Evaluation of cardiac specific Troponin I levels for diagnosis and prediction the risk of mortality in patients with acute coronary syndrome

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Abstract: Background: The detection of acute myocardial infarction (AMI) can be performed by measuring cardiac troponin, which is characterized by high in sensitivity and specificity as specific marker of myocardial cell injury. **Objective:** To assess and confirm the cut-off levels for troponin I (cTn I) to achieve better sensitivity and specificity for the diagnosing of AMI and prognostic value of cTnI in such patients. **Material and Method:** 100 subjects were admitted to the ED or CCU, they were complained from pain in chest and/or shortness of breath. Blood samples were collected at intervals of 0-3, 6-9 and 12-24 hours after admission and cTn I and creatine kinase MB (CK-MB) were determined. The specificity, sensitivity and the area under the curve (AUC) were estimated. The relation between troponin I levels and mortality at 40 days was evaluated. **Results:** The study showed that the majority of patients 76 % were males of mean age 54.3 ± 7.7 years. 65 % of studied patients had MI; approximately two thirds of them showed ST elevation (41 %) while 24 % showed non ST elevation and unstable angina represented 35 % of cases. Three cut-off values, 0.096ng/mL, 0.370 ng/mL and 0.614 ng/mL were selected to evaluate the cTnI assay sensitivity and specificity, each one of these cut-off values was evaluated at different periods (0-3, 6-9 and 12-24 hours after admission). Troponin I sensitivity for diagnosis of MI was (80, 98.5, 98.5%) and specificity was (94.3, 93.1, 97.1%) for each cut-off respectively. Three cut-off values (15-21-25 IU/L) were evaluated for CK-MB with a sensitivity (86.2, 95.4, 95.4%) and specificity (85.7, 80, 97.1%) respectively. cTnI was found to be more specific and sensitive than CK-MB in diagnosing MI cases. Regarding prediction of mortality, cTnI that measured 0 – 3 hours post admission is the best predictor of MI occurrence and death. **Conclusion:** for the diagnosis of AMI in the ED, cTn I is more sensitive than CK-MB, and is valuable in ruling out AMI when the level is lower than the cut-off value of 6 or more hours post the commencement of chest pain. cTnI best predictor of mortality in the patient with AMI.

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1. Introduction

Acute coronary syndrome (ACS) comprises unstable angina and acute myocardial infarction (AMI) (resulting in ST elevation or non-ST elevation). Recognizing a patient with ACS is important for prognosis and management [(1)]. One of the most principal source of morbidity and mortality is still ACS and it is one of the most difficult challenges to be faced in emergency department. Diagnosis of AMI in patients complaining from chest pain is the repeated electrocardiography (ECG) and measurement of biochemical cardiac indicators; cardiac troponin (cTn) and CK-MB [(2)]. Cardiac troponin is considered high in specificity than CK-MB, where cardiac troponin regulating the interaction of actin and myosin. Cardiac troponin are found in two isoforms T and I [(3)]. It is suggested that troponin I, is a subunit belonging to the troponin regulatory complex, it is encoded by 3 various genes, which are expressed at different intensity forms in various kinds of muscles, but not shown to be expressed during fetal growth in skeletal muscles and it is highly specific for the myocardial tissue [(4)]. Cardiac troponin concentration begin to elevate 3 to 12 hrs post the beginning of ischemia, high peak at 12- 24 hours, and may still high for 7 -14 days (troponin I) or 8-21 days (troponin T). Pathologically confirmed myocardial necrosis are associated with elevation in troponin concentrations and pointed to a bad prognosis in individuals with suspected ACS [(3)]. Some authors reported that the advanced age is accompanied by increase in the serum cTn levels [(5)] and though any elevation in sensitivity of cTn (hs-cTn) represents a rise of risks of cardiovascular events and mortality for long-time [(6)]. The emergency department play an important role not only in diagnosis of AMI or risk of mortality in patients but also, for identification of individuals at elevated risk for adverse result, where they might be get a profit from hospitalization and/or treatment regimens [(7)]

Objective:

The current study was aimed to assess and validate the cut-off levels for troponin I (cTn I) to achieve better sensitivity and specificity for the diagnosing of AMI and prognostic value of cTnI in such patients.

2. Material and Methods

The study included 100 patients admitted to emergency department in Tanta university hospital from March 2015 to December 2015 suffering from typical chest pain and/or shortness of breath. Patients with aortic dissection, pulmonary embolism, chronic renal failure, liver cell failure, cardiomyopathy, history of MI in previous month and cardiogenic shock were excluded. All patients were subjected to full history taking, through clinical examination, resting standard 12 lead surface electrocardiography, routine investigations including: liver and kidney function tests, blood glucose level and lipid profile.

Transthoracic echocardiographic examination:

Two dimensional, M-mode and color Doppler echocardiography was performed for each patient after admission using a Vivid 7 system (General Electric Ultrasound; Horten, Norway) and 2.5MHZ transducer. Measurements were performed according to the recommendation of the American Society of Echocardiography [(8)] without any information about the ECG findings **(Feigenbaum, 2005).**

Examination was performed for the patient in the left semi lateral decubitus with the ECG tracing with particular emphasis on:

1- **Segmental wall motion abnormalities** that was assessed qualitatively from different views and was judged to be normal, hypokinetic, akinetic or dyskinetic.

2- **Estimation of ejection fraction (EF)** with the use of apical 4-chamber view by Simpson's rule.

●Echocardiography was done also for exclusion of pulmonary embolism, aortic dissection and cardiomyopathy.

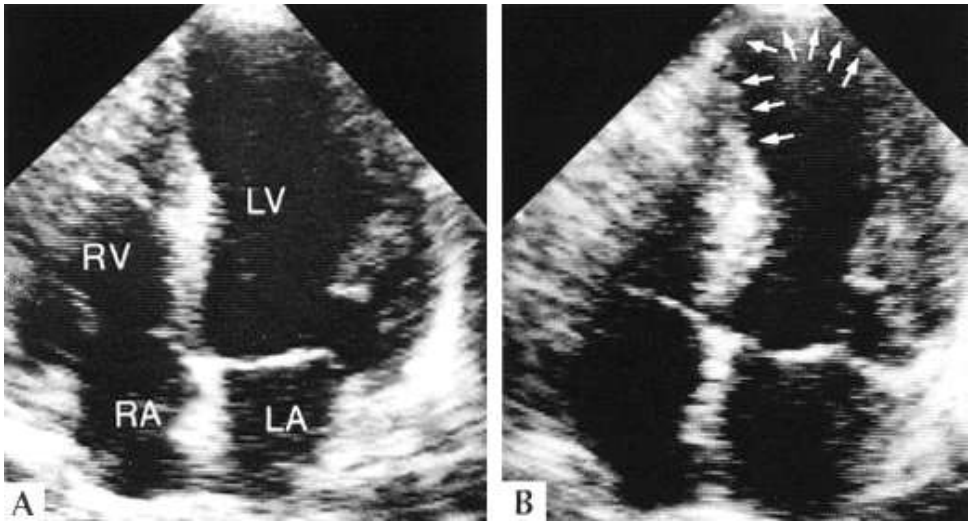

Fig. (5): Echocardiographic wall motion abnormality of coronary artery disease. A, Two-dimensional echocardiographic apical four-chamber view at end-diastole. B, Two-dimensional echocardiographic apical four-chamber view at end-systole.

Cardiac markers:

Measurement of cardiac markers CK-MB and Troponin I:

- Blood samples were collected at (0-3hrs, 6-9hrs & 12-24hrs) after onset of symptoms.
- Relation of Troponin I values and mortality at 40 days was evaluated.

I- CK-MB

Method: Immuno-inhibition. IFCC method Kinetic UV

Principle of assay:

CK-MB reagent contains an antibody inhibiting specially CK-MB subunits (i.e 100% of CK-MM and 50% of CK-MB isozymes) the remaining activity corresponding to CK- B fraction activity, is measured according to IFCC reference method for measuring CK activity. CK-MB activity is then obtained by multiplying by 2 the remaining activity.

Preparation:

Dissolve the reagent 2 in the suitable volume of reagent 1 as indicated on reagent 2 vial and wait about 15 min before use.

Sample

- Specimen: serum free of haemolysis
- Storage: samples must be analyzed immediately or stored protected from air and light for 2 days at 2-8◦C or for month at-20◦C

Reference values:

Serum (37◦C): 0-25 U/L

CK-MB activity must be compared to total CK activity (CK-MB/ total CK) x100 < 6%

The following 3 factors are indicators of damage of cardiac muscle:

- **Total CK:** Men > 171U/L Women >145 U/L
- **CK-MB** >25 U/L
- **Ratio** (CK-MB / total CK)x 100: 6-25%

Procedure:

This reagent can be used on most analyzers, semi automated analyzers and manual methods.

The application are available on request

Wave length: 340nm

Temperature: 37◦C

Read against reagent blank.

	Blank	Test
Working reagent	200 µl	200
Distilled water	10 µl	-
Sample	-	10

Mix and after 5 min incubation measure the variation of absorbance per min (ΔA/min) during 200 seconds.

Calculation:

1) Total CK activity:

Determination with CK-NAC reagent

2) CK-MB activity:

At 340 nm with 1cm light path cuvette: activity (U/L) =ΔA/min x 6 666

3) Percentage of CK-MB activity in sample:

%CK-MB = CK-MB/total CK x 100

II- Troponin I:

Principle of the Assay:-

The cTnI ELISA test is based on the principle of a solid phase enzyme-linked immunosorbent assay. The assay system utilizes four unique monoclonal antibodies directed against distinct antigenic determinants on the molecule.

Three mouse monoclonal anti-troponin I antibodies are used for solid phase immobilization (on the microtiter wells).

The fourth antibody is in the antibody-enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with the four antibodies, resulting in the troponin I molecules being sandwiched between the solid phase and enzyme-linked antibodies. After a 90-minute incubation at room temperature, the wells are washed with water to remove unbound-labeled antibodies. A solution of tetramethylbenzidine (TMB) Reagent is added and incubated for 20 minutes, resulting in the development of a blue color. The color development is stopped with the addition of 1N hydrochloric acid (HCl) changing the color to yellow. The concentration of troponin I is directly proportional to the color intensity of the test sample. Absorbance is measured spectrophoto-metrically at 450 nm.

Calculation of Results:

1) Calculate the mean absorbance value (OD450) for each set of reference standards, controls and samples.

2) Construct a standard curve by plotting the mean absorbance obtained for each reference standard against its concentration in ng/ml on graph paper, with absorbance on the vertical (y) axis and concentration on the horizontal (x) axis.

3) Using the mean absorbance value for each sample, determine the corresponding concentration of troponin I (ng/ml) from the standard curve. Depending on experience and/or the availability of computer capability, other methods of data reduction may be employed.

4) Patient samples with cTnI concentrations greater than 75 ng/ml should be diluted 10-fold with vender's Troponin I Sample Diluent. The final cTnI values should be multiplied by 10 to obtain cTnI results in ng/ml.

Statistical Analysis

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 17.0 *P* value <0.05 was considered statistically significant. And a *P* value <0.0001 was considered highly significant in statistical presentation and analysis of the present study was conducted, using the mean, standard error, unpaired student t-test, Paired t-test and ROC curve.

Results

Demographic data: The study included 76 males (76 %) and 24 females (24 %). MI patients included 52 males and 13 females but in UA male patients were 24 while female patients were 11. The mean age in the study was 54.3 ± 7.7 years old. It was in MI patients 55±7.5 years and that of UA was 52.9 ± 8.1 years.

Risk factors of ACS were compared between patients with unstable angina and patients with MI (Table 1).

ACS types and complications: (**Figure 1**)

Cardiac enzymes (cardiac troponin and CK-MB)

Upon admission with chest pain cardiac enzymes (CK-MB and cardiac specific Troponin I) were assessed for all patients three times the 1st 0 – 3 hours after admission, 6 – 9 hours after admission and 12 – 24 hours after admission. Troponin I mean on 0 – 3 hours was 0.4 ± 0.5, 6 – 9 hours was 1.2 ± 5.3 and 12 – 24 hours was 2.3 ± 6.1. CK-MB mean on 0 – 3 hours

was 26.1 ± 19.1, 6 – 9 hours was 62.3 ± 56.8 and 12 – 24 hours was 103.5 ± 95.4. Cardiac enzymes were also compared between patients with unstable angina and those with MI. MI patients showed higher cardiac enzymes levels and this was highly statistically significant (P= 0.000).

The cut-off points of CK-MB for diagnosis of MI used in the study (26 IU/L) was assessed. CK-MB sensitivity at this level is 66.2 % at 0 – 3 hrs, 93.8 % at 6 – 9 hrs and 95.3 % at 12 – 24 hrs and specificity is 100 % at 0 – 3 hrs and 97.1 % at 6 – 9 hrs and 12 – 24 hrs (**Table 2**).

The cut-off value for Troponin I for diagnosis of MI (1.5 ng/ml) was assessed**.** Troponin I sensitivity at this level is 4.6 % at 0 – 3 hrs, 10.8 % at 6 – 9 hrs and 96.9 % at 12 – 24 hrs and specificity is 100 % at 0 – 3 hrs and 97.1 % at 6 – 9 hrs and 12 – 24 hrs **(Table 3).**

Three cut-off values, 0.096 ng/mL, 0.370 ng/mL and 0.614 ng/mL were selected to evaluate the troponin I assay sensitivity and specificity. Each one of these cut-off values was also evaluated at different times (0-3, 6-9 and 12-24 hours after admission time). Three cut-off values (15- 21- 25 IU/ /L) were evaluated for CK-MB. Receiver Operating Characteristic (ROC) curve and area under the curve (AUC) were calculated to get the best CK-MB and Troponin I cut-off values for diagnosing MI among ACS patients in the study **(Figure 2,3)**. From **(Table 4)** it was apparent that troponin I was more specific and sensitive than CK-MB in diagnosing MI cases.

Predictors in the study:

Variables include total cholesterol in mg/dl, HDL level in mg/dl, troponin I level in ng/ml in 0 – 3 hrs, 6 – 9 hrs and 12 – 24 hrs were studied to find out factors that predict **mortality occurrence**. It was found that troponin I measured 0 – 3 hrs post admission significantly predicts mortality occurrence (P =0.001). Variables include total cholesterol in mg/dl, HDL level in mg/dl, troponin I level in ng/ml in 0 – 3 hrs, 6 – 9 hrs and 12 – 24 hrs were studied to find the best **mortality predictors**; Troponin I in the 1st 0-3 hours was the best predictor of mortality in the study (P =0.026)**. (Table 5).**

Table 1: Risk factors of ACS among the studied patients

Risk factor		**MI**	**UA**
Hypertension	Hypertensive	54	28
	Not hypertensive	11	7
Smoking	Smokers	39	-
	Non smokers	26	35
DM	Diabetic	41	23
	Non diabetic	24	12
Lipid profile (Mean ± SD)			
Cholesterol		208.6±52.3	183.3± 51.9
LDL		142.9±38.7	138.4±39.9
HDL		70.9±14.1	73.8±23.9
Triglycerides		256.8±86.8	268.5±72.6

Table 2: CK-MB cut-off value (26 IU/L) among unstable angina and MI patients

CK-MB level		**MI (n = 65)**	**UA (n = 35)**	**p-value**
0 – 3 hrs	**≥ 26 IU/L**	43 (66.2 %)	0 (0 %)	< 0.001*
	< 26 IU/L	22 (33.8 %)	35 (100 %)	
6 – 9 hrs	**≥ 26 IU/L**	61 (93.8 %)	1 (2.9 %)	< 0.001*
	< 26 IU/L	4 (6.2 %)	34 (97.1 %)	
12 – 24 hrs	**≥ 26 IU/L**	62 (95.3 %)	1 (2.9 %)	< 0.001*
	< 26 IU/L	3 (4. 7 %)	34 (97.1 %)	

Table 3: Troponin I cut-off value (1.5 ng/ml) among unstable angina and MI patients

Troponin I level		**MI (n = 65)**	**Unstable angina (n = 35)**	**p-value**
0 – 3 hrs	**≥ 1.5 ng/ml**	3 (4.6 %)	0 (0 %)	0.311
	< 1.5 ng/ml	62 (95.4 %)	35 (100 %)	
6 – 9 hrs	**≥ 1.5 ng/ml**	7 (10.8 %)	1 (2.9 %)	0.255
	< 1.5 ng/ml	58 (89.2 %)	34 (97.1 %)	
12 – 24 hrs	**≥ 1.5 ng/ml**	63 (96.9 %)	1 (2.9 %)	< 0.001*
	< 1.5 ng/ml	2 (3.1 %)	34 (97.1 %)	

Table 4: Sensitivity, specificity and AUC for CK-MB and troponin I cut-off values for diagnosis of MI.

Cut-off level		Sensitivity %	Specificity %	AUC
CK-MB (IU/L)	15 (0 – 3 hrs)	86.2	85.7	0.921
	21 (6 – 9 hrs)	95.4	80	0.978
	25 (12 – 24 hrs)	95.4	97.1	0.972
Troponin I (ng/ml)	0.096 (0 – 3 hrs)	80	94.3	0.861
	0.370 (6 – 9 hrs)	98.5	93.1	0.971
	0.614 (12 – 24 hrs)	98.5	97.1	0.966

Table 5: Independent predictors of mortality

Predictor	B	p-value	Adjusted OR (95 % CI)
• Cholesterol	-0.013	0.334	1.013 (0.987 – 1.040)
• HDL	-0.103	0.199	1.108 (0.947 – 1.297)
• Troponin I (0 – 3 hrs)	2.886	0.026	0.056 (0.004 – 0.712)
• Troponin I (6 – 9 hrs)	0.033	0.874	0.967 (0.641 – 1.459)
• Troponin I (12 – 24 hrs)	0.089	0.251	0.915 (0.785 – 1.065)
• Constant	3.362	0.563	0.078
Model χ^2 = 7.684		0.175	

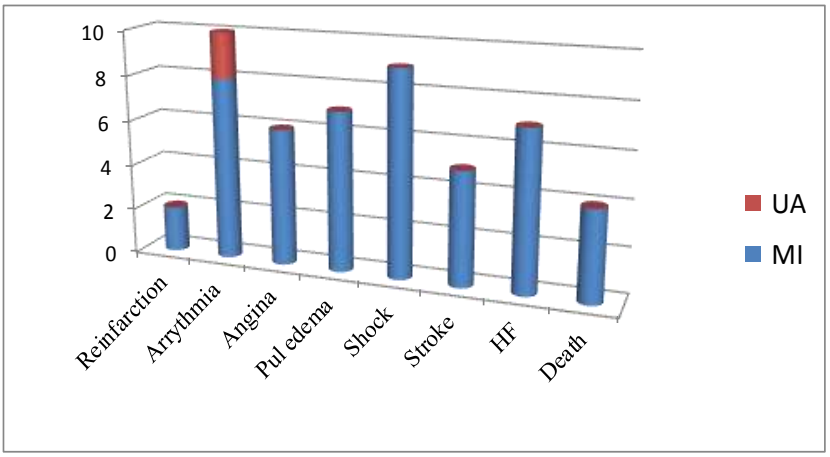

Figure (1): ACS complications in the study.

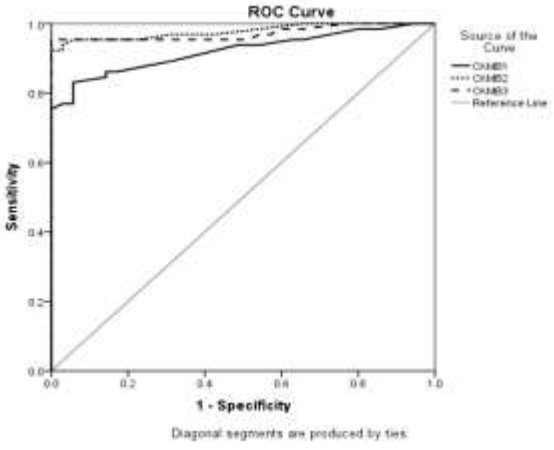

Figure 2: ROC curve for CK-MB levels at the 3 measured intervals.

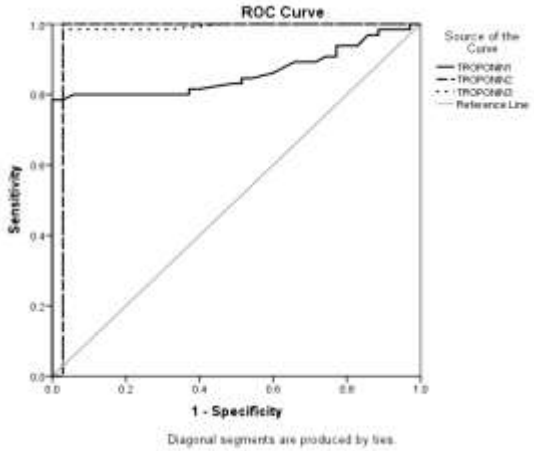

Figure 3: ROC curve for Troponin I levels at the 3 measured intervals.

4. Discussion

Sensitivity and specificity of cardiac troponin and CK-MB:

About 65% of the patients in the current study were established to have AMI. In this study, it is observed that early detection of troponin I (0-3 hrs post admission), troponin I sensitivity was nearly equal to the specificity at lower cut-off levels (0.096 ng/ml). The sensitivity and specificity were 80% and 94% respectively. After 6 -9 hrs of admission, the specificity persisted unchanged at all cut-off points (0.370 ng/ml), while the sensitivity is improved,. The sensitivity and specificity were averaged 98.5% and 93.1 respectively. In spite of increasing in the period post-admission (12 -24 hrs), no changes in the levels of sensitivity (98.5%) and specificity (97.1%), still at cut-off (0.614ng/ml). In our population, 1.5ng/mL is the best cut-off level for diagnosis of AMI and the suitable time for measuring was within 6-9 hrs post admission according to the AUC. Whereas, CK-MB quantity had a little elevation in sensitivity (95.4%) than its specificity (80%), when measured at 6-9 hrs post-admission, which was remain decrease than the level of troponin I, at cut-off (21 IU/L). The present work demonstrate for confirming diagnosis of AMI in patients, estimation of Troponin I was more sensitive and specific than CK=MB is-enzyme assay.

Several previous researches have reported comparable conclusions, mentioning that in an ischemic patients, elevation of cardiac troponin I is marker of inducing subsequently myocardial infarction and death, where the level of CK-MB not affected significantly [(9)].

In the study of Hamm et al. who studied 773 patients complaining from acute chest pain for a period of 12 hours. ECG not showing elevation in ST-segment. Levels of Troponin T & I status (positive or negative) was estimated twice at different intervals (at admission and post 6hrs from onset of pain). They reported that 63% of examined patients (773) were suffering from cardiac diseases must be admitted to the CCU [(10)]. Our results are coordinated with their results, where we obtained the same rate of patients having AMI in the ED.

Apple et al [(11)], in their study the 99th percentile level of 0.04 ng/mL was chosen as a cut-off level. The results revealed that 41 (13%) patients had AMI with clinical sensitivity (74%) and specificity (84%) values at admission, whereas the sensitivity and specificity values at 6- 24 hrs post-admission was averaged 94% and 81%, respectively. The ROC curve post 6-24 hrs post admission is more accurate (P=0.001) than at time of admission in diagnosing of AMI. Their results are in coordination with our finding in the current study.

Other investigators, Ebell et al., [(12)] found that 8hrs post-admission, troponin I was estimated for diagnosis of AMI, the sensitivity was averaged (84%) and the specificity was (81%). With regarding to our finding in the current work, the sensitivity reached 98.5%, whereas, the specificity averaged 93.1%, with 0.370 ng/mL cut-off level.

Troponin I sensitivity increased from 10% to 45% vs. the cut-off value within 1 hour of pain appearance and elevated to 90% post 8 hrs. While, the specificity elevated from 80% to 95 % after 1 and 12 hrs, respectively post appearance of chest pain. An abnormal peak level 24hrs post admission to the ED had an area under the curve of 0.99 and was very valuable for exclusion AMI in case of the troponin level was undetectable or less than the cut-off level [(13)].

Ross et al. [(14)] evaluated 153 patients complaining from chest pain in the ED. Performed ECG and cardiac markers. The sensitivity of CK-MB and ECG during diagnosis of AMI was averaged 88% and 69%, respectively. With respect to the level of troponin I (<0.6ng/ml), the sensitivity and specificity were found to be 94% and 81%, respectively at 0 or 6 hours post admission**.** With regard to the current study, the sensitivity was less (76%), while the specificity was high (90%); this variation may be attributed to the use of a high cut off value (1.0 ng/mL) and also, the variation in the sensitivity of immunological assay used in different studies. When the cut-off value of troponin I was 2.0 ng/mL in the study of Ross et al., the sensitivity and specificity was 85% and 91%, respectively, in comparison with CK-MB and ECG reports which are in agreement with our results when cut-off value of troponin I taken in account was 1.5 ng/mL.

The prognostic value of cardiac troponin

In the present study we found that early after admission (0-3hrs) at cut-off (0.375 ng/ml) the sensitivity and specificity for prediction the risk of mortality were 100% and 62.9% respectively, when time had elapsed (6-9 hrs) after admission with cut-off (0.695 ng/ml) the sensitivity and specificity were 100% and 52.6% respectively, after (12-24hrs) from admission with cut-off (3.375 ng/ml) the sensitivity and specificity were 100% and 94.8% respectively.

Due to the predictive importance of cTn raise, an adjusted analysis of 1,706 subjects obtained from 6 different investigations. The data revealed that an elevation in cTn was accompanied with elevated death (OR 2.5, 95% CI 1.9 – 3.4; P < 0.0001). Whereas, in unadjusted analysis of 1,019 subjects belonging to 8 investigations, an increase in the concentration of cTn was liked with 3.0 days prolongation in ICU stay

(95% CI 1.0 – 5.1; P = 0.004), and 2.2 days more in the hospital stay (95% CI -0.6 – 4.9; P = 0.12) [(15)].

Some researchers reported that, in a multivariate analysis troponin T level in addition to other factors such as hypertension, age, ECG changes at rest and number of antianginal drugs are independent variables for diagnosis of AMI or cardiac death. The predictive status of cTn-T was independent of an index result classification into myocardial infarction or unstable angina [(16)]**.** In contrast in our study variables like total cholesterol in mg/dl, HDL level in mg/dl, troponin I level in ng/ml in 0 – 3 hrs, 6 – 9 hrs and 12 – 24 hrs were studied to find the best mortality predictors, we found Troponin I in the 1st 0-3 hours was the best predictor of mortality (P =0.026**),** and MI occurrence (P =0.001).

Conclusion

The importance of using cTn I in diagnosis of AMI in our people is comparable to that found in other studies worldwide. We also suggested that cTn I is more advantageous than CK-MB for AMI diagnosis in the ED. This method is particularly useful in excluding out AMI at 6 or more hrs, post chest pain appearance, when the level is under the cut-off value. The sensitivity of the cTn I assay, comparable to other cardiac enzymes, is greatly reliant on the sum of hrs passed from the chest pain appearance. Cardiac Tn I assessment is valuable in appraising individuals with ACS. Detection of cTn I level is a useful marker for expectation of ACS elsewhere that provided by ECG or the demographic characteristics of the patient at admission. This permits the early detection of patients at high risk of mortality.

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