

# Cardiac Specific Troponin I as Prognostic Factor among Non-COVID-19 Mechanically Ventilated Patients in a Tertiary Government Hospital: A Prospective Study

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## ABSTRACT

**Objective.** The study aimed to investigate the relationship between cardiac Troponin I (cTnI) level and prognosis among mechanically ventilated patients in terms of mortality, prolonged mechanical ventilation, and tracheostomy rate.

**Methods.** This is a prospective cohort study conducted at Quirino Memorial Medical Center, a tertiary government hospital, over a period of ten (10) months. Seventy-six (76) mechanically ventilated adult patients admitted at the medical intensive care unit, surgical intensive care unit, medical wards, and centers for neurologic sciences were included in the study. Quantitative cardiac Troponin I (cTnI) marker was measured and correlated to prognostic outcomes: a) prolonged ventilation (requiring more than 21 days), b) tracheostomy rate, and c) mortality rate. Data were analyzed using SPSS 16.0 and logistics regression with 95% confidence interval.

**Results.** Results showed that among 76 patients, 15 patients have low cTnI levels, 11 patients have normal levels and 50 patients have elevated levels. Among patients with low cTnI levels (<0.020 ng/mL), 13 (86.7%) were extubated, 1 (6.7%) preceded tracheostomy and 1 (6.7%) expired. Those with normal range cTnI levels (0.020 – 0.060 ng/mL), 10 (90.9%) were extubated, none (0%) preceded tracheostomy and 1 (9.1%) expired. Those with elevated cTnI levels (>0.060 ng/mL), 7 (14.0%) were extubated, 7 (14.0%) preceded tracheostomy and 36 (72.0%) expired.

**Conclusion.** Analysis of the results showed a significant correlation of cTnI elevation with prognostic outcome proven by the p-value of < 0.0001. The risk of mortality among subjects with above normal cTnI levels were nine times (9x) higher compared to subjects with normal or low cTnI levels. Duration of intubation among patients with low normal and high cTnI levels did not differ significantly. Tracheostomy rate in the study was inconclusive.

**Keywords:** mechanical ventilation, cardiac specific troponin I, mortality, prognosis



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## INTRODUCTION

Mechanical ventilation, also known as positive pressure ventilation is an artificial means of respiration of the lungs. It is indicated for patients whose spontaneous breathing is insufficient to support life. Decreasing the work of breathing to avoid respiratory muscle fatigue and to reverse life-threatening hypoxemia and progressive respiratory acidosis are the primary goals of mechanical ventilation.<sup>1,2</sup>

The number of patients requiring mechanical ventilation has been increasing, especially those needing intensive and critical care. This has caused an increase in the financial burden among admitted critically patients regardless of socioeconomic status.

In May 2014, a monthly average of 82% adult patients were intubated at the Medicine Intensive Care Unit of

Quirino Memorial Medical Center and this has been amplified to 84.4% approaching the year 2015.<sup>3</sup> In Malaysia, a pre-COVID study among ICU patients reveal escalating cost of healthcare with ICU patients incurring a daily cost of stay of \$1324 at the general intensive care unit.<sup>4</sup>

Unit cost of admission per day in the ICU remain higher for ventilated patients, especially patients on prolonged intubation.<sup>4,5</sup>

Thereby, a prognosticating factor that will aid in the management of patients on mechanical ventilation will be helpful. Prognostic indicators evaluate the likelihood of outcomes developing overtime in patients with a particular clinical condition.

An observation study in 2019<sup>6</sup> evaluated possible prognostic factors associated with mortality among mechanically ventilated patients in the ICU. APACHE-II score, successful weaning and nosocomial infection were the identified independent factors associated with prognosis of patients in the ICU. In another observation study done in 2020,<sup>7</sup> the lactate and albumin ratio were used as a prognostic marker in mortality among critically ill patients.<sup>7</sup>

Troponin, a sensitive marker of myocardial injury is commonly elevated among critically ill patients.<sup>8,9</sup> The purpose of this study is to evaluate the prognostic value of cardiac Troponin I (cTnI) level in mechanically ventilated patients and its influence in health outcomes.

## REVIEW OF RELATED LITERATURE

The most frequent indication for initiating mechanical ventilation is acute respiratory failure with hypoxemia which include acute respiratory distress syndrome, heart failure with pulmonary edema, pneumonia, sepsis, complications of surgery and trauma, which accounts for about 65% of all ventilated cases, and hypercarbic ventilator failure due to coma (15%), exacerbations of chronic obstructive pulmonary disease (COPD; 13%) and a small portion under neuromuscular diseases (5%).<sup>2,4,6,9</sup>

Troponins are protein molecules found in cardiac and skeletal muscle. The troponin complex consists of subunits troponin I (TnI), troponin T (TnT), and troponin C (TnC) along with tropomyosin located on the actin filament. Each subunit has a unique function and is essential for calcium-mediated regulation of muscle contraction. Troponin T binds the troponin components to tropomyosin, troponin I inhibits the interaction of myosin with actin, and troponin C contains the binding sites for calcium that helps initiate contraction.<sup>10-12</sup>

Cardiac troponin I is a specific marker for myocardial injury (see Appendix). It contains amino acid sequence that is unique to cardiac muscle.<sup>11</sup> Troponin I isoform has a post-translational tail of 32 amino acids on the N-terminus. This sequence of cTnI isoform and the 42% and 45% difference with sequence of other isoforms have made possible generation of highly specific monoclonal antibodies with no

cross-reactivity with other non-cardiac forms.<sup>8-12</sup> It has a high sensitivity and a marker for continuing cardiac injury.<sup>12,13</sup>

Coronary disease is not the only occasion where troponin I become elevated and several studies have started to correlate troponin elevations with other diseases. Likewise, troponin I and its relationship to prognosis of non-coronary diseases, septic shock, COPD and stroke of all types have been investigated.<sup>5,8,10-14</sup>

Previous studies that predicted outcomes on intubated and critically ill patients with septic shock showed a high prevalence of cTnI. One theory of myocardial dysfunction was based on the hypothesis of global myocardial ischemia.<sup>8,10-14</sup> During critical illness, there is marked inflammatory reaction leading to ischemia of various organs including the heart. The release of cTnI from damaged myocardial cells might be an oxygen supply – demand mismatch of the myocardium. In addition, inflammatory response may increase respiratory rate which may increase work of breathing further increasing cardiac demands.<sup>8-14</sup>

Physiologically, mechanical ventilation also affects cardiovascular function. Positive pressure ventilation may worsen the function of right ventricle (RV), by airway pressure elevation because of higher transpulmonary pressure. This may lead to increased RV after load and increase in pleural pressure which also decrease the venous return limiting the diastolic filling of RV.<sup>10-12</sup> It may also affect the preload and afterload on the left ventricle (LV) by decreasing pulmonary venous pressure and LV end-systolic transmural pressure leading to decrease in LV stroke volume.<sup>10-13</sup> Both mechanisms may lead to a decrease in cardiac output with a decrease in myocardial oxygen demand.<sup>11-13</sup>

Myocardial oxygen demand increases as a consequence of fever and increase in heart rate. Other factors that contribute to reduced oxygen supply include systemic hypoxemia from respiratory failure, microcirculatory dysfunction, hypotension, and at times, anemia. Aside from ischemia, a direct cardiac insult and toxic effect of endotoxins, cytokines or reactive oxygen radicals by infectious process and inflammatory cells contribute to microinjury and myocardial cell damage.<sup>11</sup> One report revealed the role of tumour necrosis factor alpha (TNF- $\alpha$ ) altering the permeability of myocardial cells, hence escape of cTnI to the bloodstream.<sup>13,14</sup>

Increased level of serum troponin in acute exacerbation COPD may signify ongoing cardiac co-morbidity.<sup>5,11-14</sup> In one study, approximately 70% of patient with AECOPD had increased levels of troponin I at presentation.<sup>11</sup> Positive cTnI in AECOPD has also been correlated with increasing severity of pulmonary hypertension and right or left ventricular dysfunction. Increased pulmonary artery pressure from the contraction of the small pulmonary arteries can cause cardiac stress and hypoxia which results in cTnI release. In acute exacerbation, the increased work and oxygen cost of breathing, the rise in the left ventricular after load with the increased intrathoracic pressure, the aggravation of pulmonary hypertension and the presence of hypoxemia

and hypercapnia are all associated with myocardial injury.<sup>13,14</sup> In pulmonary embolism, the RV strain could be the reason for troponin release. The presence of RV overload is the same mechanism for troponin released in both pulmonary embolism and COPD.<sup>11-14</sup>

Increased level of cTnI has also been reported in cases of stroke such as ischemic, intracerebral hemorrhage and subarachnoid hemorrhage (SAH).<sup>14</sup> In all types of stroke, left ventricular systolic dysfunction has been noted. It has been suggested that cardiac abnormality is due to dysfunctional sympathetic activity triggered by acute stroke.<sup>14</sup> In SAH, the elevated cTnI is a potent predictor for the occurrence of cardiac and pulmonary sequelae. The release of catecholamines after SAH is associated with myocardial death and release of cardiac enzymes.<sup>14</sup> After catecholamine release is the development of pulmonary edema by means of increasing transmural pulmonary vascular pressure caused by activation of alpha and beta adrenoceptor and myocardial damage. Hypotension and hypoxia are the two most important secondary sequelae that influence outcome after acute stroke.<sup>14</sup>

Despite multiple studies on mechanically ventilated patients and cTnI, association between troponin elevation and prognosis are still conflicting.<sup>15,16</sup> While some studies<sup>17-19</sup> show increased morbidity and mortality with elevated troponin, there are other studies<sup>20-22</sup> who refuted this association.

## MATERIALS AND METHODS

This is a prospective cohort study which aims to investigate the relationship between cTnI level and prognosis among mechanically ventilated adult patients in terms of mortality, prolonged mechanical ventilation, and tracheostomy rate (Appendix). The study was conducted over a period of ten (10) months, at the Quirino Memorial Medical Center, Quezon City.

The subjects were mechanically ventilated adult patients, aged 18 years old and above who are admitted at the medical intensive care unit, surgical intensive care unit, medical wards and centers for neurological sciences. History-taking and physical examinations with baseline electrocardiogram analysis to rule-out cardiac pathology were done. Subjects with the following disease entities with expected elevated cardiac specific Troponin I (cTnI) levels were excluded from the study: ischemic heart disease, previous myocardial infarction, heart failure, heart trauma, cardioversion, ablation and cardiac arrest, aortic valvular disease, hypertrophic obstructive cardiomyopathy, renal insufficiency and pregnancy.

Consent for inclusion in the study was asked by the primary investigator and/or co-investigator from the patient or the next of kin of the critically ill patient in situations that the patient was deemed unfit to give consent. Patients and/or relatives who did not consent were excluded. Competency in obtaining consent was ensured since the primary investigator

and co-investigator have Good Clinical Practice certificate. The investigator gathered data from medical charts which include diagnosis on admission and date of intubation. Likewise, the relatives of the subjects were properly informed of the procedure. Three (3) mL whole blood was extracted from patients on the day of intubation or at least four days after intubation for quantitative Troponin I (cTnI) analysis. Measurement of cTnI levels was done at Department of Pathology and Laboratory, Quirino Memorial Medical Center by means of three-site sandwich immunoassay using direct chemiluminometric technology with sensitivity and specificity to be 0.89 and 0.92, respectively.

Overnight monitoring and care were provided by resident physicians. Full-time physical and respiratory rehabilitation therapies were given for all patients.

The protocol was submitted to the local ethics review board of the institution. In addition, the investigators have undergone a Good Clinical Practice workshop and have certification prior to conduction of the study. All computers used for data gathering and interpretation were password protected and files were stored in a dedicated drive. All documents (electronic and printed copies) were discarded after 6 months from the completion of the study.

## RESULTS

Gathered data were encoded in Microsoft Word format and Microsoft Excel sheet for documentation and analysis. Each statistical analysis was done using the SPSS version 10 for windows to compute for the means, standard deviation and percentages. Analysis of variance (ANOVA) was used to compare more than two groups with numerical data, and Chi-square test to compare/associate nominal (categorical) data.

Table 1 presents the demographic distribution of subjects according to gender and age. It could be seen that males dominated the gender distribution. There were 44 male subjects which made up the 57.9% of the sample. While the female subjects (n=32) filled in the 42.1% of the sample. It could be gleaned that majority of the subjects were in the age range of 41 to 50 years old (23.7%). Second in rank

**Table 1.** Demographic Characteristics of Subjects

	Frequency (n=76)	Percentage (%)
<b>Age</b>		
21 - 30	8	10.5
31 - 40	7	9.2
41 - 50	18	23.7
51 - 60	16	21.1
61 - 70	17	22.4
71 - 80	10	13.2
<b>Mean ± SD = 52.66 ± 15.30</b>		
<b>Gender</b>		
Male	44	57.9
Female	32	42.1

**Table 2.** Distribution of Subjects According to Troponin Levels

Troponin Levels (ng/mL)	Frequency (n=76)	Percentage (%)
<0.020	15	19.7
0.020 - 0.060	11	14.5
>0.06	50	65.8

Mean  $\pm$  SD = 1.35  $\pm$  3.80; Median = 0.149

**Table 3.** Distribution of Subjects According to Prognostic Outcome

	Frequency (n=76)	Percentage
<b>Prognostic Outcome</b>		
Expired	38	50.0
Extubated	30	39.5
Tracheostomy	8	10.5
<b>Days Intubated</b>		
1 - 10	38	
11 - 20	21	
21 - 30	13	
>30	4	

Mean  $\pm$  SD = 13.14  $\pm$  8.60

were the 17 subjects in the 61 to 70 years of age group. This constituted the 22.4% of the sample. This was followed by the age group 51 to 60 years old, representing 21.1% of the group. 13.2% of the subjects belonged to the 71 to 80 years old age group, while 8 subjects (10.5%) were in the 21 to 30 years old age group. The least number of subjects were in the 31 to 40 years of age, which included 8 patients (9.2%). The mean age was 52.66 years old.

Table 2 shows the distribution of subjects according to their cardiac Troponin I levels. cTnI levels ranged from 0.001 to 25.77 with a mean of 1.35. Majority of the subjects, about 65.8% had cTnI levels above 0.06. There were 11 (14.5%) subjects who had normal cTnI levels and 15 subjects (19.7%) had low levels of cTnI (<0.020).

Table 3 shows the distribution of subjects according to prognostic outcome. Out of the 76 subjects, 38 (50.0%) expired, 30 (39.5%) were extubated and 8 (10.5%) underwent tracheostomy. Days intubated ranged from 4 to 34 days with a mean of 13.14 days. Most of the patients were intubated for 1-10 days, followed by 11 to 20 days, 21 to 30 days and those who were intubated for more than 30 days.

Table 4 shows the association of Troponin I levels with the prognostic outcomes. Among 38 subjects who expired, 36 (72%) had elevated troponin levels. This showed a significantly higher mortality among those with troponin levels of above

normal, which was nine times (9x) higher than those with normal and low cTnI levels. Meanwhile, those patients who had been extubated (n=30), majority had noticeably low and normal levels of troponin. Less number of subjects who had elevated Troponin (14%) underwent extubation. Out of 8 patients who underwent tracheostomy, 7 were noticed to have elevated troponin levels. The following results showed significant association as proven by the p-value of <0.0001.

Table 5 shows the comparison of the duration of intubation according to the levels of Troponin I. The results showed a trend towards longer duration of intubation with increasing Troponin I. However, when comparing the different durations, there seemed to be no significant difference noted as proven by the p-value of 0.52.

## DISCUSSION

Cardiac Troponin I (cTnI) has been the mainstay of diagnosing acute myocardial infarction and risk stratification for future adverse cardiac events. However, coronary disease is not the only condition wherein troponin I may be elevated. Its elevation can also be correlated to other non-cardiac diseases, such as stroke, sepsis and COPD.<sup>1,2</sup>

Mechanical ventilation is a common life-saving intervention in the intensive care setting. And it has several direct and indirect effects on the lung and the upper airways, cardiovascular, renal, hepatic and gastrointestinal systems. Pulmonary effects include barotrauma, nosocomial pneumonia, oxygen toxicity, tracheal stenosis and deconditioning of respiratory muscles.<sup>2-6</sup> Organs that lie within the chest cavity which includes the heart, great vessels and pulmonary vasculature are subjected to increased intrathoracic pressures associated with mechanical ventilation, thus decreases the cardiac output as a result of decreased venous return to the right heart, altered left and right ventricular dysfunction. Renal function is also compromised with positive pressure ventilation with decreased urine volume and sodium excretion. Decreased cardiac output, undesirably affect the hepatic function with increased hepatic vascular resistance and elevated bile duct pressure.<sup>2,7-15</sup> The gastric mucosa does not have autoregulatory capability thus, mucosal ischemia and secondary bleeding may result from decreased cardiac output and increased gastric venous pressure.<sup>2,3,16</sup>

Majority of the cases included in the study were sepsis and cerebrovascular disease. The mechanism that results in the elevation of cTnI in septic patients has been based on

**Table 4.** Association of Troponin I with Prognostic Outcome

Troponin Levels (ng/mL)	Prognostic Outcome			p-value*
	Expired (n=38)	Extubated (n=30)	Tracheostomy (n=8)	
<0.020 (Low)	1 (6.7%)	13 (86.7%)	1 (6.7%)	15
0.020 - 0.060 (Normal)	1 (9.1%)	10 (90.9%)	0	11
>0.06 (Elevated)	36 (72.0%)	7 (14.0%)	7 (14.0%)	50

\*p-values = <0.0001

**Table 5.** Distribution of Subjects According to Troponin Levels and Days Intubated

Troponin Levels (ng/mL)	Frequency	Days Intubated (Mean $\pm$ SD)	p-value*
<0.020	15	11.06 $\pm$ 7.29	0.52 (NS)
0.020 - 0.060	11	12.46 $\pm$ 7.68	
>0.06	50	13.92 $\pm$ 9.16	

\*p-values >0.05 - not significant



the hypothesis of global myocardial ischemia. Myocardial dysfunction is a consequence of cardiac cell damage that prompts the release of cTnI. An oxygen supply-demand mismatch in the myocardium results from fever and tachycardia which then increases the oxygen demand of the myocardium. Concurrently, the oxygen supply of the myocardium is reduced because of systemic hypoxemia from respiratory failure, microcirculatory dysfunction and hypotension. All types of stroke (ischemic intracerebral hemorrhage, and subarachnoid hemorrhage) have been reported to have elevations of cTnI levels. Acute stroke provokes a disturbance in the sympathetic activity thereby initiating an exaggerated release of catecholamine that leads to the excessive liberation of intracellular ions and subsequent decrease in cardiac function, hence a significant increase in cTnI.<sup>12,17,21,22</sup>

## CONCLUSION

In this study, the results showed a significant correlation of elevated cTnI with increased mortality of mechanically ventilated adult patients. The risk of death among these group of patients are said to be nine times (9x) higher than those with normal and low levels of Troponin I.

Liberating the patients by way of extubation as an outcome in this study, showed those mechanically ventilated patients who had normal and low cTnI levels have a higher chance of being extubated and a possible higher chance of survival compared to those who have elevated Troponin I. Undergoing a tracheostomy procedure as another outcome in this study showed a significant correlation of elevated cTnI levels and the risk of longer ventilation which is an indication to undergo the said procedure. However, with the limited sample size and cost of tracheostomy, several subjects were not able to undergo the procedure. Moreover, it has been seen in this study that there is no significant relationship between number of days of intubation and frequency of elevation in Troponin I.

Hence, in this study, cardiac specific Troponin I is a useful parameter to determine the prognosis of mechanically ventilated adult patients in terms of mortality, extubation and undergoing tracheostomy.

In summary, elevated cardiac specific Troponin I levels can serve a prognostic factor in terms of mortality and survival of mechanically ventilated adult patients.

## Limitations of the Study

A larger sample size and a longer follow up of subjects can aid in determining stronger associations between cTnI levels and prognostic outcomes.

## Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and final approval of the version to be published.

## Author Disclosure

All authors declared no conflicts of interest.

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## APPENDIX

### Glossary of Terms/Operational Definitions

1. Mechanical Ventilation - any mechanically assisted breathing, employing either positive- or negative- pressure devices.
2. Tracheostomy - the surgical formation of an opening into the trachea through the neck especially to allow the passage of air.
3. Troponin I - one of the cardiac troponins and a structural protein that act to regulate muscle contraction.
4. Prolong intubation - at least 21 consecutive days on the ventilator for more than 6 hrs/day.
5. Intubation - the passage of a tube through the nose or mouth into the trachea for maintenance of the airway.
6. Extubation - the removal of a tube especially from the larynx after intubation.
7. Mortality - the death rate.