Original Article

Prognostic Significance of Serum Cholinesterase in Acute Myocardial Infarction

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Abstract

Background: Autonomic dysfunction has a prognostic significance in various cardiovascular (CV) disorders, particularly atherosclerotic coronary artery disease (CAD). Previous studies are few, regarding the association of parasympathetic dysfunction with increased complications in patients with the acute coronary syndrome, a subset of CAD. We aimed to study the correlation of trends in the serum cholinesterase (sChE) levels, the marker of parasympathetic activity, with the occurrence of major adverse cardiovascular events (MACEs) in ST-segment elevation myocardial infarction (STEMI) patients. **Methodology:** We prospectively observed the levels of sChE in patients with STEMI on the day of admission, day 3, and day 5 along with routine biochemical profile, electrocardiogram, echocardiography, and coronary angiography. The patients were monitored during the hospital stay and were followed up at 1 month for the occurrence of any MACE. The MACE monitored was cardiac death, complete heart block, arrhythmias, and heart failure. The sChE levels are laboratory dependent and a value between 4000 and 14000 IU/L was considered normal in our laboratory. A value <4000 IU/L is noted as a low sChE level. The receiver operating characteristic curve was plotted for the cut off value of the sChE levels to predict the outcomes of patients. **Results:** Of the 100 STEMI patients studied, the sChE levels were persistently lower in patients who had MACE compared to those without MACE during the hospital stay and at month follow-up, which was statistically significant. A sChE <3745 IU/l on day 5 predicted an increased MACE with a sensitivity of 93.55% and specificity of 92.11%. **Conclusion:** A persistently low sChE levels from the day of admission can predict MACE in STEMI patients. Larger studies with prolonged follow-up are required for the causal association in the future.

Keywords: *Major adverse cardiac events, parasympathetic nervous system, ST-segment elevation myocardial infarction, serum cholinesterase*

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Introduction

The incidence of coronary artery disease (CAD) is progressively increasing globally and affecting young people too. ST-segment elevation myocardial infarction (STEMI) occurs secondary to total occlusion in the coronary artery resulting in transmural necrosis. Time is the muscle in the management of STEMI.[1] Early recognition and restoration of normal blood flow to salvage the myocardium is the primary goal.[1] Approximately in 80% of the cases, the diagnosis of STEMI can be confirmed by electrocardiography. The remaining can be confirmed by raising cardiac enzyme levels or the presence of regional wall motion abnormality on echocardiography.[2] Cardiovascular (CV) function is closely linked to the autonomous nervous system. The autonomic imbalance, i.e., either a decreased vagal activity or an increase in sympathetic activity is associated with increased CV mortality in STEMI.[3,4] The prognostic significance of serum cholinesterase (sChE) levels in predicting major adverse cardiovascular event (MACE) in STEMI patients has been evaluated in this study.

Methodology

This study is a prospective observational study done from April 2020 to October 2021 in patients attending the Cardiology Department in Osmania General Hospital, Hyderabad. Patients with acute STEMI were included in the study. Patients with onset of symptom (chest pain) >48 h and conditions associated with decreased levels of sChE, i.e., liver disease (hepatitis, cirrhosis, and malignancy), malignancies,

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chronic renal failure, dermatomyositis, nephrotic syndrome, toxic goiter, patients receiving the sympathomimetic drug, phenothiazine derivatives, and atropine or its analogs were excluded from the study. History regarding the onset of chest pain, demographic data, and presence of comorbidities was collected from each patient. Each patient underwent an electrocardiogram for the diagnosis of STEMI, and echocardiography for the assessment of regional wall motion abnormality and left ventricular function. The biochemical profile included a complete blood picture, random blood sugars, lipid profile, serum creatinine, and serum electrolytes apart from the sChE levels.

Assessment of serum cholinesterase levels

The assessment was by the colorimetric method. Samples were collected in standard sampling tubes and were sent to the laboratory in an ice pack. The stability of the sample collected is a week when stored at 4°C–8°C and 4 weeks at −20°C. Normal values differ between the laboratories based on the testing method and the population studied. The normal level in males is between 4000 and 14,000 IU/L and in females is between 3930 and 13,800 IU/L. The sChE levels were assessed at admission, on day 3, and day 5.

Coronary angiography was done to identify the extent of CAD and the culprit artery. The sChE levels at predetermined time intervals were assessed in all the patients enrolled in the study. Patients were monitored for MACE during the hospital stay and at a 1-month follow-up. CV mortality, heart failure, arrhythmias, and heart blocks were recorded as MACE. The patients were divided into two groups based on the occurrence of MACE. The patients with MACE were categorized as a complicated group and without MACE as an uncomplicated group. The baseline characteristics, clinical profile, and sChE levels were compared between the groups.

The institutional ethics committee approved the study protocol. All the patients signed the informed consent form. SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA) was used to analyze the data. Data were entered into Microsoft excel sheets to generate graphs, tables, etc. The continuous variables were presented as mean ± standard deviation and categorical variables were presented in number and percentage. The association between the variables and sChE levels was assessed. The receiver operating characteristic (ROC) curve was plotted for the sChE levels at admission, and day 5 for the cut off to predict the probability of MACE.

Results

A total of 100 patients were studied. The mean age of the study group is 55.1 ± 11.76 years. The male:female ratio is 2.57:1 (72 males vs. 28 females). The common age group in the study was 40–49 years (34%) followed by 26%, 22%, and 12% of age 50–59 years, 60–69 years, and >70 years, respectively. Only 6% of patients belonged to age <40 years. Smokers were 58% and alcoholics were 57%. When stratified the study group according to the body mass index (BMI) (kg/m^2), 38% had BMI between 25 and 29.9, 25% had between 23 and 24.9 and only 10% had BMI >30. The baseline characteristics of the study group are described in Table 1.

Of the 100 patients, 62 patients were in the complicated group and 38 patients in the uncomplicated group. The characteristics of both groups are shown in Table 2. The sChE levels were persistently lower in the complicated group compared to the uncomplicated group and which was statistically significant [Table 2 and Figure 1]. Of the 62 patients in the complicated group, 22 (35.5%) patients died, 10 (16.13%) patients developed complete heart block, 18 (29.03%) patients had heart failure, and 12 (19.35%) patients had arrhythmias [Figure 2].

Table 1: Baseline characteristics of the study group (*n*=100)

Characteristic	Mean±SD (*n*)
Age (years)	55.1±11.76
<40	6
40-49	34
50-59	26
60-69	22
≥70	12
Males	72
Females	28
Male: female	2.57:1
History of alcohol consumption	57
History of smoking	28
BMI (kg/m^2)	25.1±4.4
<18	3
18-22.9	24
23-24.9	25
25-29.9	38
≥30	10
Angiographic profile	
Normal coronaries	22
Single-vessel disease	22
Double-vessel disease	29
Triple-vessel disease	27

All the continuous variables were denoted in mean±SD and categorical variables in number. SD=Standard deviation, BMI=Body mass index

Table 2: Comparison of the profile of patients in the complicated and uncomplicated groups

Variable	Complicated (*n*=62)	Uncomplicated (*n*=38)	*P*
Age	55.26±11.29	54.61±12.8	0.79
Male	41	31	0.1
Female	21	7	0.1
BMI	24.87±4.15	25.47±4.73	0.51
Smoker	33	25	0.22
Alcoholic	27	30	<0.01
sChE levels			
At admission	3614.15±447.09	4838.92±725.45	<0.01
Day 3	2298.65±358.69	3361.39±503.96	<0.01
Day 5	2865.39±786.42	4830.58±889.28	<0.01

BMI=Body mass index, sChE=Serum cholinesterase

There was no significant difference in the sChE levels across age or gender. The association between sChE levels and smoking history did not show any significant difference. The sChE levels did not show any association with the number of vessels having significant stenosis (>70% diameter stenosis) [Table 3]. The ROC curve was plotted for all the patients in the group to note the cutoff value of the sChE level for predicting the occurrence of MACE at admission, and day 5. The sChE level ≤4125 IU/L at admission had a sensitivity of 93.5% and specificity of 96% (area under the curve [AUC] 0.865) in predicting the MACE [Figure 3]. Similarly, a value ≤3875 IU/L on day 5 had a sensitivity of 93.55% and specificity of 92.11% in predicting the MACE [Figure 4].

Discussion

This prospective observational study of STEMI patients done in a tertiary care hospital has shown that persistent low levels of sChE from the day of admission predict the occurrence of MACE. It can be used as a prognostic marker in STEMI patients for CV mortality or occurrence of arrhythmias, and heart failure.

Most patients with CV disease have autonomic dysfunction (the imbalance in sympathetic and parasympathetic activity). The mechanisms underlying their influence on long-term CV outcomes are incompletely understood. This imbalance has led to identifying measurable biomarkers of parasympathetic activity so that risk can be predicted. The indirect measures of cardiac parasympathetic dysfunction are elevated resting heart rate, delayed heart rate recovery after exercise, and attenuated heart rate increase during exercise.[3-5] However, sChE is commonly used as a biomarker of parasympathetic activity. It is the cumulative effect of acetyl and butyrylcholinesterase.

Table 3: Association of serum cholinesterase levels with variables

Variable	sChE levels[#]		
	Day 1	Day 3	Day 5
Alcohol consumption			
Yes	4275.46±870.83	2834.75±681.94	3859.12±1308.61
No	3819.88±680.55	2527.16±607.37	3284.79±1133.80
F-statistics	8.05	5.47	5.28
P	0.005	0.02	0.02
Smoking			
Yes	4159.98±841.29	2691.97±662.70	3644.95±1325.96
No	3968.50±792.82	2717.02±677.28	3566.88±1185.38
F-statistics	1.32	0.03	0.09
P	0.25	0.85	0.76
BMI			
<18	3727.67	2640.33	3473.33
18-22.9	3895.04	2692.58	3457.71
23-24.9	4372.68	2936.88	3904.88
25-29.9	4061.42	2576.95	3609.08
≥30	3964.10	2636.00	3304.40
F-statistics	1.30	1.15	0.57
P	0.27	0.33	0.68

[#]Units (IU/L) BMI=Body mass index, sChE=Serum cholinesterase

The substrate for these is acetylcholine, the neurotransmitter of the parasympathetic system. Acetylcholine is labile and

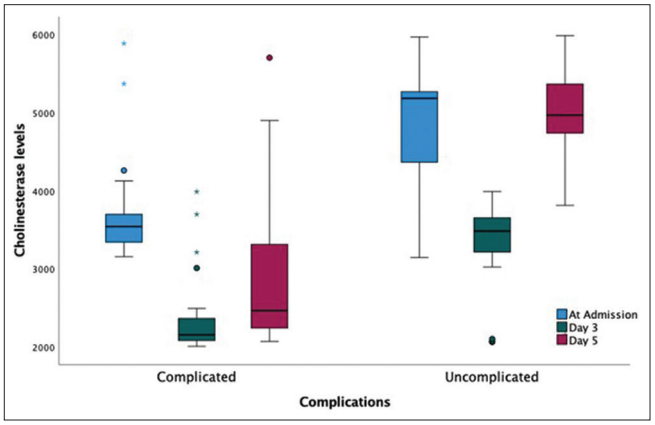

Figure 1: Box Whisker plot showing the trend of sChE levels in complicated and uncomplicated groups. sChE = Serum cholinesterase

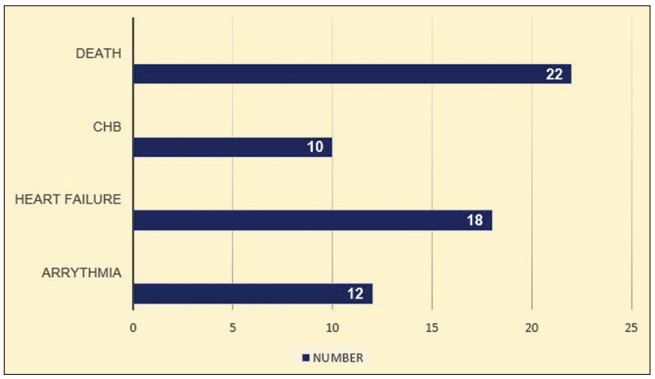

Figure 2: Bar diagram showing the type of MACE in the complicated group. MACE = Major adverse cardiovascular event

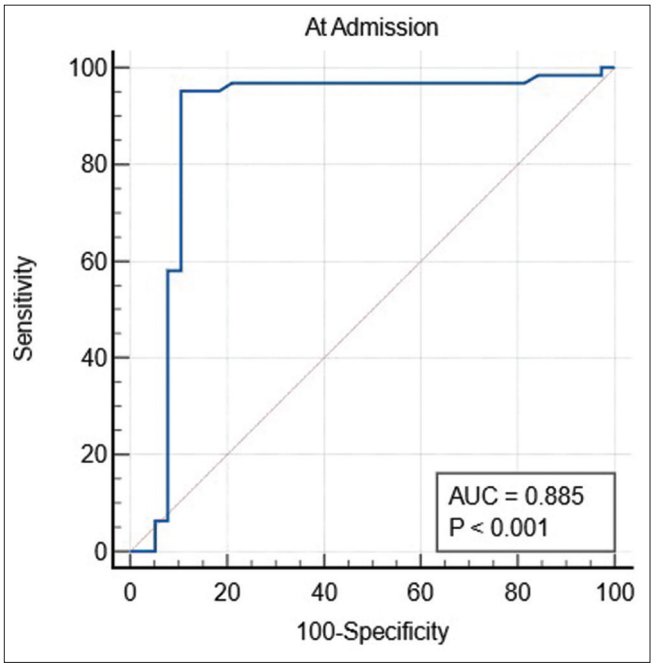

Figure 3: The receiver operating characteristic curve of sChE levels at the time of admission. sChE = Serum cholinesterase

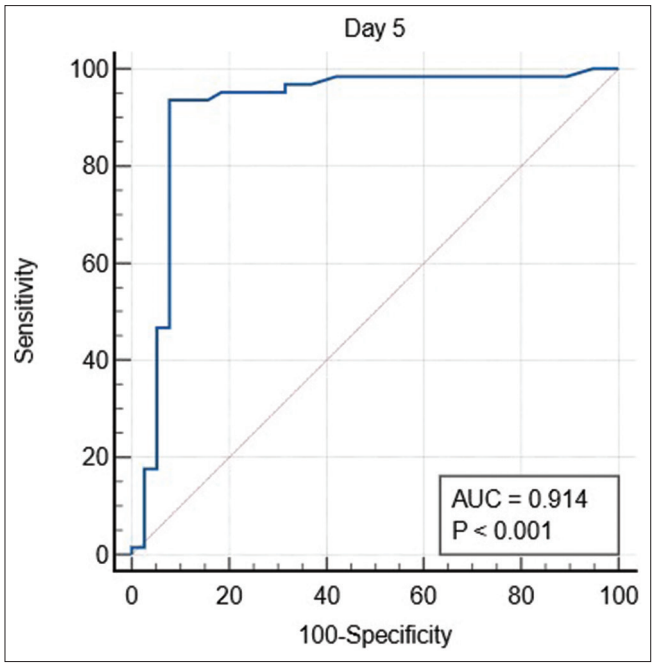

Figure 4: The receiver operating characteristic curve of sChE levels on day 5. sChE = Serum cholinesterase

difficult to use for clinical measurements. Hence, measuring sChE would be a feasible option. The parasympathetic activity is assumed as reduced by a low sChE and thereby would predict a poor prognosis.[6,7] In this study, we studied the impact of the parasympathetic activity on the prognosis of STEMI patients by assessing the sChE levels at admission, day 3, and day 5.

The sChE levels vary according to age and usually decrease with age. In this study, we did not find any correlation between age and sChE levels which is in contrast with the previous studies.[8-12] The age of the groups in the studies might have led to a conflicting association.

The sChE levels as per the gender did not show any difference, a similar observation was seen by Sato *et al*.[12] There are few studies which have reported a higher sChE levels in males compared to females.[9,10,11] A negative correlation of sChE with BMI has been observed in the past.[8,9,11,12] In our study, we found no correlation between BMI and sChE levels (give the R^2 value), and our results correlate better with the study by Mito *et al*.[10] The varying number of participants might have led to the conflictive findings. The association between sChE and smoking and alcohol consumption cannot be interpreted as they were not compared with normal people without alcohol consumption. The sChE levels were persistently lower than usual in patients with MACE compared to those without MACE since admission and it was statistically significant ($P < 0.05$). Similar trends in sChE levels were noted in the previous studies.[8,9,13] The present study is compared with the previous studies as shown in Table 4.

The cutoff level to predict the MACE was done by plotting the ROC curve. A value of <4215 U/L at admission (sensitivity 93.5% and specificity 96%, AUC 0.865) and <3875 U/L on day 5 (sensitivity 93.55% and specificity 92.11%, AUC) predicted the occurrence of MACE in STEMI patients. Previous studies did not assess the cutoff values in the prediction of MACE.

Table 4: Correlation of different parameters with sChE levels in the present study and previous studies

Parameter	Arbel et al.[6]	Goliasch et al.[8]	Calderon et al.[10]	Present study
Cardiac events	MACE (inverse)	Mortality (inverse)	Mortality (inverse)	MACE (inverse)
CRP	Inverse	-NA-	-NA-	-NA-
Sex	No	Positive	No	No
BMI	No	Positive	Positive	No
Age	No	Negative	Negative	No
Smoking	-NA-	No	-NA-	No
Alcohol	No	No	-NA-	No
Multivessel disease	No	No	-NA-	No

MACE=Major adverse cardiovascular events, CRP=C reactive protein, BMI=Body mass index, NA=Not available

The limitations of the study are small study population, other markers of parasympathetic activity such as heart rate variability and SA node recovery time were not assessed (as assessment of these values in acute coronary syndromes is not feasible). The sChE levels might have been influenced by serum proteins and liver function, inflammatory markers C-reactive protein. We did not measure these parameters in the study. A study involving a larger population and long follow-up would help in confirming the causality of the decreasing trends in sChE levels with increased MACE.

Conclusion

The decreasing trends of sChE levels in patients with STEMI had a poor prognosis compared to those with no decrease in the levels.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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