A Comparative Study on the Diagnostic Utility of Creatine Kinase-MB (Myocardial Band) Mass Estimation Over Its Activity Measurement in Patients with Acute Myocardial Infarction in a Tertiary Care Hospital in Puducherry

Nikhila Suresh Kumar[1], Sivaa Rajendran[2], Sunil Kumar Nanda[3], Mark Christopher[4], Ravichandran Kandasamy[5]

[1, 2, 3] Department of Biochemistry, Pondicherry Institute of Medical Sciences, Pondicherry, Tamilnadu, India. [4]Department of Cardiology, Pondicherry Institute of Medical Sciences, Pondicherry, Tamilnadu, India. [5]Department of Biostatistics, Pondicherry Institute of Medical Sciences, Pondicherry, Tamilnadu, India.

ABSTRACT

BACKGROUND

Cardiovascular diseases (CVDs) are one of the major health problems and leading cause of death worldwide. Acute myocardial infarction (AMI) is one of the cardiovascular diseases which has high mortality in early hours of presentation and hence early and accurate diagnosis is important to reduce the morbidity and mortality. Troponin I and CKMB (Creatine Kinase-Myocardial Band) activity are the routine biomarkers used for early diagnosis of AMI. Since there is a high degree of instability in the measurement of CKMB activity and also there are frequent non-correlation with the Troponin I levels, we aimed to estimate and compare the levels of CKMB mass and CKMB activity in patients with and without AMI.

METHODS

This comparative study included 40 cases and 40 controls. Cases were adult patients between the age group of 30 -70 years diagnosed with AMI by electrocardiogram (ECG) and positive troponin I, and controls were who presented with non myocardial infection (MI) chest pain. Blood samples were collected to estimate CKMB activity and CKMB mass.

RESULTS

The median value of CKMB activity in controls was 21 IU/L (IQR 13.25-27.75) and that in cases was 40 IU/L (IQR 30.25-94.25) and this difference is statistically significant. The median value of CKMB mass in controls was 5 ngmL (IQ 4-6) and that in cases was 19.50 ng/mL (IQR 6-61.50) which is also statistically significant in differentiating both. In Spearman correlation test, both showed a better statistical significance and correlation in cases (r = 0.787). It was evident that the median value of CKMB activity in controls was higher than that of the normal range for CKMB activity which is 8-16 IU/L, but the median value of CKMB mass in controls was well within the normal range of 5- 10 ng/mL, considering it to be a better marker for eliminating false positive results.

CONCLUSIONS

CKMB mass can be considered as a better marker than CKMB activity for accurate diagnosis of AMI along with troponin I.

KEYWORDS

Cardiovascular Diseases, Biomarker, Acute Myocardial Infarction, CKMB Mass, CKMB Activity

Corresponding Author:
Dr. Sivaa Rajendran,
Professor of Biochemistry,
Pondicherry Institute of Medical Sciences, Ganapathichetikulam,
Kalapet, Puducherry-605014, India.
E-mail: drsivaar@gmail.com

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BACKGROUND

Cardiovascular diseases are one of the major health problems and leading cause of death worldwide. About 16 million deaths occur due to CVD every year.[1] CVD currently accounts for nearly half of non communicable diseases (NCDs) which overtook communicable disease, as the world major disease burden, with CVD remaining the leading global cause of death, accounting 17.5 million deaths per year. This number is expected to grow to more than 23.6 million by 2030.[2] Cardiovascular diseases are broadly classified into CVD due to atherosclerosis and CVD due to other causes. CVD due to atherosclerosis are ischemic heart disease (heart attack), cerebrovascular disease (stroke), disease of aorta & arteries (hypertension & peripheral vascular disease). CVD due to other causes includes congenital heart disease, rheumatic heart disease, cardiomyopathies, and cardiac arrhythmias.[3]

Acute myocardial infarction - is one of the CVD which has a high mortality in early hours of presentation and can be salvageable when diagnosed early. So, early and accurate diagnosis is important to reduce the morbidity and mortality.[4] There are various risk factors behind the development of AMI –

Age

Men aged more than 45 years and women aged more than 55 years are more prone to develop AMI.

Gender

Incidence of atherosclerosis and AMI is higher in men than women in all age groups. This gender difference in AMI however narrows down with increasing age.

Family History

Family history of premature CHD increases an individual's risk for atherosclerosis and AMI. Familial coronary events are multifactorial caused by genetic components and acquired general health practice, lifestyle etc.

Lack of Physical Activity

An inactive lifestyle contributes to high blood cholesterol levels and obesity which increases risk for CAD. Individuals who exercise regularly have better cardiovascular fitness, which decreases their overall risk of heart attack. Exercise is also beneficial for lowering high blood pressure.[5] Family history of premature CHD or AMI was found to be an independent risk factor for CAD.[6] Nora et al. observed that the highest relative risk was associated with a positive family history of ischemic heart disease (IHD).[7]

Obesity

It is linked with high blood cholesterol levels, high triglyceride levels, high blood pressure and diabetes. Wilson PW et al. observed obesity to be a significant risk factor for AMI.[8]

Tobacco Use

Certain components of tobacco and tobacco combustion gases are known to damage blood vessel walls. Body response to this type of injury elicits the formation of atherosclerosis and its progression, thereby increasing the risk of AMI.[9]

Hyperlipidemia

Elevated levels of total cholesterol, low-density lipoprotein (LDL) or triglycerides are associated with increased risk of coronary atherosclerosis and AMI. Levels of high density of lipoprotein (HDL) less than 40 mg/dl also shows increased risk.[10]

Hypertension

High blood pressure and increased risk of AMI are consistently associated. The control of hypertension with appropriate medications have been shown to reduce the risk of AMI.[11]

Type 2 Diabetes Mellitus (T2DM)

Diabetes mellitus increases the risk of AMI because it increases the rate of atherosclerotic progression and affects the lipid profile adversely. Kalofoutis C et al. observed that insulin resistance, metabolic syndrome and T2DM are linked with CVD, as apparent from increased levels of CVD morbidity and mortality and from the presence of a complex array of CVD risk markers.[12]

The following events explain the underlying pathology of the coronary artery leading to atherosclerosis. The atheromatous plaque in coronary artery undergoes an acute change consisting of intraplaque hemorrhage, erosion or ulceration, rupturing or fissuring. When exposed to subendothelial collagen, the necrotic plaque contents activate the adhered platelets. This activated platelets, release their granule contents which aggregate to form microthrombin. Vasospasm is stimulated by the mediators released from platelets. Tissue factor activates the coagulation pathway, adding to the bulk of the thrombus. Within minutes, the thrombus can expand completely occluding the vessel lumen. The obstruction of coronary artery diminishes blood flow to the region of the myocardium causing rapid myocardial dysfunction, ischemia, and with prolonged vascular compromise which leads to myocardial death.

Early biochemical consequences of myocardial ischemia is the cessation of aerobic metabolism within few seconds which leads to inadequate production of high energy phosphates and accumulation of potentially noxious metabolites like lactic acid. Because of the exquisite dependence of myocardial function on oxygen and nutrients,

myocardial contractility ceases within a minute or so of the onset of severe ischemia. Such loss of function precipitates heart failure long before myocyte death occurs.[13]

The pathogenesis of AMI is the full-blown necrosis and death of the cardiac tissues due to complete block of the coronary arteries. Acute coronary syndrome (ACS) - Tthe term is applied to patients in whom there is a suspicion of myocardial ischemia. There are three types of ACS. ST elevation MI (STEMI), Non-ST elevation MI (NSTEMI), Unstable angina (UA).[14] The first two types are characterised by a typical rise and /or fall in biomarkers of myocyte injury and the later one is elicited clinically. Initial care of the patient with suspected AMI should include the early and simultaneous achievement of four goals. They are, confirmation of the diagnosis by electrocardiogram and biomarkers measurement, relief of ischemic pain, assessment of the hemodynamic state & correction of abnormalities that may be present and initiation of antithrombotic and reperfusion therapy if indicated.[15]

Cardiac biomarkers play a vital role in the diagnosis of AMI. Though the diagnosis of AMI is based on clinical presentation and ECG findings, Serum cardiac biomarkers are employed to differentiate unstable angina from other variants. Commonly used markers are cardiac troponins T & I, Creatine Kinase (CK) and its isoforms like CKMB (Creatine Kinase- Myocardial Band), myoglobin, heart type fatty acid binding protein (H-FABP).

Troponin complex is found on the thin filament (actin) of all the types of striated muscle (fast, slow, cardiac). Its function is to regulate the calcium dependent contraction of muscles. There are three types of troponins- TnT, TnI, TnC. They are designated with a letter that refers to the function of the troponin protein: TnC binds calcium: TnI inhibits the action of enzyme actomyosin adenosine triphosphate; TnT binds to tropomyosin. Troponin T and I have unique cardiac isoforms, whereas cardiac muscle and skeletal muscle share troponin C isoforms, rendering this protein unsuitable for diagnostic use. Troponin T and I are currently the gold standard for the detection of myocardial injury and are key to clinical decision making in ACS.[16]

Cardiac troponin I (24 KDa) is reported to have a unique segment containing 31 amino acids that make it different to either sTnI or fTnI (19 KDa). During the foetal development, both sTnI and cTnI are expressed in the myocardium. At the time of birth, only cTnI remains in the myocardium.[17] Cardiac troponin has not been shown to be expressed in any type of skeletal muscle during either development or disease stimuli.[18] This makes cTnI specific for the myocardial tissue and an excellent marker for the detection of myocardial injury in serum. cTnI was reported first as a biochemical marker for the diagnosis of AMI.

High cTnT and cTnI concentrations have been reported in critically ill patients who had not been diagnosed with comorbid AMI.[19] Blunt trauma to the chest, closed heart massage, external defibrillation is also reported to result in elevation of cTnT.[20]

Elevations have also been reported in cases of myocarditis and drug induced cardiac toxicity.[21] Elevated troponin levels (I and T) occur in some patients with acute pulmonary embolism. There is however, a slightly higher rate of positive results with cTnT assays in some patients with chronic renal failure and acute or chronic muscle disease.[22]

Creatine kinase is an enzyme with molecular weight of approximately 82,000 that is generally associated with ATP regeneration in contractile or transport system. It is located in muscle cells, where it is involved in the storage of high energy creatine phosphate. Every contraction cycle of muscle results in creatine phosphate use, with the production of adenosine triphosphate (ATP). These results in relatively constant levels of muscle ATP. It is composed of two subunits M and B. Three different pairs of units combine to give rise three different isoenzymes CKBB, CKMB and CKMM. CKBB is the brain isoenzyme, present in large quantity in brain and many other internal organs. CKMB is the heart specific isoenzyme and has been gold standard in the diagnosis of AMI in many laboratories.[23] This cardiac specific CKMB can be measured in serum or plasma by one of two methods.

CKMB activity assay: This measures the total activity of enzyme in serum or plasma by methods like electrophoresis, column chromatography, immunoinhibition or immunoprecipitation. These methods are non-specific, measures only active enzymes & have low analytical sensitivity (5 IU/L).[24]

However, the activity of CKMB in the serum can be influenced by the presence of other enzymes, temperature, pH, ions used in the assays and by prolonged storage.[25] These factors make it difficult to diagnose acute MI when the elevated serum CKMB activity is low. In CKMB immunoinhibition method which is commonly performed, CKM antibody is used, which inhibits M subunit of CKMB, CKMM, eventually enzyme activity of CK–B is measured. In this technique, the B subunit of CKBB and atypical CK are also measured as these are not inhibited and could give falsely high results.[26]

CKMB - mass assay: Measures the protein mass in serum or plasma by using specific antibodies against M, B or MB subunits, where mass assay measured in terms of its protein concentration rather than its biological activity and CKMB mass has been measured by electrochemiluminescence technology, sandwich principle where monoclonal antibodies against CKMB have been used so specifically the CKMB fraction is measured. Results are reported in ng/mL or µg/L.

Assays are highly specific and have high analytical sensitivity (0.3 ng/mL) and can also measure both active and inactive enzymes. Reference ranges using various methods have been reported to be 8-16 IU/L for CKMB activity and 5 - 10 ng/mL for CKMB mass.[24]

Though cardiac Troponin I (cTnI) is the preferred marker of choice, it is elevated in other non-cardiac illnesses and require serial measurements Diagnostic sensitivity of AMI improves when CKMB activity is measured along with troponin.[27]

Because of the various drawbacks associated with the CKMB activity assay, the present study was taken up to estimate and compare the levels of CKMB mass and CKMB activity in patients with and without AMI and also to analyse the diagnostic utility of CKMB mass in comparison with CKMB activity.

Aim

To assess the diagnostic utility of CKMB mass over CKMB activity in patients with acute myocardial infarction.

Objectives

1. To estimate the levels of CKMB activity in patients with acute myocardial infarction.
2. To estimate the levels of CKMB mass in acute myocardial infarction.
3. To correlate CKMB mass concentration with that of CKMB activity in these patients

METHODS

This was a cross sectional comparative study, carried out in Pondicherry Institute of Medical Sciences, Puducherry, from January 2016 to December 2016.

Inclusion Criteria

Adults between the age group of 30 - 70 years were included. The participants were categorised as cases who presented with chest pain and diagnosed as AMI with ECG changes and positive troponin I values. Those participants who presented with chest pain with normal ECG findings and negative troponin I values were categorised as controls.

Exclusion Criteria

The patients with the history of renal failure, acute stroke and myopathy were excluded from this study. Renal failure patients normally show an elevated level of CKMB levels because of regeneration of injured skeletal muscles, excessive volume overload, left ventricular hypertrophy, congestive heart failure and other analytical interferences.[28]

Since we couldn't find similar type of studies done previously, we calculated the mean and standard deviation (SD) based on the last one-year hospital data for the determination of sample size. Based on these values we considered a mean (SD) of subjects with AMI and without AMI for CKMB-activity as 40 (38) and 25 (10) respectively. At a 5 % level of significance and a power of 80 %, the minimal required sample size of 40 per each group was obtained. The blood samples were collected from the study participants with their consent and were centrifuged at 3500 rpm for 10 minutes. The separated serum samples were aliquoted in separate containers and stored at -70ºc till analysis. Serum CK_MB activity was estimated by immunoinhibition method done in a fully automated chemistry analyser and Serum CK-MB mass by ELISA (Enzyme Linked Immunosorbent Assay).

Statistical Analysis

Data were entered in MS Excel 2007 and analysed by statistical package for social sciences (SPSS) 20.0 version. Mann–Whitney test was used for comparing CKMB mass versus activity. Spearman correlation coefficient test were used for correlating CKMB mass and CKMB activity. A P value < 0.05 was considered as statistically significant.

RESULTS

A total of 80 adult individuals with AMI (n = 40) and without AMI (n = 40). Among the 40 AMI patients, 30 (75%) were male and 10 (25%) were female patients. In the age group, majority of 25 (62.5%) the patients were more than 50 years of age.

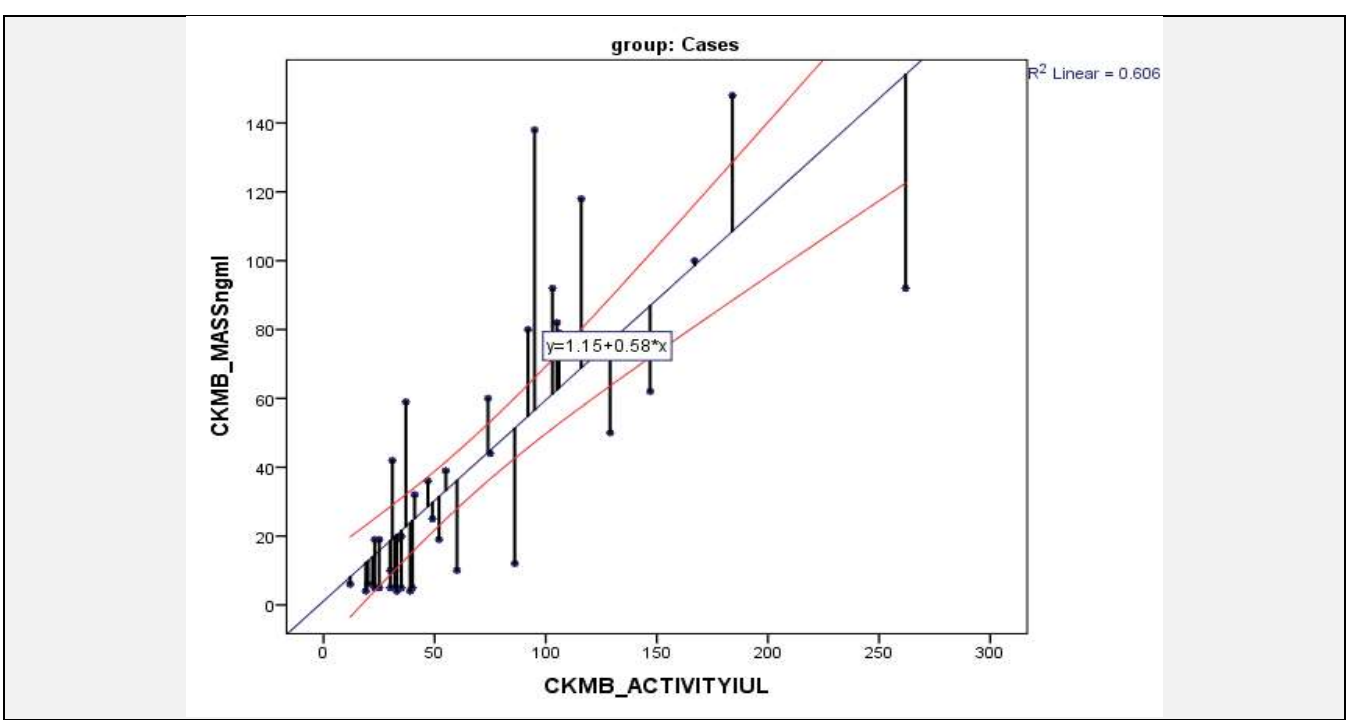

Figure 1. Correlation between CKMB Activity and CKMB Mass in Cases Using Spearman's Correlation

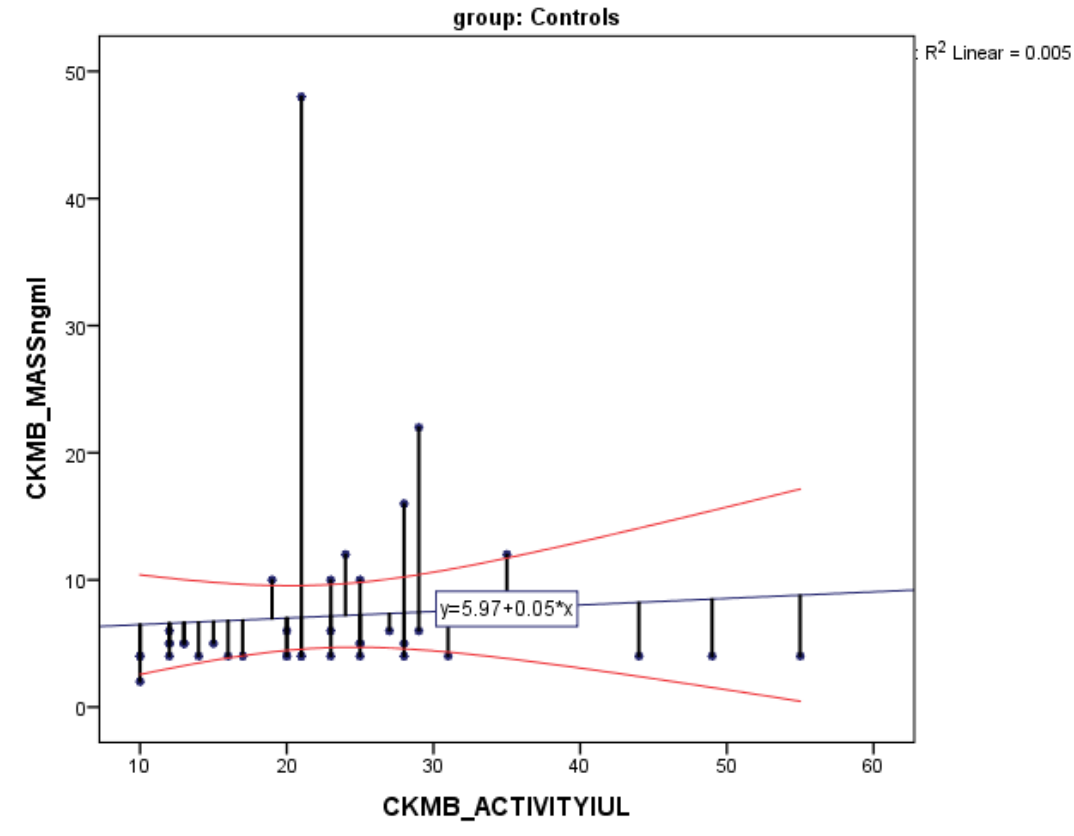

Figure 2. Correlation between CKMB Activity and CKMB Mass in Controls Using Spearman's Correlation

In total of 40 without AMI, there were 31 (77.5%) male and 9 (22.5%) female and 28 (70%) of them were more than 50 years of age. The normal range of CKMB activity is 8-16 IU/L and the normal range of CKMB mass is 5-10 ng/mL. The Mann–Whitney U Test was used to compare the levels of both CKMB activity and CKMB mass with AMI and without AMI patients. The test showed that there was statistical significance at P - value less than 0.05.

	Cases Median (IQR)	Controls Median (IQR)	P-Value
CKMB-Activity	40 (30.25 - 94.25)	21 (13.25 - 27.75)	0.001*
CKMB-Mass	19.50 (6-61.50)	5 (4-6)	0.001*

Table 1. Comparison of CKMB Activity and Mass Levels in Cases and Controls by Mann-Whitney Test

*P value < 0.05 was considered as statistically significant

Groups	P Value	r Value
Controls (n = 40)	.194	0.210
Cases (n = 40)	0.001	0.787

Table 2. Correlation between CKMB Activity and Mass among Cases and Controls

There was correlation between CKMB activity and mass among AMI patients (cases) and there was no correlation between CKMB activity and mass among non-AMI patients (controls).

DISCUSSION

Our present study included 80 subjects, out of which 40 of them had an attack of AMI and rest of the subjects are non-MI individuals. Sixty of the subjects were males and rest were females. The mean age of the control group was 55.12 ± 10.5 years, while that of cases was 54.92 ± 9.7 years. The normal range of CKMB activity is 8-16 IU/L, The median values of CKMB activity in controls were 21 IU/L (IQR 13.25 - 27.75) and that in cases were 40 IU/L (IQR 30.25 - 94.25) which is statistically significant in differentiating cases and controls. (Table 1). The normal range of CKMB mass is 5 - 10 ng/mL, The median values of CKMB mass in controls were 5 ng/mL (IQ 4 - 6)and that in cases were 19.50 ng/mL (IQR 6 - 61.50) which is statistically significant in differentiating cases from controls. (Table 1)

In our study, on applying Spearman correlation test, both parameters showed a better statistical significance correlation with troponin positive cases (Table 2 & Figure 1) and no correlation existed in controls (Table 2 & Figure 2). Even though the difference between the CKMB activity and mass levels of cases and controls showed a high statistical significance, the median value of the CKMB mass in controls were well within the normal range, but the median value of CKMB activity in controls was slightly higher than that of normal so that there is a change for false positive results. We also experienced the similar kind of situation in our lab where the CKMB values, most of time will be higher than the normal levels when the serum troponin levels are negative.

The serum measurement of CKMB mass is better than measuring activity, because the problem in measuring activity is that the enzyme becomes deactivated by environmental conditions and experimental manipulation leading to low values, and also they observed the correlation between CKMB mass & CKMB activity was initially fair and

hence patients having myocardial infarction could be diagnosed by CKMB mass rather than by CKMB activity.[27]

In a Turkish study, Ozcan O et al. observed that CKMB activity was affected more profoundly in haemodialysis, but CKMB mass was not affected by haemodialysis.[29] Pierce GF al. observed that in cases of haemolysis, due to the release of adenylate kinase enzyme from RBC, there might be an elevated CK MB values in such samples because adenylate kinase will also catalyse the same reaction as that of CKMB activity. This kind of interference is not seen with CK MB mass assay as antibodies specific for the CKMB is used and adenylate kinase has no effect on assay.[30]

Similar study was done in Washington by Elenberg PR et al. and they concluded that the two measures were comparable and could be used for the diagnosis or exclusion of AMI.[31] In a Jordan study, Algani AA et al. observed that the measurement of total creatine kinase & creatine kinase MB are useful parameters for diagnosing AMI.[32] In another study done in America, Christenson RH et al. was observed that CKMB mass assay was developed to improve both analytical & clinical sensitivity and specificity for measuring CKMB compared with enzymatic assay.[33]

Bakker AJ et al. observed that CKMB mass assay has higher sensitivity than activity assay in diagnosing AMI. It has also been reported to be more sensitive in detecting even small injuries to the myocardium that occurs in patients with no ST elevation MI.[34] Venta R et al. observed that the presence of CK-BB, macro CK type 1 or macro CK type 2 in high concentrations interfere with the results and lead to false elevation of CK-MB when activity measurement is employed. These interferences have no effects on mass assay.[35] Though our study results are in consistent with most of the studies, still large-scale studies are required to prove the utilization of CKMB mass assay as routine biomarker for diagnosing AMI.

Limitations

A large sample size would have elicited a difference in the level of correlation between the two parameters even in the controls also. We haven't classified the study group based upon the AMI types, differentiated according to their ECG pattern during the study period. Hence, we are not able to find out the diagnostic specificity of both methods in various types of AMI.

CONCLUSIONS

In our study, we estimated CKMB mass and CKMB activity levels in AMI patients and found that CKMB mass can be a better marker than CKMB activity for the accurate diagnosis of AMI along with troponin I.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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