

Research Article

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The association between elevated troponin levels and all cause 30 day mortality in critically ill patients seen at an Academic Hospital – a prospective cohort study

Jospeh D¹, Ker J¹, Rheeder P¹ and Ueckermann V^{*1}

¹Department Internal medicine, University of Pretoria, South Africa

Abstract

Purposes: Elevated cardiac troponins have been shown to be associated with mortality in critical care, but its utility is not well established, especially in the setting of renal failure. This study aimed to examine the relationship between an early elevated troponin level and all cause 30 day mortality in critically ill patients, and in the subgroup of patients with renal failure.

Methods: Serum troponin levels were collected from all patients referred to a critical care team, be they medical or surgical, within 48 hours of referral. The study was a prospective cohort over a six month period. Patients' outcome was followed up to 30 days post enrolment.

Results: A total of 202 patients were enrolled in the study over a period of 6 months. One hundred and thirty one patients survived to 30 days (64.9%). A statistically significant association with troponin elevation and mortality was found ($p = 0.008$). Higher levels of troponin were also associated with higher mortality in the subjects studied. Once adjusted for renal failure, a relative risk of death of 2.27 ($p = 0.012$) was found with troponin values above 325 ng/L.

Introduction

Cardiac specific troponins have been used as biomarkers for myocardial injury since 1989 and their usefulness in both the diagnosis and prognosis of illness is presently a topical area of research [1].

It is known that both myocardial ischaemia and myonecrosis result in troponin release, which can be detected using various assays[1]. Troponin I and T subunits in particular have cardiac specific isoforms, making them more reliable markers for myocardial injury [1,2].

While the finding of an elevated serum troponin level would indicate myocardial damage, it does not differentiate the cause of the damage.

Besides acute coronary syndromes, alternative causes for raised troponins exist. In the absence of symptomatic, electrographic, echographic and/or angiographic evidence of myocardial ischaemia, these alternative sources may need to be investigated [1,3]. The numerous causes of cardiac myocyte injury and therefore raised troponin level, are listed below (Table 1).

The interpretation of troponin elevation is dependent on three factors: The baseline troponin level; the change in troponin level at a selected time interval and the clinical setting in which troponin levels are being evaluated [1,5].

The interpretation of elevated levels of cardiac biomarkers in the critically ill patient remains a challenge. Many causes for elevations of these biomarkers may be present simultaneously, making differentiation of the aetiology much more challenging in this population. Furthermore, elevated troponins in the context of renal failure have been historically difficult to interpret [6].

Owing to the nature of the illnesses facing critically ill patients, as well as many of their treatment interventions, particularly sedation, ventilation and the use of analgesia, symptomatology appropriate for the diagnosis of myocardial ischaemia may be absent. The critically ill patient may, in addition, have confounders for the presence of electrographic features typical of myocardial ischaemia. The performance of echocardiography may also be technically difficult in this setting and the patient may not be stable enough to be offered diagnostic angiography.

It may thus be difficult to prove a primary cardiac aetiology, such as acute coronary syndrome, as opposed to the myriad of other causes, to be the aetiology of biomarker increase in this population of patients.

Evidence in the literature highlights the difficulty facing critical care physicians. In one study, it was found that, while 41% of patients studied met criteria for definite myocardial infarction, only 20% of patients were recognised by the clinical team as such [7]. This discrepancy was attributed to the technical challenges facing critical care clinicians in interpreting an elevated troponin level and in conducting diagnostic studies to prove myocardial damage.

Lim (2006) conducted a systematic review of studies done on critically ill patients to evaluate the frequency of troponin elevation and the association between this elevation and mortality, as well as length of hospital and Intensive Care Unit stay [8]. The study found

Correspondence to: Dr V Ueckermann, Physician Intensivist, MBChB, MMed(Internal Medicine), Certificate Critical Care(Phys)(SA), University of Pretoria, South Africa, E-mail: ueckermannV@live.com

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Table 1: Conditions Associated with Troponin Elevations [1-4].

Arrhythmias (Tachy- or Brady-arrhythmias and Heart Block)
Aortic Dissection
Aortic Valve Disease
Acute and Chronic Heart Failure
Apical Ballooning Syndrome
Acute Respiratory Distress Syndrome
Anaemia
Burns
Coronary Vasospasm
Cardiomyopathy
Coronary Vasculitis
Cardiac Contusion (traumatic, post-surgery, post-ablation, with pacing)
Chemotherapy
Hypertension
Infiltrative Diseases of the myocardium (e.g. Amyloidosis, Haemochromatosis, Sarcoidosis & Scleroderma)
Myocardial Infarction
Myocarditis
Myocardial Extension of Endo-/Pericarditis
Pulmonary Embolus
Sepsis/Septic Shock
SIRS
Takotsubo Cardiomyopathy
Renal Failure
Respiratory Failure
Severe Neurological Disorders (Stroke & Sub-Arachnoid Haemorrhage)
Pulmonary Hypertension – Severe
Radiofrequency Ablation
Rhabdomyolysis with Cardiac Injury
Toxins and Drugs
Extreme Exertion

that troponin elevation was observed in 12% – 85% (median 43%) of critically ill patients. The frequency was even higher amongst patients with septic shock (60%). Amongst patients with hypovolemic shock, troponin elevation was found in all patients studied. The review also showed that a raised troponin level was associated with an increased mean length of ICU stay of 3.02 days and with hospital length of stay increased by a mean of 2.18 days. Mortality was also significantly increased amongst patients who had elevated troponin levels (37.1% vs. 13.6% in those who did not show elevated levels). The mortality associated with elevated troponin levels was even higher in patients with sepsis.

Recent studies have drawn attention to the fact that elevated levels of troponin may have, if not diagnostic, at least prognostic significance in the critical care setting [9-18]. In the context of patients with renal failure, however, there has been some uncertainty about the prognostic value of elevated troponin levels.

Methods

Study Design and Setting

This prospective cohort study took place amongst adult patients referred to the medical and surgical critical care units at an academic hospital in Pretoria, South Africa, over a period of six months from August 2015 to January 2016.

Study Population

All eligible patients who were referred to, and thereafter admitted, by the critical care teams responsible for the medical and surgical

intensive care units were enrolled in the study. We aimed to enrol every admission in the study and there was therefore no selection or sampling method applied.

Patients admitted to the coronary care unit, as well as to cardiothoracic intensive care unit, were excluded in order to avoid selection bias, given the nature of the study in measuring cardiac biomarkers. Patients with a clear primary cardiac cause for troponin elevation were excluded. We also excluded any readmissions to one of these critical care units that occurred over the period of study.

Measurements

Demographic information for each patient enrolled in the study was recorded, as well as the patient's underlying clinical diagnosis. Blood samples for troponin level quantification were collected and tested on the day of admission/referral to the critical care unit (we regarded this day as Day 0). The presence or absence of renal failure was noted for each patient; this was done to review the effect renal failure would have on the results. For the purposes of this study an eGFR < 60 ml/min/1.73m² was regarded as renal failure.

Only troponin levels that were obtained within the first 48 hours of acceptance by the critical care team were included in the study, to limit timing of the collection as a source of bias. Patients who had troponin levels collected more than 48 hours post critical care referral were excluded from the study.

Troponin levels were measured by the National Health Laboratory Service (NHLs) in units of ng/L. Patients were followed from referral to the critical care team (Day 0) until Day 30. If the patient demised prior to, or on Day 30, this was noted. Similarly survival beyond Day 30 was also noted. Patients discharged from a critical care unit before Day 30 were followed up in the ward to which they were discharged, up until and including Day 30. Survival was thus defined, as survival to hospital discharge or alternatively 30 days from critical care referral. Any patients who were lost to follow-up before 30 days were excluded from the study.

Ethical considerations

All patients enrolled in the study provided researchers with informed consent. Informed consent was obtained voluntarily, from a patient who was deemed competent and capable with the assurance that the information explained to the individual was clearly understood. If a patient was unable to provide consent, owing to the nature of their illness, consent obtained from a relative (in the following hierarchical order: spouse/partner, parent, grandparent, adult child and sibling) and the patient was, where possible, re-consented when they were able. The study protocol was approved by the Faculty of Health Sciences MMed Committee, as well as the Research Ethics Committee, University of Pretoria.

Statistical analysis

Data collected was recorded in table format using Microsoft Excel. Statistical analysis was performed using Stata 13 Data Analysis and Statistical Software (*StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.*)

Results

The study was conducted for a period of 6 months in 2015 to 2016. After exclusion of 46 patients who had underlying cardiac disease, cardiac trauma or cardiac surgery, 202 patients were enrolled in the study. Of these patients 115 were medical and 87 were surgical.

The population studied showed an equal proportion of male and female subjects with 96 (47.5%) being female and 106 (52.5%) male.

There was a wide age distribution with the youngest patient being 13 and oldest 94 years of age; mean age was 50 years. One hundred and thirty six (67.3%) of patients had renal failure on admission to a critical care unit, which was defined as an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m².

Of the 202 patients studied there were 71 mortalities that occurred within 30 days of admission (35.1%), with 131 (64.9%) surviving to 30 days or discharge. As depicted in Table 2, survival was not significantly different between male and females ($p = 0.50$), nor between medical and surgical patients ($p = 0.47$). There was however a statistically significant survival difference in patients with and without renal failure ($p = 0.01$).

Association with survival and troponin is depicted in Table 3. Troponin was evaluated in quantiles with a statistically significant association with mortality found with troponin elevation the frequency of which increased with higher quantile of troponin encountered ($p = 0.008$). Once adjusted for the presence of renal failure, a potential confounder, results still showed a statistically significant relative risk of 2.27 ($p = 0.012$) for troponin above 325 ng/L (quantile 4 troponin) and overall the persistence of a statistically significant relationship with troponin elevation and mortality ($p = 0.0476$) (Table 4,5).

Discussion

Troponin elevation was found to be predictive of 30 day mortality in our population of critically ill patients. Thus, even though the etiology of elevated troponins in the intensive care unit may be difficult to elucidate, the test is a useful prognostic tool.

Our study population contained a large percentage of African patients, which was not a feature in previous studies.

We furthermore found that higher values of troponin were associated with an increased frequency of mortality in this setting.

What is noteworthy is that there is a significant risk of mortality at what may be considered a relatively low troponin level, with levels above 325ng/l being found to be significant for a more than 2-fold risk of mortality, even after results were adjusted for confounders.

The findings of this study highlight that troponin elevation has significant clinical utility in a critical care population.

Renal dysfunction is the one cause of elevated troponin that is not caused purely by an increased release of troponin, but rather a reduced

Table 2: Characteristics of Patients Studied.

N	202
Gender: Female/Male (%)	96/106 (47.5/52.5)
Ethnicity:	
African(%)	101(50)
White(%)	85(42)
Coloured(%)	7(3.5)
Indian(%)	9(4.5)
Age in years: Mean (Range)	50 (13 – 94)
Medical/Surgical (%)	115/87 (56.9/43.1)
Presence of Renal Failure on admission: Yes/No (%)	136/66 (67.3/32.7)
Survival to Day 30: Yes/No (%)	131/71 (64.9/35.1)
Troponin I Level (ng/L): Median (Range)	69.5 (10 – 35596)
Troponin I range per quantile:	
Quantile 1 (ng/L) [number of patients]	10 – 23 [51]
Quantile 2 (ng/L) [number of patients]	23 – 69.5 [50]
Quantile 3 (ng/L) [number of patients]	69.5 – 325 [51]
Quantile 4 (ng/L) [number of patients]	325 – 35596 [50]

Table 3: Association of 30-Day Mortality According to Gender, Clinical Team and Presence/Absence of Renal Failure.

	Survival to Day 30 number(%)		P = 0.50
	Yes	No	
Gender			
Male	71 (35.1)	35 (17.3)	
Female	60 (29.7)	36 (17.8)	
Clinical Team			P = 0.47
Medical	77 (38.1)	38 (18.8)	
Surgical	54 (26.7)	33 (16.3)	
Renal Failure			
No	51 (25.2)	15 (7.4)	
Yes	80 (39.6)	56 (27.7)	P = 0.01

Table 4: Association of Troponin with 30-Day Mortality.

Troponin Quantile No. (%)	Survival to Day 30		P = 0.008
	Yes	No	
1	41 (31.2)	10 (14.1)	
2	34 (26.0)	16 (22.5)	
3	32 (24.4)	19 (26.8)	
4	24 (18.3)	26 (36.6)	
Total	131 (64.9)	71 (35.1)	

Table 5: Association of Troponin with 30-Day Mortality, Adjusted for Renal Failure.

	Risk Ratio	P value	95% Confidence Interval
Quantile of Troponin			
1	-	-	-
2	1.45	0.295	0.72 – 2.90
3	1.73	0.106	0.89 – 3.36
4	2.27	0.012	1.20 – 4.28
Renal Failure Present	1.52	0.101	0.92 – 2.49
		P = 0.0476	

clearance of troponin and therefore it is the only identified cause of elevated troponin level that we adjusted for in the study. A surprising, yet highly clinically significant finding, was that troponin elevation in the presence of renal failure remained predictive of mortality.

The significance of the association of troponin elevation and mortality was not found to be significantly altered by gender, type of patient (medical or surgical), or age. The fact that age of patients in this study varied widely, strengthens the generalizability of the association between elevated troponin and outcome.

Limitations

The hospital's gatekeeping rules hampered eligibility for enrolment of the patients. While bloods were requested in a timely fashion in some cases, due to gatekeeping rules they were not processed, for various reasons.

Conclusion

Elevated troponin, while difficult to ascribe to a specific aetiology in the critical care setting, still has significant clinical utility in helping to identify patients who may have a poorer prognosis.

The association between elevated troponin and mortality remains still significant despite the presence of renal failure. This association between an elevated troponin level and mortality, in the presence of renal failure, is a novel one and has significant clinical relevance

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