



## Serum Cortisol Level as a Predictor of In-Hospital Mortality in Patients Undergoing Primary Percutaneous Intervention for ST Segment Elevation Myocardial Infarction

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### Abstract

**Introduction:** Various laboratory markers have been proposed to assess prognosis in myocardial infarction. Serum cortisol is one such laboratory marker. There are only few studies done in the recent past which prove that cortisol is a prognostic marker in STEMI.

**Methods:** We studied a total of 168 patients who presented with STEMI and underwent primary percutaneous intervention (PPCI) within 12 hours of symptom onset between April 2016 and November 2016.

**Results:** The average age of study population was  $61 \pm 0.12$  years. Males were predominant ( $n = 132, 78.57\%$ ). 155 patients survived, whereas 13 patients died in the hospital. Mean syntax score was  $16.65 \pm 5.33$  among patients who died, whereas it was  $13.11 \pm 5.62$  among survivors ( $P = 0.03$ ). Mean cortisol was significantly higher among the patients who died ( $46.13 \pm 14.61$  mcg/dl) than the survivors ( $31.16 \pm 13.16$  mcg/dl) ( $P = 0.003$ ). The ROC AUC for in-hospital mortality was 0.77 (95% confidence interval [CI], 0.645–0.897). An optimal cut-point identified from the ROC curve was a random serum cortisol concentration of 33.66 mcg/dl, with corresponding sensitivity and specificity of 69.2 % and 64 %, respectively. At a cut-point of 29.55 mcg/dl, sensitivity and specificity were 84.6 and 50 %, respectively.

**Conclusion:** This study showed that serum cortisol level is a strong predictor of mortality in patients undergoing PPCI for STEMI. Levels more than 33.66 mcg/dl can predict mortality with a sensitivity of almost 70 percent and specificity of 64 percent.

## INTRODUCTION

ST segment elevation myocardial infarction (STEMI) is one of the cardiovascular diseases carrying high mortality. Among the subgroup in STEMI, elderly patients, cardiogenic shock, anterior infarction, high sum of ST segment elevation and right ventricular infarction carry a higher mortality. Various risk

assessment scores and laboratory markers have been proposed to assess prognosis in myocardial infarction. Serum cortisol is one such laboratory marker. There are only few studies done in the recent past which prove that cortisol is a prognostic marker in STEMI.

Serum cortisol levels increase in response to acute critical illness. This involves activation of hypothalamic pituitary adrenal axis [1]. In myocardial infarction, both high and low cortisol levels have been correlated with mortality [2-5]. Though most of the studies demonstrated a high cortisol level and mortality association [2-4], a few studies also demonstrated a low serum cortisol level being associated with mortality [5]. This study was done to correlate serum cortisol with mortality and determine a cut-off value of cortisol, which can predict mortality in patients undergoing primary percutaneous coronary intervention (PPCI) for STEMI.

## METHODS

### Study Population

A total of 168 patients presented with STEMI and underwent PPCI within 12 hours of symptom onset between April 2016 and November 2016.

Subjects were not eligible if they had any of the following conditions:

1. Steroid use
2. Prior history of Myocardial infarction
3. History of recent infection
4. History suggestive of hypo/ hypercortisolism
5. Retroviral illness
6. History of hypothyroidism or hyperthyroidism

The study protocol was approved by the ethics committee of the Institution and informed consent were obtained prior to study entry.

### Methodology

STEMI was defined by the American College of Cardiology [6] as "new ST elevation as measured from the J-point in 2 or more contiguous leads with leads V1, V2, and V3 measuring at least 0.2 mV or at least 0.1 mV in the remaining leads."

All patients received a complete physical examination, assessment of coronary risk factors, medical histories and presenting clinical symptoms were also recorded. Venous blood samples were collected when the patient initially presented to the emergency department or intensive coronary care unit (ICCU) before PPCI. Serum Cortisol (in mcg/dl) and troponin T levels (in ng/ml) were calculated in the laboratory using electrochemical luminescence immunoassay (EQL). We correlated at-admission serum cortisol levels with in-hospital mortality in patients with STEMI undergoing PPCI.

### Angiographic Analysis

Coronary angiography was performed through the femoral/radial artery and the angiograms were visually evaluated by interventional cardiologists who were blinded to the study plan and to each other. A thorough analysis of each coronary angiography established the

lesion location and the percentage of stenosis. Coronary artery disease was defined as > 50% stenosis in the luminal diameter in at least one major epicardial coronary artery. All patients underwent primary PCI to culprit vessel.

The Gensini scoring system was used to define the severity of the CAD. This method grades the narrowing in the lumen of the coronary arteries as 1 for 1-25% stenosis, 2 for 26-50%, 4 for 51-75%, 8 for 76-90%, 16 for 91-99%, and 32 for total occlusion. The score is then multiplied by a factor illustrating the importance of the lesion's location. For the location scores, 5 points are assigned for left main lesion; 2.5 for left circumflex (LCX) artery and proximal left anterior descending (LAD); 1.5 for the mid-segment LAD and LCX; 1 for the distal segment of LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for the second diagonal and second obtuse marginal branches.

Gensini Score Calculation: severity score × segment location multiplying factor X collateral adjustment factor [7].

Lesions were also categorized according to number of vessels involved. Grade 0 was given smooth epicardial arteries, Grade 0.5 to plaque < 50% diameter stenosis, Grade 1 to single vessel disease, Grade 2 to double vessel disease and Grade 3 to triple vessel disease. Coronary lesions leading to ≥ 50% diameter stenosis in vessels ≥ 1.5 mm was scored separately and added together to provide the cumulative syntax score which was prospectively calculated using the SYNTAX score calculator on the baseline diagnostic angiogram.

### Statistical Analysis

The statistical comparisons for the quantitative variables describing the clinical characteristics of the groups were carried out using Independent sample t test and expressed as mean ± standard deviation. The cortisol levels were also plotted on an ROC curve. The area under the ROC (AUC) as well as the most appropriate cutoff cortisol levels were calculated. The most appropriate cutoff values were established as the ones with higher result of the sum of sensitivity and specificity. Pearson's non parametric test was used to compare serum cortisol levels with Gensini and SYNTAX score. All statistical analysis was done using statistical software IBM SPSS version 23.

## RESULTS

The average age of study population was 61 ± 0.12 years. Males were predominant (n = 132, 78.57%). 155 patients survived whereas 13 patients died. Anterior wall MI was commoner than inferior wall MI. Mean syntax score was 16.65 ± 5.33 among patients who died whereas it was 13.11 ± 5.62 among survivors (P = 0.03) (Table 1).

**Table 1.** Baseline characteristics

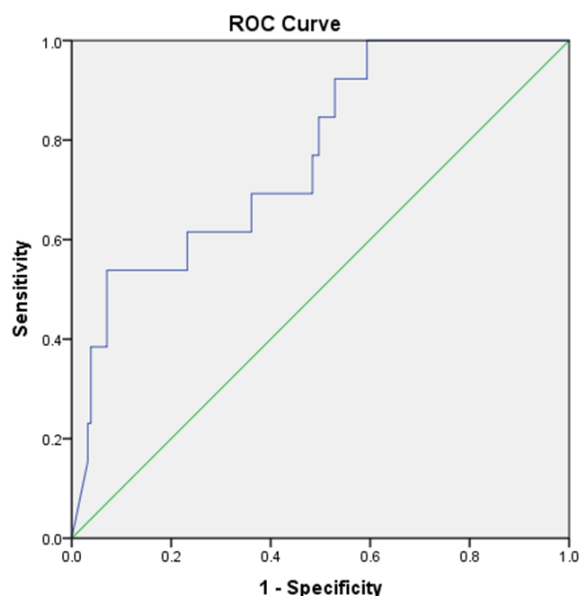
Variables	All patients (n = 168)	Survived (n = 155)	Expired (n = 13)	P value
Age (years)	61 ± 0.12	61.37 ± 9.84	60.69 ± 9.52	0.812
Male	132 (78.57)	122 (78.71)	10 (76.92)	0.895
Female	36 (21.43)	33 (21.29)	3 (23.08)	0.880
Diabetes mellitus	32 (19.04)	27 (17.42)	5 (38.46)	0.064
Hypertension	41 (24.40)	35 (22.58)	6 (46.15)	0.058
Dyslipidemia	20 (11.90)	15 (9.68)	5 (38.46)	0.002
Smokers	21 (12.5)	15 (9.68)	6 (46.15)	0.000
AWMI (Infarction in LAD territory)	87 (51.78)	78 (50.32)	9 (69.23)	0.191
IWMI (Infarction in RCA or LCx territory)	81 (48.22)	77 (49.68)	4 (30.77)	0.191
Syntax score	13.33 ± 5.57	13.11 ± 5.62	16.65 ± 5.33	0.030
Cortisol (mcg/dl)	32.32 ± 13.83	31.16 ± 13.16	46.13 ± 14.61	0.000
Gensini score	59.33 ± 26.51	57.27 ± 25.61	83.85 ± 25.72	0.001

Data in table are presented as Mean ± SD or No. (%)

(AWMI-anterior wall myocardial infarction, IWMI - inferior wall myocardial infarction, LAD – left anterior descending artery, RCA – right coronary artery, LCx – left circumflex artery)

Mean cortisol was significantly higher among the patients who died ( $46.13 \pm 14.61$  mcg/dl) than the survivors ( $31.16 \pm 13.16$  mcg/dl) ( $P = 0.003$ ). Mean cortisol level was  $36.85 \pm 13.09$  mcg/dl in females whereas it was  $31.09 \pm 13.81$  mcg/dl in males ( $P = 0.02$ ). Mean cortisol level was  $33.11 \pm 14.05$  in AWMI whereas it was  $31.13 \pm 13.31$  mcg/dl in IWMI ( $P = 0.4$ )

The ROC AUC for in-hospital mortality was 0.771 (95% confidence interval [CI], 0.645–0.897). An optimal cut-point identified from the ROC curve was a random serum cortisol concentration of 33.66 mcg/dl, with corresponding sensitivity and specificity of 69.2 % and 64 %, respectively. At a cut-point of 29.55 mcg/dl, sensitivity and specificity were 84.6 and 50 %, respectively (Fig 1).



**Figure 1.** Serum cortisol levels as a predictor of mortality in patients with ST segment elevation myocardial infarction. ROC analysis revealed that area under the curve was 0.77. The cut-off value of serum cortisol for predicting mortality was 33.66 mcg/dl.

## DISCUSSION

Our study correlated at-admission serum cortisol levels with mortality in patients with STEMI undergoing PPCI. We studied the correlation of cortisol levels with in-hospital mortality, age, distribution of MI and magnitude of coronary artery disease. Several studies have correlated serum cortisol levels with outcomes in MI [2-5, 8, 9]. However most of these studies were done few decades ago. To our knowledge this is the first study in patients with ST segment elevation MI undergoing PPCI correlating serum cortisol levels with in-hospital mortality. In-hospital mortality was 7.73 percent and mean cortisol level was significantly higher among the patients who died. In our study the cut-off for serum cortisol level to predict mortality was 33.66 mcg/dl, with corresponding sensitivity and specificity of 69.2 % and 64 %, respectively.

Zouaghi et al. [2] reported a negative association between cortisol concentration and risk of death in 34 consecutively treated patients with acute coronary syndrome. Bain et al. [3] studied serum cortisol response to acute myocardial infarction in 70 consecutive patients admitted to a coronary care unit and showed that the levels were significantly raised early in the course of the illness and prior to elevation of the cardiac specific enzyme fraction, creatine kinase MB. They also showed that very high levels (more than 2000 micromole/L) were predictive of mortality. Imran Nito et al. [4] studied thirty-six patients with myocardial infarction and correlated mortality with random serum cortisol levels. Out of these, four patients died, whereas thirty-two patients survived. Serum cortisol was significantly higher among the patients who died than the survivors. In this study, death and size of myocardial infarction were significantly correlated with a cortisol level of more than 20 mcg/dl on the day of admission. Reynolds et al. [5] demonstrated lower serum cortisol levels in patients who died than those who survived (median, 1189 nmol/L vs. 1355 nmol/L;  $P < 0.001$ ). A cortisol concentration in the bottom quartile ( $< 1136$

nmol/L) was a strong predictor of death within 30 days. Wiener showed that significant limit of cortisol level to death was found to be > 20 ug/dL. Plasma cortisol levels in myocardial infarctions with any complication were higher than in patient with infarction without any complication [9]. Prakash also found similar results, i.e. 10 out of 12 acute myocardial infarction patients with complication had cortisol levels of > 40 ug/dL.

In this study there was no correlation between serum cortisol levels with Gensini and syntax score. This establishes the fact that cortisol levels may predict in-hospital mortality in STEMI independent of the extent or severity of coronary artery disease. However, there are no previous studies correlating cortisol levels with either syntax or Gensini score. Further studies need to be conducted in STEMI with larger mortality data to establish the relation. Also, we did not find any correlation between mean cortisol levels with age and distribution of myocardial infarction. However, females had a significant higher cortisol levels compared to males.

Few limitations of this observational study merits consideration. We studied only the in-hospital mortality in patients undergoing primary PCI and correlated with serum cortisol levels and so the long term clinical outcomes were not studied. There is a diurnal variation in serum cortisol levels with levels being highest in morning and lowest at mid-night. The appropriate time to measure cortisol levels following stress remains uncertain. Though many studies conducted shows that cortisol response following acute stress is blunted, it still remains controversial. So further studies are required to study the diurnal variation in cortisol levels following STEMI.

## CONCLUSION

In our study we showed that serum cortisol level is a strong predictor of in-hospital mortality in patients undergoing PPCI for STEMI. Levels more than 33.66 mcg/dl can predict mortality with a sensitivity of almost 70 percent and specificity of 64 percent.

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## Conflicts of Interest

None

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