

## Effectiveness of cardiac markers to detect the increased cardiovascular risk in chronic kidney disease patients

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### Abstract

The manifestation of cardiovascular diseases in healthy individuals & patients of CKD differ, the latter owing more than 50% of the mortality to cardiovascular disease, should be diagnosed early of their cardiovascular condition, which is highly conducive in early treatment and reduction in mortality. The standardized tests don't apply to patients of CKD. The independent way of diagnosis is the elevation of the cardiac enzymes. In the present study, 30 CKD patients and 30 healthy controls were included to find status and cutoff values of the cardiac markers. Findings indicate significant rise in CK-MB and LDH to be an early marker to diagnose CVD in CKD patients. There was no significant rise in the TnI and AST levels, these markers seem to be unavailing in early diagnosis of CVD in CKD patients. No correlation was found between any of the cardiac markers. Considering the difference in the homeostasis and functioning of various organ systems in the control and CKD patients, these cutoff values of general population won't be conforming to the latter's condition resulting in under-diagnosis. Therefore, the cutoff values were formulated and calculated to be >13.51 and >286.49 for CKMB and LDH respectively using ROC curve analysis.

**Keywords:** Chronic kidney disease, cardiovascular disease, Cardiac markers, Troponin I, CK-MB.

### Introduction

Chronic kidney disease (CKD) is a conspicuously growing worldwide public health problem signaling varied adverse outcomes from kidney failure, cardiovascular disease (CVD) to even premature death.<sup>(1)</sup> Taking one more step into perceiving the adversities of CKD and taking into consideration the rising number in India and the world: The estimated prevalence of CKD is 800 per million population (pmp) and rapidly rising, and the incidence of end-stage renal disease (ESRD) is 150–200 pmp.<sup>(2)</sup> The estimated deaths due to chronic diseases in India are anticipated to rise from 3.78 million in 1990 (40.4% of all deaths) to 7.63 million in 2020 (66.7% of all deaths), not only India, the worldwide encumbrance of CKD is increasing rapidly.<sup>(3)</sup>

It is an ascertained fact that the increased morbidity and mortality in the patient population suffering from ESRD stems from CVD, accounting for more than 50% of all deaths.<sup>(4,5)</sup> Now, if we were to compare the manifestations of CVD in a normal person and a person suffering from CKD, albeit, the former may show signs of angina and well established signs of cardiac abnormalities, in the latter, however, the first manifestation of atherosclerosis is an emergent cardiac death or acute myocardial infarction.

The CKD patients often do not present with angina, occurring in only 17% in one study<sup>(6)</sup> and also have a speculative preponderance of abnormal baseline electrocardiograms and echocardiograms, silent myocardial ischemia and abnormal cardiac symptoms.<sup>(7)</sup> This clearly indicates the need for diagnosing CVD in this patient population early. The

diagnosis of CVDs in CKD patients, does not occur, as this patient population cannot undergo exercise stress test and may also be due to the false negative rate of pharmacological stress testing.<sup>(8)</sup> Therefore, the independent way of diagnosing acute coronary syndromes, in this patient population is the elevation of the cardiac enzymes and as a result, there is a need for standardization of assays to fully elucidate the markers for detection of CVD.

For many years, Creatine kinase, Creatine kinase-MB and other cardiac enzymes have been used for the detection of early myocardial injury. These biomarkers, however, are seen to be increased in patients with CKD. Along with these cardiac enzymes, the introduction of troponin I (TnI) has more specificity.<sup>(9)</sup>

There is paucity of data on cut off points of the cardiac markers viz. TnI, CK-MB, LDH and AST in CKD patients for the suspicion of CVD risk. There are very few studies published, of which, few indicated better and others as poor prognostic ability of serum troponin in the context of patients with CKD.<sup>(10-18)</sup> Therefore, there is a need for more research into this field of diagnosing myocardial abnormalities in patients with CKD, which holds much importance in preventing clinical scenarios where mortality of this patient population is high due to no prior preventive measures taken, owing to incompetency in diagnosis. Therefore, we hypothesized: The cut off values of cardiac markers may serve as a better indicator for CVD risk in CKD patients, and association with one another. The cut off values so formulated may differ in CKD patients as compared to healthy controls.

## Material and Methods

### Subjects

Total of 60 subjects were recruited, of which 30 were CKD patients between the age group of 35 years and above, coming on outpatient basis to dialysis unit at Bharati Hospital and Research Center, Pune. CKD patients with history of CVDs, Diabetes mellitus, HIV/HBsAg positive, Infections, sign and symptoms of other systemic diseases, pregnant women were excluded. 30 healthy age and gender matched subjects were recruited as controls. The healthy control individuals were without any history of diabetes and/or cardiovascular disorders or any major illness. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration of 1975 that was revised in 2000. The informed consent was obtained from all individual participants.

### Laboratory measurements

After complete explanation of procedure to the patients 4 ml of blood sample was collected in plain & EDTA vacutainers. The EDTA blood sample was used for estimation of TnI. The blood from plain vacutainer was allowed to settle/clot for half an hour. Serum was separated after centrifugation at 2000 rpm for 10 minutes. It was subjected for estimation of CK-MB, LDH and AST levels. Estimation of TnI was done by Fluorescent Immunoassay (ALERE, INDIA). Estimations of CK-MB<sup>(19)</sup> LDH<sup>(20)</sup> and AST<sup>(21)</sup> were done by UV Method.

### Statistical Analysis

The continuous variables were expressed as Mean  $\pm$  SD. The means of the biochemical parameters were compared by unpaired students 't' test. The correlation of cardiac markers was evaluated by Pearson's correlation coefficient, and receiver operating characteristics (ROC) curve analysis was performed to find out the effectiveness of cardiac markers with the cut off values.

## Results

The present investigation was aimed to examine association of myocardial injury markers in patients of CKD and controls. The cardiac markers viz. TnI, CK-MB, LDH and AST were studied in CKD patients and age and gender matched healthy controls.

### Comparison of cardiac markers in patients with CKD and controls:

The cardiac markers including TnI, CK-MB, LDH and AST values are depicted in table no. 1. CK-MB ( $p=0.0125$ ) and LDH ( $p<0.0001$ ) levels were found to be significantly ( $p<0.05$ ) increased in CKD patients when compared with control subjects, and there was no significant change in AST and TnI levels in CKD patients when compared to control subjects.

**Table 1: Comparison of cardiac markers in patients with CKD patients and controls**

	CKD patients	Controls	'p' value
AGE (years)	44.53 $\pm$ 18.14	49.65 $\pm$ 8.59	0.0970
TROPONIN I	0.046 $\pm$ 0.010	0.05 $\pm$ 0.0	0.0811
CK MB (IU/L)	19.46 $\pm$ 10.66	13.26 $\pm$ 7.76	0.0125*
LDH (IU/L)	495.73 $\pm$ 145.42	299.53 $\pm$ 113.73	< 0.0001*
AST (IU/L)	15.76 $\pm$ 7.18	15.30 $\pm$ 5.61	0.7826

\*Statistically significant;  
CK MB: Creatine kinase MB; LDH: Lactate dehydrogenase; AST: Aspartate transaminase

### Correlation between cardiac markers in CKD patients

The correlation between different cardiac markers in CKD patients was evaluated by Pearson's correlation coefficient; it was observed that none of the cardiac markers was found to be statistically associated with other cardiac markers. The results of Pearson's correlation between cardiac markers in CKD patients are depicted in table no. 2, the value of 'r' denotes the correlation coefficient with respective p values.

**Table 2: Correlation between cardiac markers in CKD patients**

	CKMB	LDH
AST	r = 0.01868 p = 0.9220	r = 0.3439 p = 0.0628
CKMB	-	r = 0.1405 p = 0.4591

CK MB: Creatine kinase MB; LDH: Lactate dehydrogenase; AST: Aspartate transaminase

### ROC curve analysis of cardiac markers in CKD patients

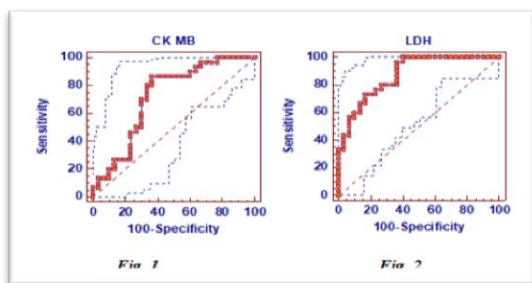
The ROC curve analysis was done for cardiac markers to find out the cut off values, for the prediction of CVDs in CKD patients. The cut off value for CKMB was found to be >13.51 with area under the ROC curve (AUC) of 0.72, 95% CI of 0.589 to 0.828 and 'z' & 'p' values of 3.19 & 0.0014 respectively with the highest sensitivity and specificity.

The cut off value for LDH was found to be >286.49 with area under the ROC curve of 0.87, 95% CI of 0.762 to 0.945 and 'z' & 'p' values of 8.54 & <0.0001 respectively with the highest sensitivity and specificity. The cut off values, AUC, standard error and 95% CI and respective 'z' and 'p' values for cardiac markers are presented in table 3, and ROC curves are depicted in figure 1 & 2.

**Table 3: Receiver operating characteristics curve analysis of cardiac markers in CKD patients**

	Cut-off value	AUC $\pm$ SE	95 % CI	'z' value	'p' value
CKMB	>13.51	0.72 $\pm$ 0.06	0.589 to 0.828	3.19	0.0014
LDH	>286.49	0.87 $\pm$ 0.04	0.762 to 0.945	8.54	<0.0001

\*Statistically significant; AUC: Area under curve; SE: Standard error; CI: Confidence interval; CK MB: Creatine kinase MB; LDH: Lactate dehydrogenase; AST: Aspartate transaminase



**Fig. 1 & 2: ROC curves for CK MB and LDH in CKD patients**

### Discussion

CKD patient population is evidently a major risk group for developing subsequent myocardial adverse outcomes.<sup>(4,5)</sup> CVD is the leading cause of death in this patient population and therefore, accurate diagnosis of acute cardiovascular syndromes is a necessity. A conscientious effort to the problem at hand is to ascertain a way of diagnosing this patient population as early as possible in order to take preemptive measures of prophylaxis and early treatment. The already established diagnosing methods are discarded in this patient population owing to their atypical cardiac symptoms and inability to undergo exercise stress test and may also be due to the false negative rate of pharmacological stress testing.<sup>(8)</sup>

Our endeavor through this research was to add on to the much needed knowledge on the various cardiac markers variation in this patient population. The incurred interpretation of the result of this research project were analogous to many researches, however were heterologous to a few too. It was found that the CK-MB and LDH levels were significantly increased in CKD patients when compared with control subjects. Moreover, no correlation was observed in the variations of all cardiac enzymes. The rise was independent of one another which indicate these enzymes have no relation whatsoever.

The "MB" in CK-MB denotes its 2 subunits M and B, combination of which, form iso-enzymes namely - CK-BB, CK-MB, CK-MM. Out of the aforementioned iso-enzymes, CK-MB has been found exclusively and in significant numbers in the myocardium, thus implying its high sensitivity and specificity for myocardial cell wall injury. Determination of CK-MB iso-enzyme has a 98% predictive value for myocardial necrosis with a positive enzyme profile and a 100% negative predictive value for the absence of necrosis with a normal profile.<sup>(22)</sup>

The raise in LDH, albeit, present in all the cells of the body, can be attributed to myocardial injury owing to the concurrent raise in the CK-MB levels. Therefore, the significant raise in the CK-MB values in patients of CKD in comparison to the controls can be imputed to the initiated myocardial necrosis in these patients thus aiding in the process of early diagnosis and treatment. As CK-MB and LDH have yielded high values in the

research, it can be ascertained that these cardiac markers can be used to veritably diagnose the cardiomyopathy in this patient population which can be treated early accordingly. It was also found that there was no significant change in AST or TnI in CKD patients as compared to control subjects.

Many studies have been conducted to elucidate the role of TnI in relation to its diagnostic and predictive role. Our study states no elevation in TnI levels as opposed to controls. Many studies, however, delineates the elevation of TnI as well as troponin T as important prognostic indicators signaling increase mortality in CKD patients owing to the anticipated cardiac complication.<sup>(10-12,15)</sup> One of which indicate troponin T to be a better prognostic marker than TnI.<sup>(12)</sup> Some studies concluded moderate or no elevation of cardiac troponin and therefore, to not have diagnostic or predictive value for subsequent adverse outcomes. Troponins in asymptomatic patients are of questionable value for risk stratification, most probably due to unspecific elevation.<sup>(14,17,18)</sup>

As the cut-off values of the cardiac biomarkers in patients of CKD and that of the controls differ, the cut off values has been calculated for the values of CK-MB and LDH. The cut off values for CK-MB and LDH were found to be 13.51 and 286.49 respectively, with the highest sensitivity and specificity.

The diagnostic and predictive value of the cardiac markers viz. TnI, CK-MB, LDH and SGOT has already been established for CVD, in normal healthy individuals. However, the correlation among them and the cut off values may differ in the individuals suffering from CKD owing to the highly deranged state of the bodily functions.

In the present study the levels of cardiac markers were estimated and compared between CKD patients and controls. According to the results, significant increase in levels of CK-MB and LDH were observed in CKD patients, which can be connoted to the risk stratification of myocardial adverse outcome. The number of false positives in various researches render them non-specific and of questionable value in diagnosis of myocardial injury in patients of CKD. However, our results suggest significant increase in the values irrespective of the falsity or veracity of the test.

Non-significant variations in levels of TnI and AST were observed which denote no probatory value of these cardiac markers in patients of CKD. Further prospective research is warranted to conclude the incoherent results in different research projects. It's highly unlikely to have a situation where none of the sample patients have cardiac adverse outcomes, and therefore, the former conclusion has been made. Moreover, no correlation was observed in the variations of all cardiac enzymes. The rise was independent of one another which indicate these enzymes have no relation whatsoever.

Considering there may be variation in cut-off values of normal healthy individuals and CKD patients, the requisite cut-off values for CKD individuals when calculated were found to be >13.51 and >286.49 for CK-MB and LDH respectively with the highest sensitivity and specificity indicating any rise of these values above the given, to be significant for CVD in CKD patients.

### Conclusions

The present study concluded, taking into consideration all the data, findings and result, that CKD patients, who are disposed to developing cardiovascular conditions causing more than 50% of mortality in this patient population, should be diagnosed early of their cardiovascular condition which would be highly conducive in early treatment and reduction in mortality. Our findings indicate the significant rise in CK-MB and LDH to be an early marker to diagnose CVD in CKD patients. However, as there was no significant rise in the TnI and AST levels, these cardiovascular markers seem to be unavailing in early diagnosis of CVD in CKD patients. Moreover, no significant correlation was found between any of the cardiovascular biochemical markers.

Considering the difference in the milieu intérieur and the functioning of various organ systems in the control and CKD patients, we infer that the cut off values of general population won't be conforming to the latter's condition resulting in mis (under) diagnosis. Therefore, the cut off values were formulated and calculated to be >13.51 and >286.49 for CKMB and LDH respectively using ROC curve analysis.

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