Raised serum cardiac troponin I concentrations predict hospital mortality in intensive care unit patients†

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Background. Recent work suggests that increased plasma concentrations of cardiac troponin I (cTnI) are common in critically ill patients and are associated with poor outcome. We measured the frequency of increased plasma cTnI concentrations during patients’ stay in a mixed medical/surgical intensive care unit (ICU) and compared our findings with hospital mortality.

Methods. Basic details, organ support, and hospital mortality were recorded for all patients treated in ICU during a 6 month period. cTnI concentrations were sampled daily for all patients, using 0.04 μg litre−1 as the upper limit of normal, and 0.12 μg litre−1 as an additional stratification point.

Results. Of 663 patients, 54% were male, with a mean (SD) age of 60 (18) yr, 65% were surgical patients, and the median Acute Physiology and Chronic Ill Health II (APACHE II) score was 15 (inter-quartile range 12–20). Increased cTnI concentrations were found in 345 patients (52%) while in ICU. One hundred and twenty patients (18%) died in hospital. cTnI concentration >0.04 μg litre−1 was associated with reduced odds of hospital survival, independent of age, medical admission, unplanned admission, APACHE II score, mechanical ventilation, and haemofiltration (adjusted odds ratio 0.25, 95% confidence interval 0.08–0.75, P=0.014). Stratification by the degree of cTnI increase revealed an incremental trend towards a lower odds of hospital survival, including for patients with ‘minor’ elevations of cTnI (0.05–0.12 μg litre−1).

Conclusions. Increased serum cTnI concentrations during ICU stay independently predicts hospital mortality, even when the threshold is low. We found a trend towards an association between ‘minor’ elevations in cTnI and higher in-hospital mortality.

Keywords: biological markers; heart; intensive care; myocardial ischaemia; troponin

Accepted for publication: 27 January 2012

Increased plasma concentrations of cardiac isoforms of troponin I (cTnI) and T are highly sensitive and specific biomarkers for cardiac myocyte damage.2 Recent work has suggested that such increases are common in critically ill patients, even where the admission problem is not primarily of cardiac origin.3 In addition, high cTn values have been associated with poor outcomes in this group of patients.3

Cardiac troponin concentrations are classically increased in the setting of acute coronary syndrome (ACS), where high cTn values almost invariably represent irreversible myocardial ischaemia and resultant myocyte death due to a primary coronary event, most commonly secondary to thrombotic coronary artery disease. Other disease processes associated with high serum cTn concentrations are: sepsis or septic shock, pulmonary embolism, severe exacerbations of chronic obstructive pulmonary disease, cocaine use, rhabdomyolysis, cardiac trauma, pericarditis, myocarditis, and acute or chronic myocyte damage after cardiac transplantation.4 Patients with renal disease also commonly have increased cTn values.5 Many of these processes do not necessarily imply irreversible myocardial ischaemia, and it has been suggested that reversible ischaemia can also contribute to high serum cTn concentrations,6 which may have particular relevance in the setting of cardiac stress and the reversible impairment of cardiac function during sepsis.

The relatively recent reclassification2 of myocardial infarction to include a type 2 infarction, occurring secondarily to an imbalance between oxygen supply and demand, may
thus be relevant in understanding the pathophysiology of high cTn values in critically ill patients in whom primary cardiac causes of myocardial damage are not clinically apparent.

In addition to allowing more accurate differentiation of non-ST elevation myocardial infarction from unstable angina, increased cTn has also been shown to have a prognostic value, both in patients with primary cardiac events and for other aetiologies, including renal disease, sepsis, subarachnoid haemorrhage, and pulmonary hypertension. In ST-elevation and non-ST-elevation ACS, this prognostic information extends to risk stratification, and it has been suggested that the extent of cTn elevation may help guide choice of treatment.

In the intensive care setting, increased cTn values appear to be common and associated with poor outcome. Lim and colleagues found a median frequency of cTn elevation during intensive care unit (ICU) stay of 43% (inter-quartile range, IQR, 21–59%) in a meta-analysis of 23 studies; this was associated with a greater risk of death in the six studies that measured outcome and adjusted for potential confounding factors [odds ratio (OR) 2.5, 95% confidence interval (95% CI) 1.9–3.4].

However, cTn threshold values used and frequency of testing differ widely in the literature, leaving clinicians with little guidance as to the significance of ‘minor’ elevations in cTn concentrations in the intensive care setting.

Our unit routinely samples cTnI for every patient each day, using a sensitive assay. Our primary objective was to survey a large cohort of unselected medical and surgical ICU patients to determine whether previous findings that increased cTnI independently predicts hospital mortality held true for our ICU population. A secondary objective was to more accurately describe the frequency and nature of cTnI elevation in our ICU patients.

### Methods

This retrospective observational study was a survey of blood test results, clinical observations, and patients’ data that had been collected routinely in the course of ICU care, and the local research ethics committee waived the need for formal ethics committee consideration.

The study cohort comprised all patients treated in the General ICU at St George’s Hospital, London, between January 1, 2008, and June 30, 2008. The General ICU in our hospital is a mixed medical/surgical unit, with cardiothoracic and neurosurgical patients being dealt with in separate units.

Age and admission type (planned vs unplanned, medical vs surgical) and Acute Physiology and Chronic Ill Health II (APACHE II) score were noted in an ICU database at the time of admission. Organ support while in ICU was recorded in the same database during the patient’s stay on the unit, as was the date of either the patient’s discharge from the ICU or their death, as appropriate. Mechanical ventilation during ICU stay was used as the criteria for recording the use of respiratory support. Although almost all patients received some form of cardiovascular support during their ICU stay, the criteria for a patient having received advanced cardiovascular support were: use of multiple i.v. vasoactive, rhythm controlling drugs, or both simultaneously, temporary cardiac pacing, or continuous cardiac output monitoring at any point. The use of a single vasoactive drug in isolation did not meet these criteria, although all patients receiving more than small doses of a single vasopressor agent routinely receive advanced cardiac output monitoring in our unit. Renal support was defined as the use of haemofiltration or haemodialysis at any point during the ICU stay.

Serum cTnI concentration is measured as part of a routine panel of blood tests for each patient at least once per day in our unit. Blood samples are analysed using a Siemens Advia Centaur TnI-Ultra Assay. The lower and upper limits of detection are 0.006 and 50 µg litre\(^{-1}\), respectively; the claimed 10% coefficient of variation is 0.03 µg litre\(^{-1}\) with a 99th centile of 0.04 µg litre\(^{-1}\). Values obtained for each patient were retrieved from the hospital’s Laboratory Information Management System database. The initial cTnI value and the maximum cTnI value were recorded. As there is some evidence that impaired renal clearance may contribute to increased cardiac troponin values, serum creatinine was recorded for the day of the maximum cTnI value. Once discharged from the ICU, the patient’s progress in hospital was recorded on a separate hospital database, which was later used to determine the date of either the patient’s discharge or their death.

### Statistical analysis

Data were analysed using SPSS 17.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean (ss) or median (IQR), as appropriate. Categorical data are presented as absolute numbers and percentages. The Kolmogorov–Smirnov test was used to determine if data were normally distributed. Correlation between the peak serum cTnI and creatinine concentrations was assessed using Spearman’s \(r\).

The primary decision limit above which a serum cTnI concentration was considered raised was 0.04 µg litre\(^{-1}\), the 99th percentile value of normal, in accordance with consensus guidelines defining myocardial infarction. A further threshold of three times this decision limit was calculated as 0.12 µg litre\(^{-1}\), following from the type 4 myocardial infarction definition in the same guidelines. The \(\chi^2\) test was used to separately test the univariable significance of cTnI elevation above each threshold.

The risk of hospital death associated with cTnI above 0.04 µg litre\(^{-1}\) was then compared with that for the reference group (cTnI ≤0.04) in a simultaneous-entry logistic regression model. The main effects were cTnI status, serum creatinine, and an interaction term. Predefined and plausible independent predictor variables (age, medical admission, planned admission, APACHE II score, organ support) were added as potential confounders. \(P<0.05\) was considered significant in this analysis. Additionally, the risk of hospital...
death for each of the two predefined strata of cTnI elevation was then compared with that for the reference group (cTnI ≤ 0.04) in similar regression models. A Bonferroni correction was applied, given the multiple testing against a single reference group, and $P \leq 0.025$ was considered significant. Age was coded in 1 yr increments, APACHE II score was encoded in 1 unit increments, serum creatinine concentration (in mmol litre$^{-1}$) was encoded as a continuous variable, and dichotomous variables were encoded as true or false. We did not allow for other variable interactions. The $B$ coefficient standard errors were inspected for indications of collinearity and other numerical problems. The Hosmer–Lemeshow goodness of fit was calculated for the model. Results for predictor variables are presented as ORs and 95% CIs. The regression models treated cases with missing values by list-wise deletion (complete case analysis). Since 6% of patients had missing APACHE II values, a sensitivity analysis was performed, using median-imputation where APACHE II values were missing.

### Results

Over the 6 month study period, 741 patients were admitted to ICU (Table 1). Forty-eight were readmissions and were excluded, as were 13 patients with missing cTnI values and a further 17 patients who were transferred to other hospitals and whose outcomes could not be traced.

Most patients had undergone surgery (65%), and most of these were planned admissions (44% of the total sample). Ten per cent (63) of the patients had an acute cardiac problem documented at the time of admission, including 29 (4%) who had suffered a cardiac arrest.

The median number of cTnI measurements made was 3 (IQR 2–5). Figure 1 shows the distribution of cTnI values during the ICU stay. cTnI was found to be increased on admission to our ICU in 38% of patients, while 52% of

Table 1  Characteristics of study cohort and outcomes. Data presented as median (range) or number (%). APACHE, Acute Physiology and Chronic Health Evaluation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range) or Number (%)</th>
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</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>358 (54%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64 (17–95)</td>
</tr>
<tr>
<td>Surgical patient</td>
<td>430 (65%)</td>
</tr>
<tr>
<td>Planned admission</td>
<td>290 (44%)</td>
</tr>
<tr>
<td>Admission APACHE II score</td>
<td>15 (3–42)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>343 (52%)</td>
</tr>
<tr>
<td>Advanced cardiovascular support</td>
<td>426 (64%)</td>
</tr>
<tr>
<td>Haemofiltration</td>
<td>75 (11%)</td>
</tr>
<tr>
<td>Duration of ICU stay (days)</td>
<td>2 (1–53)</td>
</tr>
<tr>
<td>ICU survival</td>
<td>584 (88%)</td>
</tr>
<tr>
<td>Hospital survival</td>
<td>543 (82%)</td>
</tr>
</tbody>
</table>

**Fig 1** Spread of measured cTnI concentrations at different time points. The median value is indicated with a line, with the numerical value indicating the number of results used, while the upper and lower box boundaries are 75th and 25th percentile values, respectively. Whiskers mark the highest and lowest data points within 1.5 IQR from the box boundaries. Concentrations are presented in μg litre$^{-1}$. cTnI, cardiac troponin I.
patients had a raised cTnI value at some point in their ICU stay. A cTnI value above 0.04 μg litre⁻¹ during ICU stay was a more common finding for medical patients (76%) than for planned (32%) and unplanned surgical patients (54%). Planned surgical patients in our unit were less unwell on arrival than unplanned patients [APACHE II score 14 (IQR 11–17) vs 19 (15–25), P<0.001], and this may explain some of this lower prevalence of cTnI elevation. Of patients admitted with a normal cTnI concentration, 14% developed a raised cTnI value while in ICU.

There was a significant association between the peak serum cTnI and contemporaneous creatinine concentrations (Spearman’s ρ 0.428, P<0.001).

The peak cTnI values exceeding both cutoffs (0.04 and 0.12 μg litre⁻¹) were associated with higher hospital mortality when used to dichotomize the sample (31% vs 4%, P<0.001, and 37% vs 8%, P<0.001) on univariable analysis.

Patients with a cTnI value of >0.04 μg litre⁻¹ were less likely to survive to hospital discharge, independent of age, medical/surgical and planned/unplanned admission type, APACHE II score, the use of mechanical ventilation, advanced cardiovascular support and haemofiltration, and serum creatinine (adjusted OR 0.25, 95% CI 0.08–0.75, P=0.014). Neither serum creatinine concentration nor the interaction term between this and cTnI elevation was significant in the multivariable logistic regression model (Table 2).

**Discussion**

In this study, a serum cTnI concentration above 0.04 μg litre⁻¹ while in ICU was associated with increased mortality in hospital, after adjusting for admission characteristics, age, severity of illness at admission, organ support, and serum creatinine concentrations.

Importantly, this trend was observed when patients were stratified according to cTnI values (0.05–0.12 and >0.12), although the level of significance was reduced.

Lim and colleagues reported in a study of 103 ICU patients that myocardial infarction, sepsis, and renal failure were the leading causes of raised cTn. The same group showed that systematic screening for myocardial infarction (using serial cTnI measurements and ECG recording) detected increased cTnI and myocardial infarction more often than was detected in routine clinical practice, and that increased cTnI was associated with greater mortality. Ammann and colleagues found that for a small sample of critically ill patients in whom coronary artery disease had been excluded, increased cTnI values were still associated with higher mortality.

It should be noted that our study describes cTnI measurements from one of the largest groups of consecutive unselected critically ill patients so far. Previous studies have either been smaller, have not included daily cTn measurement for every patient, or have used higher cutoffs for cTn elevation that do not reflect current consensus guidelines.

We also looked for a confounding relationship between an increased peak cTnI value and impaired glomerular filtration (as estimated by serum creatinine concentration on the same day). We found a significant correlation between creatinine concentration and cTnI elevation above 0.04 μg litre⁻¹, but neither serum creatinine nor an interaction term was a significant predictor in the multivariable analysis. As our study did not attempt to characterize the overall

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**Table 2** Multivariable logistic regression model summary. APACHE, Acute Physiology and Chronic Health Evaluation; cTnI, cardiac troponin I. The Hosmer–Lemeshow goodness of fit χ²=4.77, P=0.78. Standard error (B) <1 for all variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR for hospital survival (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97 (0.95–0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical patient</td>
<td>2.83 (1.43–5.63)</td>
<td>0.003</td>
</tr>
<tr>
<td>Planned admission</td>
<td>3.14 (1.17–8.47)</td>
<td>0.024</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>0.92 (0.87–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.35 (0.17–0.72)</td>
<td>0.004</td>
</tr>
<tr>
<td>Advanced cardiovascular support</td>
<td>0.59 (0.30–1.15)</td>
<td>0.12</td>
</tr>
<tr>
<td>Haemofiltration</td>
<td>0.32 (0.15–0.66)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.00 (0.99–1.01)</td>
<td>0.54</td>
</tr>
<tr>
<td>Interaction term</td>
<td>1.00 (1.00–1.01)</td>
<td>0.36</td>
</tr>
<tr>
<td>Peak cTnI &gt;0.04 μg litre⁻¹ during ICU stay</td>
<td>0.25 (0.08–0.75)</td>
<td>0.014</td>
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</table>

**Table 3** Likelihood of hospital survival stratified by cTnI concentration. Concentrations are presented in μg litre⁻¹. cTnI, cardiac troponin I. The Hosmer–Lemeshow goodness of fit χ²=7.86, P=0.45. Standard error (B) <1 for all variables. *P=0.05; **P=0.02. In sensitivity analysis with imputed values: peak cTnI 0.05–0.12, OR=0.25 (95% CI 0.07–0.89), P=0.032; peak cTnI >0.12, OR=0.22 (95% CI 0.068–0.69), P=0.01

<table>
<thead>
<tr>
<th></th>
<th>Peak cTnI 0–0.04 (n = 318)</th>
<th>Peak cTnI 0.05–0.12 (n = 115)</th>
<th>Peak cTnI &gt;0.12 (n = 230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality (%)</td>
<td>4</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>OR for hospital survival (95% CI)</td>
<td>Reference</td>
<td>0.27* (0.08–0.99)</td>
<td>0.24** (0.07–0.77)</td>
</tr>
</tbody>
</table>
effect of impaired renal function on survival, we did not analyse this further.

There are some limitations to our study. It was a large survey of consecutively admitted patients in our ICU. We were not able to specifically record all admission diagnoses and the presence or absence of pre-existing ischaemic heart disease or risk factors for this. In addition, the presence or absence of ischaemic ECG changes, or echocardiographic determination of myocardial infarction or heart failure, was not recorded. This information would have helped ascertain the likely cause of any observed cTn elevation, and could have informed a subgroup analysis based on known pathophysiology. For our outcome analysis, we adjusted for patient characteristics, severity of illness on admission, type of admission, and use of organ support in ICU. Unfortunately, the use of cardiovascular support was so widespread (Table 1) that it was hard to adjust meaningfully for this without recording the nature of the support required in more detail. In addition, given that for patients with a short ICU stay, the number of available troponin measurements was small (median 3, IQR 2–5), it is possible that a late troponin increase would be missed, although we consider that the majority of myocardial damage in the ICU would be likely to occur earlier in the patient’s stay.

The clinical significance of relationship between cTnI and mortality remains unclear, and there is no consensus on how increased cTn concentrations in the ICU, particularly ‘minor’ elevations, should be managed acutely or chronically in the absence of clinically apparent ischaemia/ACS. Investigation and management decisions are made especially difficult by the wide range of separate disease processes that may be involved.

Further work to help guide clinical responses to increased cTn values will be needed to distinguish between cTn’s role (i) as a marker of short-term myocardial damage secondary to other disease processes, for which the prognostic value of an increased serum concentration reflects the influence of these disease processes on outcome and for which the management response should include identification and treatment of the underlying cause, and (ii) as a marker of subclinical myocardial damage that itself exerts an effect on outcome, either during the hospital stay or later. It may be that studies should concentrate on incidental or ‘minor’ cTn elevations, since these are intuitively more likely to be ignored. ACS patients, patients in the emergency room, and even patients participating in a population-level research study can already be risk-stratified for mortality by cTn levels, and such stratification may help decide whether to opt for early coronary angiography or conservative treatment in ACS patients. Computed tomography of the coronary arteries of patients with stable angina has found that more significant plaque disease is associated with low levels of serum cTn elevation. There are no guidelines to help clinicians respond to increased cTn values in ICU in the absence of clinically apparent myocardial infarction, but it is possible that undetected thrombus-mediated ischaemia may be the cause, and thus appropriate cardiac investigations and secondary prevention may be warranted, although further work will be required to determine whether this is the case.

Until the relationship between low levels of cTn elevation and outcome is clarified, our finding that cTnI above 0.04 µg litre⁻¹ independently predicts hospital mortality should prompt clinicians to take careful note of even the ‘minor’ elevations in cTnI commonly seen in ICU patients.

**Declaration of interest**

None declared.

**References**

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