True 99th centile of high sensitivity cardiac troponin for hospital patients: prospective, observational cohort study

Mark Mariathas,1 Rick Allan,2 Sanjay Ramamoorthy,3 Bartosz Olechowski,1 Jonathan Hinton,1 Martin Azor,4 Zoe Nicholas,1 Alison Calver,5 Simon Corbett,3 Michael Mahmoudi,1,5 John Rawlins,5 Iain Simpson,5 James Wilkinson,5 Chun Shing Kwok,6 Paul Cook,2 Mamas A Mamas,6 Nick Curzen1,5,7

ABSTRACT

OBJECTIVE
To determine the distribution, and specifically the true 99th centile, of high sensitivity cardiac troponin I (hs-cTnI) for a whole hospital population by applying the hs-cTnI assay currently used routinely at a main teaching hospital.

DESIGN
Prospective, observational cohort study.

SETTING
University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, between 29 June 2017 and 24 August 2017.

PARTICIPANTS
20 000 consecutive inpatients and outpatients undergoing blood tests for any clinical reason. Hs-cTnI concentrations were measured in all study participants and nested for analysis except when the supervising doctor had requested hs-cTnI for clinical reasons.

MAIN OUTCOME MEASURES
Distribution of hs-cTnI concentrations of all study participants and specifically the 99th centile.

RESULTS
The 99th centile of hs-cTnI for the whole population was 296 ng/L compared with the manufacturer’s quoted level of 40 ng/L (currently used clinically as the upper limit of normal; ULN). Hs-cTnI concentrations were greater than 40 ng/L in one in 20 (5.4%, n=1080) of the total population. After excluding participants diagnosed as having acute myocardial infarction (n=122) and those in whom hs-cTnI was requested for clinical reasons (n=1707), the 99th centile was 189 ng/L for the remainder (n=18171). The 99th centile was 563 ng/L for inpatients (n=4759) and 65 ng/L for outpatients (n=9280). Patients from the emergency department (n=3706) had a 99th centile of 215 ng/L, with 6.07% (n=225) greater than the recommended ULN. 39.02% (n=48) of all patients from the critical care units (n=123) and 14.16% (n=67) of all medical inpatients had an hs-cTnI concentration greater than the recommended ULN.

CONCLUSIONS
Of 20 000 consecutive patients undergoing a blood test for any clinical reason at our hospital, one in 20 had an hs-cTnI greater than the recommended ULN. These data highlight the need for clinical staff to interpret hs-cTnI concentrations carefully, particularly when applying the recommended ULN to diagnose acute myocardial infarction, in order to avoid misdiagnosis in the absence of an appropriate clinical presentation.

TRIAL REGISTRATION
Clinicaltrials.gov NCT03047785.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Current guidelines recommend the use of troponin assays to help exclude or diagnose acute myocardial infarction
Manufacturers of troponin assays provide a recommended 99th centile that is based on a few hundred healthy individuals; this level is often used as the upper limit of normal when applied to the hospital population
A variety of clinical factors affect the troponin level, such as age, sex, and renal function, but little is known about the true distribution of the troponin level across the whole hospital population.

WHAT THIS STUDY ADDS
In a hospital population of 20 000 consecutive patients, one in 20 of all patients had a high sensitivity troponin I concentration greater than the manufacturer’s recommended 99th centile; in most of these patients there was no clinical suspicion of acute myocardial infarction
It is important to interpret the troponin result in hospital patients according to individual patients, their clinical presentation, and the guideline recommendations for correct diagnosis of type 1 and type 2 myocardial infarction.
These results could help to avoid misdiagnosis and inappropriate treatment.

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- These results could help to avoid misdiagnosis and inappropriate treatment.
conditions, which are secondary to ischaemia caused by increased oxygen demand or decreased supply rather than a plaque erosion, are not well recognised when the troponin test is requested or the result interpreted. Correct diagnosis is important because most patients with type 2 myocardial infarction have not been shown to benefit from the same aggressive pharmacotherapy and invasive investigation and treatment that are offered as standard in patients with type 1 myocardial infarction. Some exceptions include spontaneous coronary dissection, coronary embolism, and coronary spasm. Misinterpretation may lead to inappropriate management, including prolonged antplatelet therapy and invasive coronary angiography, with or without revascularisation.

Secondly, the assay specific 99th centile (upper limit of normal; ULN) is generally applied as a binary “rule in” or “rule out” threshold for acute myocardial infarction. Recent trial data confirm the veracity of using early cardiac troponin concentrations to confidently exclude a diagnosis of acute myocardial infarction; however, the assumption that a concentration greater than the recommended threshold implies acute myocardial infarction (and in particular type 1 myocardial infarction) 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. Consequently, new highly sensitive cardiac troponin (hs-cTn) assays allow for rapid exclusion of acute myocardial infarction, and thereby enable patients to be discharged early 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. The appropriate interpretation of raised hs-cTn, specifically in relation to the diagnosis of type 1 myocardial infarction, is therefore dependent on 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 currently recommends that the 99th centile for any assay can be calculated using 300 “healthy” men and 300 “healthy” women. However, several factors are known to affect an individual’s troponin, including age, sex, glomerular filtration rate, left ventricular function, and the presence of major inflammatory conditions. Therefore, whether the clinically applied concept of a ULN for the hs-cTn assay is appropriate requires closer scrutiny, particularly when it has been derived from a limited number of healthy individuals. Importantly, the approaches to determining the recommended 99th centile are also variable.

The objective of the CHARIOT study was to determine the true distribution of the highly sensitive cardiac troponin I (hs-cTnI) concentration, and more specifically the 99th centile, in a population of consecutive inpatients and outpatients in our hospital. Our hypothesis was that the true 99th centile of hs-cTnI in this population would differ from the manufacturer recommended ULN for this assay. This difference would highlight the potential for misinterpretation of a concentration greater than this threshold in routine clinical practice, particularly when making a diagnosis of acute myocardial infarction and especially type 1 myocardial infarction.

Methods
Study population
This was a prospective, observational study of 20,000 consecutive patients aged at least 18 years in whom a biochemistry blood test was requested for clinical reasons by their supervising doctor at our institution, University Hospital Southampton (United Kingdom). It was conducted between 29 June 2017 and 24 August 2017. We included patients regardless of the setting in which the blood test was requested. Therefore, the study population consisted of outpatients and inpatients, attendees at the emergency department, 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 patient was then excluded from further sampling so that a consecutive series of 20,000 different patients were included. During some of our analyses, we excluded patients in whom a troponin was requested for clinical reasons by the supervising doctor, and those in whom a diagnosis of acute myocardial infarction was made. This was determined by reviewing the electronic blood request forms submitted to the biochemistry department and by electronic discharge summaries.

Approvals
As part of the ethical committee process, we sought approval from the Confidentiality Advisory Group based on two unusual aspects of the methods. Firstly, patients did not know that an extra blood assay was being performed and consent was not sought or required. Secondly, except for patients who had an hs-cTnI test as part of their routine clinical care as requested by their supervising doctor, test results were nested and not revealed to either patients or their supervising clinical team; this was regardless of whether the level was greater than the recommended ULN.

Cardiac troponin I assay
The Beckman Coulter Access AccuTnI+3 assay (Brea, CA, USA) is used in routine clinical practice at our hospital. We applied this assay to measure hs-cTnI concentrations in the study population. The manufacturer’s recommended 99th centile (ULN) is 40 ng/L, which is the level we use in routine clinical practice. The coefficient of variation of the assay is less than 10% at 40 ng/L; the limit of quantification (10% of the coefficient of variation) is 20 ng/L; the limit of
were requested by the clinical team, 73% (n=1246) had presented with chest pain; arrhythmia (n=52) and suspected blackouts (n=63) were the next most common reasons for the test.

Patient location
We stratified patients according to their location when the biochemistry test was requested. Specifically, the study included 9280 (51.1%) hospital outpatients in whom the observed 99th centile was 65 ng/L, with hs-cTnI concentrations greater than the recommended ULN in 2% (n=186). There were 4759 (26.2%) inpatients and the 99th centile for this group was 563 ng/L; the hs-cTnI concentration was greater than the recommended ULN in 7.29% (n=347).

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

In the critical care setting (three intensive care units and two high dependency units; n=123), 39.02% (n=48) had hs-cTnI concentrations greater than the ULN. When we excluded all patients diagnosed as having myocardial infarction or who had an hs-cTnI test requested by the clinical team, 14.16% (n=67) of all medical inpatients (excluding those on cardiac wards) had an hs-cTnI concentration greater than the recommended ULN. For the medicine for older people wards, 20.8% (n=20) had an hs-cTnI concentration greater than the recommended ULN; for patients managed on the acute surgical unit, the corresponding figures were 4.62% (n=16), and for those on orthopaedic wards, 5.24% (n=13). In none of these patients was an acute myocardial infarction suspected or diagnosed (table 2; fig 2).

Age
There was an association between increasing age and distribution of troponin concentration. Supplementary tables 1 and 2, and figure 3 show centiles (25th, 50th, 75th, and 99th) and proportion of patients with hs-cTnI greater than the ULN according to age.

Sex
The 99th centiles for men and women were 373 and 236 ng/L, respectively. A total of 6.6% (n=622) of men and 4.38% (n=463) of women had hs-cTnI concentrations greater than the ULN. Significant differences were seen in mean hs-cTnI levels when comparing men with women (62 vs 31 ng/L, P=0.021).

Multivariable analysis
When we excluded all patients who had been diagnosed with myocardial infarction or had hs-cTnI tests requested by the clinical team (n=1829), a
multivariable analysis was undertaken. This analysis assessed the independent predictors of a patient having an hs-cTnI concentration greater than the recommended ULN (40 ng/L). Advancing age (odds ratio 1.03, 95% confidence interval 1.03 to 1.04, P<0.001), male sex (1.33, 1.14 to 1.54, P<0.001), and decreasing estimated glomerular filtration rate (0.98, 0.97 to 0.98, P<0.001) were shown to be independent predictors. Furthermore, compared with the outpatient population, inpatient location was an independent predictor of hs-cTnI concentration greater than the ULN: emergency department (2.79, 2.26 to 3.43, P<0.001); resuscitation room (9.91, 7.3 to 13.46, P<0.001); critical care units (36.62, 23.86 to 56.2, P<0.001); cardiac wards (9.08, 6.44 to 12.81, P<0.001); acute surgical unit (2.52, 1.47 to 4.33, P<0.001); medical wards (4.74, 3.45 to 6.50, P<0.001); medicine for older people wards (3.70, 2.16 to 6.34, P<0.001); and orthopaedic wards (2.24, 1.23 to 4.05, P=0.008; table 3). Supplementary table 3 shows independent predictors for the full cohort (n=20 000).

Discussion

In this large study, we found that one in 20 consecutive inpatients and outpatients at a large UK hospital had a troponin level greater than the manufacturer recommended 99th centile (ULN) for the assay. We also showed that the true 99th centile varies according to the clinical setting, age and sex of the patient, and location when the biochemistry test was requested. Two per cent of outpatients and 39% of patients in critical care units had a hs-cTnl concentration greater than the recommended ULN.

These results have important clinical implications that are almost certainly relevant to the application of all modern hs-cTn assays. Firstly, they confirmed our hypothesis that the true 99th centile for a general hospital population is not consistent with the recommended ULN. Secondly, these data raise important questions about the applicability of the quoted ULN as an arbiter of type 1 acute myocardial infarction in patients who do not give a typical history consistent with this diagnosis. Previous evidence for using “negative” hs-cTnI levels to “rule out” acute myocardial infarction is clear cut and robust. The Fourth Universal Definition recommends a diagnosis of acute myocardial infarction when there is clinical evidence of acute myocardial ischaemia and when an increase or decrease in cardiac troponin levels is detected. However, using the recommended ULN as a “rule in” test for acute myocardial infarction might not be appropriate in patients presenting with atypical symptoms and other comorbidities, such as in the emergency department or on acute medical and surgical wards. This approach could expose patients to inappropriate pharmacological and invasive treatments that have only been shown to be beneficial in true type 1 myocardial infarction populations.

These data demonstrate the importance of interpreting hs-cTnl results with caution in individual patients. The risk of potential systematic misdiagnosis of acute myocardial infarction is particularly shown by the observed 99th centile for hs-cTnI in our emergency department population (215 ng/L) and acute medical admissions (1459 ng/L). In addition, about 40% of patients in some clinical settings have hs-cTnI levels greater than the recommended ULN. It is important for frontline clinical staff to understand that using a single cutoff of hs-cTnl to diagnose acute myocardial infarction might be inappropriate and that the ULN of the assay depends on the setting and the clinical characteristics of patients. We would advocate that...
clustering from different locations, which would be expected. Further research is also required to determine whether there is an association between absolute hs-cTn concentrations and cardiovascular outcomes in such populations.

Other factors that were clearly associated with increasing hs-cTn concentrations were age and sex. Specifically, we found that almost double the proportion of patients in their 60s had hs-cTn concentrations greater than the ULN compared with patients in their 50s. In addition, levels tended to be higher in men than in women. These observations lend weight to the concept that there should be age and sex specific recommendations for the ULN.

Comparison with other studies
Previous literature in this field has confirmed the use of the newer hs-cTn assays for early exclusion of acute myocardial infarction in a robust and safe manner. However, interpretation of a single hs-cTn concentration above the supplied ULN as being an indicator of acute myocardial infarction, and, more specifically, type 1 myocardial infarction, by frontline clinical staff could lead to misdiagnosis and inappropriate investigations and treatment. Our data 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 myocardial infarction should raise a cautionary note.

Our findings raise important and interesting questions about the potential implications of the observed distribution of hs-cTn in the hospital population. Specifically, are the levels that we found in these patients, for whom the suspicion of acute myocardial infarction 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? An accumulating body of evidence suggests that hs-cTn concentrations in populations of patients with stable chronic disease states, of cardiac and non-cardiac origin, are associated with risk of cardiovascular events. Notably, in the outpatient population it has been reported that hs-cTn has been shown to be associated with an increased risk of vascular events and all cause mortality. It is conceivable that the raised hs-cTn concentrations in a patient with stable disease always indicates myocardial injury or unwellness: the so-called “never means nothing” hypothesis.

Implications of this study
The results of the CHARIOT study have important clinical implications that might be relevant to the

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**Table 2 | Distribution of hs-cTnI (ng/L) according to location when the biochemistry test was requested**

| Location                         | No of patients | Median (ng/L) | Interquartile range (ng/L) | Range (ng/L) | Proportion ≥ULN (%) (No) | 99th centile (ng/L) |
|----------------------------------|----------------|---------------|---------------------------|--------------|-------------------------|---------------------|
| Inpatients                       | 4759           | 7             | 10                        | 14994        | 7.29 (347)              | 563                 |
| Outpatients                      | 9280           | 5             | 8                         | 37255        | 2.02 (187)              | 65                  |
| Emergency department             | 3706           | 7             | 9                         | 6106         | 6.07 (225)              | 215                 |
| Resuscitation room               | 426            | 11            | 24                        | 10979        | 19.48 (83)              | 1839                |
| Critical care units              | 123            | 25            | 115                       | 13086        | 39.02 (48)              | 12097               |
| Cardiac wards                    | 269            | 14            | 28                        | 14994        | 21.56 (58)              | 3967                |
| Acute surgical unit              | 346            | 6             | 9                         | 2668         | 4.62 (16)               | 92                  |
| Medical wards                    | 473            | 12            | 22                        | 8807         | 14.16 (67)              | 1459                |
| Medicine for older people wards  | 96             | 20            | 27                        | 3508         | 20.83 (20)              | —                   |
| Orthopaedic wards                | 248            | 8             | 9                         | 402          | 5.24 (13)               | 184                 |

*HS-cTnI=high sensitivity cardiac troponin I; ULN=upper limit of normal (40 ng/L).*
The results of this study should highlight that although hs-cTnI can contribute to the diagnosis of acute myocardial infarction, frontline clinical staff should use this test in conjunction with other key factors, such as clinical history and other investigations. At present, using the 99th centile to help rule out a diagnosis of acute myocardial infarction is clear cut and is based on a “healthy” reference population. However, the recommended threshold and its application to patients presenting to hospital to rule in acute myocardial infarction is problematic, particularly when the degree of suspicion is low and other factors might contribute to the cardiac troponin concentration. Currently, the implications of detecting a hs-cTnI concentration above the supplied ULN, in terms of outcome and management, are unclear in patients in whom there is low clinical suspicion of acute myocardial infarction. A more considered approach to applying hs-cTnI concentrations would be to tailor the ULN according to the patient’s baseline characteristics and comorbidities. The feasibility of using this approach, however, has not been investigated. Further data about the potential association between hs-cTnI level and cardiovascular risk are required.

Limitations of this study
There were a number of limitations. This is an observational study of a large number of consecutive patients. Therefore, the level of detail about management and diagnoses can only be obtained from the best records available for each patient, which included electronic blood request or discharge summary data, and formalised coding records. In addition, we did not examine clinical outcomes because this was not part of our objective. We also used discharge codes in our analysis for diagnosing acute myocardial infarction, but these final diagnoses were not independently verified. Finally, this study looked at hs-cTnI concentrations in 20,000 patients based on a single sample for each patient; as a result, we could not differentiate between acute and chronic myocardial injury.

Conclusions
This study has shown that the 99th centile of high sensitivity troponin I concentration of the population in our hospital was substantially higher than the healthy reference population. However, the recommended threshold and its application to patients presenting to hospital to rule in acute myocardial infarction is problematic, particularly when the degree of suspicion is low and other factors might contribute to the cardiac troponin concentration. Currently, the implications of detecting a hs-cTnI concentration above the supplied ULN, in terms of outcome and management, are unclear in patients in whom there is low clinical suspicion of acute myocardial infarction. A more considered approach to applying hs-cTnI concentrations would be to tailor the ULN according to the patient’s baseline characteristics and comorbidities. The feasibility of using this approach, however, has not been investigated. Further data about the potential association between hs-cTnI level and cardiovascular risk are required.

Table 3 | Independent predictors of hs-cTnI concentration greater than recommended ULN in final study population (n=18,171)

| Variable                     | Predictors of manufacturer troponin ULN >40 ng/L | Predictors of non-parametric troponin ULN >189 ng/L |
|------------------------------|-----------------------------------------------|--------------------------------------------------|
| Age (per year increase)      | Odds ratio (95% CI) P                          | Odds ratio (95% CI) P                             |
| Male sex                     | 1.03 (1.03 to 1.04) <0.001                      | 1.03 (1.02 to 1.04) <0.001                        |
| Sodium (per unit increase)   | 1.33 (1.14 to 1.54) <0.001                      | 0.90 (0.66 to 1.23) 0.51                          |
| eGFR (per unit increase)     | 0.99 (0.97 to 0.98) 0.001                       | 0.99 (0.98 to 1.00) 0.001                          |
| Emergency department         | 2.79 (2.26 to 3.43) <0.001                      | 3.46 (2.14 to 5.61) <0.001                        |
| Resuscitation room           | 9.91 (7.3 to 13.46) <0.001                      | 13.79 (7.67 to 24.77) <0.001                      |
| Critical care units          | 36.62 (23.86 to 56.2) <0.001                    | 99.27 (55.51 to 177.54) <0.001                    |
| Cardiac wards                | 9.08 (6.64 to 12.81) <0.001                     | 14.91 (7.91 to 28.11) <0.001                      |
| Acute surgical unit          | 2.52 (1.47 to 4.33) 0.001                       | 0.98 (0.13 to 7.21) 0.98                          |
| Medical wards                | 4.74 (3.45 to 6.50) <0.001                      | 5.80 (2.95 to 11.42) <0.001                        |
| Medicine for older people wards | 3.70 (2.16 to 6.34) <0.001                   | 9.60 (4.00 to 23.00) <0.001                        |
| Orthopaedic wards            | 2.24 (1.23 to 4.05) 0.008                       | 2.15 (0.51 to 9.14) 0.30                          |

eGFR=estimated glomerular filtration rate; hs-cTnI=high sensitivity cardiac troponin I; ULN=upper limit of normal (40 ng/L).
than the manufacturer’s recommended ULN used in clinical practice based on the 99th centile for a healthy population. Furthermore, the 99th centile for the hospital population varied depending on the clinical setting, age and sex of the patient, and location when the test was requested; however, in all groups, a proportion of the patients had hs-cTnI concentrations greater than the recommended ULN. The study observations highlight the need for clinical staff to interpret hs-cTnI concentrations carefully and systematically when making a diagnosis of acute myocardial infarction, particularly type 1 myocardial infarction.

AUTHOR AFFILIATIONS

1Coronary Research Group, University Hospital Southampton NHS Foundation Trust, Southampton, UK
2Biochemistry Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK
3Emergency Medicine Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK
4Coding Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK
5Wessx Cardiothoracic Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK
6Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute of Primary Care and Health Sciences, Keele University, Stoke on Trent, UK
7Faculty of Medicine, University of Southampton, Southampton, UK

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Ethical 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 UK and its independent Confidentiality Advisory Group for further approval (REC reference: 17/ SC/0042; IRAS project ID: 215262).

Data sharing: No additional data are available.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no discrepancies from the study as planned (and, if relevant, registered) have been explained.

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**Web appendix:** Supplementary material