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EVALUATING TROPONIN I FOR MONITORING CARDIAC HEALTH IN CHILDREN WITH BETA-THALASSEMIA MAJOR: INSIGHTS FROM PAKISTAN

Dr.Huma Waqar[1] , Dr.Noor un Nisa[2] , Dr.Falak Abro[3], Dr.Seema Aftab[4], Taimoor Malik[5]

[1]ChildLife foundation, Karachi, Pakistan
[2,3,4] Paediatrics Department, Dow University Hospital, DUHS, Karachi, Pakistan
[5]School of Public Health, DUHS, Karachi, Pakistan

ABSTRACT

Cardiac injuries continue to be a primary source of morbidity and mortality in children with MBT, mainly due to iron overload. Cardiac biomarkers, such as Troponin I (Trop I) have appeared as encouraging procedures to identify heart issues at initial stages. This study aimed at addressing key demographic and clinical factors including the role of age, gender and iron chelation therapy in determining cardiac health outcomes in children with MBT, providing insights to conduct focused intervention and enhance patient care.This was a cross-sectional study included 205 children identified with MBT aged between 1-5 years. Patients were categorized into distinct groups that is positive or negative based on their Troponin I levels. Data related to age, gender, residence status (urban/rural), and iron chelation therapy was gathered and analysed by employing chi-square tests. Statistical significance was set at $P < .05$.Out of the total 205 patients, positive Trop I levels were observed in 31 (15.1%) of the patients. Patients not undergoing chelation therapy had significantly higher levels of elevated Troponin I compared to those receiving chelation therapy ($p < 0.001$). 27.2% of the rural participants had raised Troponin I levels while only 5.3% of urban participants had positive levels ($p = 0.002$). Children older then 10 years exhibited an elevated frequency of Troponin I levels ($p = 0.034$).The findings of this study underscore the preventive role of iron chelation therapy in mitigating cardiac complications and underline the elevated cardiac risk in rural residents along with elder children with MBT. This is consistent with evidence pointing that oxidative stress and myocardial injuries grow with age due to iron deposition in MBT patients, specifically in the absence of chelation therapy.Increased age, residing in rural settings and inadequate chelation therapy were correlated with a elevated frequency Troponin I levels in children having MBT. Routine surveillance of Trop I levels in patients with risk factors of cardiac complexities may lead to timely detection and handling of cardiac involvement, eventually enhancing outcomes for MBT patients.

Keywords: *Troponin I, Major beta thalassemia, chelation therapy, reactive oxygen species, echocardiography, MRI Cardiac biomarkers, Cardiomyopathy.*

INTRODUCTION

Thalassemia is a group of congenital blood ailment in which the formation of haemoglobin is decreased. Hemoglobin mobilizes red blood cells to carry oxygen all over the body and its deficiency results in anemia. Major beta thalassemia (MBT) is the most intense form of thalassemia which arises if both parents carry a deficient beta-globin gene, leading to minimal or no formation of beta-globin chains. This gives rise to

severe anemia, necessitating lifetime blood transfusions to prolong life (Musallam et al., 2021; Mettananda et al., 2021; Taher et al., 2022; Cohen et al. 2018).

MBT is a serious community health problem in countries located inside the "thalassemia belt" covering India, Pakistan and Mediterranean regions. About 1.5% of the world population carries the beta-thalassemia gene. In context of Pakistan, this strain is particularly notable with 6% of the population classified as carriers and an approximately 5,000 infants born per year with the condition (Ferraresi et al., 2023; Yusoff et al., 2023; Ansari et al., 2022). Over the time, attempts for management of MBT have progressed significantly including advancement in blood transfusions and the implementation of iron chelation therapies. These procedures have considerably increased the life expectancy and wellbeing of patients (Njeim et al., 2024; Tie et al., 2022; Saadatifar et al., 2021)

Unfortunately, these life-saving therapies are accompanied by certain complexities. The utmost persistent hurdle is iron overload that which takes place as a consequences of frequent blood transfusions. Surplus iron gathers in various tissues including the liver, endocrine glands, and most critically, the heart. This iron accumulation results in continuous organ injury, escalating occurrence of disorders and deaths. Among these complexities, problems related to heart, inclusive of cardiomyopathy, arrhythmias, and heart failure remains the dominant causes of death in thalassemia patients leading to nearly 70% of casualties (Shahramian et al., 2021; Galanello & Origa, 2020).

The impairment to the heart triggered by iron overload is silent and advances with the time. Iron that infiltrates heart cells produces destructive substances known as reactive oxygen species (ROS), which disrupt the heart muscle by damaging its capability to pump blood, and results in cell death (Khaled et al., 2020; Yassin et al., 2020). This state frequently remains undiscovered till considerable impairment causing indications like breathlessness and tiredness or decreased functioning of heart. Therefore, immediate diagnosis is decisive for fixing aftermath and avoiding serious issues (Shah et al., 2024; Kurban et al., 2023; Saliba et al., 2023)

Traditional procedures for detecting heart complications like echocardiography, are extensively employed as they are attainable and inexpensive. But echocardiography merely identifies irregularities including decreased ejection fraction when significant impairment has takes place. An alternative commonly established technique cardiac MRI with T2 imaging* is very responsive which can diagnose iron overload early. However, cardiac MRI is laborious and difficult to access in resource poor settings such as Pakistan (Jewad et al.,2024; Taher et al., 2022; Mettananda et al., 2021). Therefore, these restrictions demand an urgency for uncomplicated, non-surgical and economical procedures for timely cardiac evaluation.

Cardiac biomarkers, such as Troponin I (Trop I), have appeared as encouraging procedures to identify heart issues at initial stages. Trop I is a protein deployed inside the blood stream when heart muscle cells are injured. It is extensively accepted for its accuracy in confirming cardiac injury, specially in acute situation such as heart attacks. Current literature advocate that Trop I is also efficient in chronic illness like thalassemia. It can detect heart damage caused by iron overload even before structural abnormalities appear on imaging (Vaswani et al., 2020). In contrast to Serum ferritin that assess the total iron load in the body but it is affected by inflammation. On the other hand, Trop I directly reflects harm to heart tissue, indicating a more definite measure of cardiac injury (Shahramian et al., 2021; Koohi., 2021; Shizukuda et al., 2019).

Irrespective the capability of Trop I as a biomarker for cardiac problems in thalassemia, literature on its usefulness still restricted, specially in country such as Pakistan. Challenges such as inadequate access to advanced healthcare, low utilization of chelation therapy, and delayed diagnoses increase the impact of cardiac complications in these regions Exploring the role of Trop I in detecting early cardiac damage could lead to affordable and timely interventions. (Soliman et al., 2023; Ansari et al., 2022; Ansah et al., 2022).

This study aimed at addressing the limited research on the usage/utilization of Trop I as an indicator of cardiac problems in MBT, specifically in limited resources settings such as Pakistan. The primary objectives were to ascertain the frequency of elevated Trop I levels in MBT patients with cardiomyopathy and to investigate its relationship with demographic and clinical factors, like as age, gender, transfusion burden, and chelation therapy compliance. This study attempts at supporting the emergence of low cost and feasible approaches for the timely discovery and handling of cardiac complications. The study is expected to be

valuable for settings with reduced exposure to latest detection procedures where early intervention is vital for lowering thalassemia-related deaths (Zhou et al., 2024; Mutaz et al., 2019)

Literature Review

Cardiac complexities are the dominant source of illness and deaths in patients suffering from MBT, forced mainly by iron overload arising due to frequent blood transfusions. Surplus iron in the myocardium produce ROS that harm cellular structures encompassing ion channels and mitochondria causing apoptosis, fibrosis, and consequent cardiomyopathy (Taher et al., 2022). Myocardial iron surplus is a continuous status commonly remains silent for long time finally leading to obvious indication such as arrhythmias, heart failure, or limited cardiomyopathy (Mettananda et al., 2021).

The gathering of iron in myocardial tissue develops by non-transferrin-bound iron (NTBI) penetrating cardiomyocytes through L-type calcium channels. Once inside, iron facilitate the development of free radicals, giving rise to oxidative injury and damaging contractile proteins and ion transport process (Soliman et al., 2023). Studies have revealed that myocardial iron accumulation is unrelated to systemic iron levels as few patients demonstrating notable cardiac involvement even with routine serum ferritin (Galanello & Origa, 2020).

Diagnostic Modalities for Cardiac Involvement

Cardiac issues in thalassemia usually advances quietly, necessitating responsive diagnostic procedures. Echocardiography reveal harm only in later phase whereas cardiac MRI (CMR) with T2* imaging is more reliable to assess myocardial excess iron. But, its unaffordability and inadequate access in a setting with low resources such as Pakistan underscore the call for basic and more inexpensive diagnostic procedures (Lan et al., 2024; Aessopos et al., 2020; Taher et al., 2022; Mettananda et al., 2021).

Role of Troponin I as a Cardiac Biomarker

Troponin I (Trop I) is a responsive and accurate biomarker for diagnosing cardiac injury, extensively investigated in acute coronary syndromes. Its contribution in chronic situation such as thalassemia is acquiring consideration because of its capability to detect myocardial injury prior to the onset of structural injury (Vaswani et al., 2020). Latest literature has revealed raised Trop I levels in MBT patients with myocardial iron overload, even in the absence of echocardiographic irregularities. Contrary to ferritin that estimate total iron and is influence by inflammation, Trop I precisely indicate heart injury, demonstrating its reliability for detecting cardiomyopathy at initial stages (Shahramian et al., 2021; Deraz et al., 2021; Khaled et al., 2020).

Emerging Trends in Managing Cardiac Complications

Current development in the handling of thalassemia related cardiac problems centred on integration of precautionary and medicinal methods. Studies underscore the necessity for timely screening that incorporate biomarkers like Trop I with imaging modalities for extensive cardiac evaluation (Galanello & Origa, 2020). Moreover, novelty in iron chelation procedure, like mixture treatment of deferoxamine and deferiprone, have demonstrate potential in increasing myocardial iron clearance and enhancing cardiac outcomes (Taher et al., 2022; Eghbali et al., 2020).

The contribution of genetic predisposition in the variation of cardiac complexities is also growing. Particular genetic polymorphisms like those influencing antioxidant capability have been related to elevated vulnerability to iron toxicity and cardiac ailment (Shahramian et al., 2021; Aessopos et al., 2020).

Iron Chelation Therapy and Cardiac Outcomes

Iron chelation therapy is crucial for handling surplus iron in MBT patients and mitigating cardiac problems. Chelators such as deferoxamine and deferasirox eliminate excessive iron. But their success depends on patient compliance, which is usually insufficient in low resource settings (Ansari et al., 2022; Taher et al., 2022). Despite adequate chelation, cardiac issues in few patients intensifies because of factors such as

oxidative stress. Periodic monitoring utilizing procedures such as echocardiography and Trop I, is essential for extensive cardiac management (Yadav et al., 2022; Mettananda et al., 2021).

Regional Gaps in Research and Clinical Practice

In subcontinent inclusive of Pakistan, poor reach to modern diagnostics technique such as Cardiac Magnetic Resonance Imaging (CMR) and inadequate compliance to chelation therapy escalate cardiac complexities in thalassemia patients (Ansari et al., 2022). Studies from the region are limited, emphasize the necessity for extensive studies to manage the increasing burden of cardiac difficulties in thalassemia patients. This study evaluates Trop I as a cost efficient, non surgical marker for cardiomyopathy in MBT patients. It aims at guiding earlier diagnosis and handling strategies through establishing baseline data on raised Trop I levels.

Material And Methods

Study Design and Setting: This was a cross-sectional study conducted at the Department of Paediatrics, Dr. Ruth K.M. Pfau Civil Hospital Karachi, lasted for six months from January 31, 2020, to July 30, 2020.

Sample Size: Sample size was estimated using OpenEpi version 3.01. Using frequency of raised Trop I in Thalassemic patients as 16% (Vaswani et al., 2017) with confidence interval of 95% and absolute precision of 5% yields the minimum sample size of 207 patients.

Sampling Technique: Non probability convenience sampling was used to recruit participants.

Inclusion criteria

- Patients Detected with MBT via hemoglobin electrophoresis.
- Presence of cardiomyopathy confirmed by echocardiography.
- Both genders.
- 1 - 15 years of age

Exclusion criteria

- Patients whose attendants refuse to provide consent
- Patients who are critically ill and admitted in intensive care.
- Patients with congenital cardiac anomalies identified on echocardiography.

Data collection procedure: This study was conducted after obtaining approval from College of Physicians and Surgeons Pakistan. Patients visiting the Department of Paediatrics, Dr Ruth K.M Pfau Civil Hospital Karachi (CHK), fulfilling the inclusion criteria were enrolled in the study. Informed consent was obtained from all the parents/caretakers. Troponin I levels were measured by using Chemiluminescene Microparticle Imuno-assay (CMIA method) from Central Lab, CHK.

Basic demographic information, including gender, age, residence, age at diagnosis, chelation status, and Troponin I levels, was recorded on a pre-designed proforma. Bias and confounding variables were minimized by strictly adhering to the inclusion and exclusion criteria. All patients received supportive and definitive management according to institutional protocols.

Data Analysis Procedure

Data were analyzed using SPSS version 26. Frequencies and percentages were calculated for qualitative variables, such as gender, chelation status, and Trop I levels. Mean and standard deviation (SD) were computed for quantitative variables, including age, age at diagnosis, and the number of blood transfusions. To determine associations between positive Troponin I levels and categorical variables (e.g., gender, chelation therapy, residence), the chi-square test was used. Independent samples t-tests were performed to compare mean differences where applicable. A p-value ≤ 0.05 was considered statistically significant for all analyses.

Results

Demographic and Clinical Characteristics of Participants

The mean age of the patients was 10.11 ±2.91 years with 112 (54.6%) patients with ≤10 years of age and 93 (45.4%) patients with >10 years of age. Gender distribution was comparable with 105 (51.2%) males and 100 (48.8%) females. Urban residents made up 113 (55.1%) of the cohort, while 92 (44.9%) were from rural areas. Patients received an average of 4.99 ± 1.85 transfusions, with 126 (61.5%) underwent ≤5 transfusions while 79 (38.5%) undergone >5 transfusions. Among the participants, Iron chelation therapy was found in 112 (54.6%) patients (Table-01).

Troponin I Levels

Out of the total 205 patients, positive Trop I levels were observed in 31 (15.1%) of the patients (Figure-1). Among males (n = 105), 24 (22.9%) tested positive, whereas among females (n = 93), only 7 (7%) had elevated Troponin I levels (p-value 0.002) (Table-02). The Table-03 compares the prevalence of positive Troponin I levels between patients aged ≤10 years and those >10 years. Among the 112 patients aged ≤10 years, 9 (8%) had positive Troponin I levels, while 103 (92%) had negative levels. Similarly, among the 93 patients aged >10 years, 22 (23.7%) had positive Troponin I levels, and 71 (76.3%) had negative levels. The difference in positive Troponin I levels between the two age groups was statistically significant (p = 0.034).

Among patients with five or fewer transfusions, 19 (15.1%) had positive Troponin I levels, while 12 (15.2%) of those with more than five transfusions also tested positive (p=0.783, Table-04). The analysis revealed a significant association among residence status and positive Troponin I levels (p = 0.002) as 27.2% of the rural participants had raised Troponin I levels while only 5.3% of urban participants had positive levels (Table-05).

Patients not undergoing chelation therapy had significantly higher levels of raised Troponin I in oppose to those receiving chelation therapy (p < 0.001).Only 9(8%) of the children getting chelation therapy exhibited positive Troponin I levels, whereas 103 (92%) showed negative levels. On contrary, 22(23.7%) of children who did not receive iron chelation therapy demonstrated positive Troponin I levels, while 71(76.3%) exhibiting negative levels (Table-06).

Discussion:

Beta-Thalassemia Major (BTM) is a severe form of inherited anemia that poses significant health challenges, particularly in regions with high carrier rates such as Pakistan. The findings of this study highlight the vital role of Troponin I (Trop I) as an encouraging biomarker for timely identification of cardiac problems in children with BTM. With 15.1% of participants demonstrating elevated Troponin I levels, the current study contributing to the existing body of knowledge and highlight the significance of elevated awareness and dedicated surveillance of cardiac health in this vulnerable population. Raised troponin levels have been linked with accumulated deaths in different setting, indicating the need of timely diagnosis and handling of cardiac complexities. (Mediani et al., 2024; Shahramian et al., 2021; Vaswani et al., 2020; Hayek et al., 2020; Blankenberg et al., 2016).

Troponin I is a protein released when cardiac muscle cells are damaged, resulting in a valued marker for determining myocardial injury. Its validated effectiveness in acute coronary syndromes is firmly established. However, its utility in chronic situation such as thalassemia is also acquiring attention (Zhou et al., 2024; Kadhim et al., 2024; Ghafoor et al., 2023)

A study conducted by by Vaswani et al. (2020), have revealed that myocardial damage due to iron overload can be indicated by raised Trop I levels. The capability of Trop I to identify cardiac trauma prior to structural alterations are evident on imaging modalities underscoring its ability to serve as a standard tool in managing BTM. In our study, raised Trop I levels were notably linked with non-adherence to iron chelation therapy, aligned with the findings of Taher et al. (2022). These results underline the key role of compliance to treatment routines in alleviating iron overload and decreasing the risk of cardiac injuries (Ansah et al. 2023; Koohi et al. 2019; Kadhim et al., 2024). The gender differences noted in raised Trop I levels, with

male children exhibiting higher prevalence as compared to female children, presents central considerations concerning the biological and social aspects that can lead to these differences. (Khaled et al., 2020)

The findings exhibit a significantly inflated occurrence of raised Troponin I levels in children aged >10 years (23.7%) in contrast to those aged ≤10 years (23.7 vs. 8%, p = 0.034), indicating that elder children can encounter extensive cardiac stress, possibly due to persistent iron overload and its mounting cardiotoxic effects. This is consistent with studies demonstrating that despite chelation therapy, oxidative stress and myocardial injuries grow with age due to iron deposition in BTM patients (Karakaş et al., 2023; Aessopos et al., 2021). These findings emphasize timely and adequate chelation therapy to reduce long term cardiac dilemma along with detailed cardiac management in elder children to handle possible risks.

The study exhibited a significant difference in positive Troponin I levels among rural and urban patients (p = 0.002). Rural residents showed a substantially higher frequency (27.2%) contrast to urban participants (5.3%) These results underline likely inequalities in health care access and cardiac management among rural and urban populations. Insufficient health care facilities, delayed identification and lack of routine cardiac assessments can lead to this discrepancy in rural areas. Previously, high proportions of cardiac problems in rural settings have been linked to limited health care facilities and inadequate access to focused care (Ahmed et al., 2022; Khattab et al., 2020). Moreover, lower prevalence of elevated Troponin I levels in urban setting may be associated to better disease handling and access to extensive health care infrastructure. Managing these differences through focused mediation and enhancing access to specific care in rural settings is vital for decreasing the burden of cardiac complications in children with beta-thalassemia major (Kadhim et al., 2024; Pepe et al., 2022).

In the current study positive troponin, I levels were substantially lesser among patients who underwent iron chelation therapy in oppose to those who did not (6.3% vs. 25.8%, p < 0.001). These figures highlight the preventive role of chelation therapy in reducing cardiac complications related to thalassemia. Adequate chelation therapy plays a crucial role in handling iron overload which is essential element enhancing cardiac abnormalities in patients with MBT. Earlier findings have also illustrated the cardioprotective influence of chelation therapy, relating enhanced survival rates to improved iron regulation (Zhang et al., 2024; Ali et al., 2021). This underscores the significance of timely initiation and compliance to chelation therapy to counter myocardial injuries and boost long term outcomes.

Conclusion

In conclusion, our study indicated the adequacy of Trop I as a biomarker for cardiac damage in MBT patients. Routine surveillance of Trop I levels in patients with risk factors of cardiac complexities may lead to timely detection and handling of cardiac involvement, eventually enhancing outcomes for MBT patients. Future studies are essential to confirm our findings and to explore the potential of Trop I as a biomarker for cardiac complications in MBT patients.

Based on our study, raised Trop I levels were detected in a considerable segment of beta-thalassemia major (BTM) patients along with noticeable differences across demographic and clinical aspects including residence, age at diagnosis, and gender. These results advocate a possible relationship among Trop I levels and the burden of cardiac complexities in this study group. While Trop I exhibits promise as a biomarker for detecting patients at risk, future studies are desirable to confirm its clinical utilization, specifically in the situation of iron overload and chelation therapy.

Future Directions

To further establish the utility of Trop I as a biomarker for cardiac injuries in MBT patients, researchers must concentrate on conducting longitudinal studies that evaluate the predictive value of Trop I levels in connection to extended cardiac outcomes. These studies should incorporate diversified populations to warrant general applicability of findings. Moreover, investigating the integration of Trop I surveillance with curent diagnostic modalities like echocardiography and cardiac MRI may improve the overall evaluation of cardiac health in thalassemic patients.

Additionally, future studies into the underlying mechanisms of cardiac damage in MBT patients, specifically concerning the role of oxidative stress and genetic predisposition is warranted. Comprehending these mechanisms may facilitate to develop targeted treatments aimed at reducing cardiac damages.

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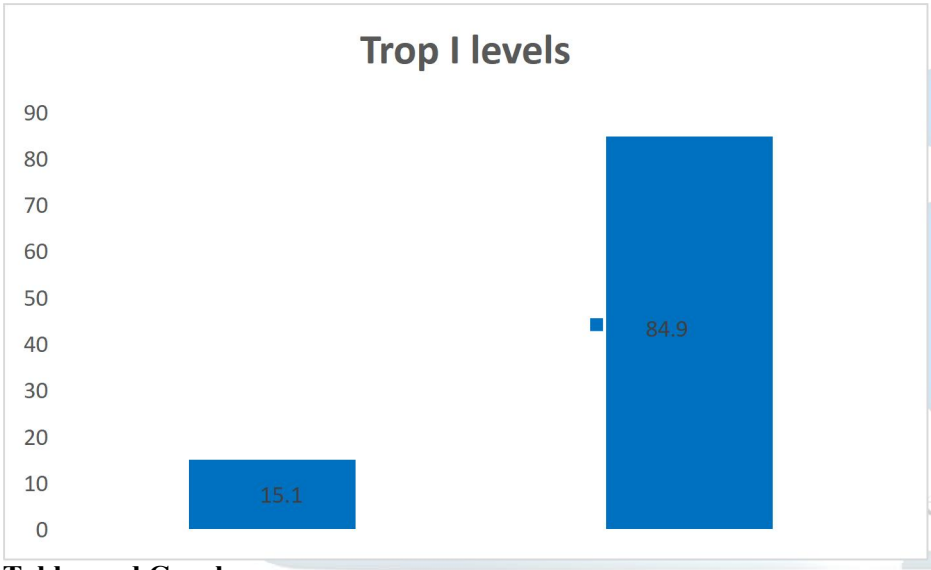

Tables and Graphs

Figure-01: Trop I levels of Participants

Table-01: Demographic and Clinical Characteristics of Participants

Variable		Frequency	Percentage
Age (Years)	10.11 ±2.91		
Age Group			
≤10		112	54.6
>10		93	45.4
Gender			
Male		105	51.2
Female		100	48.8
Residence			
Urban		113	55.1
Rural		92	44.9

Number of transfusions 4.99 ± 1.85		
≤5	126	61.5
>5	79	38.5

Table-02: Relationship between positive troponin I levels and Gender (n=205)

Gender	Positive Troponin I Level		Total	p-value
	Yes	No		
Male	24 (22.9)	81 (77.1)	105 (100)	
Female	7 (7)	93 (93)	93 (100)	0.002
Total	31 (15.1)	174 (84.9)	205 (100)	

Table-03: Relationship between positive troponin I levels and Age Group (n=205)

Age Group	Positive Troponin I Level		Total	p-value
	Yes	No		
≤10	9 (8)	103 (92)	112 (100)	
>10	22 (23.7)	71 (76.3)	93 (100)	0.034
Total	31 (15.1)	174 (84.9)	205 (100)	

Table-04: Relationship between positive troponin I levels and Number of Transfusion (n=205)

Number of Transfusion	Positive Troponin I Level		Total	p-value
	Yes	No		
≤5	19(15.1)	92 (84.9)	126 (100)	
>5	12 (15.2)	67 (84.8)	79 (100)	0.783
Total	31 (15.1)	174 (84.9)	205 (100)	

Table-05: Relationship between positive troponin I levels and Residence (n=205)

Residence	Positive Troponin I Level		Total	p-value
	Yes	No		
Rural	25(27.2)	67(72.8)	92 (100)	
Urban	6 (5.3)	107 (94.7)	113(100)	0.002
Total	31 (15.1)	174 (84.9)	205 (100)	

Table-06: Relationship between positive troponin I levels and Chelation Therapy (n=205)

Iron chelation therapy	Positive Troponin I Level		Total	p-value
	Yes	No		
Yes	9 (8)	103 (92)	112 (100)	
No	22 (23.7)	71 (76.3)	93 (100)	<0.001
Total	31 (15.1)	174 (84.9)	205 (100)	