Relation of Troponin I Levels With Postoperative Mortalitiy and Morbidity Rates In Patients Followed In Intensive Care Unit After Congenital Cardiac Surgery Whose Ages Between 7 Days and 16 Years Old

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ABSTRACT

Introduction: Troponin I is the most important predictive marker of myocardial injury. Myocardial injury has been reported as most significant cause of morbidity and mortality in pediatric cardiac surgery. In this study, we aimed to evaluate the effects of troponin I on postoperative mortality and morbidity in child population.

Materials and Method: Ninety-nine patients to whom underwent congenital cardiac surgery were included in this study. Perioperative and postoperative, troponin I values at 24th and 48th hours were recorded. Patients were divided into two groups according to troponin I values at 24th hours (lower and higher than 15 ng/ml, respectively). Aortic cross clamp time, cardiopulmonary bypass (CPB) time, intubation time, the duration of intensive care unit stay and medication of inotropic agents were recorded.

Results: Postoperative troponin I levels at 24th hours were higher than 15ng/ml in patients who underwent congenital cardiac surgery and were related with significantly higher CPB, aortic cross clamp, intubation time and longer stay in intensive care unit.

Conclusion: Higher troponin I levels at 24th hours are associated with increased morbidity in patients who undergo congenital cardiac surgery.

Keywords: Congenital cardiac surgery; Mortality, Morbidity, Troponin I.

Konjenital Kardiyak Cerrahi Sonrası Yoğun Bakım Ünitesinde Takip Edilen 7 Gün ile 16 Yaş Aralığındaki Hastalarda Troponin I Seviyelerinin Postoperatif Mortalite ve Morbidite ile İlişkisi

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ÖZET

Giriş: Troponin I miyokardiyal hasarın tahmininde önemli bir belirteçtir. Pediyatrik kardiyak cerrahide miyokardiyal hasarın en önemli mortalite ve morbidite nedeni olduğu anlaşılmıştır. Bu çalışma ile konjenital kalp ameliyatı olan çocuklarda troponin I değerlerinin postoperatif mortalite ve morbidite üzerine etkisini değerlendirmek amaçlanmıştır.

Hastalar ve Metod: Konjenital kardiyak cerrahi uygulanan 99 hastanın perioperatif, postoperatif 24. ve 48. saatteki troponin I değerleri kaydedildi. Hastalar hesaplanan cutoff değerine göre 24. saat troponin I seviyelerine göre iki gruba ayrıldı (15 ng/ml'den yüksek olanlar ve olmayanlar). Hastaların aortik kros klemp süreleri, kardiyopulmoner bypass süresi, entübasyon süresi, yoğun bakımda kalış süresi ve inotropik ajan düzeyleri kaydedildi.

Bulgular: Konjenital kalp ameliyatı olan hastalarda postoperatif 24. saatte ölçülen troponin I seviyelerinin 15 ng/ml'nin üzerinde olmasının: Kardiyopulmoner bypass süresi, aortik kross klamp süresi, entübasyon süresi ve yoğun bakım kalış süresini anlamlı olarak arttırdığı gösterildi.

Sonuç: Konjenital kalp ameliyatı olan hastalarda postoperatif 24. saat yüksek troponin I düzeyleri yüksek morbidite riski ile uyumludur.

Anahtar Kelimeler: Konjenital kalp ameliyatı, Mortalite, morbidite, Troponin I.

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Introduction

With technological improvement in anesthesia of cardiac surgery, cardiopulmonary bypass (CPB) and continuation of extracorporeal circulation, there has been significant development in pediatric and adult cardiac surgery. It is well known that, myocardial injury secondary to surgery or CPB, affects cardiac functions; therefore increases morbidity and mortality (1).

Pediatric open heart surgery is a special operation that has variety of success rates, depending on the quality of technique. Intraoperative myocardial tissue injury, affects postoperative cardiac functions which is directly related with morbidity and mortality (2).

Cardiac troponins are quite sensitive and specific markers for miyocardial injury. High specificity of troponin is derived from spesific isoforms of cardiac troponin T and I. Therefore, CK and CK-MB increase with a result of skeletal muscle, but are not relevant with cardiac troponins (3, 4). Several studies have showed that cardiac troponin I levels are safely can be used as an indicator of myocardial damage both in pediatric and adult cardiac surgery. Increased troponin I levels have been associated with postoperative complications like delayed extubation time, necessity of higher inotropic support and mortality (5-7).

In this study we aimed to evaluate the affects of troponin I on postoperative mortality and morbidity in patients between 7 days - 16 years old who underwent congenital cardiac surgery.

Material and Methods

Study subjects

Ninety-nine patients between 7 days and 16 years old, who were operated in Siyami Ersek Thoracic and Cardiovascular Surgery Center due to congenital cardiac disease, were included in this study. Patients who had liver and kidney failure was excluded. The indications for operation were as follows: Transposition of the great arteries (TGA) (n: 14), atrioventricular canal defect (AVCD) (n: 6), Glenn shunt (n: 2), ventricular septal defect (n: 34), atrial septal defect (n: 7), tetralogy of Fallot (TOF) (n: 18), cor atrium (n: 1), anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) (n: 2), double outlet right ventricle (DORV) (n: 4), supravalvular aort stenosis (n: 2), truncus arteriosus (n: 1), Total anomalous pulmonary venous connection (TAPVD) (n: 3), VSD and aortic coarctation (n: 1), AVCD and DORV (n: 1), VSD and ASD (n: 1), supraaortic ridge (n: 3).

All subjects gave their consent for inclusion in the study. The investigation conforms with the principles outlined in the Decleration of Helsinki. The study was approved by the local ethics committee.

Anesthesia and Surgical Protocol

All patients included in the study underwent the same anesthesia protocol. For sedation 3 – 5 mg/kg intramuscular (IM) ketamine was performed; afterwards arterial line and venous angiocatheter was inserted. We administered 0.1 mg/kg intravenosus (IV) midazolam, 5 – 10 mcq/kg Fentanyl (IV), 0.1 mg/kg Vecuronium (IV) for induction of anesthesia. To maintain anesthesia during operation, before and after CPB 0.1 mcg/kg/m Fentanyl and Sevoflurane, during CPB in every 30 minutes 0.5 – 1 mg Vecuronium, 5 – 10 mcg/kg Fentanyl and 0,5 – 1 mg midazolam was performed.

Following sternotomy, standart aortic and bicaval cannulation was administered. Activated clotting time was held over 400 seconds by 300 U/kg heparin IV infusion. CPB membrane oxygenator (Minimax Plus, Medtronic Inc. , Minneapolis, MN USA) and roller pump (Sarns Inc. USA) was used. Primary solution was prepared with lactate, whole blood (to hold hematocrite over 20%), albumin 20%, mannitol and heparin. After cross-clamping aorta, to save myocardial tissue, blood cardioplegia at +4 °C with an initial dose of 20 ml/kg and maintenance in every 20 minutes 10 ml/kg was performed. Ultrafiltration was applied starting from warming period of CPB.

Design of the Study

Blood samples for troponin I levels were taken from all patients on preoperative, postoperative first, 24th and 48th hours. The following data below were recorded.

- Duration of aortic cross clamp and operation time.
- Lactate levels of peroperative, first, 24th and 48th hours.
- Levels of inotropic agents performed after CPB was determined by Vasoactive-Inotropic Score.

  Inotropic score = [Dopamine (μgr/kg/min) + Dobutamine (μgr/kg/min) + Adrenalin (μgr/kg/min) x 100]
- Duration of mechanical ventilation and stay in intensive care unit.

Statistical Analysis

Number Cruncher Statistical System 2007 (NCSS), Power Analysis & Sample Size 2008 (PASS), Statistical Software 2008 (Utah, USA) programs were used in this study. Descriptive statistical methods (mean, standart deviation, median, frequency, ratio, minimum and maximum) was used in statistical evaluation. Student T test was performed for comparison of normally distributed variables and Mann Whitney U test for the parameters that were not normally distributed. The repeated Measures ANOVA (variance analysis of repeated measures) for normally distributed in-group comparison and corrected Bonferroni test for binary comparisons were used. Freidman test was used to compare groups that were not normally distrubuted and Wilcoxon Signed Ranks were applied for binary comparisons. ROC analysis and diagnostic screening tests were used to detect cut off points according to presence of morbidity and/or mortality. Significance was assessed at $p<0.01$ and $p<0.05$.

Results:

The study was composed of 99 patients and 49,5 % (n: 49) of the participants were female. The median age of the patients was 38 ± 41,9 months (range; 26-192) . The distributions of descriptive properties of the cases were shown in Table 1. Mortality was observed in 3% (n:3) of the patients.

Preoperative and postoperative first, 24th and 48th hour troponin I levels were demonstrated in Table 2 and Figure 1.

The changes of preoperative, postoperative first, 24th and 48th hours Troponin I levels, were statistically significant (p=0,001; p<0,01). The increase in postoperative 1th, 24^{th} and 48^{th} hour troponin levels were significantly higher than the preoperative levels (p=0,001; p=0,001; p=0,001; p<0,01, respectively). Postoperative 24^{th} and 48^{th} hour troponin I levels were in a decreasing trend when compared to preoperative levels (p=0,001; p=0,001; p<0,01, respectively). Postoperative 48^{th} hour levels were siginificantly lower than 24^{th} hours levels (p=0,001; p<0,01).

24^{th} hours troponin levels were significantly different (p=0.012; p<0.05) and troponin levels in 24^{th} hours were notably higher (Table 3). Based on this data, ROC analysis for 24^{th} hours Troponin levels and cut-off values for diagnostic screening tests were calculated.

The cut-off point of 24th hours troponin level for prediction of morbidity and mortality was 15 with a sensitivity of 58,82%; specificity of 67,69%; positive predictive value of 48,78% and negative predictive value of 75,86% (Table 3). Area under ROC curve was 65,5% with 5,9% standart deviation (Figure 2). Postoperative 24th hour troponin I levels were demonstrated in Table 4. The cross clamping, bypass, intubation and intensive care stay time were significantly shorter in the group with troponin levels < 15 in the postoperative 24th hours, compared to those with troponin levels ≥ 15 (p<0,05).

The patients who had intensive care unit staying time shorter than 5 days had significantly lower postoperative 24th hours troponin levels than those with longer stays (p:0,029; p<0,05) (Table 5).

The cases without any morbidity and/or mortality had significantly lower 24th hours troponin levels than those who sufferred morbidity and/or mortality (p:0,012; p<0,05) (Table 6).

Regarding the mortality rates there was not any statistically difference between preoperative, postoperative 1st and 24th hours troponin levels (p>0,05). However, postoperative 48th hours Troponin levels were significantly higher in deceased patients than the survivors (p<0,023; p<0,05) (Table 7).

Discussion

The heart, in pediatric population, faces more metabolic changes when exposed to ischemia, cardioplegic arrest and reperfusion. Myocardial injury was demonstrated to be the most important reason of mortality and morbidity in pediatric cardiac surgery (5–8). Therefore, operator should pay attention to protect myocardial tissue in congenital cardiac surgery. The presence with complex defects and intervention to more than one anomaly have an effect upon morbidity and mortality (9).

Troponin T and I have been found to be more specific in pediatric cardiac surgery rather than CK-MB and myoglobin in determining myocardial tissue injury (8, 9).
Datas regarding troponin T and I for diagnosis and follow up of infantile and pediatric population have recently been reported. Previous studies demonstrated the superiority of Troponin I to Troponin T in determining myocardial injury after surgery (10–12). Therefore, we prefered troponin I in our study as it reflects injury better. According to troponin I cut off values of 15 ng/ml at

postoperative 24th hours, we classified patients into two groups. In our study, the highest troponin I levels were recorded in the postoperative 24th hours (13).

Immer et al (14) performed a study in 73 patients who underwent congenital cardiac surgery. Patients were assigned in two groups according to postoperative 24th hours troponin I levels (higher or lower than 35 ng/ml). The group with higher troponin levels significantly had more liver and kidney dysfunction, necessity of vasoactive agents and longer intubation times (14). In our study, the patients with postoperative 24th hours troponin I levels higher than 15 ng/ml, had significantly longer intubation time. Contrary to findings reported by Immer et al. (14), there was not any statistically relationship between troponin I levels and necessity of inotropic agents in our study.

Several studies demonstrated that troponin I levels higher than 100 ng/ml, was related with increased mortality in pediatric population (12,14,15). However, recently studies pointed out that high troponin levels were not associated with high cardiovascular risk or mortality in infants who underwent congenital cardiac surgery (16,17).

In our study, troponin levels were found under 100 ng/ml in 2 of the 3 deceased patients. Troponin values of these patients in postoperative 48th hours were significantly higher compared to remaining living patients. Consequently, troponin levels continued to stay higher in patients who ended up with mortality.

Recent studies showed that variety of congenital cardiac disorders and surgery altered troponin levels (8, 12, 18). Imura et al (18) stated that troponin I levels, aortic cross clamp and CPB time and frequency of postoperative inotropic medication were significantly higher in complex TGA group than basic TGA in pediatric population. This difference was related with myocardial injury due to incision. In our study, aortic cross clamp time and duration of bypass were significantly longer in patients who had troponin I levels higher than 15 ng/ml in postoperative 24th hours.

Previous studies pointed out the relation of higher postoperative troponin I levels with major complications in adult cardiovascular surgery (1). Following pediatric surgery, intubation and intensive care unit stay time which have effects on morbidity and mortality, were found significantly longer, as shown in our study (19). Despite, in infant population, troponin I levels stated higher (12, 20); Bojan et al (13) declared the unnecessity of routine troponin I use in infants under 1 years old.

Consequently, the use of cardiac markers has been increasing during treatment of patients with congenital heart disease, however there is not any valid guideline regarding the routine use of these markers. Troponin I is one of the most significant markers establishing myocardial injury in congenital cardiac surgery. In our study, postoperative 24th hours Troponin I levels higher than 15ng/ml were significantly related with longer CPB, aortic cross clamp, intubation and intensive care unit staying time in patients who underwent congenital cardiac surgery. Routine use of troponin I during follow up in congenital cardiovascular surgery may be useful in estimation of postoperative morbidity and mortality.

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Table 1: Distribution of descriptive features

	Min-Max	Mean±SD
Age (month)	0,26-192,0	38,07±41,95
Cross time (minute)	16,0-223,0	74,89±44,42
Bypass time (minute)	31,0-323,0	105,05±58,62
Intubation time in ICU (hour)	2,0-504,0	48,13±79,35
ICU stay (day)	1,0-31,0	4,68±5,46

		N	%
Gender	**Female (1)**	49	49,5
	Male (2)	50	50,5
Mortality	**Survival**	96	97,0
	Exitus	3	3,0
Inotropic agents	**0**	5	5,1
	1	19	19,2
	2	38	38,4
	3	27	27,3
	4	10	10,1

Table 2: Troponin values

Troponin(ng/ml)	**Min-Max**	**Mean±SD (median)**	***[a]p***	***[b]Post-hoc***
[1]Pre-op	0,00-50,00	0,91±5,39 (0,02)	***0,001*****	***1<4<3<2***
[2]Post-op 1st hour	0,07-98,0	24,82±23,30 (17,50)		
[3]Post-op 24th hours	0,99-84,51	16,55±15,18 (12,21)		
[4]Post-op 48th hours	0,00-153,00	11,65±19,57 (6,83)		

[a]Friedman test *[b]Wilcoxon signed ranks test* ***p<0,01*

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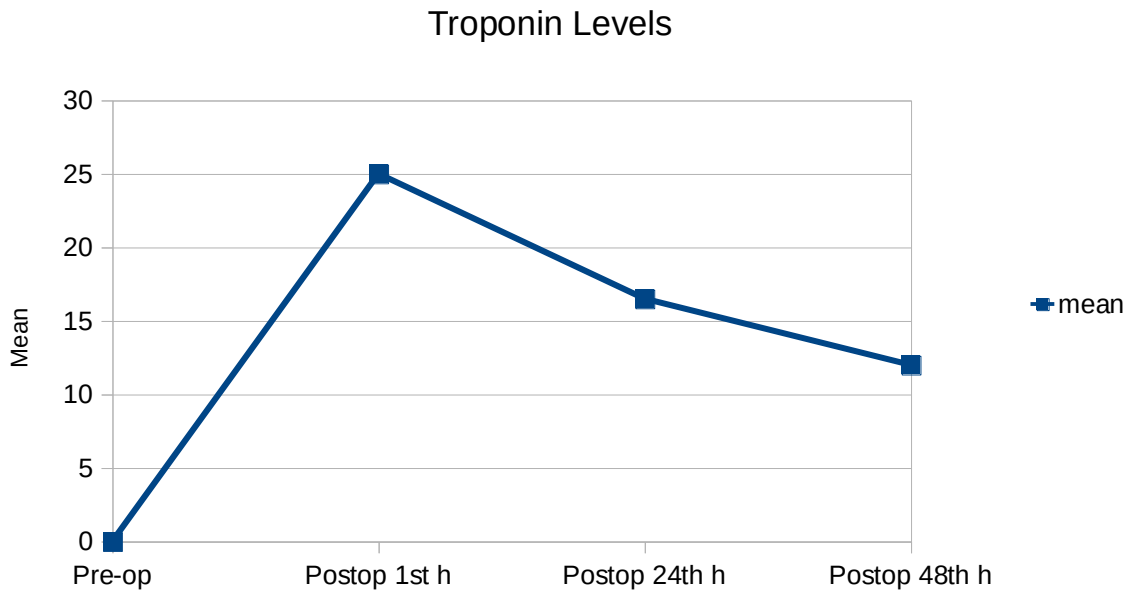

Figure 1: Distribution of troponin values

Table 3: Diagnostic scanning features of 24th hours troponin levels and analysis of ROC curve

	Diagnostic Scan	ROC Curve	*P*					
	Cut off	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**Area**	**95% Confidence Interval**	
24th hours troponin levels	***≥15***	58,82	67,69	48,78	75,86	**0,655**	0,552-0,747	***0,009****

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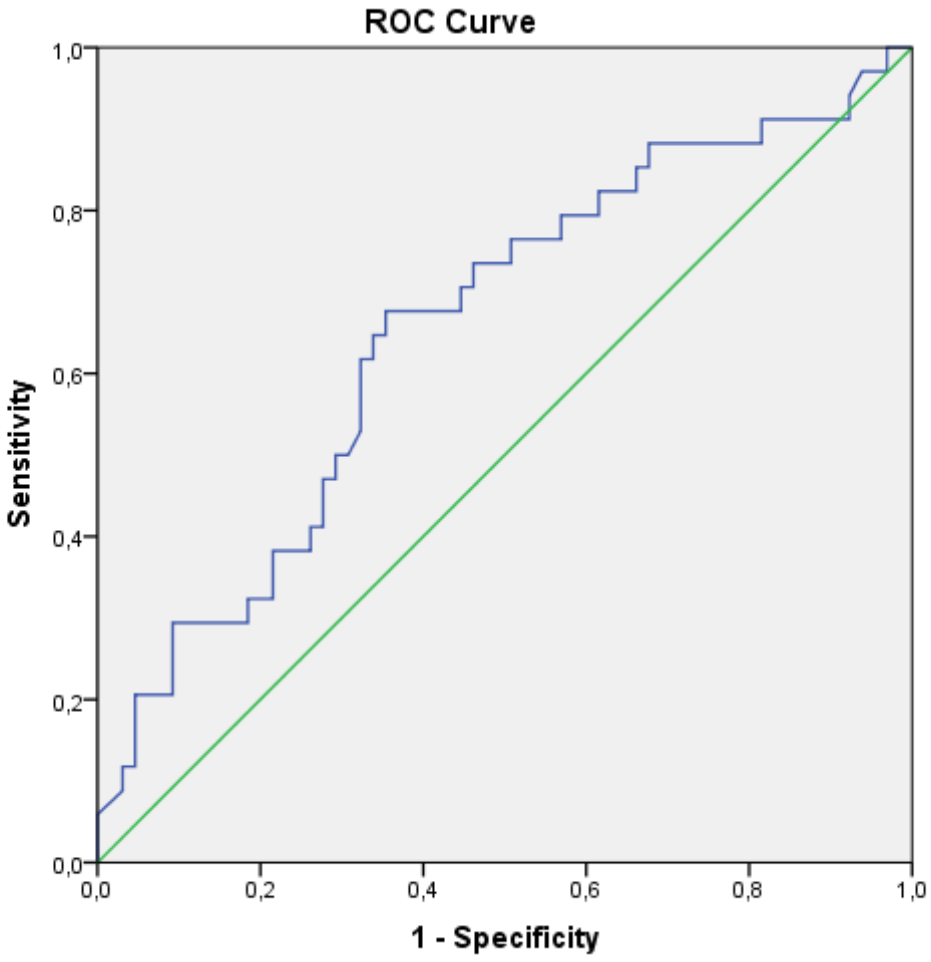

Figure 2: ROC curve of 24th hours troponin levels in morbidity and/or mortality

Table 4: Evaluation of postoperative 24th hour troponin I levels

	Postop 24th hours Troponin < 15 ng/ml (n=58)	**Postop 24th hours Troponin ≥ 15 ng/ml(n=41)**	***P***
	Mean±SD	**Mean±SD**	
Cross time (min); *(median)*	64,51±38,47 (52,50)	89,56±48,46 (80,00)	***[e]0,003*****
Bypass time (min); *(median)*	90,46±46,42 (75,50)	125,68±67,86 (109,00)	***[e]0,003*****
Intubation time (hour); *(median)*	31,50±42,82 (12,00)	72,86±110,02 (24,00)	***[e]0,022****
ICU staying time (day); *(median)*	3,53±3,60 (2,15)	6,31±7,06 (4,00)	***[e]0,003*****

[e]Mann Whitney U test *[f]Student t test* **p<0,05* ***p<0,01*

Table 5: Relation between post-op 24th hours troponin levels and morbidity

	Morbidity (-) (n=66)	**Morbidity (+) (n=33)**	***P***
	Mean±SD (median)	**Mean±SD (median)**	
Postop 24th hour troponin	14,22±13,26 (10,35)	21,22±17,74 (16,20)	***0,029****

Mann Whitney U test **p<0,05*

Table 6: Relation between post-op 24th hours troponin levels and morbidity and/or mortality

	Morbidity and/or mortality		***P***
	No (n=65)	**Yes (n=34)**	
	Mean±SD (median)	**Mean±SD (median)**	
Postoperative 24th hour troponin	13,48±11,93 (10,24)	22,42±18,82 (16,42)	***0,012****

Mann Whitney U test **p<0,05*

Table 7: Troponin levels and mortality rates

Troponin	Mortality		*P*
	No (n=65)	**Yes (n=34)**	
	Mean±SD (median)	**Mean±SD (Median)**	
Preop	**0,94±5,47 (0,02)**	**0,02±0,01 (0,02)**	***0,603***
Postop 1st hour	**24,12±22,42 (16,97)**	**47,12±44,23 (25,60)**	***0,198***
Postop 24th hours	**16,03±14,67 (11,72)**	**33,31±25,15 (22,80)**	***0,086***
Postop 48th hours	**10,50±17,54 (6,59)**	**48,75±44,91 (38,19)**	***0,023***

Mann Whitney U test ****p<0,05***