**Association between Troponin Level and Medium Term Mortality in 20,000 Hospital Patients**

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**Funding:**

Unrestricted Research Grant from Beckman Coulter (BC) for the high sensitivity troponin assays. BC had no role in the design, execution, analysis or interpretation of the study

**Financial Disclosures/Potential Conflicts of Interest:**

N. Curzen – unrestricted research grants from: Boston Scientific; Heartflow; Beckman Coulter. Speaker fees/consultancy from: Abbot Vascular; Heartflow; Boston Scientific;

Travel sponsorship – Edwards; Biosensors, Abbot, Lilly/D-S; St Jude Medical, Medtronic.

Michael Mahmoudi, Mamas A. Mamas are on the editorial board of Heart

**Data sharing statement:**

Due to the nature of the data sharing agreement with NHSDigital , the data from this study cannot be shared.

**Author contributions:**

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**Acknowledgement:**

Parts of this work have previously been included within the lead author’s thesis

**Abstract**

*Introduction:* Cardiac troponin (cTn) concentrations above the manufacturer recommended upper limit of normal (ULN) are frequently seen in hospital patients without a clinical presentation consistent with type 1 myocardial infarction, and the significance of this is uncertain. The aim of this study was to assess the relationship between medium term mortality and cTn concentration in a large consecutive hospital population, regardless of whether there was a clinical indication for performing the test.

*Method:* This prospective observational study included 20,000 consecutive in-hospital and outpatient patients who had a blood test for any reason at a large teaching hospital, and in whom a hs-cTnI assay was measured, regardless of the original clinical indication. Mortality was obtained via NHS Digital.

*Results:* A total of 20,000 patients were included in the analysis and 18,282 of these (91.4%) did not have a clinical indication for cTnI testing. Overall, 2825 (14.1%) patients died at a median of 809 days. The mortality was significantly higher if the cTnI concentration was above the ULN (45.3% versus 12.3% p<0.001 log rank). Multivariable Cox analysis demonstrated that the log10 cTnI concentration was independently associated with mortality (hazard ratio 1.76 (95% confidence interval 1.65 – 1.88)). Landmark analysis, excluding deaths within 30 days, showed the relationship between cTnI concentration and mortality persisted.

*Conclusion:* In a large, unselected hospital population, in 91.4% of whom there was no clinical indication for testing, cTnI concentration was independently associated with medium term cardiovascular and non-cardiovascular mortality in the statistical model tested.

**Introduction**

A cardiac troponin (cTn) above the manufacturer defined upper limit of normal (ULN) is a central requirement for the diagnosis of type 1 myocardial infarction (T1MI) (1-3). Newer troponin assays have an ability to measure down to very low concentrations (4-7). It has been widely demonstrated that cTn concentrations are frequently above the ULN in a range of in- and outpatient cohorts and this observation is seen with increasing frequency with increasing sensitivity of cTn assays (8-11). Furthermore, there is increasing evidence that elevated cTn concentrations outside the context of T1MI are associated with adverse prognosis in a range of chronic conditions (8, 9, 12-20). In our previous work, which included 20,000 consecutive patients most of whom had no indication for the test, we demonstrated that 1 in 20 patients had a cTnI concentration (using an assay that approaches the criteria to be a high sensitivity assay) above the ULN and that this was associated with one year mortality across inpatients, outpatients and the emergency department (9, 11). The aim of this follow-on study was to assess the relationship between the snapshot cTnI concentration and medium-term mortality, and, specifically, to examine the relationship of the assay to cardiovascular and non-cardiovascular causes of death. Our hypothesis was that the snapshot cTnI, taken in most cases without a clinical indication, would be associated with medium-term mortality, thus acting as a biomarker for this outcome.

**Method**

*Participants*

This follow up study included all the patients from the original CHARIOT study, which has been described previously in detail (9, 11). Briefly, CHARIOT was a prospective, observational study of 20,000 consecutive and unselected patients who underwent a biochemistry blood test for any indication at a large teaching hospital. Patients were included if they were 18 years or older and required a biochemistry blood test whether they were an inpatient, outpatient or in the emergency department. In addition to the biochemistry tests requested by the clinical team, a cTnI test was added onto the first blood test performed following the start of the study, regardless of whether there was a clinical indication for performing this test. In accordance with our ethical approval (see below) the cTnI result was hidden and not revealed to the supervising clinical team, unless they had specifically requested the assay for clinical reasons, or to the patient.

*Ethical approval*

The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, and received the appropriate approvals from the Research Ethics Committee, Confidentiality Advisory Group and the Health Research Authority, United Kingdom. The study was included on the clinicaltrials.gov registry (NCT03047785). A substantial amendment approved follow up to two and half years (Confidentiality Advisory Group 17/CAG/0083, Research Ethics Committee 17/2C/0042). According to the approved study protocol, the patients included in the CHARIOT study did not know that they were included in a study.

*Patient public involvement*

The original and follow up applications to ethics and confidentiality advisory group for CHARIOT were supported by the Chairman of the British Cardiac Patients Association. The patients making up the CHARIOT population by protocol did not know that they were in a study, but information, including a privacy notice, was placed on the research section of University Hospital Southampton’s website.

*cTnI assay*

The cTnI concentrations were measured using the Beckman Coulter Access AccuTnI+3 assay (Beckman Coulter, Brea, California). This was the higher sensitivity troponin assay in routine clinical use at our institution at the time of the study. This assay approaches the level of sensitivity required to be defined as a high sensitivity assay but does not quite meet these criteria as defined by the International Federation of Clinical Chemistry (21). This assay does still have good performance at the levels used in this study. The manufacturer-provided 99th percentile is 40ng/L and this was used as the ULN in routine practice. The coefficient of variation at 40ng/L is less than 10%, the limit of quantification is 20ng/L, limit of detection 8ng/L and the limit of blank 5ng/L. Serum was collected in serum separator tubes and stored at room temperature for up to 24 hours. CTnI concentrations were measured using the DxI800 platform (Beckman Coulter, Brea, California).

*Mortality data*

According to the ethical approval, NHS Digital were given the NHS number, gender, date of birth and study specific identifier for each patient. NHS Digital then returned whether the patient was alive or not, with the date and cause of death, as applicable. These data were then matched to the CHARIOT database using the study-specific identifier.

*Statistical analysis*

Continuous variables were summarised using the median with the interquartile range (IQR) and categorical variables were expressed as the number and percentage for each group. The Chi squared test was used for comparisons between categorical variables and the Mann Whitney U test for continuous variables. Kaplan Meier curves were used to illustrate the mortality events over time (starting from when the blood test was taken) stratified by whether the cTnI concentration was above or below the ULN. The log rank test was used to determine if there was a statistical difference between the populations. An additional landmark analysis was performed excluding patients that died within 30 days to eliminate the impact of short term mortality. Multivariable analysis was performed by creating a Cox proportional hazards model with adjustments for age, gender, estimated glomerular filtration rate (eGFR), clinical location (outpatient (OPD), inpatient (IPD), emergency department (ED)), whether the cTnI concentration was requested by the clinical team and the hs-cTnI concentration. For the multivariable analysis, the cTnI concentration was log10 transformed given the highly positively skewed distribution of this variable. The cTnI data were also split into categories according to the ratio between the cTnI concentration and the ULN (0, >0 to <0.25, 0.25 to <0.5, 0.5 to 1 and >1). The proportional hazards assumption was evaluated for categories of hs-cTnI relative to the ULN using the log (-log(survival)) versus log (time) graph to ensure that this assumption was met. Additional sensitivity analysis explored whether the relationship was consistent across each of the patient locations (OPD, IPD, ED). Further, a multivariable Cox model was fitted for the entire cohort for, firstly, non-cardiovascular mortality and, secondly, cardiovascular mortality using a cause specific competing risk approach. The cause of death was based on the ICD 10 code given by NHS Digital. All analyses in this study were performed using SPSS version 27.0 (SPSS, IBM Corporation, Armonk, New York).

**Results**

The study included 20,000 consecutive patients over the age of 18 years who underwent a biochemistry blood test, regardless of the indication for the test, between the 29th of June and 24th August 2017 at University Hospital Southampton NHS Foundation Trust. There were 1,718 (8.6%) patents in whom the cTnI assay was performed as requested by the supervising clinician, and the remaining 18,282 patients (91.4%) only had the assay performed as part of this research study, in which case the result was not released to the patient or their clinical team.

There were 1,085 (5.4%) patients with a cTnI concentration above the ULN, as previously reported (11). The median age of the entire cohort was 61 years (IQR 43 – 73 years) with 52.9% female and Table 1 summarises the baseline characteristics. There was only one patient with a missing variable (eGFR) and as a result this patient was excluded from analyses requiring this variable.

A total of 1782 (8.9%) patients died at one year, and by the median follow-up of 809 (IQR 793 – 822 days) days a total of 2825 patients had died (14.1%) ((OPD 873 (9.3%), IPD 1,102 (22.3%), ED 850 (14.9%)). The mortality was 44.8% in patients with a cTnI concentration above the ULN, compared with 12.4% below the ULN (Supplementary figure 1 p<0.001). When a landmark analysis was undertaken excluding patients that died within 30 days (Figure 1), the snapshot cTnI concentration above the ULN remained associated with both 30 day and medium-term mortality (both p<0.001).

On multivariable Cox regression analysis (which included age, gender, eGFR clinical location (outpatient (OPD), inpatient (IPD), emergency department (ED)), whether the cTnI concentration was requested by the clinical team and the hs-cTnI concentration as variables), the log10 cTnI concentration remained independently associated with mortality in the statistical model tested (HR 1.76 (95%CI 1.65 – 1.89) (Table 2). When the cTnI variable was split into its ratio with the ULN, there was a gradual significant step up in hazard ratio beyond 0.25 ULN (0 as reference, >0 to <0.25 HR 0.986 (95%CI 0.820 – 1.185), 0.25 to <0.5 HR 1.505 (95%CI 1.244 – 1.821), 0.5 to 1 HR 1.941 (95%CI 1.577 – 2.390), >1 HR 2.516 (95%CI 2.034 – 3.112), Figure 2, Supplementary Table 1). The proportional hazards assumption was met for categories of hs-cTnI relative to the ULN using the log (-log(survival)) versus log (time) graph (supplementary figure 2). On sensitivity analysis for each of the patient locations (OPD, IPD, ED), the statistical relationship between log10 cTnI concentration and mortality remained consistent (Supplementary Table 2). In all of these models there was a reduction in the hazard of mortality if the cTnI test was requested by the clinical team (except for the OPD cohort where cTnI was rarely requested by the clinician).

The most common cause of death was malignancy (1,308 (46.3%)), followed by cardiovascular mortality (363 patients (12.8%) (Table 3). On multivariable analysis, the log10cTnI concentration was independently associated with both non-cardiovascular and cardiovascular mortality in the statistical model tested, although with a greater hazard for cardiovascular mortality (HR 1.985 (95%CI 1.861 – 2.118) and HR 2.527 (95%CI 2.198 – 2.904) respectively) (Supplementary tables 3-4).

**Discussion**

The CHARIOT study has explored the relationship between a snapshot cTn test in 20,000 consecutive hospital patients, the vast majority (91.4%) of whom had no clinical indication for this test, and medium-term mortality. To our knowledge, this is the largest ever hospital cohort in which this has been undertaken. This study has several important findings. First, the snapshot cTnI concentration was significantly associated with medium-term mortality in the entire cohort. Second, this relationship remained statistically significant after excluding early mortality within 30 days. Third, the cTn concentration was associated with both cardiovascular and non-cardiovascular mortality. Finally, the relationship persisted irrespective of the setting in which hs-cTnI was taken (OPD, IPD, ED).

This study adds to the evidence already available, largely in populations in whom the test was performed for clinical reasons, that demonstrates that cTn is a marker of prognosis for populations of stable patients in outpatients, acutely unwell patients and patients with specific disease processes, both cardiovascular and non-cardiovascular (2, 8, 9, 12, 13, 15, 19, 20, 22-31). Specifically in the outpatient population the BiomarCaRE study also demonstrated that the cTn concentration was associated with both cardiovascular and non-cardiovascular mortality as seen in our study (32).

In the current study, over 91% of the patients had no clinical reason to have the snapshot cTnI measured. Furthermore, the current study demonstrates that, in the minority of the study population who had cTn concentrations measured as part of their clinical care, there was actually a lower hazard of mortality. Therefore, previous studies that only include patients in whom the test was requested are likely to illustrate only a limited picture of the true prognostic potential of these assays in hospital populations as a biomarker of risk. This somewhat paradoxical observation could be explained by the fact that cTn assays are primarily requested to exclude T1MI in patients presenting with chest pain, the vast majority of whom are clinically well at presentation. Patients in whom cTn was not requested may represent a group of patients who are more unwell and hence more likely to have elevated cTn concentrations

Whilst the consecutive nature of the cohort in this study, combined with the outcome data provided by NHS Digital, do provide a clear picture of the prognostic value of cTnI assays, further research is now required before testing cTn concentrations outside of those patients with a presentation consistent with T1MI can be considered as part of routine clinical practice. Firstly, further data are needed to confirm these findings across multiple sites and healthcare settings. Secondly, if this relationship between a snapshot cTnI test and medium-term mortality is confirmed, the next step would be to determine whether this increased risk can be modified. In a study of over 250,000 patients across five centres in the UK with a mixture of cTn assays demonstrated that a concentration above the ULN was associated with a 3.2 hazard of mortality at three years (15). Whilst this study only included patients in whom the test was clinically requested, it did demonstrate that those patients without acute coronary syndromes who went on to have angiography had improved clinical outcomes (15). This is an observational study and it maybe that the patients chosen for angiography were a highly selected group. However this highlights the need for further research to examine the presence or absence of comorbidities such as coronary artery disease and left ventricular function in these patients. Whilst a clear strategy for managing patients with cTn concentrations above the ULN outside the context of T1MI requires further research, clinicians considering how to interpret and manage these patients in clinical practice should involve the patient in any discussions.

*Limitations*

There are several limitations associated with this study. First, this was a single centre study and therefore has all the standard potential limitations associated with this design. Second, whilst the absolute number of patients and consecutive nature of their recruitment in this study has advantages, this also meant that it was not possible to gather extensive demographic and comorbidity data that could otherwise be utilised in multivariable modelling. It is therefore important, when interpreting this study, to accept that there will be potentially important variables that are known to affect cTn concentrations that have not been included in the multivariable analysis and may thereby represent confounding factors. It seems biologically unlikely that cTn concentration per se poses a long term mortality risk but more likely that it represents a broad spectrum of both cardiovascular and non-cardiovascular whether previously diagnosed or as yet concealed comorbidity that increases the long term mortality risk. Finally, whilst the assay used in this study was in use at our centre (and others) at the time as a high sensitivity assay, it does not quite meet the performance needed to be classified as a true modern high sensitivity assay (33). However, we do not expect this to have a major effect on the relationship described but it maybe that modern true high sensitivity assays change the relationships at concentrations below the ULN.

In conclusion, in a consecutive cohort of 20,000 hospital patients who had a cTnI test added onto their routine blood sampling, regardless of whether there was any clinical indication to do so, and in 91.4% of whom no such indication existed, the cTnI concentration was independently associated with medium term mortality in the statistical model tested. These findings suggest that a snapshot cTn in a hospital population may represent a biomarker of overall medium term mortality.

**Tables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | **Entire cohort (n=20,000** | **Alive (n=17,175)** | **Died (n=2,825)** | **P value** |
| Sex  Male  Female | 9420 (47.1%)  10580 (52.9%) | 7859 (45.8%)  9316 (54.2%) | 1561 (55.3%)  1264 (44.7%) | <0.001 |
| Troponin requested by clinical team | 1718 (8.6%) | 1508 (8.8%) | 210 (7.4%) | 0.018 |
| Location  OPD  IPD  ED | 9345 (46.7%)  4947 (24.7%)  5708 (28.5%) | 8472 (49.3%)  3845 (22.4%)  4858 (28.3%) | 873 (30.9%)  1102 (39.0%)  850 (30.1%) | <0.001 |
| Median (IQR) age | 61 (43 – 74) | 58 (40 – 71) | 77 (67 – 86) | <0.001 |
| eGFR | 90 (71 – 90) | 90 (75 – 90) | 73 (49 – 90) | <0.001 |
| cTnI concentration (ng/L) | 6 (3 – 12) | 6 (2 – 10) | 13 (7 – 28) | <0.001 |

OPD=outpatients department; IPD=inpatients department; ED=emergency department; eGFR=estimated glomerular filtration rate

Table 1: Baseline demographics comparing those who died at follow up with those alive at the end of follow up

|  |  |  |
| --- | --- | --- |
| **Variable** | | **Mortality HR (95% CI)** |
| Age (years) | | 1.048 (1.044 – 1.051) |
| Male gender | | 1.217 (1.127 – 1.314) |
| eGFR | | 0.994 (0.992 – 0.996) |
| cTnI requested by clinical team | | 0.616 (0.529 – 0.717) |
| Clinical location | OPD | Reference |
| IPD | 2.012 (1.831 – 2.210) |
| ED | 1.556 (1.404 – 1.725) |
| Log (10) cTnI | | 1.764 (1.653 – 1.883) |

Table 2: Multivariable outputs for all-cause mortality

OPD=outpatients department; IPD=inpatients department; ED=emergency department; eGFR=estimated glomerular filtration rate

|  |  |
| --- | --- |
| **Cause of death** | **Number (percentage)** |
| Malignancy | 1308 (46.3%) |
| Cardiovascular | 363 (12.8%) |
| Old age | 221 (7.8%) |
| Respiratory | 217 (7.6%) |
| Neurological | 150 (5.3%) |
| Gastrointestinal | 128 (4.5%) |
| Bacterial infection | 122 (4.3%) |
| Other/unknown | 94 (3.3%) |
| Accident/substance misuse | 73 (2.6%) |
| Endocrine | 44 (1.6%) |
| Renal/urological | 44 (1.6%) |
| Viral infection | 29 (1.0%) |
| Systemic disease | 21 (0.7%) |
| Haematological | 11 (0.4%) |

Table 3: Cause of death

**Figures**

Figure 1: Landmark analysis at 30 days comparing mortality depending on whether the cTnI concentration was above or below the ULN.

Figure 2: Adjusted hazards of mortality with cTnI of 0 as reference (>0 to <0.25 HR 0.986 (95%CI 0.820 – 1.185), 0.25 to <0.5 HR 1.505 (95%CI 1.244 – 1.821), 0.5 to 1 HR 1.941 (95%CI 1.577 – 2.390), >1 HR 2.516 (95%CI 2.034 – 3.112). Bars represent 95% confidence intervals

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