Review Article

Population differences and high-sensitivity troponin values: a narrative review

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Background and Objective: The 99th percentile upper reference limit (URL) of high-sensitivity troponin is used as a diagnostic threshold for acute myocardial infarction. It is not established if troponin differs across different populations. This narrative review discusses 99th percentile URLs of high-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity cardiac troponin T (hs-cTnT) derived from healthy reference populations in different populations across different geographic locations.

Methods: Articles investigating high-sensitivity troponin in healthy reference populations which reported sex-specific 99th percentile URLs, with a minimum of 800 subjects, and written in English were included. Besides more recent articles identified from PubMed and Google Scholar until December 2022, we included studies in the systematic review previously published by Kimenai in 2018 that met our inclusion criteria. Studies that did not use high-sensitivity troponin assays were excluded.

Key Content and Findings: Nineteen articles (9 with hs-cTnT studies and 15 with hs-cTnI studies) were identified. The largest difference in hs-cTnT across studies was 19.6 ng/L, but very little difference was seen between similarly designed studies. The biggest difference in hs-cTnI (Abbott ARCHITECT STAT) was 22.9 ng/L. Expectedly, as hs-cTnI is not standardized differences exist between studies using different analytical platforms from different vendors. Reference cohort compositions and statistical treatment varied across all studies limiting comparison.

Conclusions: Population differences in high-sensitivity troponin values do not appear to be very different across similarly studied populations for hs-cTnT in different countries. More differences are noted for hs-cTnI. Differences in 99th percentile hs-cTn URLs between populations are influenced by many variables including composition of the reference cohort and statistical methods employed. Male sex, increasing age, comorbidities such as subclinical heart disease, renal dysfunction and dysglycemia, and including outliers in analysis can raise hs-cTn 99th percentile URLs. Existing study designs investigating 99th percentile URLs of troponin have been heterogenous making it challenging to compare population differences in troponin concentrations. The jury is still out on whether troponin values differ across populations. Reference cohorts should include a representative distribution of the regional population composition in the applicable geographic area as recommended by expert committees.

Keywords: High-sensitivity cardiac troponins (hs-cTn); 99th percentile upper reference limits (99th percentile URLs); population differences

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Introduction

Background

Cardiovascular disease (CVD) is the leading cause of death globally (1). An estimated 17.9 million people died from CVD in 2019. Timely diagnosis and intervention of acute myocardial infarction (MI) is crucial in optimizing outcomes and are enabled by high-sensitivity cardiac troponins (hs-cTn) as recommended by the European Society of Cardiology (ESC) and the American Heart Association (AHA) (2-4). As part of the contractile apparatus in striated cardiac and skeletal muscle, cardiac troponin (cTn) I and T are released from injured myocardium, making them useful markers for diagnosing myocardial injury and MI (5-7). The population 99th percentile upper reference limit (URL) is particularly important as it is the threshold used to diagnose myocardial injury and MIs (8). Troponin is also increasingly being interpreted as a continuous biomarker for prognostication and risk stratification (9-14).

Rationale and knowledge gap

Over the last decade, more hs-cTn assays have been developed. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) states that for a troponin assay to be labelled as high-sensitivity, the total imprecision [% coefficient of variation (CV)] at the 99th percentile has to be ≤10%, and the assay should be able to measure concentrations above the assay's limit of detection (LOD) in at least 50% of healthy individuals of both sexes (7). High-sensitivity troponin assays and improvements in analytical platforms have also enabled measuring high-sensitivity troponins with lower limits of detection and more precise analytical sensitivity. This has revealed differences in high-sensitivity troponin values between sexes, different ages and health statuses. It is unclear if there are differences in 99th percentile URLs of hs-cTn derived from healthy subjects from different geographical populations.

Objective

Several studies have explored high-sensitivity troponins in different geographical locations, and some have compared 99th percentile URLs derived from different racial populations (15-17). We aim to provide an updated view of whether there are population differences in the 99th percentile URLs of high-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity cardiac troponin T (hs-cTnT) derived from healthy reference populations in different populations across different geographic locations. We present this article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-73/rc).

Methods

The IFCC Committee on Clinical Application of Cardiac Bio-Markers (C-CB) has only recently advised that for the 99th percentile URL to have a robust confidence interval (CI) of 95%, 800 subjects (400 female and 400 male) have to be studied (18). Articles investigating high-sensitivity troponin in healthy reference populations which reported sex-specific 99th percentile URLs, with a minimum of 800 subjects, and were written in English were included. Besides more recent articles identified from PubMed and Google Scholar until December 2022, we also included studies that were previously published in a systematic review by Kimenai *et al.* (19) that met our inclusion criteria. Studies that did not use high-sensitivity troponin assays were excluded. For analysis, articles were grouped and compared according to hs-cTnT versus the respective hs-cTnI assay platforms. For studies that reported more than one cohort, only cohorts that met the inclusion criteria were used for analysis. In studies where there were more than one cohort that met all inclusion criteria, the cohort with the strictest criteria for cohort selection (biochemical screening for co-morbidities—renal dysfunction, subclinical heart disease, and diabetes) was chosen for inclusion. Male sex, older age, renal dysfunction, subclinical heart disease, and diabetes are associated with higher troponin values and can raise the 99th percentile URLs. In addition, exclusion of outliers using stricter methods compared to others (e.g., Tukey > Reed, Dixon > no exclusion of outliers) can result in lower results. These factors were taken into consideration when reviewing the 99th percentile URLs. The 99th percentile URLs were compared across geographical locations where possible.

Results

Overall, 19 articles [articles from Kimenai *et al.* (19) =9, articles from additional search = 10] were included in this review. The articles comprised of nine hs-cTnT and 15 hs-cTnI studies including five articles which reported on both hs-cTnT and hs-cTnI assays. All nine hs-cTnT studies were conducted with the hs-cTnT Roche Elecsys assay. The 15 hs-cTnI studies comprised hs-cTnI Abbott ARCHITECT

STAT assay (10 studies), Siemens ADVIA Centaur hs-cTnI assay (2 studies), Beckman Coulter Access hs-cTnI assay (1 study), Ortho Clinical Diagnostics VITROS hs-cTnI assay (1 study), and Singulex Clarity hs-cTnI assay (1 study).

hs-cTnT (Roche Elecsys)

Studies using hs-cTnT included in this review are slightly easier to compare as hs-cTnT assays are from a single vendor, Roche. Studies using hs-cTnT are shown in *Table 1* (12,16,20-26). The nine studies that assessed the 99th percentile of hs-cTnT were conducted in eight different countries and five different analyzers were used (cobas e170, e411, e601, e602, and e801). The inclusion criteria for screening of healthy subjects varied in their biochemical screening for co-morbidities (vide supra). Two studies screened for all three subclinical disorders and three studies did not screen for any subclinical conditions in their reference cohorts.

The overall 99th percentile URLs ranged from 13.6 to 28.0 ng/L, the 99th percentile URLs in females ranged from 7.9 to 24.0 ng/L and the 99th percentile URLs in males ranged from 14.4 to 34.0 ng/L. The largest difference in 99th percentile hs-cTnT URLs across studies was 19.6 ng/L between males in the study by Odsæter *et al.* (25) in Norwegians and the Cardiovascular Health Study (CHS) in Americans by Gore *et al.* (26). The 99th percentile URLs from the study by Odsæter *et al.* (25) were consistently the lowest while the 99th percentile URLs from the CHS reported by Gore *et al.* (26) were consistently the highest. It is worth noting that the cohort studied by Odsæter *et al.* (25) was thoroughly screened with all 3 biochemical parameters for subclinical disease and used Tukey, a stricter technique for identifying outliers while the CHS cohort studied by Gore et at. (26) was older (median age 72 versus 43 years), did not screen for dysglycemia, and did not exclude any outliers.

Comparing the studies by Zhang *et al.* (20) in Chinese and Odsæter *et al.* (25) that screened for all three subclinical conditions with exclusion of outliers, the maximum difference in 99th percentile hs-cTnT URL was 5.1 ng/L in females. Odsæter *et al.* (25) used Tukey, a stricter technique to identify outliers, while Zhang *et al.* (20) used Reed-Dixon. The Odsæter *et al.* (25) study used the cobas e801 whereas the Zhang *et al.* (20) employed the cobas e170. These differences in outlier treatment and analyzer platforms may have contributed to the difference.

If we exclude the study by Odsæter *et al.* (25) which had stricter outlier treatment, and the CHS Atherosclerosis Risk in Communities Study (ARIC) cohorts in Gore *et al.* (26) which had cohorts that were older than the other studies (72 and 61 years) in *Table 1*, there was little difference in the 99th percentile hs-cTnT URLs (maximum difference was 6.2 ng/L in males) between Chinese, Singaporeans, Australians, Germans, Dutch, Scottish, and Americans.

The study by Fitzgerald *et al.* (16) (n=1,301) conducted at 7 US sites concluded that the hs-cTnT 99th percentile URLs (18.5–20.0 ng/L) and median values (3.0–3.7 ng/L) were generally consistent across different populations (Asian, African American, Caucasian, Hispanic, non-Hispanic) (16). From *Table 1*, hs-cTnT 99th percentile URLs across populations in Asia, Oceania, Europe and North America also do not seem to be very different.

hs-cTnI assays

Concentrations of hs-cTnI vary widely across assays and are difficult to compare as hs-cTnI are not standardized. As such we have segregated them by the respective assay platforms as far as possible.

hs-cTnI (Abbott ARCHITECT STAT)

Studies we reviewed using the Abbott ARCHITECT STAT assay are shown in *Table 2* (12,22-24,27-32). Between the 10 studies from 15 different countries, three different analyzers (ARCHITECT ci16200, ARCHITECT i1000SR, and ARCHITECT i2000SR) were used. Reference cohort inclusion criteria varied between studies. One study screened for all three subclinical diseases (vide supra) while four studies did not screen for any subclinical disease.

In *Table 2*, the overall 99th percentiles ranged from 13.0 to 28.9 ng/L, the 99th percentile URLs in females ranged from 11.0 to 22.7 ng/L, and the 99th percentile URLs in males ranged from 20.0 to 42.9 ng/L. The largest difference was the male 99th percentile URLs which had a difference of 22.9 ng/L between the studies by Hickman *et al.* (30) and Kimenai *et al.* (24)/Ji *et al.* (29) in Australians and the Dutch/South Koreans, respectively. The overall 99th percentile URLs differed by 15.9 ng/L between Kimenai *et al.* (24) and the Australian cohort in Ungerer *et al.* (22). The lowest female 99th percentile URL was similarly from the study by Kimenai *et al.* (24) while the highest 99th percentile URL was from the cohort by Li *et al.* (27) in Chinese. The cohort in Kimenai *et al.* (24) was screened for both renal dysfunction and subclinical heart disease and excluded outliers using Dixon, while both these diseases and outliers

Table 1 Demographics, biochemical exclusion criteria for reference cohort selection and statistical methods of articles reporting sex-specific 99th percentile URLs for hs-cTnT (Roche Elecsys hs-cTnT assay)

Study location	Author [year]	Participants (n)	Females (%)	Mean/ median/ age range (years)	Platform	Biochemical parameters used to exclude subjects from reference cohort			99th percentile (ng/L)			Statistical method
						eGFR <60 mL/ min/1.73 m^2	Abnormal HbA1c or fasting glucose	Abnormal BNP or NT-proBNP	Overall	Female	Male	
Asia												
China	Zhang [2020]	932	63.0	NR	Cobas e170	Yes	Yes	Yes	16.0	13.0	18.0	NP/Reed-Dixon
Singapore	Aw [2017]	1,086	50.0	52.2	Cobas e601	Yes‡	No	No	17.0	12.0	18.6	NP
Oceania												
Australia	Ungerer [2016]	2,004	35.2	40.0	Cobas e601	No	No	No	15.9	9.6	18.1	NP
Europe												
Germany	Giannitsis [2020]	827	50.9	56.0	Cobas e411, cobas e602	No	No	No	16.8	13.3	19.2	NP/Dixon
Netherlands	Kimenai [2016]	1,540	52.4	57.0	Cobas e601	Yes	No	Yes	15.0	12.0	16.0	NP/Dixon
Norway	Odsæter [2020]	983	49.8	43.0	Cobas e801	Yes	Yes	Yes	13.7±0.1	8.0±0.1	14.5±0.1	NP/Tukey
Scotland	Welsh [2019]	19,501	58.3	18–98	Cobas e411	No	No	No	NR	14.4†	20.7†	NP/LTV >5 SD
North America												
USA	Fitzgerald [2020]	1,301	50.4	48.0	Cobas e601	Yes	No	Yes	O 19.2, AA 18.5, C 20.0, NHL 19.2	13.5–13.6	21.4–22.2	NP
	Gore [2014]	DHS 1,978, ARIC 7,575, CHS 1,374	DHS 55.9, ARIC 60.8, CHS 64.4	DHS 43.2, ARIC 61.0, CHS 72.0	NR	Yes	No	Yes	DHS 14.0, ARIC 21.0, CHS 28.0	DHS 11.0, ARIC 15.0, CHS 24.0	DHS 17.0, ARIC 26.0, CHS 34.0	NP

†, estimated using weighted mean of subgroups; ‡, eGFR <90 mL/min/1.73 m^2. AA, African American; ARIC, Atherosclerosis Risk in Communities Study; C, Caucasian; CHS, Cardiovascular Health Study; DHS, Dallas Heart Study; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; hs-cTnT, high-sensitivity cardiac troponin T; LTV, log-transformed values; NHL, non-Hispanic Latino; NT-proBNP, N-terminal pro B-type natriuretic peptide; O, overall; NP, non-parametric; NR, not reported; SD, standard deviation; URL, upper reference limit.

Table 2 Demographics, biochemical exclusion criteria for reference cohort selection and statistical methods of articles reporting sex-specific 99th percentile URLs for hs-cTnI (Abbott ARCHITECT STAT hs-cTnI assay)

Study location	Author [year]	Participants (n)	Females (%)	Mean/ median/ age range (years)	Platform (ARCHITECT)	Biochemical parameters used to exclude subjects from reference cohort			99th percentile (ng/L)			Statistical method
						eGFR <60 mL/ min/1.73 m^2	Abnormal HbA1c or fasting glucose	Abnormal BNP or NT-proBNP	Overall	Female	Male	
Asia												
China	Li [2017]	1,485	50.8	36.0	i2000SR	Yes	Yes	No	28.0	22.7	31.1	NP
Singapore	Aw [2013]	1,120	46.7	50.4	i2000SR	Yes	No	No	25.6	17.9	32.7	NP
South Korea	Ji [2016]	854	50.1	49.8	i2000SR	Yes	Yes	Yes	18.0	19.0	20.0	NP/Reed
Oceania												
Australia	Hickman [2019]	1,007	52.6	48–92	ci16200	No	Yes	No	NR	15.8†	42.9†	NP
	Ungerer [2016]	2,004	35.2	40.0†	i2000SR	No	No	No	28.9	20.2	31.3	NP
Europe												
Germany	Giannitsis [2020]	827	50.9	54.0	i2000SR	No	No	No	16.0	12.5	27.4	NP/Dixon
Netherlands	Kimenai [2016]	1,540	52.4	57.0	i2000SR	Yes	No	Yes	13.0	11.0	20.0	NP/Dixon
Scotland	Welsh [2019]	19,501	58.3	56.0	i2000SR	No	No	No	NR	14.5†	31.6†	NP/LTV >5 SD
	Zeller [2015]	4,039	49.6	50.0	i2000SR	Yes	No	No	26.0	19.4	32.5	Hajek's method
		3,865	49.6	49.0	i2000SR	No	No	Yes	21.7	14.8	25.9	Hajek's method
9 European countries‡	Krintus [2014]	1,769	56.1	56.1	i2000SR/ i1000SR	No	No	No	19.3	11.4	27.0	NP/Reed

†, estimated using weighted mean of subgroups; ‡, Austria, Belgium, Denmark, France, Germany, Italy, Norway, Poland, Spain. eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; hs-cTnI, high-sensitivity cardiac troponin I; LTV, log-transformed values; NP, non-parametric; NT-proBNP, N-terminal pro B-type natriuretic peptide; NR, not reported; SD, standard deviation; URL, upper reference limit.

Table 3 Demographics, biochemical exclusion criteria for reference cohort selection and statistical methods of articles reporting sex-specific 99th percentile URLs for hs-cTnI (Siemens ADVIA Centaur hs-cTnI assay)

Study location	Author [year]	Participants (n)	Females (%)	Mean/ median/ age range (years)	Platform	Biochemical parameters used to exclude subjects from reference cohort			99th percentile (ng/L)			Statistical method
						eGFR <60 mL/ min/1.73 m^2	Abnormal HbA1c or fasting glucose	Abnormal BNP or NT-proBNP	Overall	Female	Male	
Europe												
Italy	Clerico [2019]	1,325	49.3	18–86	Centaur XPT immunoassay system	Yes	Yes	Yes	40.1	32.4	43.4	NP/Tukey
Norway	Odsæter [2020]	983	49.8	43.0	Centaur XPT immunoassay system	Yes	Yes	Yes	53.0	35.0	55.0	NP/Tukey

hs-cTnI, high-sensitivity cardiac troponin I; eGFR, estimated glomerular filtration rate; NP, non-parametric; NT-proBNP, N-terminal pro B-type natriuretic peptide; URL, upper reference limit.

were not excluded from the cohorts in Ungerer *et al*. (22) and Hickman *et al*. (30), thus contributing to their higher hs-cTnI values. Subclinical heart disease and outliers were also not excluded from the cohort in Li *et al*. (27). It is thus not surprising that there are differences between these studies.

Furthermore, the cohort studied in Ungerer *et al.* (22) had a higher proportion of males in the cohort (35.2% of cohort was female). The sex-specific 99th percentile URLs in Ungerer *et al.* (22) were comparable to other studies in *Table 2*, thus the higher overall 99th percentile URLs can likely be attributed to the larger proportion of males in the reference cohort. The age distribution of the reference cohorts in *Table 2* were similar except for the cohort in Li *et al.* (27). The study by Li *et al.* (27) had a younger cohort (mean age 36 years) and did not screen for subclinical heart disease nor exclude any outliers. With these effects canceling each other out very little difference in the 99th percentile hs-cTnI URLs is seen.

Focusing on the studies by Kimenai *et al*. (24) and Ji *et al*. (29) in South Koreans that screened for both renal dysfunction and subclinical heart disease and excluded outliers, the maximum difference in 99th percentile URLs was 8 ng/L in females.

The studies by Giannitsis *et al.* (23) in Germans, Welsh *et al.* (12) in Scottish, and Krintus *et al.* (31) conducted in nine European countries did not exclude subjects with subclinical diseases using biochemical parameters but excluded outliers. The maximum difference in 99th percentile URLs was similar in these studies (maximum difference was 4.6 ng/L in males).

Although differences in 99th percentile hs-cTnI URLs were observed in *Table 2*, at least some of these differences can be attributed to differences in cohort composition and inconsistent treatment of outliers.

hs-cTnI (Siemens ADVIA Centaur)

Studies reviewed using the Siemens ADVIA Centaur assay are shown in *Table 3* (25,33). Both studies used the ADVIA Centaur XPT Immunoassay System and were conducted in two different countries. Each study reported multiple 99th percentile URLs with different permutations of screening for subclinical disease and statistical methods to derive the 99th percentile URLs. The 99th percentile URLs reported by Odsæter *et al.* (25) in Norwegians were higher than by Clerico *et al.* (33,34) in Italians although not by a large magnitude (maximum difference 12.9 ng/L). Overall, female, and male 99th percentile URLs were 40.1 versus 53 ng/L [90% confidence interval (CI): 41–61 ng/L], 32.4

versus 35 ng/L (90% CI: 26–59 ng/L), and 43.4 versus 55 ng/L (90% CI: 42–61 ng/L), respectively. On closer examination, each 99th percentile URL reported fell within the 90% CI of the corresponding 99th percentile URL from the other study. It is likely there was no difference between the two different populations within Europe. There were no other studies identified that were conducted in other geographical regions to compare against.

hs-cTnI (Beckman Coulter Access, Ortho Clinical Diagnostics VITROS, Singulex Clarity)

There was a single study each for the Beckman Coulter Access, Ortho Clinical Diagnostics VITROS, and Singulex Clarity assays (*Table 4*) (34-36). These studies were conducted in two different countries. Although the Singulex Clarity assay is no longer commercially available, we have included it in this review due to its superior sensitivity with an LOD of 0.80 ng/L and a measurable hs-cTnI of >99% in both females and males that may provide additional insights (37). As hs-cTnI assays are not standardized across platforms, we did not compare the results across the studies. All three studies screened their reference populations for subclinical renal dysfunction, subclinical diabetes, and subclinical cardiac disease. Two different methods used to handle outliers (Dixon and Tukey) were employed.

Limitations

Troponin concentrations are affected by sex, age, renal function, diabetes, and cardiac dysfunction. We need to understand how each of these variables influence troponin concentrations so as to be thoughtful about the effects they have on the 99th percentile URLs when comparing different populations.

Sex

Troponin concentrations are higher in males. Differences in troponin concentrations between sexes have been brought up in all the platforms but the magnitude of discrepancy varies by analyzer platform. Higher troponin concentrations observed in males than females are likely due to physiological differences that influence cardiovascular health (8,38-40). Our previous study with cardiac magnetic resonance imaging (MRI) demonstrated that left ventricular mass in females are smaller (39 g/m^2) than in males (50 g/m^2) (41,42). Cardiac mass and volumes were independently associated with hs-cTnI (Abbott ARCHITECT STAT) concentrations. The concentrations of Abbott ARCHITECT STAT hs-cTnI in transgender men and women who are prescribed testosterone and estrogen were similar to cisgender men and women, suggesting that hormones are also driving the difference in hs-cTnI (Abbott ARCHITECT STAT but not Beckman Coulter Access) values between sexes (43). It has been well demonstrated that sex-specific thresholds for diagnosing MI optimizes the performance of troponins especially in females (44,45). Reference cohorts used to derive 99th percentile URLs should have an equal sex representation and sex-specific limits should be used for comparison across populations.

Age

Several studies have found increased troponin concentrations with age (16,23,30,33-36,41,46,47). There seems to be a stronger correlation with troponin in older populations when comparing groups aged above and below age 40–65 years (23,33,34,47,48). The slope when plotting age against hs-cTnI concentrations in a healthy cohort (n=1,302) is nearly constant from 18 to 55 years of age before steadily increasing and reaching levels up to 3 times higher at 85 years (34). The development of a relationship between troponin and age later in life is consistent with age-related accumulation of cardiovascular risks and disease. Elevations in troponin concentration with age may also be attributed to physiological processes such as increased release of troponin due to myocyte turnover, cardiomyocyte proliferation and increased cardiac mass (49). In older cohorts, the 99th percentile URL has less discriminatory power due to comorbidities and higher prevalence of individuals with troponin levels above the URLs (50-55). Stratifying troponins according to age-adjusted URLs improves their diagnostic and prognostic performance (50,56,57). Furthermore, troponin reference limits should also be derived from a reference population that reflects the age demographics of patients who present with chest pain. An age-specific 99th percentile URL at every decade after 40 years will likely optimize diagnostic accuracy of hs-cTn in the elderly. However, recruiting a reference population of sufficiently sized healthy elderly is difficult. It is noteworthy that less rigorous selection of the reference population for derivation of the 99th percentile URL were accepted in the past for cardiac biomarkers in the past (58). A practical solution could be a 3-band age-specific diagnostic threshold as has been done for N-terminal pro B-type natriuretic peptide (NT-proBNP): <50, 50–75, >75 years to optimize clinical specificity (59). We similarly need to be particularly

Table 4 Demographics, biochemical exclusion criteria of reference cohort selection and statistical methods of articles reporting sex-specific 99th percentile URLs for hs-cTnI (Beckman Coulter Access hs-cTnI, hs-cTnI Ortho Clinical Diagnostics VITROS, and Singulex Clarity hs-cTnI assays)

Study location	Author [year]	Participants (n)	Females (%)	Mean/ median/ age range (years)	Platform	Biochemical parameters used to screen reference cohort			99th percentile (ng/L)			Statistical method
						eGFR <60 mL/ min/1.73 m^2	Abnormal HbA1c or fasting glucose	Abnormal BNP or NT-proBNP	Overall	Female	Male	
Beckman Coulter Access hs-cTnI assay												
Europe												
Italy	Clerico [2019]	1,302	49.9	18–86	Dxl800	Yes	Yes	Yes	15.8	13.6	18.7	NP/Tukey
Ortho Clinical Diagnostics VITROS hs-cTnI assay												
Asia												
China	He [2022]	2,183	51.9	20–95	VITROS 5600 Immunodiagnostic System	Yes	Yes	Yes	11.1	9.6	12.5	NP/Dixon
Singulex Clarity hs-cTnI assay												
Europe												
Italy	Agnello [2019]	1,110	31.0	41	Clarity system	Yes	Yes	Yes	5.0	4.4†	5.1†	NP/Tukey

†, estimated using weighted mean of subgroups. eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; hs-cTnI, high-sensitivity cardiac troponin I; NP, non-parametric; NT-proBNP, N-terminal pro B-type natriuretic peptide; URL, upper reference limit.

conscious of the age distribution of the reference cohort used to derive the 99th percentile URL when using these thresholds clinically and when comparing different cohorts.

Comorbidities

Subclinical heart failure will raise troponins as myocardial dysfunction affects the distribution of troponin (18). The IFCC C-CB recommends screening for subclinical heart disease using NT-proBNP >125 ng/L or BNP >35 ng/L. Some groups have suggested more thorough screening for subclinical cardiac disease in reference populations with electrocardiograms (ECGs) and cardiac imaging. History and eGFR >90 mL/min/1.73 m^2 alone were non-inferior to cardiovascular magnetic resonance imaging (CMRI) in 779 subjects to exclude underlying cardiac disease (25). Other studies have likewise demonstrated that there is minimal or no incremental benefit of ECG or cardiac imaging over natriuretic peptides for reference cohort screening (23,26,32). Besides NT-proBNP is convenient and effective in identifying subclinical cardiac dysfunction since screening with cardiac imaging would increase barriers to deriving 99th percentile URLs.

Although the clearance of cTn is not well understood, a dual clearance model has been proposed where at high concentrations, as seen in MI, cTn is predominantly hepatically degraded, while at lower levels, such as in chronic heart failure, renal clearance dominates and can partially explain higher troponin concentrations in individuals with renal dysfunction (60,61). Troponin increases with declining eGFR even between eGFR 60–90 mL/min/1.73 m^2 (56,62,63). Reduced eGFR is linked to cardiovascular risk factors and CVD, yet few studies take into account the effect of stage 1 and stage 2 chronic kidney disease (CKD) on troponin levels which also increase with age (26,29,41,64,65). Our previous analysis eGFR of 60–90 mL/min/1.73 m^2 concurred and for every 10 mL/min/1.73 m^2 decrease in eGFR from 90 mL/min/1.73 m^2 there was a significant step-wise increase in hs-cTnT (41). The sensitivity of troponin for predicting of future MI or mortality is improved when excluding patients with eGFR <90 mL/min/1.73 m^2 (57). In line with the recommendation to exclude subclinical cardiac disease (66), a stricter eGFR exclusion criterion of <90 mL/min/1.73 m^2 would be appropriate to exclude subclinical CKD in view of the close cardio-renal connection in CKD. Besides, screening for stage 1 and 2 CKD is less costly and labor intensive than ECGs and cardiac imaging. It is important to take note of the renal status of the reference cohort as any overt or subclinical decline in renal function can elevate troponin levels.

The association of dysglycemia and raised troponin concentrations has also been demonstrated. While the impact of diabetes mellitus [odds ratio (OR) 1.4] on elevated troponin is less than cardiomyopathy (OR 2.2) and renal insufficiency (OR 2.8) it can still contribute to troponin differences if not accounted for (67,68).

Statistical methods

Of all the variables discussed when comparing population troponin values, one largest impact on the 99th percentile URL is the statistical methods employed in their derivation (69). The distribution of hs-cTn values is highly skewed to the right. In the Odsæter study (25), the male 99th percentile URL could vary from 55 to 144 ng/L solely based on different treatment of outliers. We suggest that more rigorous methods to exclude outliers, such as Tukey, should be considered. Larger reference cohorts may have to be recruited to mitigate against these outlier effects.

Conclusions

While not comprehensive, our review provides an overview of the current evidence base on population differences in hs-cTn. High-sensitivity troponin values do not appear to be very different across different populations similarly studied when using hs-cTnT. However, when using hs-cTnI (Abbott ARCHITECT STAT), some differences in the 99th percentile hs-cTnI URLs may be noted—male hs-cTnI 99th percentile URLs were higher in Australian than Dutch cohorts with different compositions of subclinical disease and statistical handling of outliers. Differences in hs-cTnI (Abbott ARCHITECT STAT) were less prominent when comparing cohorts of more similar composition. Differences in 99th percentile URLs between populations are influenced by many variables including selection criteria of the reference cohort and statistical methods used in their derivation. Male sex, increasing age, comorbidities such as subclinical heart disease, renal dysfunction and dysglycemia, and including outliers in analysis can raise hs-cTn 99th percentile URLs. Existing studies investigating 99th percentile URLs of troponin have employed varied selection criteria for the reference populations and statistical treatment making it challenging to compare population differences in troponin concentrations. The jury is still out on whether hs-cTn values differ across different populations. Further studies employing appropriately sized cohorts (of at least 800), uniform screening criteria

and statistical methods are needed. Age-specific diagnostic thresholds for troponin may also be needed akin to that for NT-proBNP. Reference cohorts should continue to include a representative distribution of the regional population composition in the applicable geographic area as recommended by expert committees.

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