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Evaluation of the Relationship between Serum Troponin Levels and the Incidence of Cardiac Complications in Patients with Unstable Angina and Myocardial Infarction

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Abstract

Background and Aim: Many people die annually due to nosocomial complications caused by heart diseases around the world. Several diagnostic methods have been proposed to determine the severity and prognosis of these patients, which can estimate the rate of myocardial involvement and the severity of nosocomial complications in these patients. Among cardiac markers, troponin is more sensitive and specific than other markers and can even shows mild necrosis and mild myocardial muscle injuries. The present study aimed to evaluate the statistical indicators related to the qualitative serum troponin levels, obtained from the follow-up of cardiac complications in patients with a diagnosis of unstable angina and acute myocardial infarction.

Materials and Methods: In this prospective study, 400 patients with unstable angina and acute myocardial infarction evaluated for serum troponin levels, mortality and cardiac and non-cardiac complications during recent hospitalization. Required data were extracted from clinical findings, electrocardiogram, echocardiography and tests, especially quantitative serum troponin levels, which was measured serially. Also, complications of the disease during hospitalization and patients' outcome were recorded. Then, their complications in groups with higher troponin than normal troponin range were compared and statistically analyzed.

Results: Out of 400 patients, 41% were diagnosed with unstable angina and 59% with acute myocardial infarction. The mortality rate during hospitalization was 13 cases (3.25%). No statistically significant relationship was found between patients' age and quantitative troponin levels (p = 0.365). There was a significant inverse relationship between serum troponin and percentage of Ejection Fraction (r= -0.407, p <0.0001). Comparison of the results related to troponin levels in the two groups of dead and alive groups showed that the levels of troponin are higher in the dead group than in the alive group. Also, there was a direct and significant relationship between increased troponin levels and mortality and cardiac complications (p <0.0001).

Conclusion: According to the results of the present study, 236 hospitalized patients had troponin level higher than normal troponin range. Mortality rate during hospitalization was 13 cases (3.25%). All dead patients had higher troponin levels than normal level and even 69.23% of dead cases showed troponin levels above 50 (Ng/ml) Nano gram per milliliter. Hence, based on the results of this study, serum troponin as a biomarker can detect myocardial damages and it was found as a suitable indicator for predicting mortality in these patients.

Keywords: Cardiac Troponin, Unstable Angina, Acute Myocardial Infarction, Biomarkers, Mortality, Ejection Fraction

Introduction:

Heart disease, especially myocardial infarction (MI), and its complications are common causes of mortality worldwide (1). Despite major diagnostic and therapeutic advances, high mortality rates (up to 30%) in patients with MI still indicate adverse effects on life and exorbitant diagnostic and therapeutic costs for patients and the community (2). These concerns have prompted researchers to focus on the prevention of complications of MI, while taking into account advances and timely treatment measures. One way to prevent this is to identify and control people at risk. In the case of MI, these factors include hypertension, diabetes, and hyperlipidemia. Cardiac troponin measurements are used to detect myocardial injury and support the diagnosis of acute myocardial infarction. Studies show that high levels of cardiac specific troponin-I before MI is one of the prognostic signs (3-5). In addition to troponin, other cardiac biomarkers such as myoglobin and CPK-MB are used clinically to diagnose ischemia and myocardial necrosis. These biomarkers have greatly helped in the early diagnosis and treatment of heart patients (6). There are three types of troponin (I, T and C). Cardiac troponin I

(cTnI) and T (cTnT) are protein components that play a major role in cardiac muscle contractions. cTnI and cTnT are specific biomarkers for the diagnosis of necrosis and myocardial damage. Both troponin I and T are elevated in heart injury (7, 8). The results of other studies suggest that elevated troponin T and troponin I as specific biomarkers are associated with an increase in mortality. In fact, troponin is a predictor factor of mortality rate in patients with cardiovascular disease (9). Elevated troponin concentrations are not only seen in patients with acute coronary syndrome and may also increase in other clinical conditions and in other acute and chronic diseases (10). On the other hand, the evaluation of patients' clinical symptoms along with cardiac biomarker tests should be considered. Even a low level increase in cardiac troponin T or I in patients with acute coronary syndrome should be carefully evaluated by sequential testing. Also, patient with higher troponin levels benefit more from early treatment (11). Assessment of cardiac biomarkers, including troponin, has also been helpful in classifying coronary artery disease. Cardiac biomarkers can detect non-ST-segment elevation myocardial infarction (NSTEMI) in heart patients without electrocardiogram changes and differentiates NSTEMI from unstable angina and in this classification, more patients are divided into MI category (12). Serial measurement of serum troponin instead of other biomarkers is an independent prognostic factor for morbidity and mortality in coronary artery disease but as mentioned, other background disease that increase troponin level such as pulmonary thromboembolism, renal failure and sepsis should be considered (13). However, increased troponin level in non-cardiac diseases, as a prognostic factor, indicates a poor prognosis and a higher risk of mortality (14). Various measurement methods for evaluation of cardiac biomarkers, including the bedside method, can be beneficial to making decisions for patient management and reducing duration of hospitalization (15).

Given the importance of prognosis of cardiac patients and complication of their hospitalization and its relationship with cardiac biomarkers including troponin levels, the present study was conducted to evaluate the complication of patients admitted to hospitals of Shahid Beheshti University of Medical Sciences and its relationship with troponin levels. In the present study, statistical indices related to serial troponin level tests were statistically analyzed. Identifying the predictors of survival in heart patients and identifying acute phase biomarkers in these patients plays a major role in effective treatment and reduction of mortality in these patients. Also, by finding additional and more comprehensive information about cardiac bio-enzymes, a new diagnostic method can be achieved with more specificity and sensitivity than conventional methods. Also, by determining the effect of troponin levels in diagnosing heart damages and predicting the complication of hospitalization of patients with unstable angina and acute myocardial infarction, more effective treatment can be planned to improve hospital complications in these patients**.**

Methods

The present study was a non-interventional and prospective study. The statistical population of the present study included patients with acute myocardial infarction and unstable angina referred to Shahid Beheshti University hospitals, including Shahid Modarres Heart Specialized Center and Imam Hossein Hospital. Data were collected through a checklist and a questionnaire. The present study was a non-interventional study conducted on 400 patients referred to the emergency, and CCU units of Shahid Beheshti University hospitals with a diagnosis of unstable angina and acute myocardial infarction. The data required for this study were collected from hospitalized patients over a period of twelve months from 2019 to 2020. In the present study, the complications of patients during recent hospitalization were examined and the highest levels of troponin enzyme were measured and information such as demographic characteristics of patients was extracted. Among these people, the results of venous blood samples, troponin levels and other hospital information were collected. In this sampling of patients, the troponin levels were measured using a quantitative method and in the form of serial tests for each patient.

The serum troponin levels were measured by intravenous blood sampling and serial tests for each patient and the highest level was considered for each patient during recent hospitalization and serum troponin level higher than 0.10 Ng/ml was reported higher than normal range. Then, the data were analyzed using statistical analysis methods. It should be noted that the level of significance for the tests used in this study was considered at 0.05 and values less than 0.05 were considered statistically significant**.**

Ethical considerations:
The present study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (Ethical Code: IR.SBMU.MSP.REC.1398.824). The researchers were committed to adhere to ethical principles during the study, and without any intervention or manipulation outside the treatment process, the complication of patients' hospitalization was investigated. Also, there was no change in the process of diagnosis and treatment of patients and no additional costs were imposed on patients of the study. Patients' participated in this study voluntarily and after obtaining informed consent and it did not affect patients' legal rights. Also, they were ensured that all the information received from them and even their names will remain confidential.

Inclusion and exclusion criteria
 Inclusion criteria included patients over 18 years of age who referred with symptoms such as shortness of breath, chest pain, heart attack and other symptoms related to heart disease and were diagnosed with unstable angina and myocardial infarction. Other patients with other causes of increased troponin, including pulmonary embolism, sepsis, and renal failure, as well as patients with a diagnosis other than unstable angina and acute myocardial infarction were not included in the study. Those who did not have the mentioned symptoms were excluded from the study. Also, patients who suffered cardiac arrest or died before entering the emergency department were excluded from the study**.**
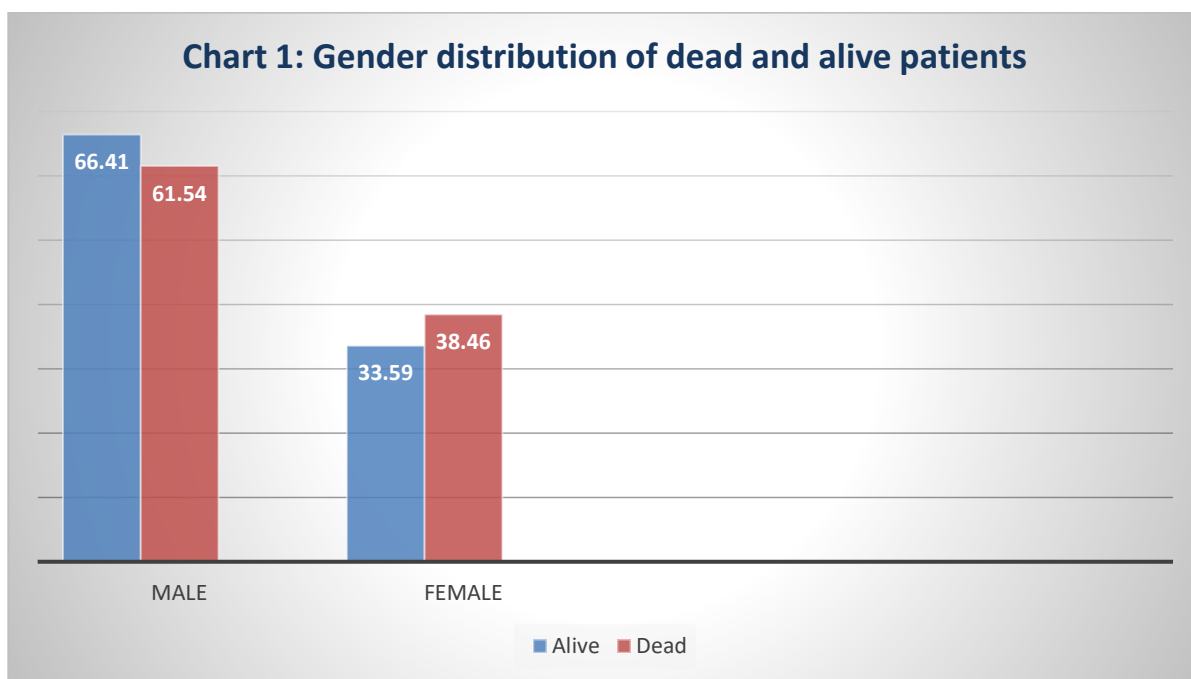
Results
Based on the results of the present study, 400 patients were eligible for the study, 40% of patients were smokers or substance abusers, 24.50% had hyperlipidemia, 53% of patients had hypertension and 34% were diabetic. Also, 265 (66.25%) of the patients in this study were male and 135 (33.75%) were female. Finally, 164 (41%) patients were diagnosed with unstable angina and 236 (59%) were diagnosed with myocardial infarction by a specialist physician. Among the patients with unstable angina, 21 patients (5.25%) showed a slight increase in troponin levels above normal during hospitalization. Finally, 13 (3.25%) cases of mortality were recorded and 83.25% of patients with stable vital signs were discharged alive from the hospital by diagnosis of treating physician. In addition, 52 people gave personal satisfaction and two people left the hospital without notice. The mean age of patients participating in this study was 62.81 years and the median age of these people was 57 years. Also, the oldest patient was 95 years old and the youngest one was 25 years old. Also, 50% of the people were less than 62.50 years old (Table 1).

Table 1: Statistical indices related to patient age

variable	Minimum	Maximum	Mean	Variance	Mode	Median	SD
Age (year)	25	95	62.81	170.10	57	62.50	13.04

Out of 387 patients survived, 257 people (66.41%) were male and 130 people (33.59%) were female. In contrast, out of 13 patients who died, 8 cases (61.54%) were male and 5 cases (38.46%) were female, so the highest of dead patients, like alive patients, were male (Chart 1).

Chart 1: Gender distribution of dead and alive patients

	Alive	Dead
MALE	66.41	61.54
FEMALE	33.59	38.46

■ Alive ■ Dead

The mean troponin of the whole study population was 17.40 Ng/ml and their median was 0.97 In other words, half of the troponin levels are less and the other half are more than 0.97, most people have a troponin level of 0.01 and this value is the lowest value reported for troponin levels, which is within the normal range based on the defined laboratory kit. Also, 59% of all subjects had a troponin level greater than 0.10. The minimum troponin level was 0.01 and the maximum troponin level in this study was 80 Ng/ml. Also, the mean troponin level was higher in dead patients (Table 2).

Table 2: Results of central indices and dispersion of troponin levels

variable	Minimum	Maximum	Mean	Variance	Mode	Median	SD
Troponin (Ng / ml)	0.01	80	17.40	710.26	0.01	0.97	26.65

Also, studies on the relationship between age and troponin levels showed that there is no statistically significant relationship between patients' age and troponin levels (p= 0.365). The results of correlation between age and troponin are shown in Table 3.

Table 3: Results of age and troponin correlation coefficient test

Test result	p-value	correlation coefficient
There is no statistically significant relationship between age and troponin.	0.365	-0.032

The mean troponin in the female population was 8 and the mean troponin in the male population was 21.88, indicating a higher mean level of troponin in the male population than female population. In the troponin

statistical data set in the male population, the most frequently repeated value of troponin was 80 Ng/ml, which was the highest value reported for troponin levels. Other results of troponin levels separately based on gender are shown in Tables 4 and 5.

Table 4: Results of troponin level statistical indices in females

Females	Minimum	Maximum	Mean	Variance	Mode	Median	SD
troponin	**0.01**	**80**	**8**	**301.13**	**0.01**	**0.04**	**17.35**

Table 5: Results of troponin level statistical indices in males

Males	Minimum	Maximum	Mean	Variance	Mode	Median	SD
troponin	0.01	80	**21.88**	**842**	**80**	**4.55**	**29**

Follow-up of patients during hospitalization finally showed all 13 cases of mortality in this study, had higher troponin levels than normal. Nine of the dead patients (69.23 %) had the serum troponin level above 50 Ng/ml. In the alive patients, in 78 patients (20.15%), troponin was above 50 Ng/ml, which indicates higher troponin levels in the dead group than in the alive group. The results of comparing the percentage of frequency of high troponin levels separately in the two dead and alive groups are shown in Chart 2**.**

Chart 2: Distribution of troponin levels above 50 ng/ml
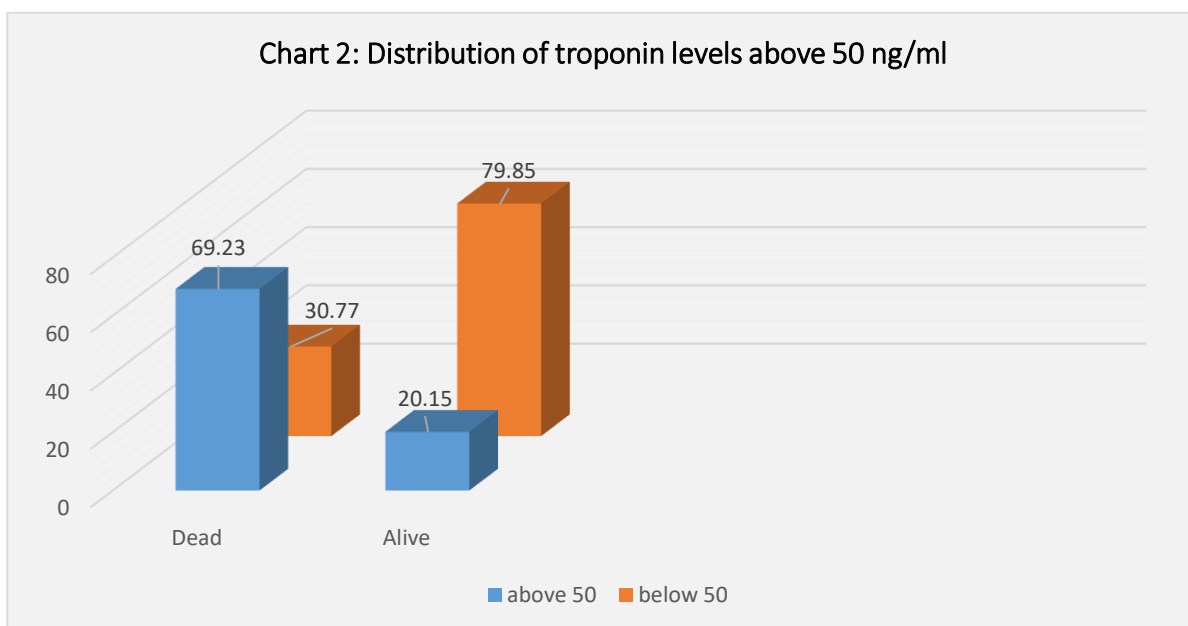
Out of 400 study patients, 57 patients (14.25%) suffered cardiac complications such as cardiogenic shock, cardiac arrest, pulmonary edema, etc., so that 4% of them suffered cardiac arrest and 3.50% of them suffered shock and hypotension and 85.75% of patients did not have any cardiac complications during hospitalization. Most of the complications in patients included cardiac arrest, shock, hypotension and pulmonary edema. Twenty four (6%)

cases had dangerous ventricular arrhythmias such as Ventricular Tachycardia and Ventricular Fibrillation during hospitalization and after myocardial infarction.

To evaluate the relationship between troponin and cardiac complications during hospitalization, a two-point correlation test was used (correlation coefficient= 0.237). The results of this test revealed a direct and significant relationship between troponin levels and cardiac complications during hospitalization ($p < 0.0001$). Also, to examine the relationship between troponin and the type of coronary artery involvement diagnosed in patients' angiography, Kruskal-Wallis nonparametric test was used Based on this test, no statistically significant relationship was found between troponin and the number of arteries involved in patients' angiography ($p = 0.076$).

Evaluation of the relationship between troponin and EF percentage

The mean EF (Ejection Fraction) percentage of these people was 44.57, so that most of these people had an EF of 55%. The lowest and highest EF values were reported at 10% and 60%, respectively, but half of these people had an EF of less than 50%. Spearman correlation coefficient test showed an inverse relationship between troponin and EF percentage among patients ($r = -0.407$, $p < 0.0001$). Due to the inverse relationship between troponin and EF percentage, calculated by echocardiography, the higher the troponin, the lower the EF percentage in these patients. In fact, as one parameter goes up, the other parameter decreases (Table 6).

Table 6: Results of Spearman correlation coefficient test

correlation coefficient	p-value	Type of relationship	Test result
-0.407	<0.0001	inverse	There is an inverse relationship between troponin and EF percentage among patients

Comparison of EF percentage in three groups of STEMI, NSTEMI and UA patients

Based on Table 7, it is concluded that the EF percentage is not the same among the three groups of patients STEMI (ST-Segment Elevation MI), NSTEMI (Non-STEMI) and UA (Unstable Angina) and the levels of this variable in these 3 groups of patients are significantly different since the significance of Kruskal-Wallis test is very small and less than 0.05. The mean values of EF percentage are presented for all three groups. According to the results of the table below, it the EF percentage in UA patients is higher than NSTEMI and STEMI patients, and EF percentage in NSTEMI patients is higher than STEMI patients (Table 8).

Table 7: Kruskal-Wallis test results

Test statistic	Degrees of freedom	p-value
72.26	2	<0.0001

8: Rank mean of EF percentage in patients

Disease type	Rank mean	The result of comparing the EF percentages in patients
UA	234.18	UA> NSTEMI > STEMI
NSTEMI	164.07	
STEMI	132	

Discussion

According to the results of the present study, troponin levels above 50 Ng/ml were compared in two dead and alive groups. In the dead group, 69.23% of patients had troponin levels above 50 Ng/ml. In the alive group, only 20.15% had very high levels of troponin. During hospitalization, 59% of patients reported higher troponin than normal range. Also, in 5.25% of patients, troponin levels during hospitalization exceeded the normal level. The mean level of troponin in the whole population was 17.40 Ng/ml and the median level of troponin is 0.97 Ng/ml.

The level of troponin that was repeated more often was 0.01, which was the same level of troponin that was repeated more often in the female population. However, higher levels of troponin were more common in the male population, and the mode of troponin in the male population was 80 Ng/ml. The mean age of patients participating in this study was 62.81 years. There was no statistically significant relationship between age and troponin level. The gender of most of dead patients, as in surviving patients, was male. The mean of troponin level in the male population was higher than female population (21.88 vs. 8).

The mean age of patients in our study was higher than the mean age reported in other studies such as Salehi et al. and Bashardoost et al. (16, 17). In terms of other demographic information such as gender, our results were in line with results of other studies such as Salehi and Shahsavari (16, 18). In our study, mean cardiac troponin concentration was higher than that reported in the study conducted by Bashardoost et al. (17). Our study was in line with previous studies such as Morinigo, Gonzalez-Del-Hoyo, Van der Linden, Welsh, and serum troponin levels were strongly associated with mortality and cardiac complications in heart patients (19-22).

Conclusion
Follow-up of the patients in the present study during their hospitalization revealed that 16 patients (4%) suffered heart attacks and subsequently cardiac arrest. Also, 13 (3. 25 %) cases of death occurred during the hospitalization of patients in this study. In all dead patients, troponin before cardiac arrest was higher than normal range. Eventually, 83.25% of patients with stable vital signs were discharged from the hospital by a specialist. Also, 21 patients (5.25%) with unstable angina showed an increase in quantitative troponin levels during hospitalization. According to the results of this study, there is a direct association between troponin levels and cardiac complications during hospitalization, which is statistically significant (p<0.0001). Also, studies have indicated that most heart complications occur in patients who have higher levels of troponin. The frequency of high troponin levels in the dead group was higher than the alive group. There was direct and significant relationship between troponin and cardiac complications during hospitalization (P <0.0001).

Examining of the statistical indices of troponin levels showed that the mean troponin of patients in this study was 17.40 and its median was 0.97. The mean of troponin in males was higher than females. Also, there was no statistically significant relationship between patients' age and serum troponin levels (p = 0.365). There was an inverse relationship between troponin levels and the EF percentage in patients and this relationship was statistically significant (p <0.0001). In general, according to the results of the present study, the serum troponin level of 59% of patients admitted with a diagnosis of unstable angina and acute myocardial infarction was reported higher than normal during their recent hospitalization. Regarding life-threatening arrhythmias that occur after myocardial infarction 24 cases (6%) of dangerous ventricular arrhythmias such as Ventricular Tachycardia and Ventricular Fibrillation were observed during hospitalization. Thus, presence of different levels of troponin in patients plays always a prognostic role for patients because its high levels can indicate the severity of cardiovascular complications. In other words, for patients with heart failure, high level of troponin is dangerous and has a negative impact on heart function. Since troponin is not naturally detectable in the blood of healthy people, it may increase several times higher than normal. Serial measurement of troponin is a very useful diagnostic method and is currently the selective troponin marker for myocardial damages.

Given the effect of troponin on cardiac and non-cardiac patients and since many people suffer the complications of cardiovascular disease in their lives, steps should be taken for developing standards for prevention, early diagnosing, and reducing of hospital complications in the patients who are at risk. Hence, it is recommended to take early diagnostic measures and timely treatment in patients with high serum troponin levels to prevent complications and sudden death. One of these measures is transfer of patient to Cath lab and doing angioplasty without wasting time. Based on the results of this study, troponin was a suitable indicator for predicting mortality in studied patients. Considering the relationship between troponin and mortality, it should be noted that this valuable marker predicts mortality risk**.**

Acknowledgments

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