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Prognostic Relevance of Serum Ferritin on Short Term and Long term Outcome in Patients with Acute Myocardial Infarction

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ABSTRACT

Background and Objective: Over the decades coronary artery disease appears to be an emerging cause of mortality and morbidity. Previous studies suggested elevated serum ferritin as a risk factor for development of AMI. However its role with regard to outcome and prognosis of AMI still remains a matter of debate. With this background, the present study was aimed to estimate the prognostic relevance of serum ferritin in relation to short term and long term survival outcomes in patients with AMI.

Methods: The study was a hospital based observational study conducted with a total number of 100 patients, with first AMI (50 suffered STEMI and 50 with NSTEMI diagnosis) admitted within 12 hours of the onset of chest pain to coronary care units (CCU) at MKCG Medical College & hospital over a period of one year. Serum ferritin was measured using an ELISA assay by a special kit. The patients were divided into three groups according to Serum ferritin level. i.e. (1st tertile: <120 ng/ml, 2nd tertile: 120 to 220 ng/ml and 3rd tertile: >220 ng/ml). Baseline characteristics, LV Ejection Fraction, Killip functional class and outcomes were compared among three different groups of serum ferritin.

Results: There was a significant correlation between serum ferritin and LV ejection fraction (p=0.01), Killip class (p=0.03) and mortality (p=0.03). Lower and higher levels of ferritin (1st and 3rd tertiles, ≤ 120; >220 ng/ml, respectively) were associated with a higher incidence of HF during hospitalization and death at 1 year.

Conclusion: Raised serum ferritin is associated with worse short term and long term outcome following myocardial infarction.

Key words: Acute myocardial infarction, Coronary artery disease, Prognosis, Serum ferritin

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INTRODUCTION

Acute myocardial infarction (AMI), is currently a leading cause of mortality and morbidity with high economic costs worldwide. Smoking, hypertension, obesity, diabetes and dyslipidemia have been established as useful predictors for AMI. Observational and epidemiological studies have identified a host of new and potential risk factors for atherothrombotic vascular diseases over the last few decades. In this growing list of new and emerging risk factors, the entities like elevated blood levels of homocysteine, fibrinogen, inflammation and infection, atherogenic lipoprotein, elevated triglyceride, and number of genetic polymorphism are of particular interest. Apart from these, there is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including coronary heart disease (CHD) [1]. Serum iron is essential for oxygen metabolism, especially in the chain that generates adenosine triphosphate through oxidative respiration in the mitochondria [2]. A surfeit of total body iron is considered to have multiple deleterious effects. In myocardial tissue in particular, it is hypothesized to be causative of myocardial infarction especially in genetically vulnerable individuals. Excessive iron is converted intracellularly into hemosiderin, ferritin and free iron which in turn promotes free radical induced oxidative damage [3,4]. Ferritin is the most accurate

yardstick of total body iron as there is an intricate relationship between its intracellular and extracellular levels. The connection between body iron and coronary artery disease was first noted by Jerome Sullivan in 1981 [5]. National Health and Nutrition Examination Survey (NHANES III), first time reported a significant positive association in iron storage and heart disease risk between 1988-1994. Since then several studies have been conducted to assess the association of serum ferritin and AMI. Results of some studies have been in favour of ferritin being a risk factor for AMI [4,6] while others have not [7]. The conflicting results could be due to methodological variation in measuring iron stores or study design. Hence, the role of serum iron store (or its surrogate ferritin) in AMI is unclear. However a few literatures is available regarding prediction of serum ferritin in outcome of AMI [8]. That's why we have taken up the study to find out both short term and long term outcome of AMI in relation to serum ferritin.

MATERIALS AND METHODS

Study design

Our study was a hospital based observational prospective study conducted in M.K.C.G. Medical College, Berhampur from June 2019 to June 2020.A total no of 100 patients of acute myocardial infarction (50 STEMI and 50 NSTEMI) were included in the study. STEMI was diagnosed from typical chest pain associated with ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous precordial leads (for the diagnosis of anterior wall MI) as well as ≥ 0.1 mV in II, III, and aVF leads (for the diagnosis of inferior wall MI) except in V2, V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years, ≥ 0.25 mV in men <40 years, or ≥ 0.15 mV in women. NSTEMI was diagnosed from typical chest pain with raised troponin I values.

Definitions

Killip classification of acute myocardial infarction

Class I: No evidence of heart failure.

Class II: Findings consistent with mild to moderate heart heart (e.g.S3 gallop, lung rales less than one-half way up the posterior lung fields or jugular venous distension.

Class III: Overt pulmonary edema.

Class IV: Cardiogenic shock.

Inclusion criteria

Patients having typical chest pain with any two of the following criteria.14 (1) Chest pain of < 12 hours duration, (2) ST elevation > 1 mm in at least two consecutive leads, (3) increased cardiac markers (creatine phosphokinase-MB (CPK-MB) two times the upper limit of normal), and (4) presumably new onset bundle-branch block were included for the study.

Exclusion criteria

Patients with neoplastic and liver disease.

Primary/ secondary hemochromatosis.

Alcohol abuse.

Tuberculosis.

Febrile conditions

Use of oral anticoagulant therapy within a 4-week time period before recruitment.

Smoking, known cardiomyopathy, hemodynamically significant valvular heart disease.

Diabetes and surgery or trauma within the previous month.

ESR > 20 mm/hr indicating the presence of inflammation/ infection, that could potentially lead to elevated ferritin concentration were excluded from the study.

Variables

All patients were subjected to routine investigations including hemogram, renal function test, lipid profile, liver function test, ECG, Transthoracic echocardiography. Serum ferritin analysis was done by ELISA kit for all cases. The normal reference value of serum ferritin was 10-120 ng/ml. Patients were divided into three groups on the basis of serum ferritin(1st tertile:<120 ng/ml,2nd tertile:120 to 220 ng/ml and 3rd tertile:>220 ng/ml) [8].

The study protocol was approved by Institutional Ethical Committee, M.K.C. G. Medical College, Berhampur. Informed consent was obtained from each of the individual patient. Study was conducted in accordance with 1964, Declaration of Helsinki and its subsequent amendment.

Aim and objective

To assess the prognostic significance of serum ferritin in short term and long term outcome of AMI.

End point

In-hospital death and 1-year death, in-hospital heart failure (Killip Class ≥ 2) and 1-year follow-up (L.V ejection fraction <50% and NYHA Class ≥ 2) were the parameters for assessing short term &long term

Table 1: Demographic data.

Students (N=40)	
Age in years	20.38 (± 1.6)
Year of study	
First year	n=20
Second year	n=11
Third year	n=9
Lecturers (N=27)	
Age in years	44.5 (± 9.76)
Experience in years	10.19 (± 5.8)

Table 2: Mean modal scores for lecturers and students.

Mode	Lecturers (N=27) Mean (± Std dev)	Students (N=40) Mean (± Std Dev)
Visual	6.44 (± 2.38)	5.98 (± 2.57)
Auditory	6.22 (± 2.68)	6.43 (± 2.88)
Read & write	5.07 (± 2.73)	4.83 (± 2.04)
Kinaesthetic	4.96 (± 1.81)	4.70 (± 2.67)

outcomes respectively. Other secondary endpoints were reinfection and ischemic cerebrovascular accident at 1 year of follow-Up. Medical records were reviewed to determine vital status and the cause of death. When this information was unavailable in the medical record, we telephoned patients or their families. Information regarding cardiovascular events such as non-fatal AMI, stroke/CVA, and re-hospitalization due to recurrence of AMI was also obtained.

Statistical analysis

The program IBM SPSS Statistics, version 20 for Windows 10, was used to perform the statistical analysis. Continuous variables were shown as mean ± standard deviation and compared according to serum ferritin tertiles by ANOVA. Categorical variables were shown as absolute values and/or percentages and compared using the chi-square test. The associations were considered statistically significant in the presence of a p-value < 0.05. The predictive value of ferritin levels over the risk of in-hospital and 1-year adverse events was determined by the odds ratio, with a 95% confidence interval (95% CI) using Kaplan–Meier survival curves analysis.

RESULTS

Baseline characteristics

Out of total of 100 AMI patients studied. Maximum no of patients belonged to high ferritin tertile followed by low value of ferritin tertile and minimum no of patients of myocardial infarction belong to medium tertile (Figure 1). The baseline, clinical and laboratory characteristics of the total population according to ferritin tertiles are shown in Tables 1 and 2. There was no significant difference in the various baseline characteristics between the three values of serum Ferritin (Table 1). Also there was also no significant difference in distribution of STEMI and NSTEMI among the three tertiles of Serum Ferritin (p=0.76) (Table 2). On transthoracic echocardiography, there was a statistically significant reduction in LVEF in 2nd & 3rd third tertile of Serum Ferritin (Table 3). Killip classification for functional status showed no significant association among three values of serum tertiles (Table 4).

Prognosis and outcome

Regarding the short-term prognosis: the in-hospital outcome was compared amongst the three groups. Recurrent angina showed a trend towards relation with ferritin (2 in first tertile,10 in second tertile and 8 in third tertile) but statistically not significant (p=0.09). Heart failure showed a similar pattern (4 in first tertile,6 in second tertile and 8 in third tertile) but p value of 0.1. Mortality was statistically strongly correlated with ferritin level (1 in first tertile,2 in second tertile and 5 in third tertile) with a p value of 0.03 (Table 5). In our

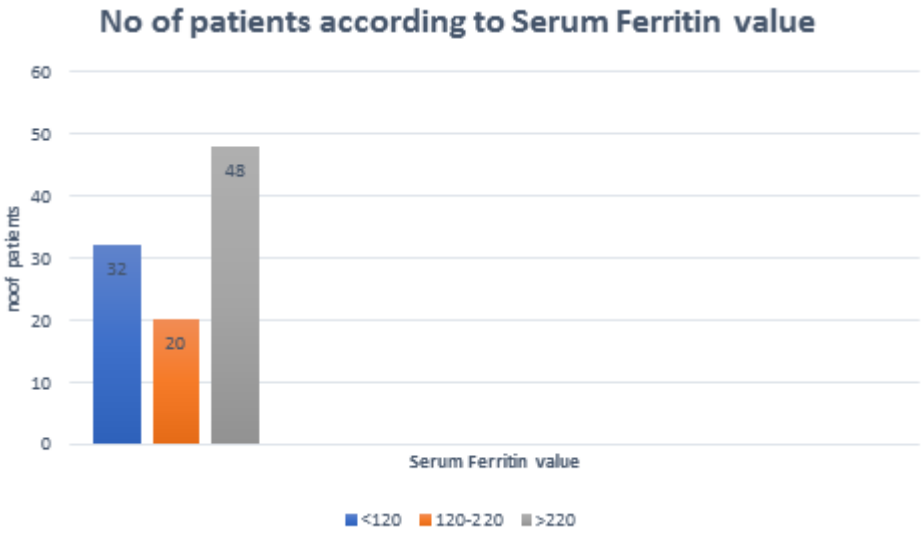

Figure 1: Serum ferritin concentrations among patients with with myocardial infarction.

Table 1: Comparison of baseline characteristics among three tertiles of serum ferritin.

	S. Ferritin values			
Characteristics	**<120 ng/ml**	**120 -220 ng/ml**	**>220 ng/ml**	**P value**
Age<60 years	20	18	20	0.22
Males	18	36	17	0.86
Smoking	12	8	6	0.27
DM	11	7	10	0.56
HTN	16	12	8	0.12
Dyslipidaemia	16	14	10	0.38
Renal failure	2	1	0	0.77
Obesity	5	3	2	0.47
DM: Diabetes Mellitus, HTN: Hypertension, p<0.05 is significant				
There was no significant difference in the various baseline characteristics between the three values of serum Ferritin				

population, regarding ferritin levels, the 2nd and 3rd tertiles were associated with occurrence of more adverse events, with statistical significance in terms of in-hospital HF, recurrent angina and death within 1 year follow up. Table 5 depicts that on short-term prognosis, around 1% (n=1) of the patients died during hospitalization and 10% (n=10) showed evidence of heart failure a. Long-term impact, approximately 6% (n=6) of the patients died in the first year of follow-up at 1 year , out of which maximum belonged to highest tertiles of serum ferritin value(>220ng/ml)i.e. n=4.and 10% (n=10) developed HF criteria during the clinical follow-up of 1year out of which maximum belong to high ferritin tertile(n=5) followed by low serum ferritin value(n=4) .Regarding the serious outcome in the form of reinfection and Cerebrovascular Accidents at 1year follow up ,maximum incidence of reinfection occurred in high serum ferritin tertile (n=10) followed by medium serum ferritin tertile (n=6) which is statistically significant with p value of 0.0138(<0.05).Similarly occurrence of CVA at 1year follow up is maximum in high serum ferritin tertile (n=2) with 1in each low and medium serum ferritin tertile which is statistically not significant.

Kaplan–Meier survival curves analysis (Figures 2 and Figure 3) shows adverse events i.e. HF and Death during follow up year. In our population, regarding ferritin levels, the 2nd and 3rd tertiles were associated with

Table 2: Comparison of types of acute coronary syndrome among three values of serum ferritin.

Type OF ACS	1st Ferritin Tertile <120ng/ml	2ndFerritin tertile 120-220 ng/ml	3rd Ferritin Tertile >220ng/ml	P value
STEMI	12	24	14	0.76
NSTEMI	14	25	11	
ACS=Acute coronary syndrome, p<0.05 significant				
STEMI: ST Elevated Myocardial Infarction				
NSTEMI: Non ST Elevated Myocardial Infarction				
Out of 50 STEMI patients, 12 belonged to first tertile,24 to second tertile and 14 to third tertile. Out of 50 NSTEMI patients,14 were in low ferritin,25 in intermediate and 11 in high ferritin group. There was no significant difference in distribution in the three tertiles (p=0.76)				

Table 3: Left ventricular ejection fraction values according to serum ferritin tertiles.

LVEF (in %)	1st Ferritin tertile <120 ng/ml	2nd Ferritin tertile 120-220 ng/ml	3rd Ferritin tertile >220 ng/ml	P value
<35	2	4	9	0.01
35-45	12	18	8	
45-55	10	15	5	
>55	2	12	3	
Results expressed as n (%) or mean ± median. LVEF: left ventricular ejection fraction.				
In the first tertile, 2 patients had EF less than 35%,12 had EF 35 to 45%, 10 had EF 45 to 55% and 2 had EF more than 55%.In the second tertile, the corresponding numbers were 4,18,15 and 12.In the highest tertile, the distribution was 9, 8, 5 and 3. There was a significant difference between the 4 groups (p-value: 0.01).				

Table 4: Killip functional classes according to serum ferritin level.

Functional class	1st ferritin tertile <120ng/ml	2nd ferritin tertile 120-220 ng/ml	3rd ferritin tertile >220 ng/ml	P value
Class I	4	6	6	
Class II	10	12	6	0.03
Class III	10	12	10	
Class IV	2	19	3	
P<0.05 is significant				
The functional status of patients (Killip class) was also compared across the groups. In the lowest tertile,10 patients each were in class II and class III but 4 were in class 1 and 2 in class IV. In the middle tertile,12 patients each were in class II and class III but 6 were in class I and 19 were in class IV. In the highest tertile,10 patients were in class III whereas 6 patients each were in class II and class III and 3 were in class IV. This was found to be significantly different with a p value of 0.03.				

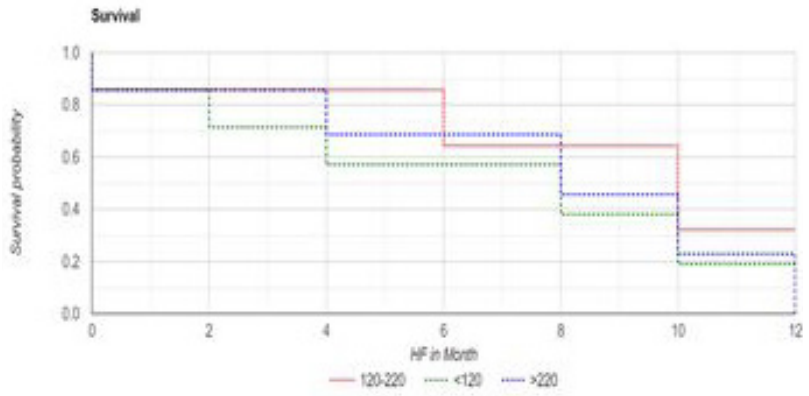

Figure 2: Kaplan–Meier survival curves for HF in patients with three serum ferritin tertiles.

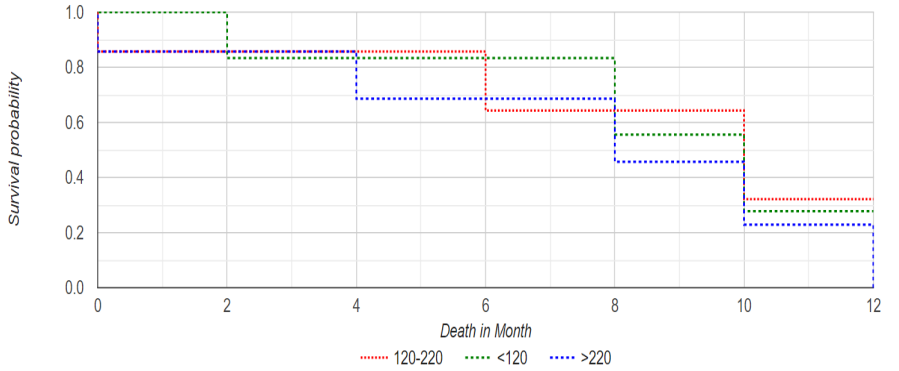

Figure 3: Kaplan–Meier event survival curves for mortality or readmission for HF in patients with three serum ferritin tertiles.

Table 5: Comparison of in -hospital short term outcomes among three tertiles of serum ferritin values.

Outcome	1st ferritin tertile <120 ng/ml	2nd ferritin tertile 120-220 ng/ml	3rd ferritin tertile >220 ng/ml	P value
Recurrent Angina	2	10	8	0.09
Heart Failure	4	6	8	0.1
Death	1	2	5	0.03

The in-hospital outcome was compared amongst the three groups. Recurrent angina showed a trend towards relation with ferritin (2 in first tertile, 10 in second tertile and 8 in third tertile) but statistically not significant(p=0.09).Heart failure showed a similar pattern (4 in first tertile,6 in second tertile and 8 in third tertile) but p value of 0.1.Mortality was statistically strongly correlated with ferritin level (1 in first tertile,2 in second tertile and 5 in third tertile) with a p value of 0.03

Table 6: Short and long term outcomes according to serum ferritin levels.

Events	1st ferritin tertile (< 120 ng/mL)	2nd ferritin tertile (120 -220 ng/mL)	3rd ferritin tertile (> 220 ng/mL)	P value
HF at 1 year	4	1	5	0.0446*
Reinfarction at 1 year	1	6	10	0.0138*
CVA at 1 year	1	1	2	0.786
Death at 1 year	1	1	4	0.616

HF: heart failure; CVA: cerebrovascular accident, p<0.05 significant

the occurrence of more adverse events, with statistical significance in terms of in-hospital HF and 1-year death. (log-rank P<0.0001 and P=0.0002, respectively) (Table 6).

DISCUSSION

The present study shows that baseline clinical characteristics or type of MI had no relation with serum ferritin. However, raised ferritin is associated with worse NYHA class and lower ejection fraction. Also, mortality and raised serum ferritin show a statistically significant correlation. Similar findings were found in a study conducted by Tatiana Duarte et al., 2018 who conducted a study taking 280 pts and analyzing both short term and long term prognostic outcome of Acute Coronary Syndrome in relation to serum Ferritin level [8].

Iron is an important element in multiple physiological processes in the body but excess iron is known to accelerate atherosclerosis [9]. Iron deficiency has been proven to be a frequent finding in heart failure worsening the outcome .Also, its correction leads to reduced morbidity and sense of wellbeing. Hence, parenteral iron is indicated in HF ref patients with iron deficiency (class IIa in ESC guidelines) [10]. However, the importance of iron and ferritin in coronary artery disease remains to be elucidated.

Serum ferritin(>200 ug/l) has been found to increase the risk of MI by 5 times [11]. Serum ferritin levels could be a prime decisive factor of myocardial ischemic burden during periods of ischemia [12]. A raised ferritin level has been found to double the risk of AMI in males [13]. Dominguez-Rodriguez showed that reduced serum iron and ferritin is associated with adverse outcome in acute coronary syndrome [14]. A study on young patients of CAD revealed that ferritin was an independent discriminating factor for CAD in males with the highest quartile having an odds ratio of 1.62 compared to the lowest quartile [15]. Hoque et al. found a significant correlation between serum ferritin and acute coronary syndrome(p<0.001) [16]. A recent metaanalysis of 11 studies concluded that serum ferritin in AMI is higher than in controls [17]. On the contrary, Frey concluded that there was no relation between MI and ferritin [18]. Similarly, Sempos et al. negated any relation between serum ferritin and cardiovascular disorders or mortality.19Ascherio A also concluded that serum iron does not increase risk of CAD in men [7].

The plausible mechanisms of the culpability of serum ferritin are many. There is a significant rise in ferritin concentration of monocytes when exposed to hydrocortisone. Stress which is an established risk factor for AMI could trigger this process [19]. Ferritin could act along with other traditional risk factors by promoting

free radical generation which in turn causes LDL oxidation and plaque formation. This could also explain raised CRP levels in AMI.20A genetic component to causality have also been proposed. For example, persons with wild allele of tag SNP rs9366637 were more likely to suffer from CAD than mutant allele [15].

Tuomainen reported an association between increased body iron stores and excess risk of AMI. The concentration ratio of serum transferrin receptor (TfR) / ferritin was utilized as indicator of body iron stores25. Salonen, reported in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) that the high stored iron level, as assessed by elevated SF concentration, is a risk factor for CAD. On the other hand Bozzini's angiography based study could not support a role for biochemical or genetic markers of iron stores as predictors of the risk of CAD or its thrombotic complications [20]. In our population, the 1st and 3rd tertiles of ferritin levels were associated with the occurrence of more adverse events, with statistical significance in terms of in-hospital HF and 1-year death.

CONCLUSION

The current study revealed raised serum ferritin was associated with worse outcomes and increased mortality following AMI .Larger studies to further explore this relationship are in order.

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CONFLICT OF INTEREST

None to be declared.

SOURCE OF SUPPORT

Nil.

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