, using the 5th generation hs-cTnT electro-chemiluminescent (ECL) immunoassay on the Cobas e601 module, looking closely into the manufacturer precision assessment section of our kit's package insert (**supplementary appendix B**) and comparing it to the results of our intermediate precision studies (**table 1**), showed that, for the Cobas e411 analyzer %CV equal to 15% and 5.2% were calculated for intermediate precision at mean value of 7.5 ng/L and 13.5 ng/L, yet regarding the Cobas e601 module (immunoassay unit) of the Cobas 6000 modular analytical system (used in the current study), %CV equal to 8.6 and 5.2 were calculated for intermediate precision at mean values of 6.5 ng/L and 11.0 ng/L. Thus, the manufacturer adopted the higher %CV of the less precise Cobas e411 as the overall %CV used to determine the LOQ of the kit, claiming the limit of quantitation (LOQ) at 13.0 ng/L would guarantee a (%CV) of <10% on all its platform, when in reality as proved by the manufacturer own study and confirmed by our precision study (revealing a CV of 7.7%, at mean 10 ng/L) (please refer to results section), the Cobas e601 module is, in fact, more precise than the e411 and a lower LOQ of 10.0 ng/L can thus be adopted and still guarantee a (%CV) of <10% as recommended. As for establishing a valid p99 URL for serum hs-cTnT, there is much debate concerning both, the selection of a healthy reference population in determining cTns p99 values. However, recent studies have shown that the selection criteria applied to define a healthy reference population may greatly influence the derived p99 values for cTns (Aw et al., 2018). Unfortunately to date, no evidence-based guidelines or universal protocols have been formally implemented to support laboratories and manufacturers in establishing p99 URLs for cTns (Benjamin et al., 2017). In multiple studies, several approaches have been proposed, ranging from data collection from self-reported questionnaires to screening with laboratory surrogate biomarkers, cardiac imaging techniques and other diagnostic tests, in order to evaluate the health status of individuals constituting a normal reference population (Krintus et al., 2015).

Sandoval and Apple suggested that the screening and enrolment of presumably healthy individuals into a study to determine the p99 URL for cTn assay should minimally address the following, clinical history for known cardiovascular disease and medication usage, surrogate biomarkers for diabetes and renal dysfunction, appropriate non-parametric statistical analysis, possible inclusion of an imaging modality if financially feasible and a description of specimen type used (Apple et al., 2017).

The current study was based on collecting serum samples from 240 apparently healthy young adult Egyptian volunteers aged 18–45 years, divided into 120 males and 120 females for measuring serum cTnT using the 5th generation hs-cTnT assay. The current study identified that gender was an important factor influencing its serum concentrations. Comparing serum hs-cTnT among the two genders revealed a significantly higher level among male compared to female subjects ($p<0.001$). Consequently, the derived p99 value for hs-cTnT in this study in female participants was lower (12.58 g/L) than that of male participants (19.6 ng/L)**.** This observation was in agreement with Collinson et al whom reported a clear difference between men and women in the examined subgroups for the Roche hs-cTnT ECL immunoassay (Collinson et al., 2012). Several other studies support the existence of a discrepancy between percentile values of hs-cTnT in men and women (Kimenai et al., 2016; Monneret et al., 2018; Mueller et al., 2016; Ungerer et al., 2016; Welsh et al., 2018; Yang et al., 2016).

Studies concerning gender-specific lower thresholds for women for the diagnosis of ACS have not shown consistent results. Shah et al. (2015) proposed that women-specific lower diagnostic thresholds for cTn may double the diagnosis of ACS in women and identify those at high risk of re-infarction and death (Shah et al., 2015). On the other hand, a study by Giménez et al. (2016) done on a larger sample size,

demonstrated that gender-specific troponin thresholds did not improve diagnostic accuracy, and hence has proposed that the p99 should remain the standard of care for both genders (Rubini Gimenez et al., 2016).

In our study, the effect of age was obvious on serum hs-cTnT levels when participants were divided according to an age cutoff value of 36 years, where serum hs-cTnT levels were significantly lower in 119 subjects aged <36 years old compared to 121 subjects aged 36 years old or more ($p<0.001$), with a proposed p99 URL value of 10.0 ng/L and 12.6 ng/L respectively with excluding of outliers.

Furthermore, the clinical utility of depending on the p99 as the URL for cardiac troponins is becoming less relevant with the recent emphasis on using the dynamic changes in serial hs-cTn values, also known as hs-cTn delta, for identifying acute myocardial injury. However, the choice between using a relative or absolute hs-cTn delta remains a topic of discussion. Additionally, there are growing considerations regarding potential differences in troponin deltas that may be significant across different sexes and racial or ethnic groups (Wright et al., 2024). This approach is gaining more importance especially with development of highly sensitive assays which by definition can detect >50% of normal subjects above LOD. Such approach is of even greater importance for hs-cTnT because of the greater gap between p99 URL mostly <20 ng/L and MI decision making limit of 100 ng/L, such an equivocal gap doesn't exist when using hs-cTnI assays. Such approach with >20% increase may lead to earlier diagnosis even before crossing MI decision making limit of 100 ng/L.

Such a wide equivocal gap of hs-cTnT, may also extends the clinical significance of our findings beyond patients with ACS to include patients with non-ischemic cardiac injury, Askin et al., 2020 reported that elevated hs-cTnT levels in this population are increasingly recognized as markers of non-ischemic cardiac injury, including heart failure with preserved ejection fraction (HFpEF), myocarditis, chemotherapy-induced cardiotoxicity and cardiomyopathies, as well as systemic conditions such as sepsis or chronic kidney disease (Askin et al., 2020). The gender-specific URLs established in our study (12.6 ng/L for females vs. 19.6 ng/L for males) may refine the detection of subtle myocardial injury in women, who are disproportionately affected by non-ischemic pathologies yet often underdiagnosed due to uniform diagnostic thresholds optimized for male physiology. Similarly, the lower age-stratified URL (10.0 ng/L for individuals <36 years) could enhance early identification of non-ischemic cardiac injury in younger patients where minor troponin elevations may otherwise be dismissed as "normal" under conventional criteria.

Finally, comparing our gender specific p99 results of 19.6 ng/L for males and 12.6 for females, to the data available from the IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) (v06, 2024) which contains the most up-to-date assessment of High-Sensitivity Cardiac Troponin I and T Assay Analytical Characteristics Designated by Manufacturer (**supplementary appendix D**), revealed comparable gender specific p99 URL results (especially among females) to studies in united states package inserts, 22 ng/L for males and 14 ng/L for females, when compared to the much lower p99 in European inserts 17 ng/L for males and 9 ng/L for females. Which may be an interesting point in future studies to find out the main reason(s) behind that.

5. Conclusion

Adopting a universally unified p99 URL of 14.0 ng/L for the hs-cTnT assay does not reflect the p99 URL value of all reference populations with varied demographic, age and gender characteristics. Instead, the establishment and use of locally driven age and gender specific p99 value as an URL for hs-cTnT assay would benefit the patient in early diagnosis of Acute coronary syndromes and decrease false diagnosis with the hs-cTnT assay, a problem with major clinical and public health ramifications. Furthermore, these stratified thresholds may extend their utility beyond ischemic heart disease, aiding in the early detection of myocardial injury in non-ischemic cardiac conditions such as heart failure, myocarditis, or systemic diseases, where subtle troponin elevations are clinically significant but often misinterpreted under uniform reference limits. Further studies are needed to verify and measures the impact of applying such locally driven age and gender specific p99 URL cutoff values to improve the diagnostic performance of hs-cTnT in males by decreasing over-diagnosis and improve assay's sensitivity among females by decreasing under-diagnosis.

The Cobas e601 module is more precise than the Cobas e411, and a lower LOQ of 10.0 ng/L (compared to the 13 ng/L assigned in the package insert) can be adopted for the Cobas e601 module while still guaranteeing a %CV of <10% as recommended.

Study limitations

Although a sample size of 120 healthy subjects per stratum is substantial according to CLSI document E28–A3, it may still fall short of the more recent number recommended by the Cardiac Biomarkers Group of the International Federation of Clinical Chemistry (IFCC).

Although the Reed's criterion (used in our study) is recommended for detecting outliers, it may not be fully reliable for detecting some high values especially in our male group, using other methods for detecting outliers may affect the results with our sample size. With that said, it seems like such high "normal" males is the reason behind the more recent expert's option for increasing sample size when evaluating cardiac troponins so as to add more of these high normal males so they wouldn't be considered outliers anymore and would then be included into a more realistic p99.

Assessing NT-proBNP levels would have helped in excluding clinically healthy individuals who might have minor cardiac abnormalities, including heart failure with preserved ejection fraction (HFpEF).

Though Determining the p99th in a young/middle-aged population (18-45 years) may not adequately represent the true URL for the broader older population evaluated for suspected myocardial damage, yet as per our title implies, we were concerned more with these younger age group. we still

recommend broadening age range to include older subjects in future studies.

Data availability

The data sets analyzed in the current study are available from the corresponding author upon reasonable request.

Abbreviations

CK-MB :
Muscle brain fraction of creatine kinase

CLSI:
Clinical Laboratory Standard Institute

FAG:
Antigen –binding fragment

cTn:
Cardiac troponins

C-TnC:
C-terminal domains of TnC

hs-cTnT:
High-sensitivity-Cardiac troponin-T

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Contributions

A.T. and A.R. carried out most of the methodology. M. L. supervised the case selection and conducted the clinical part. A.A and A.T wrote and revised the manuscript. All authors have reviewed and approved the final version of the manuscript.

Ethics declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the Declaration of ICH GCP guidelines and applicable local and institutional regulations and guidelines which govern IRB operation. All the procedures were approved by the (Alexandria University, Medical Research Institute ethics committee, IORG#0008812) (ethics approval number:E/C.S/N.T84/2019). Written informed consent was obtained from all participants in the study population.

It is not a clinical trial

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests..

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