Long-term outcomes of minor troponin elevations in the intensive care unit

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SUMMARY

The aim of our study is to determine the short-term and long-term outcomes of intensive care unit (ICU) patients with minor troponin elevations. The retrospective study compared ICU patients with peak troponin elevation less than 0.1 ng/ml to those with only negative tests during their hospital stay. Data were gathered from ICUs at Beth Israel Deaconess Medical Center between 2001 and 2008. A total of 4224 patients (2547 controls and 1677 positives) were analysed. The primary outcome was mortality at one year. Secondary outcomes were 30-day mortality and hospital and ICU lengths of stay. After adjusting for age, sex, Simplified Acute Physiology Score, Sequential Organ Failure Assessment and combined Elixhauser score, we found that minor troponin elevations (peak troponin elevation between 0.01 and 0.09 ng/ml) were associated with a higher one-year mortality (Hazard Ratio 1.22, P <0.001 for binary troponin presence; Hazard Ratio 1.03, P <0.001 for each 0.01 ng/ml troponin increment). This relationship held for the subgroup of seven-day post-discharge survivors (Hazard Ratio 1.26, P <0.001). Minor elevations of troponin also significantly increased the net reclassification index over traditional risk markers for mortality prediction (net reclassification score 0.12, P <0.001). Minor troponin elevation was also associated with 30-day mortality (odds ratio 1.33, $P=0.003$). Importantly, troponin testing did not increase the adjusted mortality odds ($P=0.9$). Minor elevations in troponin substantially increase one-year, all-cause mortality in a stepwise fashion; it was also independently associated with 30-day mortality. We propose that minor elevations in troponin should not be regarded as clinically unimportant, but rather be included as a prognostic element if measured. We recommend prospective ICU studies to assess prognostic value of routine troponin determination.

Key Words: troponin, intensive care unit, outcome research

Serum troponin assay is an integral part in the diagnosis of acute myocardial infarction[1]. Troponin serves as both a diagnostic and a prognostic tool in the assessment of patients with suspected acute coronary syndrome[2]. The specificity for myocardial injury increases with rising levels of troponin elevation[3].

Several reports have shown that a significant portion of patients with critical illness have positive troponin during an intensive care unit (ICU) stay[4]. The aetiology of this troponin rise is debated. A minority of patients with troponin elevation during critical illness have evidence of atherosclerotic plaque rupture or ST elevation myocardial infarction[5]. Troponin elevations in critically ill patients may occur in the setting of flow-limiting coronary artery disease, microvascular dysfunction and myocardial strain causing an oxygen demand/supply mismatch[6]. Several reports have shown that moderate troponin elevations are independently associated with worse clinical outcome even when an acute coronary syndrome is excluded[7].

The majority of literature on troponin elevations in critical illness has focused on moderate troponin elevations (>0.1 ng/ml). With the advent of more sensitive troponin assays, it becomes clear that a significant fraction of patients with critical illness have troponin elevations[4]. These minor troponin elevations (<0.1 ng/ml) are often described as non-specific and referred to as "troponin leak". Recently, Reynolds et

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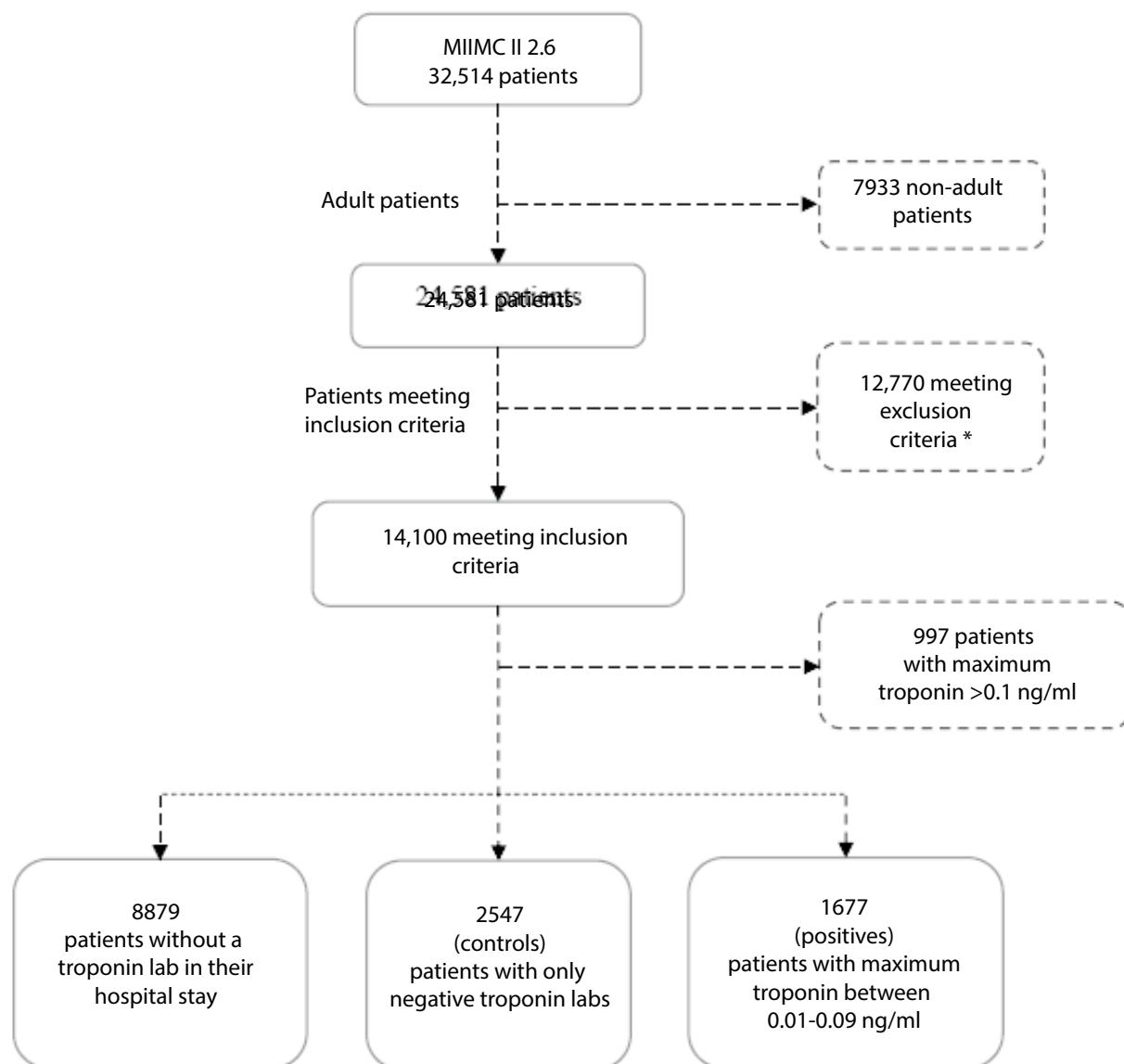§ MS, Research Affiliate, Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts, USA
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FIGURE 1: Patient cohort selection process.

| 8879 patients without a troponin lab in their hospital stay | 2547 (controls) patients with only negative troponin labs | 1677 (positives) patients with maximum troponin between 0.01-0.09 ng/ml |

Patients were excluded if they were acute coronary syndrome patients, had no admitting severity scores, or were admitted before July 2003 (when use of current troponin assay began).

al have shown that a minor elevation of troponin T (0.05 to 0.12 ng/ml) is associated with higher hospital mortality (19 versus 4%) compared to patients with normal troponin T[8]. Their study population (n=663) comprised 65% surgical patients. In another report studying mostly medical ICU patients with sepsis, however, neither minor nor moderate troponin elevations independently predicted mortality[9].

It is unclear whether, in a diverse, critically ill patient population, minor troponin elevations predict clinical outcome independent of comorbidities or severity of illness. The aim of this study was to determine the long-term (one-year) and short-term (30-day) mortality of critically ill patients with minor troponin elevation in whom an acute coronary syndrome was excluded, using the Multiparameter Intelligent Monitoring for Intensive Care II (MIMIC-II) database[10]. This data will shed light onto the understanding of the clinical significance of minor troponin elevations.

MATERIALS AND METHODS

Setting and study population

Study data were based on the MIMIC-II database, a high-resolution database developed and maintained by the Laboratory of Computational Physiology at Massachusetts Institute of Technology[11]. The database contains continuous physiologic signals such as electrocardiogram and invasive blood pressure waveforms, as captured by the bedside monitors. The 2.6 version of the database contains retrospective data for 26,870 adult hospital admissions recorded between 2001 and 2008, gathered from four ICUs at the Beth Israel Deaconess Medical Center's (BIDMC) medical intensive care unit (MICU), surgical intensive care unit (SICU), coronary care unit and cardiac surgery recovery unit.

Clinical data in the MIMIC-II database is acquired from the hospital's clinical information system, providing laboratory results, nursing notes and nurse-validated physiological data such as blood pressure and heart rate. The database was developed by a partnership between Massachusetts Institute of Technology (Cambridge, MA, USA), Philips Healthcare (Andover, MA, USA) and BIDMC (Boston, MA, USA) and is available for use in the public domain. Dates of death were acquired using patient social security numbers from the Massachusetts death records. The creation and use of the MIMIC-II database was approved by the Institutional Review Boards of both BIDMC and Massachusetts Institute of Technology (IRB Protocol 2001-P-001699/3).

All adult patient records in the database were screened for purposes of inclusion, with only the first hospital admission considered for analysis for those with multiple admissions. Our analysis focused on patients with minor troponin elevations, which we defined as values between 0.01 ng/ml and 0.09 ng/ml. Patients were excluded if they had an International Classification of Diseases Ninth Revision code for Acute Coronary Syndrome or had any troponin reading equal or above 0.1 ng/ml. We also excluded patients admitted before July 2003, as it was not known what troponin assay was used before then. The analysis was restricted to the MICU and SICU patients.

Troponin test assay information

The BIDMC core laboratory has used the Roche cardiac troponin T immunoassay since July 2003. Its analytical measuring range is 0.01 to 25 ng/ml. The assay has a standard error of 0.0055 ng/ml at a concentration of 0.095 ng/ml and 0.011 ng/ml at a concentration of 0.3 ng/ml.

Exposure, covariates and endpoints

The primary study outcome was one-year mortality. Secondary outcomes were 30-day mortality, ICU length-of-stay and hospital length-of-stay. Data regarding each patient's age, sex, Simplified Acute Physiology Score (SAPS), Sequential Organ Failure Assessment (SOFA) score laboratory values, vital signs, International Classification of Diseases Ninth Revision diagnoses and Disease Related Group were extracted. Medical comorbidities were represented by the Elixhauser scores for 30 comorbidities based on International Classification of Diseases Ninth Revision codes.

Data analysis

Patient variables and outcomes in groups with no troponin test, all negative troponin tests and at least one positive troponin test between 0.01 and 0.09 ng/ml were compared using a Kruskal-Wallis test (extension of Wilcoxon rank-sum test for more than two groups) for continuous variables and a chi-square test for categorical variables. Elixhauser scores were combined into a single weighted score using the method described by van Walraven et al and used as a covariate[11].

Patients were first split into ten groups based on maximum in-hospital troponin level. Cox regression models were then built to test the association between troponin level and the primary outcome, using the method for corrected prognosis described by Chang et al[12]. Covariates included in the models were age, sex, SAPS, SOFA score and Elixhauser score. For the SOFA scores, we took into account the score on the day of the peak troponin level. Presence or absence of a vasopressor on the day of peak troponin level was also included in the analysis. We performed a stepwise adjustment for the Cox regression in the following manner: beginning with using only troponin to predict one-year mortality and then adding (in sequence) age, gender, Elixhauser score, admission SAPS, SOFA score on the day of peak troponin and vasopressor use on the day of peak troponin. We reported the hazard ratio with 95% confidence interval (CI) and P value for the troponin value for each of these additions. Thereafter, troponin levels were represented as a binary variable with cut-offs at each 0.01 ng/ml interval, and a separate Cox regression model was created to confirm the significance of serum troponin at each cut-off (i.e. any test level between 0.01 and 0.09 ng/ml is considered equal).

We performed four sensitivity analyses by adding other possible explanatory variables to the model one at a time. We ran four separate models, adding in: 1) the number of troponin tests taken, 2) the

Table 1
Patient characteristics

Variable	Troponin status			
	Not tested	Negative	Positive	*P* value
Demographics				
Sex (male %)	54%	49%	52%	<0.001
Age (y)	56 IQR 29	63 IQR 26	74 IQR 21	<0.001
SAPS	12 IQR 7	12 IQR 6	15 IQR 7	<0.001
SOFA score	5 IQR 6	4 IQR 5	6 IQR 6	<0.001
Selected comorbidities and diagnoses				
Cardiovascular disease	45%	60%	74%	<0.001
COPD	6%	8%	12%	<0.001
Diabetes	10%	15%	19%	<0.001
Sepsis	4%	5%	7%	<0.001
Chronic renal disease	3%	3%	12%	<0.001
Combined Elixhauser score	2 IQR 3	2 IQR 4	4 IQR 6	<0.001
Troponin measurements				
Number of troponin measurements taken	0 IQR 0	2 IQR 2	3 IQR 2	<0.001
Hours from admission to maximum troponin measurement	N/A	18 IQR 19	28 IQR 71	<0.001
Laboratory measurements				
Haematocrit closest to maximum troponin measurement	N/A	35 IQR 9	32 IQR 8	<0.001
Creatinine closest to maximum troponin measurement	N/A	1 IQR 0	1 IQR 1	<0.001
Mortality				
Survivor ICU LOS (days)	2.0±2.4	2.1±2.8	2.9±4.2	<0.001
Survivor hospital LOS (days)	6±7	7±8	9±10	<0.001
In-hospital mortality	10%	9%	20%	<0.001

P value represents two-way comparison between troponin negative and positive patients. IQR=interquartile range, SAPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment, COPD=chronic obstructive pulmonary disease, ICU=intensive care unit, LOS=length-of-stay.
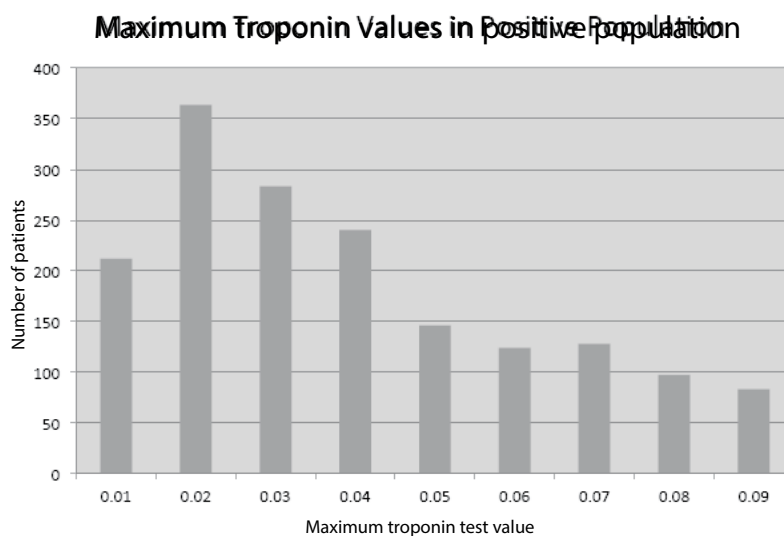

FIGURE 2: Distribution of troponin levels among patients with minor troponin elevations.

creatinine measurement occurring nearest to the maximum troponin level, 3) maximum SOFA score, and 4) the number of days from admission to the day of the maximum troponin value. If these additional variables do not impact the reported hazard ratio and significance of the troponin measurement, they are unlikely to be confounding the relationship of the serum troponin with the outcome.

The relationship between troponin and mortality was further investigated with landmark analysis to create an estimate of per-group time to death probabilities unbiased by the group assignment. Landmark analysis was introduced in 1983 as a way to estimate the probabilities associated with the time to an event in different groups, unbiased by the inherent "landmark time" associated with a response[13,14]. We selected a fixed time after discharge (seven days) as a landmark for conducting survival analysis, and only patients alive at the landmark time were included in this analysis.

The use of troponin as a biomarker was evaluated using the reclassification analysis method detailed by Pencina et al[15]. Net Reclassification Improvement was estimated as the proportion of patients with an improved reclassification score based on the serum troponin level with respect to the primary outcome (one-year survival).

Multivariate logistic regression was performed to test the relationship between troponin levels and secondary outcomes, adjusted for the same confounding variables.

All data processing and modelling was performed using MATLAB R2011a (MathWorks Inc., Natick, MA, USA).

RESULTS

Patient population

We limited our analysis to the first hospital stay of MICU and SICU adult patients without acute coronary syndrome (14,100). Of these, 997 patients had a peak troponin elevation greater than 0.1 ng/ml and were excluded from further analysis. In our remaining cohort of 13,103 patients, 8879 patients had no troponin determination throughout their hospital stay, 2547 patients had serum troponin checked but no positive result (control group) and 1677 patients had a maximum troponin measurement of less than or equal to 0.09 ng/ml (Figure 1).

Table 1 represents the characteristics of patients with no serum troponin checked, with serum troponin checked but without any positive result and with minor troponin elevations (peak serum troponin between 0.01 and 0.09 ng/ml).

Troponin testing does not increase adjusted mortality odds

In univariate analyses (Table 1), patients tested for troponin differed from those not tested in that they were older, had higher Elixhauser scores and stayed in the ICU and hospital for longer. We then performed multivariate logistic regression adjusted for age, sex, SAPS and SOFA score to determine whether simply having a troponin test ordered (regardless of test result) was a predictor for in-hospital mortality. We determined that having troponin checked during the hospital stay was not an independent predictor of in-hospital mortality (odds ratio 0.97, 95% CI 0.85 to 1.11, $P=0.68$). We therefore excluded patients without a single troponin checked (8879) from further analysis.

Population characteristics of patients with troponin tests

Patients with no positive troponin test in their ICU stays were used as the control group for the remainder of the study. Patients with at least one positive troponin test between 0.01 and 0.09 ng/ml were used as the positive group. The study cohort consisted of 4224 patients (2547 controls and 1677 positives). Patients with negative troponins differed from those with minor troponin elevation in that they were more likely to have a lower SAPS/SOFA score. The distribution of the peak troponin level in the positive group is depicted in Figure 2. Note that the group with the highest troponin level (0.09 ng/ml) in our study is the smallest subset of the study population (83 patients total). Most troponin measurements were done in the first three days of the ICU stay and the rate of testing decreased significantly thereafter (Appendix Figure 1).

Minor troponin elevation increases one-year mortality hazard

Cox regression was performed on the cohort with confounders described previously (age, sex, SAPS and SOFA score) using the maximum troponin value obtained from any test in the first hospital admission as a continuous variable (i.e. varying continuously from 0.01 to 0.09 ng/ml). As shown in Figure 3, there was a distinct separation between the control group and patients with a positive troponin value during their hospitalisation. In addition, each 0.01 ng/ml increment in peak troponin concentration was accompanied with an increase in one-year mortality (Serum Troponin Hazard Ratio=1.05 for each 0.01 ng/ml troponin increment, 95% CI 1.03 to 1.07, $P<0.001$).
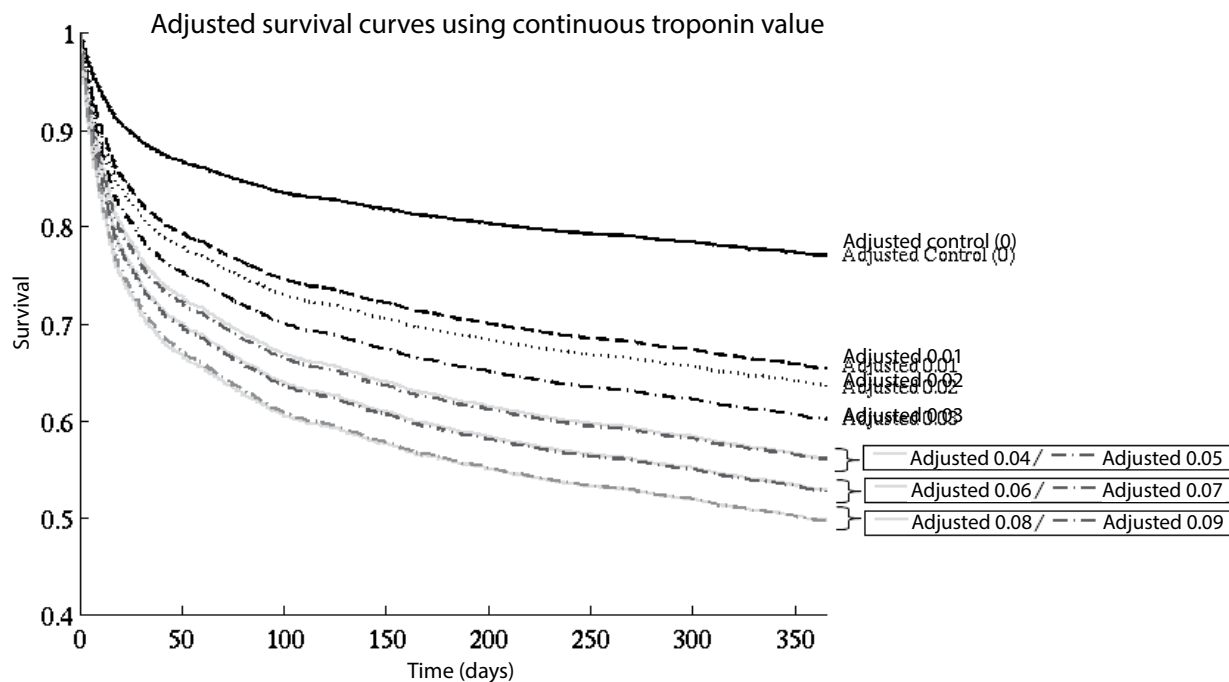
FIGURE 3: Multivariate adjusted one-year survival curves from unstratified Cox regression models based on peak serum troponin. Results have been adjusted for age, sex, SAPS, Elixhauser score and SOFA score on day of peak troponin and use of vasopressor on day of peak troponin. SAPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment.
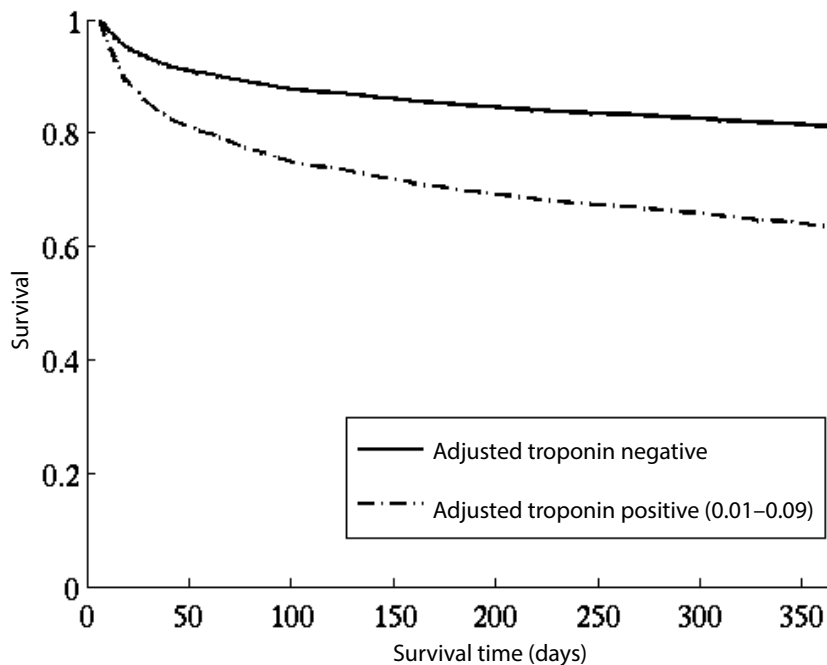

FIGURE 4: Landmark analysis for mortality between 7 and 365 days post-discharge. Curves shown are multivariate adjusted for age, sex, SAPS, SOFA score and Elixhauser score. SAPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment.

Table 2
Cox regression results for one-year mortality outcome

Covariates (stepwise addition of variables)	Hazard ratio	95% CI lower bound	95% CI upper bound	P value
Serum troponin	2.11	1.90	2.37	<0.001
+ gender + age	1.70	1.52	1.90	<0.001
+ admitting SAPS	1.37	1.21	1.53	<0.001
+ Elixhauser score	1.25	1.12	1.41	<0.001
+ SOFA on day of peak troponin + vasopressor (Y/N) on day of peak troponin	1.23	1.09	1.38	<0.001

CI=confidence interval, SAPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment.

For subsequent analyses, serum troponin was represented as a binary variable—negative for patients in whom all troponin tests were negative and positive for those with a peak serum troponin level at cut-offs of 0.01 ng/ml, 0.02 ng/ml, 0.03 ng/ml and so forth, through 0.09 ng/ml. Cox regression was performed using troponin group (positive or negative), sex, age, SAPS, combined Elixhauser score and the SOFA score on the day of peak troponin, adding the vasopressor (Y/N) on the day of peak troponin. The presence of a positive troponin was found to be associated with an increased one-year mortality hazard for all the analyses (Serum Troponin Hazard Ratio 1.15, 95% CI 1.02 to 1.29, $P=0.02$). The hazard ratios of the other cofactors are given in Table 2.

Landmark analysis for one-year mortality was performed on the subgroup of seven-day survivors. We found that proportional hazard rates remained significant when the same confounding variables were included (Serum Troponin Hazard Ratio 1.26, 95% CI 1.11 to 1.44, $P <0.001$). Corresponding survival curves are shown in Figure 4.

Sensitivity analysis was performed with four potential confounding variables in turn: the number of troponin tests, the creatinine level nearest the maximum troponin, maximum SOFA score and the test date of the maximum troponin level. The addition of these variables did not significantly change the estimated hazard ratio or P value associated with the troponin variable. In all cases, the estimated hazard ratio for the troponin variable was at least 1.22, and the estimated P value was less than 0.001.

The validity of troponin as a biomarker for poor clinical outcome was further investigated through calculation of its Net Reclassification Improvement. The reclassification of one-year survivors and non-survivors were separately analysed, which yielded a Net Reclassification Improvement score of 0.122 with a P value <0.001 (z-statistic=3.65). This means that an additional 12.2% of patients were accurately classified by the inclusion of serum troponin into the Cox regression model.

Secondary outcomes

After adjusting for differences in age, sex, SAPS and SOFA score, a positive troponin was not found to be associated with the ICU length-of-stay and hospital length-of-stay among hospital survivors. However, it was found to be associated with 30-day mortality (Serum Troponin Odds Ratio 1.33, 95% CI 1.10 to 1.61, $P=0.003$).

DISCUSSION

Moderate elevations (>0.1 ng/ml) of troponin in critically ill patients have been associated with worse clinical outcome[7]. It has been unclear whether a minor (<0.1 ng/ml) elevation of highly sensitive troponin has prognostic value in critically ill patients. Using a retrospective evaluation of the MIMIC-II database we showed that: 1) troponin elevations in the range of 0.01 to 0.09 ng/ml are independently associated with increased one-year mortality, 2) the increase in mortality increases in a stepwise manner with each 0.01 ng/ml increase, and 3) the addition of troponin to traditional prognostic tools such as SAPS, SOFA score and Elixhauser score increases the predictive value and modestly improves the Net Reclassification Index for one-year mortality.

Troponin elevation in the ICU population is very common. In a meta-analysis, the median incidence of troponin elevation was 43% (interquartile range 21 to 59%)[7]. An increased level of troponin in critically ill patients, however, is not necessarily associated with coronary artery disease. Ammann et al studied consecutive patients with a positive troponin of at least 0.1 ng/ml admitted to the ICU for reasons other than acute coronary syndrome[16]. They excluded a flow-limiting stenosis with stress echocardiography in 72% of the patients after recovery from the acute illness. We suspect that the prevalence of clinically significant coronary stenosis would even be lower among patients with peak elevation of serum troponin less than 0.1 ng/ml, although no study has looked at this.

A meta-analysis with 1706 patients, with multivariate adjustment for confounding variables, showed that moderate troponin elevation (at least 0.1 ng/ml) was an independent predictor of death with an odds ratio of 2.5 (95% confidence interval 1.9 to 3.4)[7]. With the advent of more sensitive troponin assays, investigators have attempted to evaluate the clinical significance of minor elevations (<0.1 ng/ml). Reynolds et al showed that patients with minor elevations of troponin had worse clinical outcome among mostly surgical ICU patients[8]. But a recent study of mostly medical patients with sepsis concluded that neither minor nor moderate troponin elevation was independently associated with worse clinical outcome[9]. Our analysis, the largest study to date evaluating troponin levels in critically ill patients, showed that minor elevations of troponin were associated with poorer short-term and long-term clinical outcome. In addition, we demonstrated that minor troponin elevations confer additional prognostic information beyond traditional clinical risk scores. This finding is important given that physicians tend to ignore minor troponin elevations and ascribe them to demand ischaemia of little clinical significance[17].

A restricted cubic spline function was developed to evaluate the relationship between peak troponin level and survival time after adjustment for the same covariates. Two models, one that included the entire study cohort and another that included only those with a serum troponin between 0.01 and 0.1 ng/ml, are presented in the appendices.

The limitations of this study include cited shortcoming of the retrospective study design[18]. We also do not have data on further cardiac testing to assess the aetiology of minor troponin elevation, although, as stated earlier, based on the literature, a minority of these patients have flow-limiting stenosis.

The physiologic response of a patient to stress or disease is the main determinant of the outcome[19]. Bion suggests this response is dependent on three factors: severity of the acute insult, the treatment given and the patient's degree of physiologic reserve[20]. Of the three factors, the physiologic reserve is the least characterised. Physiologic reserve accounts for the difference in clinical outcome that two patients with identical mortality risks (as traditionally defined by age, severity of illness and comorbidities) and treatment may have. Bion placed a large emphasis on the importance of cellular processes in response to stress as the major determinant of this physiologic reserve. Prior studies have attempted to measure aspects of the physiologic reserve. In a recent paper

also using the MIMIC-II database, the dynamic variables surrounding a hypotensive event were found to significantly improve mortality prediction independent of the illness acuity and the patient's comorbidities among patients with sepsis[21].

Recent literature from the VISION study and from the University Health Network in Canada on non-cardiac surgical patients was able to show that troponin elevations below the threshold for a diagnosis of a myocardial infarction were associated with an increased 30-day mortality[22,23]. The VISION study is a prospective analysis where troponin was measured in the first three days postoperatively[22]. The Canadian study was retrospective and showed an association between postoperative troponin elevation in non-cardiac and non-transplant surgical patients and increased mortality at 30 days[23]. Our study looked at critically ill patients from both MICU and SICUs, hence encompassing a wider range of patients.

We showed that minor troponin elevation provided prognostic information on top of traditional mortality risk factors, including age, severity of illness and chronic medical conditions. This association with poor long-term outcome continued after landmark analysis among seven-day survivors, which reduces the contribution of the critical illness on the one-year survival. These findings suggest that minor troponin elevation represents an inherent patient variable that is neither captured by the severity of the acute condition nor the chronic medical comorbidities but which significantly affects the outcome of critical illness.

We hypothesise that troponin elevation is a marker of the physiologic response to acute illness to which Bion alluded[20]. We, therefore, propose further research that will evaluate routine measurement of troponin in the ICU. While it is true that troponin elevation within this range will not change medical management, it may provide additional information beyond currently available prognostic markers.

CONCLUSIONS

In summary, we showed that minor elevations in troponin substantially increase one-year all-cause mortality in a stepwise fashion; it was also found to be independently associated with 30-day mortality. We propose that minor elevation in troponin should not be regarded as clinically unimportant given that it has prognostic significance among critically ill patients.

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