The True 99\textsuperscript{th} Percentile of High-Sensitivity Cardiac Troponin for the Hospital Population: An Observational Cohort Study

\textbf{The CHARIOT Study}

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Keywords
High sensitivity troponin, 99th percentile, hospital population

Word Count 3541

Funding: Unrestricted Research Grant – Beckman Coulter

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Competing interests:
M. Mariathas – none declared
R. Allan – none declared
B. Olechowski – none declared
S. Ramamoorthy – none declared
M. Azor – none declared
Z. Nicholas – none declared
A. Calver – none declared
S. Corbett – none declared
M. Mahmoudi – none declared
J. Rawlins – none declared
I. Simpson – none declared
J. Wilkinson – none declared
C. Kwok- none declared
M. Mamas- none declared
P. Cook – none declared
N. Curzen – unrestricted research grants from: Boston Scientific; Haemonetics; Heartflow; Beckmann Coulter. Speaker fees/consultancy from: Haemonetics, Abbot Vascular; Heartflow; Boston Scientific. Travel sponsorship – Biosensors, Abbot, Lilly/D-S; St Jude Medical, Medtronic.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
Abstract

Objective

Clinicians use the cardiac troponin (cTn) assay to aid in the diagnosis of an acute myocardial infarction (AMI). Each assay manufacturer provides the 99th percentile for cTn levels in a group of healthy individuals, and this level is taken as the upper limit of normal (ULN). The objective of this study was to determine the distribution, and specifically the true 99th percentile, for the whole hospital population, using the cTn assay currently employed routinely at our institution.

Design

Prospective study of 20,000 consecutive patients undergoing blood sampling for any reason at a large teaching hospital. Hs-cTnI concentrations (Beckman Coulter Access AccuTnI+3 assay) were nested for analysis in all cases except those in whom the supervising physician had requested hs-cTnI for clinical reasons.

Setting

University Hospital Southampton NHS Trust (UHS).

Participants

20,000 consecutive individuals, inpatient or outpatient, undergoing blood tests at UHS for any clinical reason.

Main outcome measures

Distribution of hs-cTnI concentrations of all study patients, and specifically the 99th percentile.
Results

The 99th percentile of hs-cTnI for the whole population (n=20,000) was 296 ng/L, compared to a manufacturer quoted 99th percentile of 40 ng/L (currently used clinically as the ULN). In 1 in 20 (5.4%, n=1080) of the total population hs-cTnI concentrations were above 40 ng/L. After exclusion of individuals diagnosed with an acute myocardial infarction (AMI) (n=122), or those in whom troponin was requested (n=1707), the 99th percentile for the remainder (n=18,171) was 189 ng/L. The 99th percentile for inpatients (n=4759) and outpatients (n=9280) was 563 ng/L and 65 ng/L, respectively. Patients from the emergency department (n=3706) had a 99th percentile of 215 ng/L, with 6.1% (n=225) above the quoted ULN. 39.02% (n=48) of all individuals from the critical care units (n=123) and 14.16% (n=67) of all medical inpatients had a hs-cTnI concentration above the quoted ULN.

Conclusions

In 20,000 consecutive patients undergoing a blood test for any reason at this hospital 1 in 20 have a hs-cTnI above the supplied ULN. These data highlight the need for clinical staff to interpret hs-cTnI concentrations carefully, particularly when applying the supplied ULN to diagnose AMI. The use of hs-cTnI to diagnose AMI in any patient could lead to misdiagnosis in the absence of an appropriate clinical presentation.

Trial Registration

The study is registered with Clinicaltrials.gov, number NCT03047785.
Introduction
The use of increasingly sensitive troponin assays for the exclusion or diagnosis of acute myocardial infarction (AMI) has become universal. The diagnosis of AMI is now defined by a rise and/or fall of cardiac troponin (cTn) concentration, now the gold standard biomarker (1), with at least one value above the 99th percentile derived from a reference population of healthy individuals in the context of an appropriate clinical presentation (3-5).

Under most circumstances, the troponin assay is requested by front line clinical staff to determine whether or not a patient is experiencing a Type 1 myocardial infarction (T1MI), which is due to coronary plaque rupture or erosion, since robust evidence has demonstrated symptomatic and prognostic benefit from the application of early pharmacological and interventional treatment strategies in such patients. However, particularly with the advent of newer assays, this strategy has 2 potential challenges.

Firstly, elevated cTn concentrations, particularly in patients not presenting with a typical history of cardiac pain, are often due to myocardial injury or Type 2 myocardial infarction (T2MI) (6, 7), which is secondary to ischaemia due to either increased oxygen demand or decreased supply rather than a plaque erosion event (8-10). This is not well recognized when the troponin test is requested, or the result interpreted, and is especially important because the majority of patients with T2MI have not been shown to benefit from the same aggressive pharmacotherapy and invasive investigation and treatment that is offered as standard in cases of T1MI (11), with some exceptions including spontaneous coronary dissection, coronary embolism and coronary spasm (10, 12). In fact, such misinterpretation may lead to inappropriate management, including prolonged antiplatelet therapy and invasive coronary angiography, with or without revascularization.

Secondly, the assay-specific 99th centile (ULN) is generally applied as a binary “rule in” or “rule out” threshold for AMI. Whilst recent trial data confirm the veracity of the use of early cTn concentrations
to confidently exclude the diagnosis of AMI (13-16), the assumption that a concentration above that level implies AMI (and in particular a T1MI) is often inappropriate. Both of these potential issues may be compounded in clinical practice by the increasing sensitivity of the available assays that are able to detect troponin at much lower concentrations than previously (5). Consequently, new highly sensitive cardiac troponin (hs-cTn) assays (17-21) allow for rapid exclusion of AMI, and thereby facilitate the early discharge of patients from hospital. Furthermore, modern hs-cTn assays can detect troponin in more than 50% of the general population, with some assays able to detect troponin in everyone (22). The appropriate interpretation of the “elevated” hs-cTn, particularly in relation to the diagnosis of T1MI, is therefore dependent upon a clinical presentation consistent with this diagnosis, and in particular, a history of cardiac-sounding chest pain, according to the guidelines.

The International Federation of Clinical Chemistry and Laboratory Medicine Task Force on Clinical Applications of Bio-Markers (IFCC TF-CB) currently recommends that the 99th percentile for any assay can be calculated using 300 ‘healthy’ men and 300 ‘healthy’ women (23). Given the number of factors that are well known to affect an individual’s troponin (23), including age (24), gender (25), glomerular filtration rate (26), left ventricular function (27), and the presence of significant inflammatory conditions (28), the appropriateness of the clinically applied concept of an ULN for the hs-cTn assay requires closer scrutiny, particularly when it was derived from a limited number of healthy individuals. Importantly, the approaches to determining the supplied 99th percentile are also variable (29-31).

The aims of this study were to determine (a) the true distribution of hs-cTnI concentration in an unselected all-comer hospital population, both inpatient and outpatient, and, more specifically, (b) the 99th percentile for this population using 20,000 consecutive patients. Our hypothesis was that the true distribution of hs-cTnI in this population would differ from the supplied ULN for this assay, thereby highlighting the potential for misinterpretation of a value above this level in routine clinical
practice, particularly the validity of applying the latter as the binary arbiter of the diagnosis of AMI, especially T1MI.

Methods

Study population

This was a prospective, observational study that included 20,000 consecutive patients aged at least 18 years in whom a biochemistry blood investigation was requested for clinical reasons determined by their supervising physician at our institution, a large University teaching hospital in the United Kingdom. Patients were included regardless of the setting in which the blood test was requested, so that the study population included outpatients and inpatients, emergency department attendees, elective and emergency admissions, and every specialty within the hospital. For each patient included in the study only one troponin measurement was performed on the first biochemistry blood sample that became available during the study period. That individual was then excluded from further sampling, in order that a consecutive series of 20,000 different patients were included. For some of the study analysis, patients who were discharged from hospital with a diagnosis of AMI or in whom a hs-cTnI level was requested by the clinical team, which was determined through a review of the electronic blood request forms submitted to the biochemistry department and via electronic discharge summaries, were excluded.

Ethics & Regulatory Approval

This research project was undertaken according to the principles of Good Clinical Practice and the Declaration of Helsinki. The study was approved by the local ethical committee who then referred it to the Health Research Authority (HRA) UK and its independent Confidentiality Advisory Group (CAG)
for further approval (Rec reference: 17/SC/0042, IRAS project ID: 215262). The CAG approval was required based upon 2 unusual aspects of the methodology. Firstly, the method did not require knowledge or consent from patients that an extra blood assay was being performed. Secondly, apart from those in whom a hs-cTnI was requested as part of their routine clinical care by their supervising clinician, the result of the hs-cTnI test was nested and never revealed to either patient or their supervising clinical team, regardless of whether the result was above the supplied ULN. The study is registered with Clinicaltrials.gov, number NCT03047785.

**Cardiac troponin I assay**

The Beckman Coulter Access AccuTnI+3 assay (Beckman Coulter, Brea, CA, USA) is employed in routine clinical practice at our Trust and was used to measure hs-cTnI concentrations in the study population. The supplied 99th percentile (ULN) is 40 ng/L, which is the level used in routine clinical practice at our institution. The coefficient of variation (CV) of the assay is <10% at 40ng/L, the limit of quantification (LOQ 10% CV) is 20ng/L; the limit of detection (LOD) is 8ng/L; the limit of blank is 5ng/L. For those patients in whom troponin had not been requested for clinical reasons, the hs-cTnI concentration was measured for every individual using serum which was surplus to clinical need. An automated, bespoke system was put in place in Biochemistry to ensure each individual was only included once in the study. Serum was collected into serum separator tubes and stored at room temperature for up to 24 hours before cTnI levels were measured through the use of the DxI800 platform (Beckman Coulter, Brea, CA, USA). Quality control of the assay was undertaken on a daily basis as is routine in clinical practice.
Data Collection

Baseline demographic data were limited to those derived from electronic request forms for blood tests and, for inpatients, from electronic discharge summary codes. These data, together with the troponin levels and other study data were collected on a bespoke database for later analysis.

Patient and public involvement

The British Cardiac Patients Association (BCPA) assisted the researchers in review of the study protocol, with particular reference to the lack of consent of participants. A letter of support for our methodology from the Chairman of the BCPA was submitted to the HRA/CAG as part of our study application.

Statistical Analysis

The 99th percentile for the study population was defined using a non-parametric procedure based on frequency tables. Statistical analyses were performed using IBM SPSS V.22.0 (SPSS, IBM Corporation, Armonk, New York, USA). We used Stata 14.0 (College Station, USA) to perform multiple logistic regressions to identify factors associated with elevated highly sensitive troponin above 40 ng/L. Variables in the model included age, male sex, serum sodium, estimated glomerular filtration rate and location.
Results

A total of 20,000 consecutive patients were included in CHARIOT between 29/06/2017 to 24/08/2017. The median age was 61 (standard deviation 20 years) and 52.9% were female, (n = 10,580).

The 99th percentile hs-cTnI concentration for the whole study population (n=20,000) was 296 ng/L, with 1 in 20 (5.4%; n=1080) of the patients having a hs-cTnI concentration above the supplied ULN (40 ng/L). Once all patients who had been diagnosed with an AMI on discharge or in whom a hs-cTnI level had been requested on the basis of a clinical suspicion of MI had been excluded, this left 18,171 patients in whom the 99th percentile was 189 ng/L, with 4.6% (n=836) above 40 ng/L (Figure 1). Baseline characteristics are shown in Table 1.

Of the 1707 patients in whom hs-cTnI concentrations were requested by the clinical team, 73% (n=1246) had presented with chest pain, with arrhythmia (n=52) and suspected blackouts (n=63) the next most common reason for the test.

Patient Location

Patients were stratified according to their location at the time the biochemistry test was requested.

Specifically, the study included 9280 (51.1%) hospital outpatients in whom the observed 99th percentile was 65 ng/L, with hs-cTnI concentrations above the supplied ULN in 2% (n=186). 4759 (26.2%) of the study population were patients admitted. The 99th percentile for this inpatient group was 563 ng/L, and the hs-cTnI concentrations were above the supplied ULN in 7.29% (n=347).

A total of 5708 patients had their blood sampling in the emergency department (ED). Of this group, 1551 (27.2%) had hs-cTnI concentrations requested by the ED clinicians. The 99th percentile for the remaining ED population (n= 3706) was 215 ng/L, with 6.07% (n=225) of these having hs-cTnI
concentrations above the supplied ULN. Patients managed in the resuscitation room (n=426) of the ED had hs-cTnl concentrations above the ULN in 19.48% (n=83).

For patients managed in the critical care environment (3 intensive care and 2 high dependency units) (n= 123), 39.02% (n=48) had hs-cTnl concentrations above the ULN.

Once all patients who had either been diagnosed with MI or hs-cTnl requested by the clinical team were excluded, a total of 14.16% (n=67) of all medical inpatients (excluding cardiac) had hs-cTnl concentrations above the supplied ULN. 20.8% of patients from the medicine for older people (MOP) (n= 20) also had hs-cTnl concentrations above the supplied ULN. 4.62% (n=16) of patients managed on the acute surgical unit had hs-cTnl above the ULN. For orthopaedic patients 5.24% (n=13) had hs-cTnl concentrations above the ULN. In none of these patients was an acute MI suspected or diagnosed (Table 2; Figure 2).

Age

There was an association between increasing age and distribution of troponin concentration. Percentiles (25th, 50th, 75th, and 99th) and proportion of patients with hs-cTnl above the ULN according to age is shown in supplementary Table 1 and Figure 3.

Gender

The 99th percentiles for males and females were 373 ng/L and 236 ng/L, respectively. 6.6% (n=622) of male and 4.38% (n=463) of females had hs-cTnl concentrations above the ULN. Significant differences were seen in mean hs-cTnl levels when comparing males to females (62 vs 31 ng/L, p=0.021).
Multivariable analysis

Once all patients who had either been diagnosed with MI or had hs-cTnI concentrations requested by the clinical team (n=1829) were excluded, a multivariable analysis was undertaken to assess the independent predictors of an individual having a hs-cTnI concentration above the supplied ULN (40 ng/L). Advancing age (odds ratio (OR) 1.03(1.03 to 1.04), p<0.001), male gender (OR 1.33, (1.14 to 1.54), p<0.001) and reducing estimated glomerular filtration (OR 0.98(0.97 to 0.98), p<0.001) were shown to be independent predictors. Furthermore, when compared to the outpatient population, location in the ED (OR 2.79 (2.26 to 3.43), p<0.001), resuscitation room(OR 9.91 (7.3 to 13.46), p<0.001), critical care units (OR 36.62(23.86 to 56.2), p<0.001), cardiac wards (OR 9.08, (6.44 to 12.81), p<0.001), acute surgical unit (OR 2.52(1.47 to 4.33), p<0.001), medical wards (OR 4.74(3.45 to 6.50), p<0.001), MOP wards (OR 3.70 (2.16 to 6.34), p<0.001) and orthopaedic wards (OR 2.24 (1.23 to 4.05), p=0.008) were independent predictors for hs-cTnI concentration above the ULN (table 3). Independent predictors for the full cohort (n=20,000) are shown in the Supplementary table 3.

Discussion

This study, which is to our knowledge the largest of its kind, has shown that 1 in 20 consecutive all-comer patients at a large UK hospital have a troponin level that is greater than the supplied 99th centile (ULN) for the assay. Our data also demonstrate that the 99th centile varies according to the clinical setting, age and gender, and location, with a range of 2% of outpatients and 39% of patients in critical care settings having a cTnI greater than the supplied ULN.

These results have important clinical implications that are almost certainly relevant to the application of all modern hs-cTn assays. Firstly, they confirm our original hypothesis that the true 99th centile for a general hospital population is not consistent with the supplied ULN. Secondly, these data raise
important questions about the applicability of the quoted ULN as an arbiter of Type 1 AMI in patients who do not give a typical history consistent with this diagnosis. The previous evidence for the use of cTnI levels to rule out AMI is clear cut and robust (14-16, 32). The Fourth Universal Definition(3) recommends the diagnosis of AMI when there is clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values. However, the utility of the supplied ULN as a “rule in” test for AMI in patients presenting with atypical symptoms and other comorbidities, such as in the context of ED or acute medicine and surgical patients, is flawed and potentially exposes such patients to inappropriate pharmacological and invasive treatment that has only been shown to be beneficial in true T1MI populations. This study highlights the importance of interpreting hs-cTnI results with caution in an individual patient. The risk of potential systematic misdiagnosis of AMI is particularly illustrated by the observed 99th centile for hs-cTnI in our subpopulations of ED (215 ng/L) and acute medical admissions (1459 ng/L), and that close to 40% of patients in some clinical settings have hs-cTnI levels above the supplied ULN. It is particularly important for frontline clinical staff to understand that using a single cutoff of hs-cTnI to diagnose AMI may be inappropriate and that the ULN of the assay will depend on the clinical environment as well as clinical characteristics of patients. We would advocate that clinical staff are aware of the current guidelines in diagnosing AMI, which are not always adhered to, and also that they have a very clear indication for requesting the test.

Our analysis highlights a number of factors that are associated with “elevated” hs-cTnI results as judged by the supplied reference, including mode of presentation. Thus, 7.29% of all inpatients in this study had an “elevated” hs-cTnI concentration, including 6.07% of ED patients and 19.48% of those admitted to the resuscitation room. It is more predictable that nearly 40% of patients admitted to a critical care setting have an elevated concentration. However, the finding that our observed 99th centile for hs-cTnI concentrations was 65ng/L in outpatients, and that 2% of these patients who attended the hospital only for a clinic appointment had a concentration above the supplied ULN, highlights the need for a review of quoted distribution of hs-cTn assay in a hospital setting. Further
research is now required to understand whether there is an association between absolute troponin concentration and outcome in such populations.

Other factors that were clearly associated with increasing hs-cTn concentrations were age and gender. Specifically, almost double the proportion of patients in the 7th decade of life have hs-cTnI concentrations above the ULN when compared patients in their 6th decade of life. Together with the tendency for higher levels in males compared to females in our study, these observations lend weight to the concept that there should be age- and gender-specific quoted levels for ULN.

**Strengths of this study**

Previous literature in this field has confirmed the utility of the newer hs-cTn assays for early exclusion of AMI in a robust and safe manner (14-16, 32). However, interpretation of a single hs-cTnI concentration above the supplied ULN as being an indicator of AMI, and, more specifically, a T1MI, by front line clinicians has the potential to lead misdiagnosis and inappropriate investigations and treatment. The data presented here indicate that the prevalence of troponin levels above the supplied ULN in an important proportion of patients in whom there is no clinical suspicion of acute MI should raise a cautionary note.

The current findings also raise the important and interesting question about the potential implications of our observed distribution of hs-cTnI in the hospital population. Specifically, are the levels that we observe in these patients, for whom the suspicion of AMI is low (for example outpatients), actually abnormal? Do the levels indicate myocardial injury in their own right, and, if so, are they associated with adverse outcome, perhaps as biomarkers for future cardiovascular risk? There is an accumulating body of evidence that suggests that hs-cTn concentrations in populations of stable patients with chronic disease states, of both cardiac and non-cardiac origin, are indeed associated
with risk of cardiovascular events (33-42). Notably, in the outpatient population it has been reported that cTnl has indeed been shown to be associated with an increased risk of vascular events and all-cause mortality (43, 44). It is conceivable that the “elevated” hs-cTn concentrations in a stable patient always indicates myocardial injury or unwellness: the so called “never means nothing” hypothesis (45).

**Implications of this study**

The results of this study have significant implications for patient care. The notion of using a single binary value above the ULN of any assay to diagnose whether a patient has suffered an acute MI is flawed. This is highlighted by the observed 99th percentile in the CHARIOT study population which is over seven times higher than the ULN supplied by the manufacturer. Further, the observed frequency of hs-cTnl above the supplied ULN in our study, regardless of location, in patients in whom there was no clinical suspicion of acute MI or myocardial injury raises concerns about the utility of a 99th percentile value from a ‘healthy population’. In particular, applying this supplied 99th centile value to determine the management of patients who are typically older, have more comorbidities, higher incidence of subclinical cardiac disease and in a worse physical condition than the reference healthy population may be flawed.

The results of this study should highlight to front line clinicians that whilst hs-cTnl can contribute to the diagnosis of AMI, this should only be when used in conjunction with other key factors such as the clinical history and other investigations (9, 24, 25, 29, 46-50). At present, the use of the 99th percentile to help rule out a diagnosis of AMI is clear and this is based on using a ‘healthy’ reference population. However, the use of this threshold level and its application to patients presenting to hospital to rule in AMI is problematic, particularly where the degree of suspicion is low and there are other factors that will contribute to the cTn concentration obtained in an individual. Currently, the implications of detecting a hs-cTnl above the supplied ULN, in terms of outcome and management, are unclear in
patients in whom there is low clinical suspicion of AMI. A more considered approach to application of cTnI concentrations would be a more tailored ULN according to the patient’s baseline characteristics and comorbidities. The feasibility of this approach, however, remains unanswered. Further data regarding the potential association between hs-cTnI level and CV risk are required.

Limitations of this study

There are a number of limitations. Firstly, this is an observational study of a large number of consecutive patients. Necessarily, therefore, the level of detail with regard to management and diagnoses can only be obtained from the best records available for each patient, which included any electronic blood request or discharge summary data and formalised coding record. Secondly, this study has not looked at clinical outcomes since this was not part of our objective. Thirdly, in our analysis we have used discharge codes for diagnosis of AMI, but have not independently verified these final diagnoses. Finally, this study has looked at hs-cTnI concentrations in 20,000 patients based on a single sample for each patient, as a result this study cannot differentiate between acute and chronic myocardial injury.

Conclusions

This study has shown that the 99th percentile of the hospital population is substantially higher than the supplied ULN used in clinical practice according to the manufacturer provided 99th centile for a healthy population. Furthermore, the 99th percentile for the hospital population varies depending on the clinical acuity, location, age and gender of the individual, but in all subgroups there is a proportion of the patients in whom the hs-cTnI concentrations are above the clinically applied ULN. This is the largest study to date to evaluate hs-cTnI levels in an unselected cohort of 20,000 consecutive patients.
and the observations from this study highlight the need for clinicians to interpret hs-cTnI concentrations carefully and systematically when attempting to diagnose AMI, particularly Type 1 MI.

**Funding Sources**

Beckman Coulter (Brea, CA, USA) provided an unrestricted research grant for the study. The company had no involvement in the data collection, analysis or interpretation; trial design; or patient recruitment. Further, the company had no role in the writing of the manuscript or decision to submit it for publication.

**Data Sharing**

No additional data is available.

**Transparency declaration**

Professor Nick Curzen affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Acknowledgements**

The authors acknowledge the help of Mr Keith Jackson, Chairman of the British Cardiac Patients Association, in his assessment of the method and support for our CAG submission.
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