HIGH-SENSITIVITY TROPONIN-T LEVEL AFTER PEDIATRIC CONGENITAL HEART DISEASE SURGERY

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ABSTRACT

Cardiac tissue ischemia can be assessed by a troponin biomarker in adults. However, its effectiveness after pediatric open-heart surgery is still being debated despite the increased demand for congenital heart surgeries. This study assesses the relationship of troponin T levels with many surgical, biochemical, and prognostic variables.

This prospective, longitudinal study included 70 patients collected over one year. These patients underwent open-heart surgery and required a cardiopulmonary bypass machine at the Cardiac Center in Erbil, Iraq. Troponin T measurements were taken 4 times for each patient: the day before the operation, 4 and 24 hours post-surgery, and on the discharge day from the hospital. These measurements were correlated with many variables.

The study revealed significantly higher troponin levels in children younger than three years old and in those with Fallot surgeries. Most patients with high 4-hour troponin levels developed short-term complications. Furthermore, significant correlations were observed between troponin levels with the duration of the whole operation and the durations of these specific procedures: cardiopulmonary bypass, aortic cross-clamp, and inotropic support. We also found that high troponin levels, particularly 4 hours post-surgery, can predict a longer-than-usual stay in the intensive care unit and hospital, as well as short-term complications.

INTRODUCTION

Congenital heart diseases (CHD) are considered the most common birth defects worldwide, with more than 1.0% of all live births in the United States of America (Jenkins et al., 2019; Martin et al., 2017). However, with the reported rise in CHD prevalence globally, the proper access to healthcare, diagnostic technologies, and ways of treatment varies around the world. This variation affects the reported prevalence of CHD as well as its outcome and prognosis, with marked heterogeneity in different regions. Furthermore, it has been reported that there is evidence of significant unmet diagnostic needs in Africa and Asia (Liu et al., 2019).

Open-heart surgery includes certain procedures that are used for different durations during the surgery, mainly cardiopulmonary bypass (CPB), aortic cross-clamp (ACC), and CPB hypothermia. The CPB is a machine that temporarily takes over the functions of the heart and lungs. It mechanically oxygenates and circulates the blood in the body by bypassing the heart and lungs. The ACC is a special instrument used to clamp the aorta to separate the systemic circulation from the heart's outflow. By CPB hypothermia, the metabolic rate is decreased, which in turn leads to a decline in oxygen consumption; thus, there will be a delay in the time of apoptosis induction (Mirzaei et al., 2015; Zavriyev et al., 2021).

Any cardiac surgery is definitely accompanied by a certain degree of damage to the heart muscle. This damage will elaborate the cardiac troponins, which are structural proteins that form part of the cardiac myofilament complex (Mangla et al., 2019).

Troponin consists of three main subtypes: troponin T, I, and C. Among them, troponin T and I are myocardial-specific proteins and are useful as precise markers for myocardial injury (Abiko et al., 2018; Yasuda & Shimokawa, 2009). Recently, the detection of low troponin concentrations has been established by using the available highly sensitive cardiac troponin T (hs-cTnT) commercial assay. This assay can detect a

minute amount; thus, it elevates the precision of the measurement (Abiko et al., 2018). The justifications for the study are:

1. The prediction of the outcome and complications after cardiac surgery is not well recognized and needs improvement (Murni et al., 2019).

2. So far, there has been no well-established cardiac biochemical marker following heart surgery in the pediatric population as in adults (Gallacher et al., 2021). However, hs-cTnT was chosen because of its availability and it is more related than troponin I to both cardiac and non-cardiac outcomes (Welsh et al., 2019).

3. Up till now, there are no clear-cut values for both cardiac forms, the T and the I, in young children (Carmona et al., 2008; Wada et al., 2018).

4. The time to measure the troponin is a subject of debate in children. Also, the value that is regarded as a risky cut-off remains controversial (Thygesen et al., 2018; Wu et al., 2018; Bohn et al., 2019; Kavsak et al., 2014; Su et al., 2019). Four and 24 hours after Intensive Care Unit (ICU) admission measurements have been chosen for comparison, and the earlier detection is the better, as it is shown by other studies to be more related to outcomes. (Su et al., 2019; Immer et al., 1999).

MATERIALS AND METHODS

This prospective, follow-up, longitudinal study has been carried out at the Cardiac Center, Surgical Specialty Hospital, Erbil, Iraq. It is the only center in Erbil where CHD surgeries are carried out. The study was conducted from April 2021 to April 2022. The sample size was 70 patients.

Each patient was followed up in the hospital from admission until discharge. Serial measurements of serum hs-cTnT have been done: pre-operatively (baseline), four hours after ICU admission, 24 hours after ICU admission, and on the day of discharge from the hospital. However, the hs-cTnT was chosen because it is the standard test by the Cardiac Center laboratory. Renal function tests (RFT), complete blood count (CBC), and liver function tests were measured before and 12–20 hours after ICU admission. Troponin measurements were done by the Cobas e 411 analyzer by Roche Diagnostics in 2019. The test follows the sandwich and electrochemiluminescence immunoassay principles, with a total duration of about 18 minutes.

The variables related to the surgery details, CPB, ACC, operation, intubation (ventilation) durations, type of the intervention, and the lowest temperature achieved were obtained from the medical records, nurses, and doctors. Inotropic support included any use of noradrenaline, adrenaline, dopamine, dobutamine, and milrinone, even in small amounts.

The ages of the patients were classified into four groups: infants and toddlers (< 3 years), preschoolers (3-5 years), schoolers (6-11 years,) and adolescents (≥ 12 years) (Militaru & Martinovici, 2005).

The troponin measurements were divided into 3 groups based on the value that is close to the mean $\pm$ standard deviation and taking into account the most statistically significant classification that is associated with perioperative variables (Immer et al., 1999).

The surgeries were divided into 6 groups, similar to some other studies (Mirzaei et al., 2015; Imura et al., 2001; Murni et al., 2019), with adjustments according to the frequency. The categories of the surgeries were divided as follows:

a. Tetralogy of Fallot (TOF) total correction surgeries: classic TOF, double outlet right ventricle (TOF type), and double chamber right ventricle with ventricular septal defect (VSD). This group can also be subdivided into whether a transannular patch was used or not.

b. VSD surgeries: VSD alone, VSD with patent ductus arteriosus, VSD with subaortic ridge, and VSD with tricuspid valve repair.

c. Atrial septal defect (ASD) surgeries: ASD secundum alone (ASD²), sinus venosus, ASD² with pulmonary valve stenosis underwent commissurotomy, ASD² with mitral valve repair, and partial A-V canal.

d. Atrioventricular canal (A-V canal) surgeries: complete and intermediate A-V canal

e. Subaortic ridge resection surgeries.

f. The other surgeries: mitral valve repair, supravalvular aortic stenosis, and aortic valve replacement (Gupta et al., 1999). This group involved surgeries that were done once during the data collection.

The ICU duration has been divided into two groups, as children usually remain about one day after the operation and as a definition for

prolonged ICU stay (Baggish et al., 2004), and this was also applied to the hospital stay.

The occurrence of complications was divided into two groups: those who have complications and those without complications. The complications that were studied included: pleural and pericardial effusion, chylothorax, acute renal failure, temporary pacemaker, permanent heart block (necessitating permanent pacemaker), acute liver failure, chest infection, pneumothorax, re-operation of the patient in the same period of stay(redo), cerebrovascular accident, arrhythmia, and death (Murni et al., 2019; Javed et al., 2021).

Inclusion criteria:

Any patient from birth to 21 years old who had open-heart surgery in the center during the period of data collection for the study was included.

-Exclusion criteria:

1. Any child with an abnormal troponin level before the operation.

2. Patients who had no troponin measurement for any reason (for example, the parents' refusal of the test).

3. Any patient who underwent cardiac surgery without CPB and ACC.

4. Those who died soon after the surgery, before the assessment of the Tn4 (troponin measurements at the 4th hour from admission to the ICU).

Statistical analysis was performed using SSPS 26 for Windows in addition to the Excel program for graphs. A p-value of < 0.05 was defined as significant, and a p-value of < 0.001 was regarded as highly significant. The research was approved by the scientific and ethical committees of Hawler Medical College. The meeting code is 8 and the paper code is 2.

RESULTS

All troponin values before surgery were within the normal range per age; 27 of the 70 samples were undetectable (< 0.003 ng/ml). The mean ± SD of Tn4 was 2.27 ± 2.093 ng/ml; the median was 1.655 ng/ml; and the range was from 0.474 to 12.99 ng/ml. Tn4 in relation to age is shown in Table 1

Table(1):- Troponin measurements at the 4th hour from admission to the ICU (Tn4) in relation to age

Age (years)	N	Troponin (ng/ml) 4 hours after ICU admission			P-value
		< 2 No.(percent)	2 – 3.9 No.(percent)	≥ 4 No.(percent)	0.016*
Infant and Toddler	21	5(23.8)	11(52.4)	5(23.8)	
Preschooler	23	15(65.2)	4(17.4)	4(17.4)	
Schooler	18	13(72.2)	5(27.8)	0(0.0)	
Adolescent	8	4(50)	3(37.5)	1(12.5)	
Total	70	37(52.9)	23(32.9)	10(14.3)	

*Fisher's Exact test

Fifty percent of those with high Tn4 levels were infants and toddlers, compared to 40% of them being preschoolers and 10% being adolescents (Figure 1).
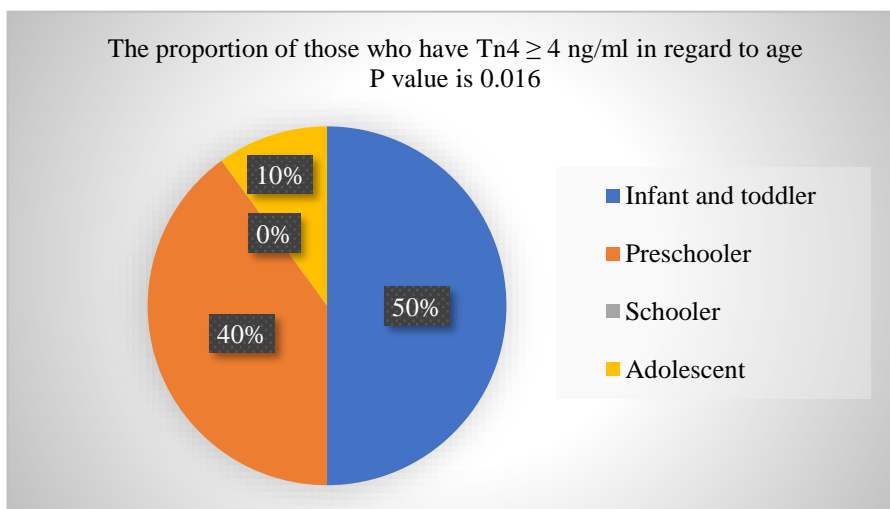
Fig.(1): -Tn4 levels in relation to age (Fisher's exact test)

Out of the 70 patients, only one died before doing Tn24 (troponin measurements at the 24th hour from admission to the ICU). The mean (of the 69 patients) $\pm$ SD of Tn24 was ~ 0.963 $\pm$ 0.676 ng/ml, the median was 0.794, and they ranged from 0.188 to 3.82. Tn24 decreased from Tn4 in all of the cases except one.

**Table 2**:- Troponin measurements at the 24th hour from admission to the ICU (Tn24) in relation to age

Age (years)	N	Troponin (ng/ml) 24 hours after ICU admission			P-value
		< 0.750 No.(percent)	0.750 - 1.4 No.(percent)	≥ 1.5 No.(percent)	0.044*
Infant and Toddler	20	4(20.0)	10(50.0)	6(30.0)	
Preschooler	23	13(56.5)	6(26.1)	4(17.4)	
Schooler	18	11(61.1)	7(38.9)	0(0.0)	
Adolescent	8	4(50.0)	3(37.5)	1(12.5)	
Total	69	32(46.4)	26(37.7)	11(15.9)	

*Fisher's Exact test

More than fifty percent of those with a high level of Tn24 were infants and toddlers, compared to ~36% of them being preschoolers and ~9.1% being adolescents (Figure 2).
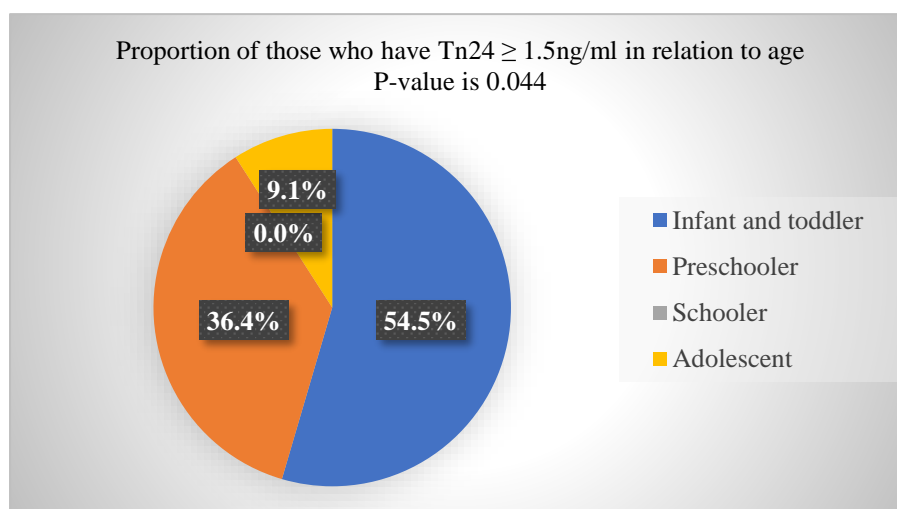

Fig.(2): -Tn24 levels in relation to age (Fisher's exact test)

The mean ± SD of troponin on the day of discharge from the hospital was ~ 0.406 ± 0.386 ng/ml, with a median of 0.291 and ranging from 0.007 to 2.24. All the patients showed a decrease in troponin levels from that of Tn24.

The medians of troponin levels with the range for each type of operation are described in Table 3.

Table (3):- Median and range of Tn4 measurements for each type of surgery

Surgery type	No.	Median(range) of Troponin 4 hours after ICU admission in ng/ml
TOF Repair	32	2.905(0.897-12.99)
VSD Repair	20	1.320(0.598-5.060)
ASD Repair	10	0.935(0.487-1.480)
A-V canal repair	2	1.77(1.050-2.490)
Subaortic ridge resection	3	0.479(0.474-0.491)
Others	3	0.877(0.511-2.410)
Total	70	1.655(0.474-12.99)

r= 0.837
P-value < 0.001
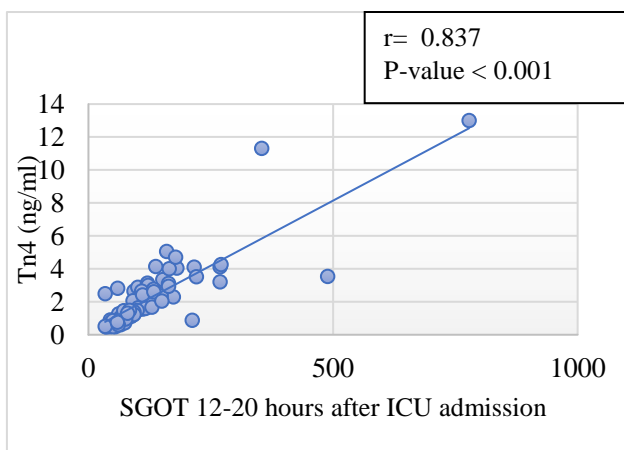
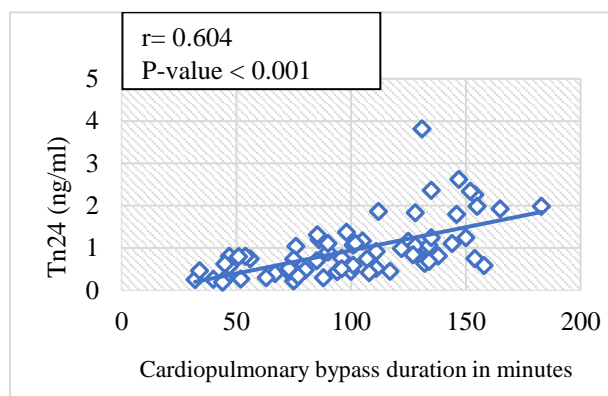**Fig.(3):-** Correlation between SGOT and Tn4

r= 0.755
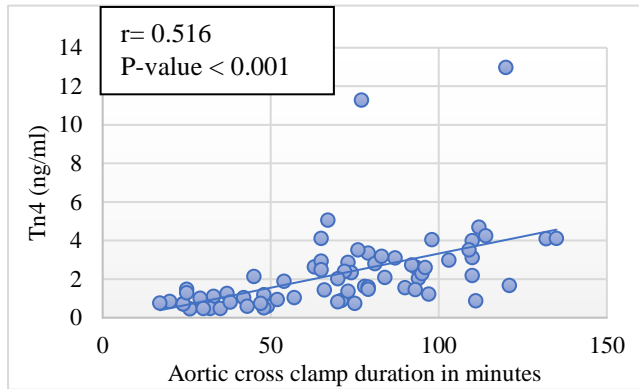P-value < 0.001
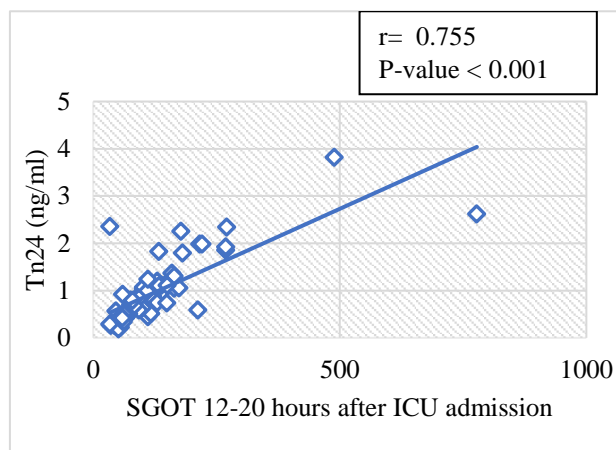
Fig.(4):- Correlation between SGOT and Tn24

A moderate positive (r = 0.4-0.7) highly significant correlation was detected with CPB, ACC, and operation duration (Figures 5, 6, 7, 8, 9, and 10).
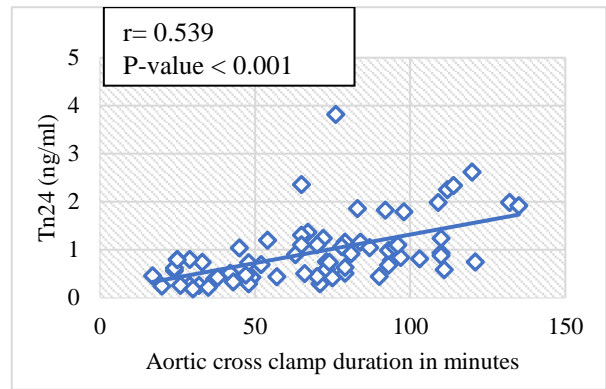

r= 0.486
P-value < 0.001
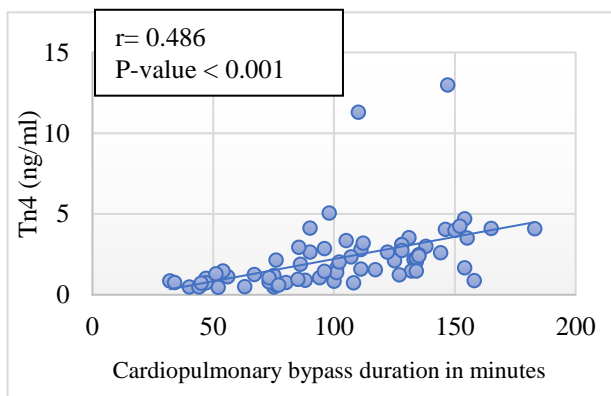
Fig.(5):- Correlation between CPB and Tn4

r= 0.604
P-value < 0.001

Fig.(6):- Correlation between CPB and Tn24
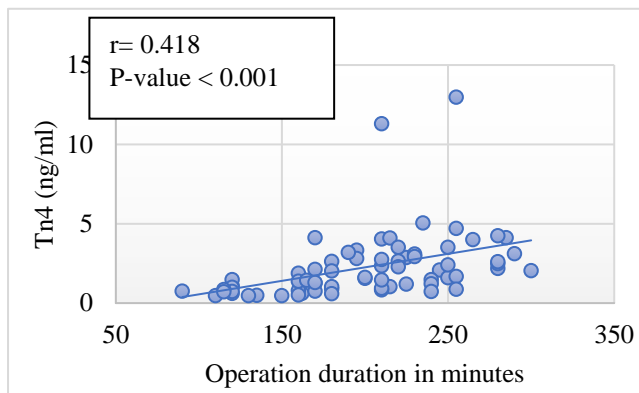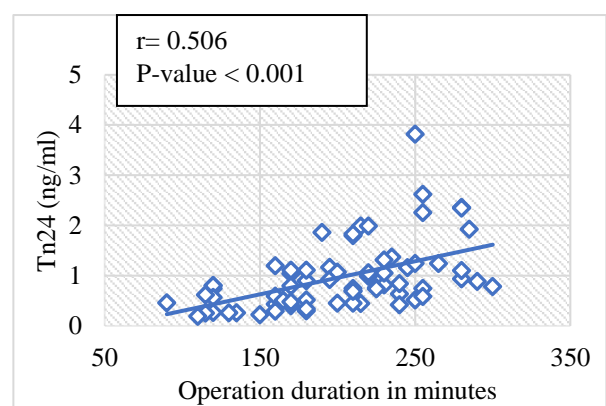
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Fig.(7): -Correlation between ACC and Tn4
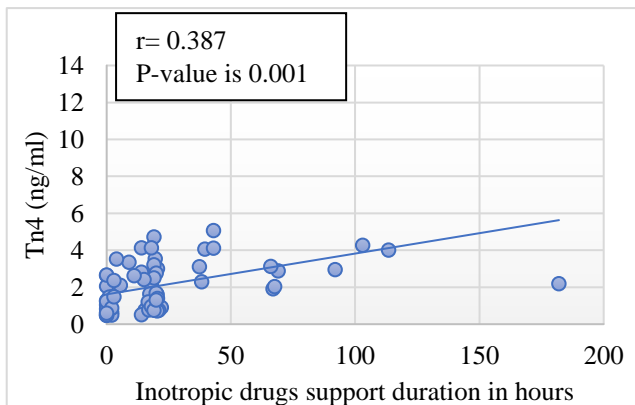

Fig.(8):- Correlation between ACC and Tn24

Fig.(9):- Correlation between operation and Tn4

Fig.(10):- Correlation between operation and Tn24

Weak positive ($r < 0.4$) significant correlation with inotropic support duration (Figures 11 and 12).

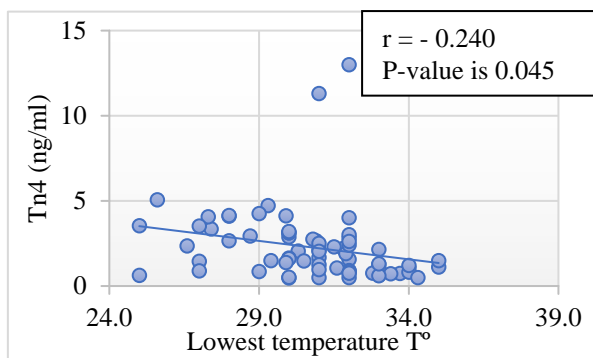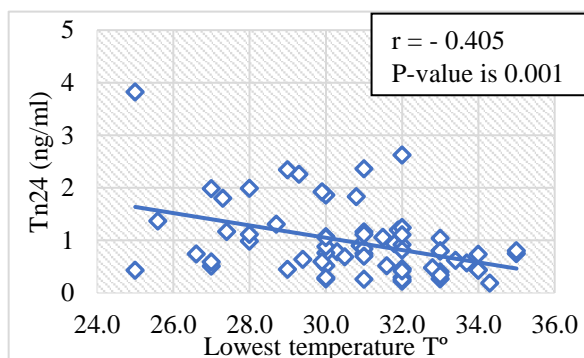**Fig.(11)**: -Correlation between inotropic support duration and Tn4
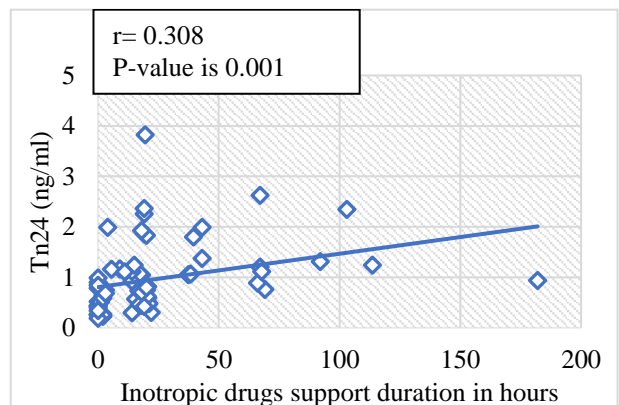
Fig.(12)`:- Correlation between inotropic support duration and Tn24

A weak negative ($r > - 0.4$) significant correlation with the lowest temperature reached during the operation was seen while a moderate one with that of 24 hours (Figures 13 and 14).

**Fig.(13)**:- Correlation between lowest T° and Tn4

Fig.(14): -Correlation between lowest T° and Tn24

No significant Pearson correlations were found with the ventilation duration, WBC count, neutrophil count, and lymphocyte count.

The patients who remained in the ICU for ≤ 24 hours were 53 out of 69 (~77%). [One patient was excluded because she died before discharge from the ICU]. In terms of troponin, only one (~ 2.7%) of 37 patients with Tn4 < 2 ng/ml remained in the ICU for more than 24 hours, while 6 (~ 67%) of 9 patients with Tn4 ≥ 4 ng/ml remained more than 24 hours (Figure 15).
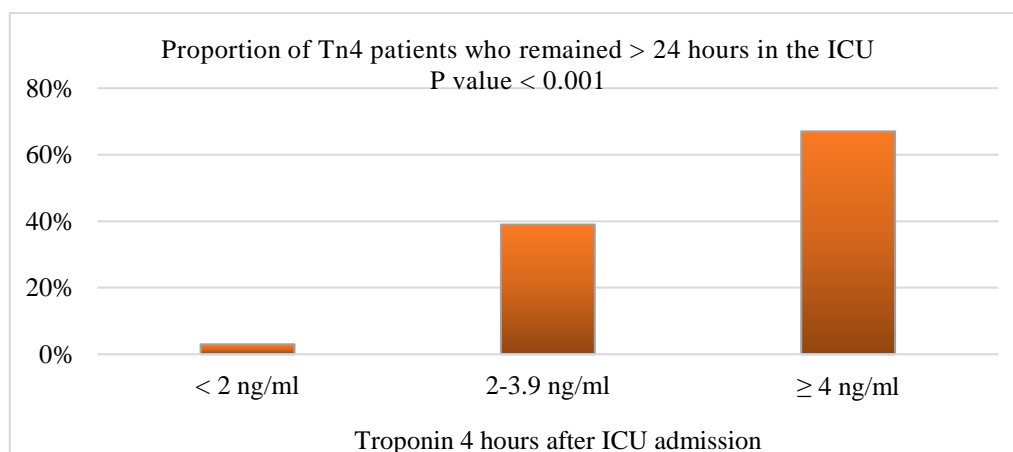
Fig.(15): -ICU stay in relation to troponin 4-hour levels (Chi-Square test)

The difference between the means of Tn4 in those who remained > and ≤ 24 hours is statistically highly significant (Table 4).

Table(4): -The means of Tn4 in those who remained ≤ and > 24 hours in the ICU

ICU stay duration	N	Mean of 4-hour troponin level	P-value
≤ 24 hours	53	1.638 ng/ml	< 0.001*
> 24 hours	16	3.803 ng/ml	

*T-test comparing 2 means

Regarding Tn24, zero of 32 patients with Tn24 < 0.750 ng/ml remained in the ICU for more than 24 hours, while five (~ 45%) of 11 with Tn24 ≥ 1.5 ng/ml, remained more than 24 hours (Figure 16).

Fig.(16): ICU stay in relation to Tn24(Chi-Square test)

The difference between the means of Tn4 in those who remained > and ≤ 24 hours is also statistically highly significant (Table 5).
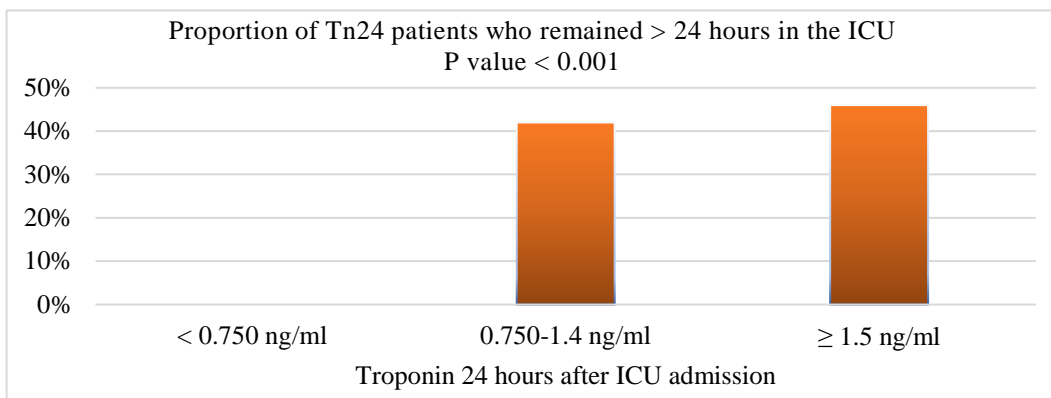
Table (5):- The means of Tn24 in those who remained ≤ and > 24 hours in the ICU

ICU stay duration	N	Mean of 24-hour troponin level	P-value
≤ 24 hours	53	0.822 ng/ml	< 0.001*
> 24 hours	16	1.430 ng/ml	

*T-test comparing 2 means

Of 37 patients with Tn4 levels of < 2 ng/ml, 26 (~ 70%) were discharged within 6 days from their hospital admission, while ~ 67 % of those who had Tn4 levels of ≥ 4 ng/ml were discharged after the 6th day (Table 6).

Table (6): -Hospital stays duration in relation to Tn4

Troponin 4-hours levels	N	Hospital stays duration		P-value
		≤ 6 days No.(percent)	> 6 days No.(percent)	
< 2 ng/ml	37	26(70.3)	11(29.7)	0.011*
2 – 3.9 ng/ml	23	8(34.8)	15(65.2)	
≥ 4 ng/ml	9	3(33.3)	6(66.7)	
Total	69	37(53.6)	32(46.4)	

*Fisher's Exact Test

The mean of hospital stay duration in those with high Tn4 was about 12 days while it was 6.7 days for those with low Tn4 levels (Figure 17).
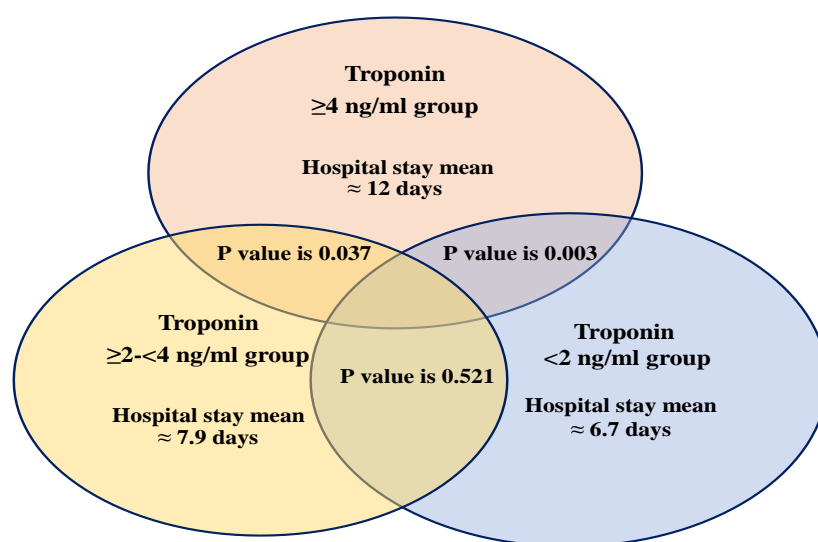
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Fig.(17):- The means of the hospital stay durations of Tn4 groups (Anova test)

Regarding Tn24 levels in relation to the hospital stay, it was found that ~ 72% of those who had Tn24 < 0.750 ng/ml were discharged within 6 days, while ~ 64 % of those with Tn24 ≥ 1.5 ng/ml were discharged after the 6th day (Table 7).

Table (7): -Hospital stay in relation to Tn24

Troponin 24-hour levels	N	Hospital stays duration		P-value
		≤ 6 days No.(percent)	> 6 days No.(percent)	
< 0.750 ng/ml	32	23(71.9)	9(28.1)	0.018*
0.750 - 1.4 ng/ml	26	10(38.5)	16(61.5)	
≥ 1.5 ng/ml	11	4(36.4)	7(63.6)	
Total	69	37(53.6)	32(46.4)	

*Chi-Square test

The differences between the means of the hospital stay duration in Tn24 groups were not significant statistically between each other; the P-value > 0.05.

Only one patient died, and his troponin level was 11.3 ng/ml. However, another patient survived with a higher troponin level (12.9 ng/ml) but with a long ICU stay, elevated liver enzymes, and pleural effusion.

About 38% of those with Tn4 < 2 ng/ml had complications; on the other hand, 90% of those with Tn4 ≥ 4 ng/ml had complications (Table 8).

Table(8):- the relation of Tn4 with the presence of complications

Troponin 4-hours levels	N	Presence of any complications		P-value
		Yes No.(percent)	No No.(percent)	
< 2 ng/ml	37	14(37.8)	23(62.2)	0.012*
2 – 3.9 ng/ml	23	10(43.5)	13(56.5)	
≥ 4 ng/ml	10	9(90.0)	1(10.0)	
Total	70	33(47.1)	37(52.9)	

* Chi-Square test

While no significant relation was found between complications and Tn24, P-value > 0.05.

DISCUSSION

In parts of Iraq (including areas of the Kurdistan region), a study stated that pediatric cardiac surgeries in Iraq were not well-developed before 2010. But the surgeries have increased over time through cardiothoracic surgery programs in underserved countries. At that time, neonatal cardiac surgery started for the first time in Iraq (Almandel et al., 2013). The other one stated that many children in Iraq are waiting to have complex surgeries done for their congenital

heart diseases, and even more infants are born every day with complex congenital heart illnesses. There is a great need for surgeons and support staff that can do complex surgeries with good recovery (Philips, 2012). This may explain the relatively high mean age in the current study, the absence of neonates, and the very low number of infants. An important observation in the study was that the level of the 24-hour troponin measurements showed a decrement from that of the 4-hour troponin measurement in all of the cases except one. (Su et al., 2019) also found the same result; the troponin T tends to decrease gradually from the 4-hour and on after the operation.

Despite the fact that nearly one-third of the patients in this study were in the preschool age group ($\geq$ 3 - < 6 years), the hs-cTnT level was significantly higher in children under the age of three. Similarly, (Malhotra, et al., 2013) observed that, despite there were no significant differences detected in perioperative variables (CPB, ACC durations, and CPB T°), higher levels of cTnT were found in younger children than in older ones. In addition to that, (Mildh, et al., 2006) also found that significantly high troponin T was measured in the first 24 hours after operation in infants in comparison to children (2.18 ng/ml versus 0.53 ng/ml). Even though in our study an obvious relationship was seen in children less than 3 years with cTnT, a larger sample size, including more infants, is required for more confirmation. This may be explained on the basis that infant's myocardium is more sensitive to injury and in turn releases more cTnT than in older children or adults, even though the infant myocardium can recover and return to contract normally after the injury (Malhotra, et al., 2013; Mildh, et al., 2006).

In a comparison between the medians of troponin in our study and another big study, it was found that our troponin levels were a little bit lower than those in their study except for ASD repair (Mildh, et al., 2006). This could be explained by the fact that our study operations were done at an older age than theirs, and also that they included more complex or risky surgeries that recently couldn't be done in the center. Regarding ASD, this may be due to the fact that we involved not only isolated ASD in the group but associated lesions also.

The relation between troponin levels and the type of surgery showed statistically higher levels in TOF cases, and about 50% of TOF surgeries had troponin levels between 2 and 4 ng/ml. It is stated that high troponin is associated with complex congenital heart surgery (Su et al., 2019; Wada et al., 2018). Moderately positive, statistically significant correlations for both 4- and 24-hour troponin levels were detected with CPB, ACC, and operation durations. In a similar way, those parameters strongly correlate with and can affect the troponin level on the first postoperative day (Wada et al., 2018). A moderately negative, statistically significant correlation was found between troponin 24-hour levels and the lowest temperature reached during the operation, similar to what was found in a study by (Cosgrave et al., 2006). Meanwhile, a weak one was found between troponin 4-hour levels and the lowest temperature. In a study, they found no difference in respect to heart muscle injury and ischemia between hypothermic and normothermic open-heart surgery in children (Poncelet et al., 2011). A weakly positive, statistically significant correlation was found with inotropic support duration, unlike a study (Wada et al., 2018) which found a moderate positive correlation.

Our study revealed that high troponin levels are associated with prolonged or longer-than-usual periods of stay in both the ICU and hospital, especially with the early measurements. (Boroński et al., 2022) also found that troponin T concentration is a beneficial tool to predict the postoperative status, ICU duration, and duration of hospital stay.

Our data revealed a significant relationship between high troponin levels and short-term complications. Similarly, (Mildh et al., 2006) reported that high troponin can predict postoperative outcome and complications and, in a study (Su et al., 2019), it is said that troponin carries important prognostic value for both morbidity and mortality in infants. In line with our findings, (Bottio et al., 2006) reported that outcome during a hospital stay can be predicted by the measurement of troponin I.

In contrast to our study, a study reported that high troponin levels do not necessarily predict death or severe cardiovascular events after CPB in young patients (Murni et al., 2019). In contrast to adults, in the pediatric groups, high troponin levels are not necessarily followed by serious complications (Malhotra, et al., 2013).

Nevertheless, some authors like (Momeni et al., 2017) did not find any relation between cTnT level and death after cardiac surgery and stated that cTnT is not routinely recommended for monitoring patients.

In the current study, only one child died in the ICU after surgery and his troponin level was too high (the case was complicated by renal failure). On the other hand, a female patient survived and her troponin level was even higher.

CONCLUSION

Higher troponin T levels were observed in children under 3 years of age compared to other age groups. The results also suggest that troponin T may serve as a marker that correlates well with the CPB, ACC, and operation durations; not only with these but also with the type of the surgery. The high troponin level early after ICU admission is also significantly associated with prolonged or more-than-usual ICU and hospital stays. Additionally, the complications may be predicted by early troponin measurements. These findings may call for earlier measurements

RECOMMENDATIONS

• To include more patients from this center, or even other cardiac centers in Sulaymaniyah and Duhok cities thus will ensure more sample size and more infant age groups in the study. By doing this, the relation of the troponin measurements with death can be studied with more confidence.
• Expand the follow-up of the patient after they leave the hospital may be for months to assess the relationship with long-term complications.

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