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Serum procalcitonin levels in AMI patients in predicting the Clinical outcome

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Abstract-

Background and Aim: Procalcitonin (PCT), a 14-kilodalton, Calc-1 gene-coded protein, consisting of 116 amino acids, issecreted under normal conditions, from thyroid C-cells. Physiological levels of PCT in serum are negligible.[1]To determine if procalcitonin can be used to predict the clinical outcome in acute Myocardial Infarction -(M.I.) patients.

Methods-This was a prospective analytical study on patients with acute myocardial infarction, admitted under the department of General Medicine, JIPMER, from July, 2020 to June 2021. The Institute Ethics Committee (Human Studies) approved the protocol on 6th July,2020. All patients both males and females, above 18 years of age, admitted in JIPMER under the Department of General Medicine, with definitive evidence of acute myocardial infarction, within 24 hours of admission were enrolled in the study.

Results-After obtaining informed consent, 268 cases of acute M.I. were enrolled in the study. Baseline data and blood samples were collected for all 268 patients. Of these, 54 patients were excluded (24 had turned COVID-19 positive and were lost to follow up, while 30 were found to have infection on follow-up, or data were not available during follow-up). At the end of the study, hsCRP and procalcitonin levels were estimated for all the 214 patients and were followed up till 1 month after discharge. Mean age of the study population was 56.53±11.43 years, 73.4% of the cases were males with 22.5% were aged > 65 years. Out of 214 cases STEMI vs NSTEMI was 72% and 28% respectively.59.35% of the patients had poor clinical outcome during the studyperiod.Mean hsCRP value of the sample populationwas 73.52 +/- 63.87 mg/L. Thedifference in hs-CRP values between poor and good clinical outcome groups was statistically not significant.Median procalcitonin value in our study population was 2085.12 (801.40 - 6841.40) pg/mL.There was no statistical significance in procalcitonin values among patients with poor and good clinical outcome groups.There was a statistically significant difference in clinical outcome between different Killip's classes (p-value (p value <0.001) and between patients with different ejection fraction (p <0.01). The difference in procalcitonin values between poor and

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not poor clinical outcome patients was statistically not significant probably because both poor and not poor clinical outcome classes had patients with statistically comparable ejection fraction (p-value 0.036) and Killip's classes (p-value 0.02).Levels of procalcitonin and hsCRPwere compared in acute myocardial infarction patients.hsCRP and procalcitonin levels in acute myocardial infarction patients are poorly correlated in the study population. Strength of correlation was 0.01

Conclusion-Acute M.I. is one of the leading causes of cardiovascular mortality around the world. Procalcitonin was elevated in both STEMI as well as NSTEMI patients without any statistical difference between poor vs good clinical outcome groups.The difference in procalcitonin values between poor and good clinical outcome patients was statistically not significant probably because both poor and good clinical outcome classes had patients with statistically comparable ejection fraction (p-value 0.036) and Killip's classes (p-value 0.02). This comparable distribution probably resulted in statistically insignificant difference between poor and good clinical outcome groups. Further studies with larger sample sizeare required to confirm this difference in procalcitonin in different Killip's classes and between different ejection fraction groups for attributing this as the reason for no statistical significance in procalcitonin levels between poor and not poor clinical outcome groups.

Keywords- Procalcitonin, Acute Myocardial Infarction, Ejection Fraction, Coronary Arterial Disease, NSTEMI.

INTRODUCTION

Procalcitonin (PCT), a 14-kilodalton, Calc-1 gene-coded protein, consisting of 116 amino acids,is secreted under normal conditions, from thyroid C-cells. Physiological levels of PCT in serum are negligible.[1]In response to stress (tissue damage, hypotension, infections), procalcitonin messenger RNA (mRNA) is elevated in human extra-thyroidal tissues. Thus, serum PCT levelsan indicator of the systemic inflammation and an acute-phase marker.[1]Systemic inflammation is a cardinal feature of myocardial infarction (MI). Bio markers like myoglobin, creatinine kinase -MB (CK-MB), Troponin-T and Troponin-I have been found to be increased in acute MI. Highly sensitive C-reactive protein (hsCRP) is another molecule that is almost always increased in MI.

Procalcitonin is another new cardiac marker in acute MI.[2]Normal value of serum procalcitonin is <0.05ug/L.[3]According to previous studies,[4] procalcitonin has been found to increase in serum approximately 2-3 hours after ACS. Serum PCT has been found to reach its maximum value after 12-24 hours of the episode. PCT has been found to reach the baseline (<0.05 ng/ml) after 1 week.[4]Cardiovascular disease caused more than 2·1 million deaths in India in 2015 at all ages, or over a quarter of all deaths.[5]Myocardial infarction, commonest coronary artery disease (C.A.D.), accounts for 15% of the fatalities yearly.[6]

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If identified and managed early, myocardial infarction has been found to have superior clinical outcome (diminisheddeath and disability). Thrombolysis has the best prognosis, ifgiven within 6 hours of myocardial infarction. Hence, timely recognition of myocardial infarction is an absolute necessity.Not many studies have been conducted in India,on the use of procalcitonin in predicting clinical outcome in acute MI patients. Procalcitonin levels could be used in predicting clinical outcome in acute M.I. patients.

MATERIALS and METHODOLOGY

This was a prospective analytical study on patients with acute myocardial infarction, admitted under the department of General Medicine, JIPMER, from July, 2020 to June 2021. The Institute Ethics Committee (Human Studies) approved the protocol on 6th July,2020.

All males and females, above 18 years of age, admitted in JIPMER under the Department of General Medicine, with definitive evidence of acute myocardial infarction, within 24 hours of admission.

The study excluded patients with

- Clinical /microbiological evidence of infection
- Previous malignancy (except basal cell skin carcinoma)
- Suspected or known immunocompromised state
- History of (or at high risk for) tuberculosis or HIV-related disease
- Those using systemic anti-inflammatory agents
- Unconscious patients

Sample size calculation:

Assuming alpha error of 5%, power of 80%, expected area under the curve 0.7, proportion of poor clinical outcome as 10%, 10% as non-responders, we need 210 patients for the study. Sample size calculated using MedCalcsoftware.Convenient sampling from eligible consenting patients.

Methodology-

Acute MI patients were identified based on the "fourth universal definition of myocardial infarction".[12]Inclusion and exclusion criteria were applied and eligible candidates were enrolled.Consent was taken from the patients and baseline clinical data of the patients were collected. (age, gender, hospital number, contact details, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, room air saturation, STEMI or NSTEMI, site of infarction, ejection fractionand killip'sclass)

DATA ANALYSIS

Data analysis was done using STATA VERSION 14 software. Continuous variables with normal distribution expressed as mean with standard deviation.Categorical variables were expressed

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asnumbers with proportions (n (%).Correlation between procalcitonin level and clinical outcome in acute MI patients was compared using Mann Whitney test.hsCRP and procalcitonin levels in acute myocardial infarction patients were compared using scatter diagram.Appropriate tests of statistical analysis were used for the remaining data analysis.

RESULTS

Figure 1- Age distribution

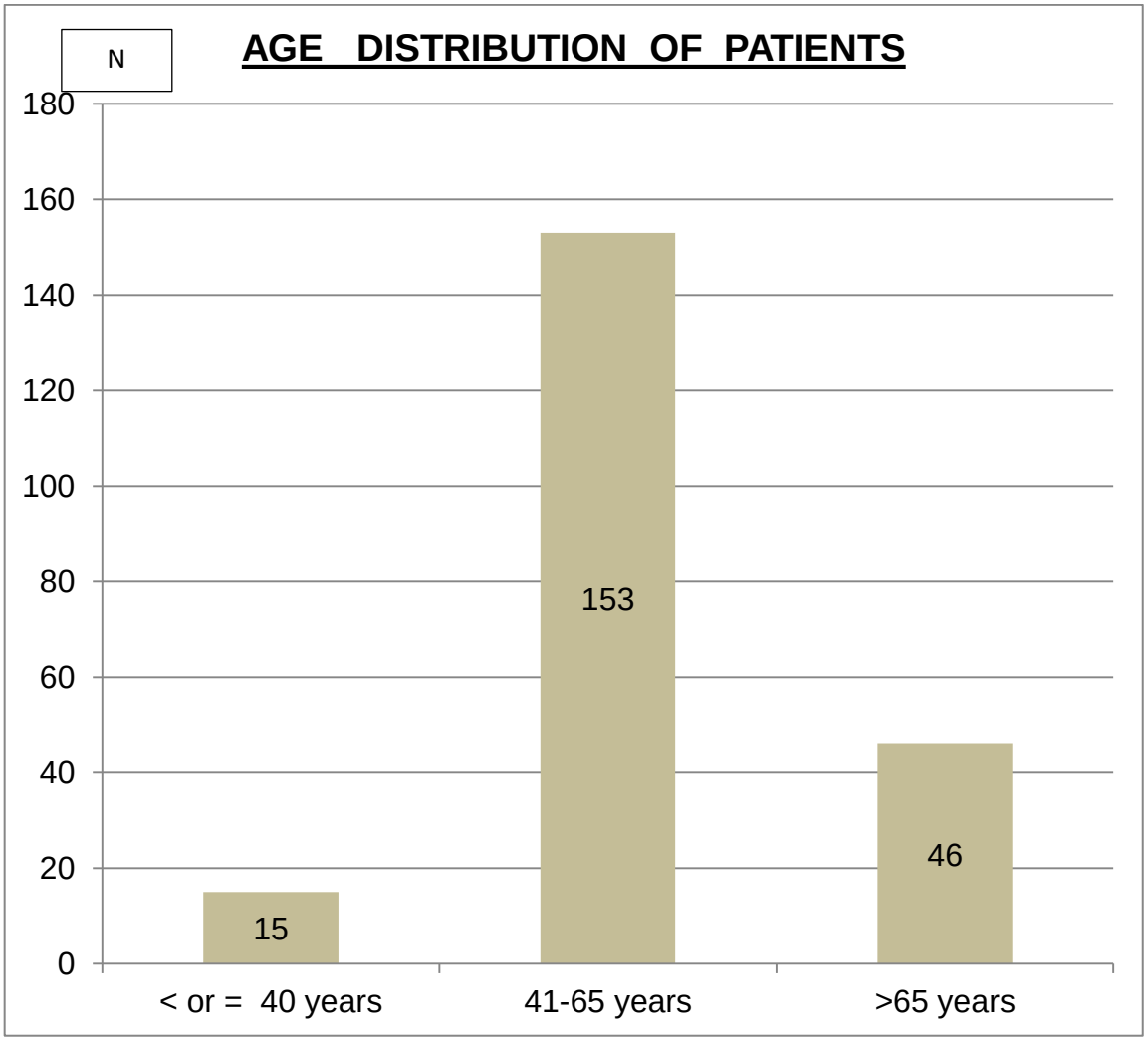

Figure. 2 Sex distribution of patients

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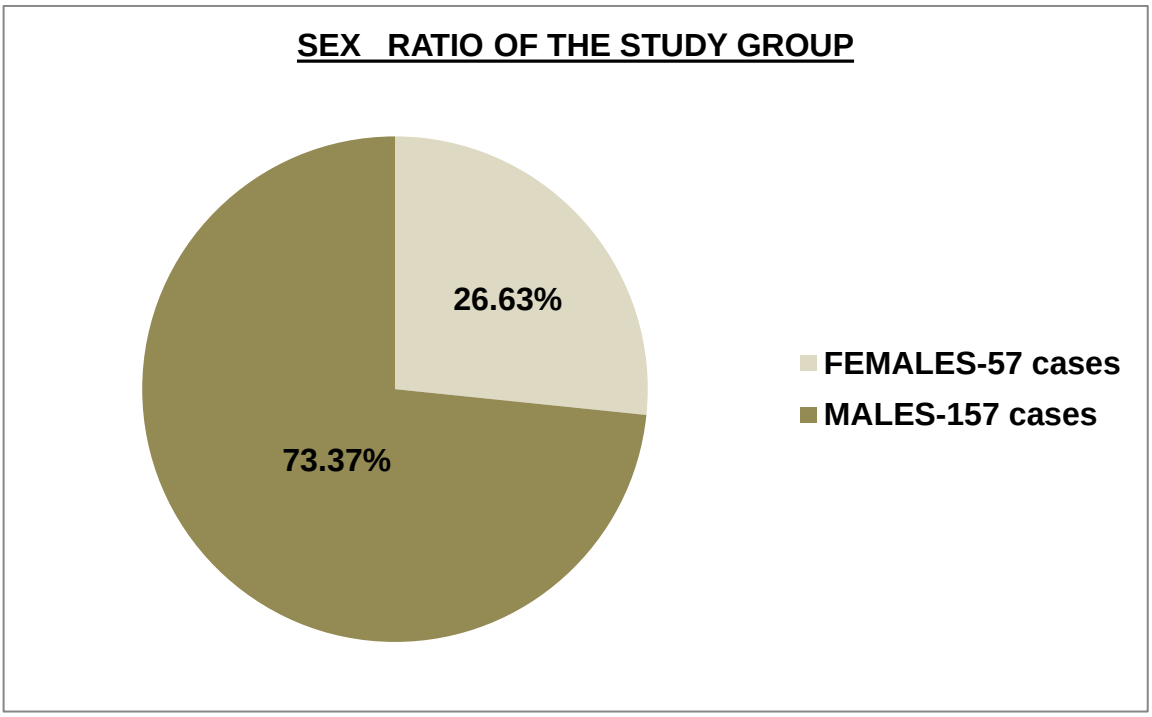

As per figure 1 and 2 71.5% of the patients [153 patients] were in the 41-65 years age group. Young patients [≤40 years] constituted only a small fraction - 7%[15 patients].In our study, the mean age of acute myocardial infarction patients was 56.53 ±11.43 years. Mean age of STEMI patients was 55.49 ±10.84 years. Mean age of NSTEMI cases was 59.2±12.53 years. The study population comprised predominantly of males (157, out of 214), accounting to 73.37% of the sample population.

Table 1- Baseline coronary artery disease in acute M.I. patients

	NSTEMI 60 (%)	**STEMI 154 (%)**	**M.I. 214 (%)**
K/C/O CAD	14 (23.33)	31 (20.12)	45 (21.03)
NOT A K/C/O CAD	46 (76.67)	123 (79.88)	169 (78.97)

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Nearly one-fifth of the patients (21.03%, n=45) had history of Coronary Artery Disease(CAD), while the majority of them were symptomatic for the first time for CAD.In our study, previous history of CAD was found in 20.12% and 23.33% among STEMI and NSTEMI patients respectively. Both STEMI and NSTEMI had nearly equal prevalence of baselineCAD.

Table 2- Ejection fraction (E.F.) in NSTEMI vs STEMI patients

As per table 2 4.67% had ejection fraction <20%, 54.67% had ejection fraction 20-40%, 30.37%

	E.F.IN STEMI PATIENTS N (%)	**E.F.INNSTEMIPATIENTS N (%)**
<20 %	7 (4.55%)	4 (6.67%)
20-45 %	102 (66.23%)	35 (58.33%)
46-50 %	33 (21.43%)	11 (18.33%)
NORMAL %	12 (7.79%)	10 (16.67%)

had ejection fraction 45-50% and 10.28% had ejection fraction >50%. Mean ejection fraction was 39.63 ± 9.8%.Very few patients had ejection fraction(E.F.)>50%- 10.28 % (n=22). 59.34% of the population (n=127) had E.F.< 45%.

Table 3- Presenting heart rate in acute myocardial infarction patients

HEART RATE	**N(214)**	**%**
<60 / min	16	7.48
60-100 / min	169	78.97
>100 / min	29	13.55
Total	214	100

Bradycardia was observed in only 7.48% of acute myocardial infarction patients, while 13.55% had tachycardia. Majority of the patients (78.97%) had normal heart rate at presentation.Nearly

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three-fourth (78.50%) of the patients in the study group had systolic blood pressure in the normal range (90-140 mm Hg), while a small proportion of the patients(1.41%) presented with S.B.P.< 90 mm Hg. Only 43 patients (20.09 % of the study population) had high S.B.P. at presentation. More than half the patients (127 patients, 59.35%) had poor clinical outcome. Of this, 92 patients had STEMI and 35 patients had NSTEMI. 59.7% of STEMI patients (n=92) and 58.33% of NSTEMI patients (n=35) had poor clinical outcome.

Table 4- Baseline characteristics of patients who died during the study period

	IN HOSPITAL DEATH(N=5)	DEATH DURING 1 MONTH FOLLOWUP (N=4)
MALES	3	4
FEMALES	2	0
DIABETIC	3	2
HYPERTENSIVE	2	2
H/O ALCOHOL CONSUMPTION	2	4
H/O SMOKING	2	4
H/O C.A.D.	2	1
S.B.P. ≤ 90 mm Hg	4	2
PULSE RATE <60/min	1	0
NSTEMI	3	4

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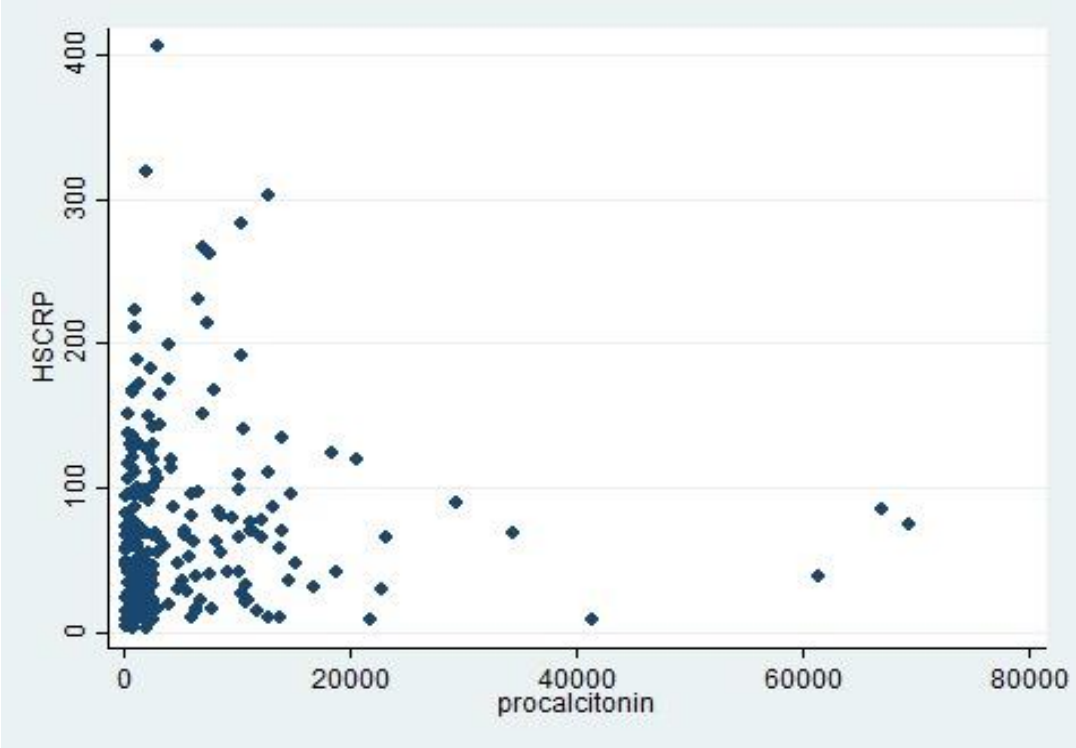
STEMI	2	0
KILLIP'S CLASS	3 IN CLASS 4, 1 EACH IN CLASS 1 AND 3	1 IN CLASS 4, 2 IN CLASS 3 AND 1 IN CLASS 2
EF <20%	3	2

Of the 5 patients who died during hospital stay, 3 were males and 2 were females. 3 patients had diabetes, while 2 of them had hypertension. 2 of them were alcohol consumers and 2 of them were smokers. 2 of them had previous history of C.A.D. Most of them (4 out of 5) presented with hypotension, but only 1 had bradycardia. 3 of them had NSTEMI, while 2 of them had STEMI. 3 of them had very low EF (EF <20%).All 4 patients who died during 1 monthfollowup period after discharge were males. 2 patients had diabetes and 2 patients had hypertension. All 4 patients were alcohol consumers and smokers. Only 1 of them had previous history of C.A.D.. 2of they presented with hypotension, but no one had bradycardia. All 4 of them had NSTEMI. 2 of them had very low EF (EF <20%).

Figure3. Correlation between hsCRP and procalcitonin levels in acute myocardial infarction patients



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hsCRP and procalcitonin levels in acute myocardial infarction patients were compared using scatter diagram and we found that they are poorly correlated in the study population. Strength of correlation was 0.01.

DISCUSSION

In our study, 268 cases of acute MI were enrolled.54 cases were excluded in due course of the study and the remaining 214 were followed up and analysed, in terms of baseline clinical and demographic data, procalcitonin and hsCRP levels. They were also evaluated in terms of clinical outcome. Clinical outcome in different groups were also assessed. Correlation between hsCRP and procalcitonin was also evaluated.Andrie et al, in theirstudy on 87 patients with M.I. complicated by cardiogenic shock, treated with acute revascularization and intraaortic balloon counterpulsation (IABP) support, documented the mean age of patients 67.78 ± 13.4 years.[7]Mean age in myocardial infarction group, in the study by Bayir et al, on100 patients with A.C.S. admitted to the emergency department and 100 healthy control subjects, was 61 ± 14 years.[8] In a prospective trial by Dai et al, constituting 400 STEMI, 400 unstable angina patients and 400 controls, mean age in STEMI group was 65.1 ± 1.8 years.[9]

In our study, the mean age of acute myocardial infarction patients was 56.53 ±11.43 years. Mean age of STEMI patients was 55.49 ±10.84 years. Mean age of NSTEMI cases was 59.2±12.53 years.

Increased risk of MI in males is well established by the previous studies. In the study conducted by Reindl et al, on 141patients with STEMI treated with primary PCI, men were 83% andwomenwere only 17%.[10]Dai et al, in their study,observed that STEMI population constituted predominantly of males (71% were males).[9]In our study, similar to previous studies, males constituted majority of the sample population (73.37% males compared to 26.63% females).

Reindl et al, in his study, registered 17 % prevalence of diabetes mellitus in STEMI patients.[10]Dai et al, in his study, noted that in the STEMI population, 31.5 % were diabetics.[9]

In our study, 55.60% of the study population had diabetes, while 44.40% did not have diabetes. The prevalence of diabetes was 53.4% in NSTEMI and 56.4% in STEMI patients. The prevalence of diabetes in acute myocardial infarction group, STEMI group and NSTEMI group was much higher compared to previous studies.

Prevalence of hypertension in A.C.S. patients was 58.4%, as per documentation by Ataogˇlu et al, in their study on 77 A.C.S. patients.[2] In patients with acute M.I., the recorded prevalence of hypertension 55%, according to Kafkas et al(Kafkas et al, in his study on 60 patientswithacute M.I.).[4]Bayir et al, in his study comparing 100 patients with A.C.S. and 100 healthy controls, estimated a 35% prevalence of hypertension in acute coronary syndrome patients and 31% in controls.[8]

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Various studies have documented a wide range of smoking rates in acute myocardial infarction patients, varying from as high as 80%[4] to as low as 35.6%.[7] Some large scale studies have registered prevalence of smoking as low as 26% in STEMI patients (Dai et al).[9]The prevalence of smoking in acute myocardial infarction patients, STEMI patients and NSTEMI patients in our study was 38.32%, 43.50% and 25% respectively. These findings were comparable with the findings in the previous studies.

History of CAD in patients presenting with acute M.I. has been highly variant in different studies. In a study on patients with cardiogenic shock due to acute M.I., Andrie et al documented previous history of CAD in 48.3% of the patients.[7] Whereas, Kafkas et al, in his study on 60 patientswithacute M.I., documented history of CAD in only 21.7% of the patients.[4]
In our study, previous history of CAD was identified in 21.03%, 20.12% and 23.33% of acute myocardial infarction patients, STEMI patients and NSTEMI patients respectively. This prevalence of CAD was comparable to the previous studies.

Most of the previous studies were either exclusively for hypotensive patients (acute coronary syndrome with cardiogenic shock) or did not mention hypotension in acute myocardial infarction patients. In his study, Kafkas et al, recorded that 8.3% of the acute myocardial infarction patients had hypotension at presentation.[4]

The ratio of NSTEMI to STEMI varied from study to study. Andrie et al, in his study on acute myocardial infarction patients, noted that 50.6% had STEMI, while 49.4% had sustained NSTEMI.[7] In the study conducted by Kafkas et al, 81.7% had STEMI, while only 19.4% had NSTEMI.[4]Ataoglu et al documented unstable angina, STEMI and NSTEMI in 18.05%, 43.05% and 38.9 % of the sample population respectively.[2]In our study, we found that 28.04% of the population had sustained NSTEMI, while 71.96% had STEMI.

Andriéet al, in their study, noted that mean ejection fraction in M.I. patients with cardiogenic shock was 35.2 ± 11.6%. 27.6% had ejection fraction less than 30%.[7]Ataoglu, in his study on acute coronary syndrome patients, documented a mean ejection fraction of47.34 ± 9.51%.[2]Reindl et al, in his study on STEMI patients, registered a mean ejection fraction of 49% (42-56%).[10]
In our study, we found that 4.67% had ejection fraction <20%, 54.67% had ejection fraction 20-40%, 30.37% had ejection fraction 45-50% and 10.29% had ejection fraction >50%. Mean ejection fraction was 39.63 ± 9.8%.

hsCRP and procalcitonin levels in acute myocardial infarction patients were compared using scatter diagram and we found that they are poorly correlated in the study population. Strength of correlation was 0.01.Previous studies in myocardial infarction have assumed different cut-offs in acute coronary syndrome and acute myocardial infarction patients, based on cut-off values in control cases. Atoaglu et al noted that elevated PCT levels (<48 hours of admission), predicted

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elevated in-hospital and 6-month mortality.[2]Picariello, et al[1] noted that in MI cases complicated by cardiogenic shock without infections, only survivors had progressive fall in procalcitonin levels.Patel T, et al[11]noted that 24 hour procalcitonin value had significant in-hospital and 30-day mortality predictive value. Reindl, et al[10]concluded that after PCI for STEMI, procalcitonin levels in the immediate period did not reflect the degree of tissue damage visualized by cardiac MRI.

Procalcitonin values were elevated in MI patients with poor clinical outcome. The difference in procalcitonin values between poor and good clinical outcome patients was statistically not significant probably because both poor and not poor clinical outcome classes had patients with statistically comparable ejection fraction (p-value 0.036) and Killip's classes (p-value 0.02). This comparable distribution probably resulted in statistically insignificant difference between poor and not poor clinical outcome groups. We couldn't find studies comparing procalcitonin in different Killip's classes and between different ejection fraction groups. Further studies are required to confirm if there is statistically significant difference between different Killip's classes and between different ejection fraction groups.

CONCLUSION

Acute M.I. is one of the leading causes of cardiovascular mortality around the world. Procalcitonin level was elevated in acute M.I. patients. But there was no statistically significant difference in procalcitonin values between acute M.I. patients withpoor and not poorclinical outcome.Hence, procalcitonin cannot predict poor clinical outcome in acute myocardial infarction patients. Our study wasn't adequately powered to show a significant relation. 30-day mortality rate after an episode of acute M.I. was 4.205%.hsCRP and procalcitonin levels in acute myocardial infarction patients were poorly correlated with strength of correlation 0.01.

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