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Original Research Article

A Clinical Study on Prognostic Predictive Value of Ferritin Levels in Acute Coronary Syndrome Patients in a Tertiary Care Hospital

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Abstract:

Background: Aim of the Study to evaluate the association between Ferritin levels and adverse cardiovascular outcomes in patients with acute myocardial infarction during short- or long-term follow-up.

Materials: 124 patients with Acute Coronary Syndrome were included in a cross-sectional study by comparing their clinical parameters and serum Ferritin levels after inclusion criteria were satisfied between January 2022 and December 2024. Patients aged 18 years and above were included. Patients with myocardial infarction, ST-elevation myocardial infarction (STEMI), or non-ST segment elevation myocardial infarction (NSTEMI) were included. Patients with Serum Ferritin values more than 300ng/mL were considered as abnormal and included in the study. Proper clinical history, past CVS history was elicited. After thorough clinical examination cardiac stress test, ECG study for ST depression, ST elevation, T-wave inversion, or presences of Q waves were undertaken. Serum Troponin levels were estimated. Normal Serum Ferritin levels (SF) were considered 300–400 µg/l as the upper limits for the adult males and 150–200 µg/l as the upper limit of normal for adult females.

Results: The serum Ferritin values estimated at 06 months intervals were correlated with the post ACS events among the subjects for a period of 32 months and it was observed that that MACE (12.09%), mortality (13.70%%), LVEF (09.67), HF (25%) and LVA (02.41%) were noted in patients equally with varying levels of serum Ferritin either low or high. There were no cardiovascular events in 46 (37.09%) patients.

Conclusions: In this study it was observed that both low and high serum Ferritin values were associated with adverse events in patients with ACS both during their hospital stay and at more extended follow-up periods. ECG changes of ischemia were more in patients Ferritin levels more than 300ng/ml. The levels of Ferritin were not linked to increased mortality risk, accentuated LVEF decline, left ventricular aneurysm formation during follow-up. The study recommends closer monitoring of serum Ferritin levels and timely therapeutic interventions for high-risk patients with ACS as elevated serum Ferritin can be a potent factor for predicting AMI especially STEMI. More elaborate studies are required with larger numbers to confirm the correlation.

Keywords: Ferritin, Acute Coronary Syndrome, LVEF, Mortality risk, STEMI and Prognosis.

Introduction

Human body iron metabolism and it homeostasis are reflected by the Ferritin which is an essential protein. [1] It is noted as a biomarker of the inflammation process in many tests assessing the function of organs like liver, kidney, Heart and endocrine glands. [2] A biological process exists to evaluate the acute or chronic inflammation occurring in the human body involved in controlling Ferritin levels. [3]

The assay of Ferritin levels benefits the physician in assessing the association of adverse outcomes in the general population and patients with various pathological conditions. [4] Hence a low of High levels of Ferritin indicates the all-cause morbidity and mortality in certain general population studies. [4] A Danish population study has quoted after a long term study of 23 years) that there was a significant higher rate of all-cause and cardiovascular (CVS) mortality in patients with raised Ferritin levels above ≥200 µg/L. [2] In an English longitudinal study based on the aging, it was observed that women with low Ferritin levels had a higher risk of mortality and that men with highest levels of Ferritin showed an incidence of mortality during their 7.7-year follow-up period. Such conclusions highlighted the possibility of gender-specific risk stratification. [3] Ferritin levels were also used as a biological prognostic marker in predicting the prognosis in patients with chronic diseases of Kidney, Liver and its levels above 1500ng/mL were considered significant over a period of five year follow up. [4] A Japanese study showed that Ferritin levels above 496ng/mL were associated with chronic diseases and especially CVS and infectious diseases. [5]

Such correlation was observed in Hemodialysis patients rather than in peritoneal dialysis patients. [5] It was also observed that high Ferritin levels were linked not only to CVS risk factors but also to metabolic syndromes. [6] Another study in the literature related the high Ferritin levels independently to coronary artery calcium score, suggesting the potential role of Ferritin in the early detection of atherosclerosis. [7] They also found that high levels of Ferritin were associated with greater risk of developing Atrial fibrillation. [8] A study in 2003 observed that the role of Ferritin levels and ischaemic heart disease was debatable and needs extensive studies as the study could not connect the two from their trial. [9]

In contrast another study in 2012 found nearly fivefold higher risk of acute myocardial infarction (AMI) in patients with Ferritin values more than 200 µg/L, an effect maintained after multivariate analysis. [10] Regarding the prognostic value of Ferritin levels in the Acute coronary syndrome (ACS), a meta-analysis of seven studies showed following a long term follow up, a high risk of adverse outcome in patients with low Ferritin levels with ACS. [11]

ACS is defined as decreased blood flow to the coronary myocardium resulting in ST-segment elevation myocardial infarction or non–ST-segment elevation ACS, (STEMI OR NON-STEMI) which includes unstable angina and non–ST-segment elevation myocardial infarction. The common risk factors are age above 65 years, currently smoking, being treated for hypertension, diabetes mellitus, hyperlipidemia. BMI above 25Kg per m^2, family history of coronary artery disease in early age were also considered. [12]

Most predictive symptoms of ACS were included chest discomfort (substernal or spreading to the arms or jaw), with or without palpitations. Ferritin is a soluble 450 kDa protein. It is present in all the cells but mainly in high concentrations in marrow macrophages, the spleen and the liver.

Cellular Ferritin provides intracellular storage of bio-available iron in a safe and readily accessible form. It protects cells from iron-mediated free radical formation and toxicity resulting from the Fenton reaction between iron and hydrogen peroxide. [13]

A small amount of Ferritin is found in the serum and plays no role in iron transport or cellular iron uptake with a half-life of 30 hours and entirely consists of L chains and 50 to 80% glycosylated which occur intracellularly. [14] Ferritin is measured by immunoassays e.g. enzyme-linked immunosorbent assay (ELISA), immuno chemiluminescence (Abbott Architect assay, ADVIA Centaur assay, Roche ECLIA assay) or immunoturbidometric assay (Tinta-quant assay).

Another biomarker useful in the diagnosis of ACS is Cardiac Troponin levels. [15] The magnitude of Troponin values of hs- cTn ng/l (more than 20ng.l) elevation correlates with the extent of myocardial injury in ACS with subsequent risk of adverse outcome. (16) In the present study the aim was to evaluate the association between Ferritin levels and adverse cardiovascular outcomes in patients with acute myocardial infarction during short- or long-term follow-up.

Materials

Study populations involved 124 patients attending the department of General Medicine and Cardiology with Acute Coronary Syndrome. An ethics committee of the institute approved the study and committee approved consent form and proforma were used.

Type of Study: A cross-sectional study.

Institution of study: Kannur Medical College and Hospital, Kannur, Kerala.

Year of Study: January 2022 to December 2024.

Inclusion Criteria: Patients aged 18 years and above were included. Patients with myocardial infarction, ST-elevation myocardial infarction (STEMI), or non-ST segment elevation myocardial infarction (NSTEMI) were included. Patients with Serum Ferritin values more than 300ng/mL were considered as abnormal and included in the study. Patients willing to participate in the study were included. Patients willing to undergo tests for Ferritin levels were included.

Exclusion Criteria: Patients below 18 years were excluded. Patients with chronic infectious diseases or metabolic diseases were excluded. Patients on peritoneal or hemodialysis were excluded. Patients with immune compromised diseases were excluded. Patients on repeated blood transfusions were excluded. Patients with GIT malabsorption syndromes were excluded. Patients with chest pain that can be reproduced with palpation or varies with breathing or position were excluded.

All the patients were elicited of their history of presenting complaints, past CVS history and thorough clinical examination was done. Prior abnormal cardiac stress test results were noted. Electrocardiography changes that predicted ACS include ST depression, ST elevation, T-wave inversion, or presences of Q waves were noted.

Elevated Troponin levels without ST-segment elevation on electrocardiography suggested non–ST-segment elevation ACS. Patients with ACS received coronary angiography with percutaneous or surgical revascularization. Other important management considerations included initiation of dual antiplatelet therapy and parenteral anticoagulation, statin therapy, beta-blocker therapy, and sodium-glucose cotransporter-2 inhibitor therapy.

Additional interventions shown to reduce mortality in patients who have had a recent myocardial

infarction include smoking cessation, annual influenza vaccination, and cardiac rehabilitation. Normal Serum Ferritin levels (SF) were considered 300–400 µg/l as the upper limits for the adult males and 150–200 µg/l as the upper limit of normal for adult females (Association for Clinical Biochemistry, 2012; Worwood et al, 2017), (17). The variations are according to the age, ethnic origin and sex. The mean SF values in neonates are high (around 200 µg/l) and remain so for nearly 2 months. From 2 to 12 years mean values approximate 30 µg/l for both boys and girls (Worwood, 1982).

In this age group values higher than 100 µg/l are considered in the context of inflammatory disease, malignant disease or juvenile hereditary haemochromatosis. In this study SF values more than 300ng/mL were considered as abnormal and included in the study. Troponin values of hs- cTn ng/l (more than 20ng/l) elevation correlates with the extent of myocardial injury in ACS with subsequent risk of adverse outcome. The prognostic value of serum Ferritin on short- or long-term outcomes, including major adverse cardiovascular events (MACE), mortality, left ventricular ejection fraction (LVEF), heart failure or development of a left ventricular aneurysm were observed and considered. All the patients were followed up for 30 months and examined at regular intervals of 06 months.

Statistical Analysis: All statistical data were analyzed using SPSS version 19.0 and AMOS version 19.0 statistical packages. The demographic characteristics of the sample were reported as means, and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Correlation and significance was calculated using student T test.

Results

Among the 124 patients included in this study as per the inclusion criteria, there were 87 (7.16%) male patients and 37 (29.83%) female patients. There were 04 (03.22%) patients aged 18 to 27 years, 09 (07.25%) patients aged 28 to 37 years, 28 (22.58%) patients aged 38 to 47 years, 31 (25%) patients aged 48 to 57 years, 29 (23.38%) patients aged 58 to 67 years, 26 (20.96%) patients aged 68 to 77 years. History of abnormal stress test results was recorded from 34 (27.41%) patients, Peripheral artery disease was noted in 43 (34.67%) patients and CAD was noted in 47 (37.93%) patients.

Symptoms of sweating was noted in 61 (49.19%) patients, pain in the right arm and shoulder was complained by 12 (09.67%) patients, Pain in both the arms was complained by 25 (28.22%) patients, pain in the left arm and shoulder was complained by 48 (38.70%) patients, Chest compressing pain was complained by 41 (33.06%) patients, and Absent chest wall tenderness was elicited in 38 (30.64%) patients. (Table 1) Hypotension was noted in 42 933.87%) patients, and Heart murmurs were noted in 13 (10.48%) patients. ECG abnormalities like ST segment depression was noted in 78 (62.90%) patients, Ischaemic changes in were noted in 88 (70.96%) patients and both ECG changes were noted in 40 (32.25%) patients. (Table 1) The ECG changes noted were statistically significant clinical sign in the diagnosis of the ACS in this study. (p value less than -0.05 was taken as significant)

Table 1: Showing the demographic data and diagnostic signs and symptoms in the study subjects, (n-124)

Observations	Number	Percentage	P value
Gender			
Male	87	70.16	0.114
Female	37	29.83	
Age in Years			
18 to 27	04	03.22	
28 to 37	09	07.25	0.234
38 to 47	28	22.58	
48 to 57	31	25	
58 to 67	29	23.38	
68 to77	26	20.96	
History			
Abnormal stress test	34	27.41	0.301
Peripheral artery disease	43	34.67	
CAD	47	37.93	
Symptoms			
Sweating	61	49.19	
Pain in the right arm or shoulder	12	09.67	0.112
Pain in both the arms	25	28.22	
Chest compressing pain	41	33.06	
Pain in left arm and shoulder	48	38.70	
Absent chest wall tenderness	38	30.64	
Physical examination			

Low B.P	42	33.87	0.100
Heart Murmur	13	10.48	
ECG			
ST segment depression	78	62.90	
Ischemic ECG changes (T wave inversion, ST segment depression, Abnormal Q wave)	88	70.96	**0.014**
Both	40	32.25	

The Cardiac Troponin levels- in terms of hs- cTn ng/l were estimated among the patients and the incidence was tabulated in the Table 2. There was statistical significance in the values of Troponin, correlating with the diagnosis of ACS in the study.

Similarly Serum Ferritin levels were assayed in all the subjects and found the values were tabulated in Table 2. There was statistical significance in the values of serum Ferritin, correlating with the diagnosis of ACS in the study.

Table 2: Showing the Troponin and Serum Ferritin values in the subjects (n-124)

Biomarkers	Number- %	P value
Cardiac Troponin levels- hs- cTn ng/l		
Below 20	21 – 16.93	**0.001**
20 to 40	14- 11.29	
40 to 60	28- 22.58	
60 to 80	34- 27.41	
80 to 100	17- 13.70	
100 to 150	10- 08.06	
Serum Ferritin Levels in ng/mL		
Below 300	21- 16.93	
300 to 400	25- 20.16	**0.001**
400 to 500	28- 22.58	
500 to 600	21- 16.93	
600 t0 700	11- 08.87	
700 800	13- 10.48	
Above 800	05- 04.03	

All the subjects were followed up for 32 months at an interval of 06 months and post MI events were recorded in the subjects. MACE was observed in 11 (08.87%) of the subjects, 17 (13.70%) deaths were recorded among the 124 subjects included in the study. LVEF was noted in 12 (09.67%) of the patients, Heart Failure was noted in 31 (25%) of the patients, Left ventricular aneurysm was noted 03 (02.41%) of the patients and the remaining 46 (37.09%) patients had no events in the period of follow up. (Table 3)

Table 3: Showing the final follow up outcomes in the study correlated with serum Ferritin levels (n-124)

Follow up outcomes	Number	Percentage	P value
Major adverse cardiovascular events (MACE)	15- 12.09	**08.87**	
Mortality	**17- 13.70**	**13.70**	
Left ventricular ejection fraction (LVEF)	**12- 09.67**	**09.67**	
Heart failure	**31- 25**	**25**	**0.001**
Left ventricular aneurysm	**03- 02.41**	**02.41**	
Total	**74- 59.67**	**59.67**	
Uneventful	46- 37.09	37.09	

In this study the clinical signs and symptoms and other parameters were compared in patients with Ferritin levels below 300ng/dL with patients with above 300ng/dL values. It was observed that there were no statistical differences except to ECG changes related to ischemia (p value <0.05), (Table 4)

Table 4: showing the clinical symptoms and signs and final outcome of Acute Coronary syndrome patients with low and High levels of Ferritin (n-124).

Clinical and Lab findings	Ferritin Below 300ng/mL	Ferritin Above 300ng.mL	P value
Symptoms			
Sweating	15- 71.42	75- 61.98	
Pain in the right arm or shoulder	12- 57.14	77- 63.63	
Pain in both the arms	13- 30.00	81- 66.94	
Chest compressing pain	10- 61.90	56- 46.28	0.133
Pain in left arm and shoulder	09- 42.85	63- 52.06	
Absent chest wall tenderness	14- 66.66	48- 39.66	
Physical examination			
Low B.P	15- 71.42	81- 66.94	
Heart Murmur	16- 76.19	78-64.46	0.127
ECG			
ST segment depression	10- 61.90	91- 75.20	
Ischemic ECG changes (T wave inversion, ST segment depression, Abnormal Q wave)	13- 30.00	85-70.24	**0.001**
Both	09- 42.85	71- 58.67	
Final outcomes			
MACE-17	03- 14.28	12- 09.67	
MORTALITY- 15	03- 14.28	14- 11.29	
LVF- 12	02- 09.52	10- 08.06	0.230
HF- 31	04- 33.33	27- 21.77	
LVA- 03	04- 19.04	02- 01.61	
UNEVENTFUL-50	01- 04.76	38- 30.64	

The serum Ferritin values estimated at 06 months intervals were correlated with the post ACS events among the subjects for a period of 32 months and it was observed that MACE (12.09%), mortality (13.70%%), LVEF (09.67%), HF (25%) and LVA (02.41%) were noted in patients equally with varying levels of serum Ferritin either low or high. There were no cardiovascular events in 46 (37.09%) patients. **(Table 5)**

Table 5: Showing the correlation between final outcomes and the serum Ferritin levels in the study (n-124)

Serum Ferritin Levels in ng/mL	MACE-15 12.09%	MORTALITY-17 13.70%	LVEF-12 09.67%	HF-31 25	LVA-03 02.41%	UNEVENT-FUL-4637.09%)
Below 300-21	03- 01.61	03- 02.41	02- 01.61	04- 04.03	01- 00.80	08- 07.25
300 to 400- 15	02- 01.61	02- 01.61	01- 00.80	04- 03.22	00- 00	06- 04.83
400 to 500- 22	01- 01.61	03- 02.41	02- 01.61	04- 04.22	00- 00	12- 09.67
500 to 600- 26	03- 02.41	03- 04.03	01- 00.80	06- 04.83	01- 0.80	12- 09.67
600 to 700- 15	02- 03.22	03- 03.22	02- 02.41	04- 03.22	01- 10.80	03- 02.41
700 800- 12	02- 01.61	01- 00.80	02- 01.61	03- 04.03	00- 00	04- 03.22
Above 800- 13	02- 01.61	02- 01.61	02-01.61	06- 04.83	00- 00	01- 0.80
Total- 124	15	17	12	31	03	46- 37.09
P value	**0.133**					

Discussion

The present study was aimed to evaluate the association between Ferritin levels and adverse cardiovascular outcomes in patients with acute myocardial infarction during short- or long-term follow-up. During the last decade there were spurt in the studies concentrating upon the metabolism of Iron (Ferritin) especially among the Cardio vascular patients with ischaemic heart disease in particular. (18) The guidelines of European Society of Cardiology (ESC) recommended estimation of Ferritin and Transferrin saturation to screen for iron deficiency among the Heart failure patients since 2021. (19) The society also recommended iron supplementation in ASC patients with LVEF <50% whenever the Ferritin levels are <100ng/mL and Transferrin saturation <20%. (19) But the current

guidelines of ESC did not recommend treating the STEMI and non-STEMI patients with Iron supplements with a potential prognostic value. (20) Hence the role of iron deficiency particularly Ferritin levels in patients with STEMI and non STEMI types require deeper introspection and more scientific studies. In the present study 124 patients were included with 87 (7.16%) males and 37 (29.83%) female patients. 04 (03.22%) patients were aged 18 to 27 years, 09 (07.25%) were aged 28 to 37 years, 28 (22.58%) were aged 38 to 47 years, 31 (25%) were aged 48 to 57 years, 29 (23.38%) were aged 58 to 67 years, 26 (20.96%) were aged 68 to 77 years. 34 (27.41%) patients had history of abnormal stress tests, 43 (34.67%) had peripheral artery disease and CAD in 47 (37.93%) patients. Symptoms like sweating was observed in 61 (49.19%) patients, pain in the right arm and shoulder in 12 (09.67%) patients, Pain in both the arms in 25 (28.22%) patients, pain in the left arm and shoulder in 48 (38.70%) patients, Chest compressing pain in 41 (33.06%) patients, and Absent chest wall tenderness in 38 (30.64%) patients. (Table 1) Hypotension was noted in 42 (33.87%) patients, and Heart murmurs were noted in 13 (10.48%) patients. ECG abnormalities like ST segment depression was noted in 78 (62.90%) patients, Ischaemic changes in were noted in 88 (70.96%) patients and both ECG changes were noted in 40 (32.25%) patients. (Table 1) The ECG changes noted were statistically significant clinical sign in the diagnosis of the ACS in this study. (p value less than 0.05, hence was taken as significant) Serum Ferritin levels fall in patients with disease related to iron-deficient states and increases in inflammatory conditions; its levels falling absolutely when the iron is reduced due to functional causes. [18]

There seems to be a pathophysiological link between cardiovascular outcomes of ACS and Oxidative stress and promotion of inflammation and atherosclerosis. [19] Few studies recorded an established fact that the serum Ferritin increased low-density lipoprotein oxidation, causing progression of atherosclerosis and acts as a risk factor for progression and injury of the coronary arteries endothelium. (20, 21) In another study the author observed that the Ferritin levels acted like a marker of inflammation than a marker of iron metabolism especially in overweight and obese patients characterized by a pro-inflammatory state. [22]

Such data explains the mystery behind the adverse clinical events occurring after ACS not only with low Ferritin levels but also high Ferritin levels in the serum. [22] Studies by Singh S [23] and Malthesh M and Gosavi S et al [24] investigated serum Ferritin levels in AMI patients focusing on the post ACS events like mortality, MACE, the decline of LVEF, left ventricular aneurysm development, recurrent angina, heart failure, and duration of hospitalization concluded that the role of Ferritin in risk of mortality and MACE stratification were somewhat discrepant; however their studies were heterogeneous.

The studies were conducted for different follow up periods and with varying outcome definitions. In one study the mortality was assessed as a post MI event only during 30 days of follow-up [20] and in another study it was for 12 months. [21] In this study the clinical signs and symptoms and other parameters were compared in patients with Ferritin levels below 300ng/dL and above 300ng/dL values. It was observed that there were no statistical differences except to ECG changes related to ischemia. (Table 4) There was no statistical significance noted as to the effect of high serum Ferritin levels in regards to the post cardiac ischaemia events in the study. (p value was more than 0.05). There were discrepancies in the selection of population characteristics and clinical settings also such as in one study the patients with STEMI who underwent primary PCI within 6 h from symptoms onset (19), while the other in other studies they included STEMI patients treated by primary PCI within 12 h from symptoms onset [20] and in some studies patients of both, STEMI or non-STEMI were treated with PCI after 5 days. [22] The serum Ferritin values estimated at 06 months intervals were correlated with the post ACS events among the subjects for a period of 32 months and it was observed that MACE (12.09%), mortality (13.70%%), LVEF (09.67%), HF (25%) and LVA (02.41%) were noted in patients equally with varying levels of serum Ferritin either low or high. There were no cardiovascular events in 46 (37.09%) patients. (Table 5) It was observed by few studies that ACS patients with markedly low or increased Ferritin values showed a higher in-hospital and 30-day mortality rates. [25] Hence in future including estimation of Ferritin levels of serum in ACS patients would help in risk stratification and help in achieving the increased prognostic performance, separating the high-risk patients who could benefit from closer monitoring. In addition to mortality risk stratification, estimation of serum Ferritin levels also could be used as a risk marker for left ventricular aneurysm development. [17] In that study the authors used a wide range of serum Ferritin levels varying from 7.0 to 323 ng/mL. In another study the high Ferritin levels were found to be linked to an accentuated LVEF decline in STEMI patients treated by PCI, [18] Nevertheless, the association between ferritin and LVEF should be evaluated in a contemporary cohort of patients, with currently available guidelines-directed therapies for heart failure patients.

Limitations: The data selected in this study was small, with inhomogeneity hampered and limited the

generalizability of the results. There was no consensus existed on the cut-off ferritin values.

Conclusions

In this study it was observed that both low and high serum Ferritin values were associated with adverse events in patients with ACS both during their hospital stay and at more extended follow-up periods. ECG changes of ischemia were more in patients Ferritin levels more than 300ng/ml. The levels of Ferritin were not linked to increased mortality risk, accentuated LVEF decline, left ventricular aneurysm formation during follow-up. The study recommends closer monitoring of serum Ferritin levels and timely therapeutic interventions for high-risk patients with ACS as elevated serum Ferritin can be a potent factor for predicting AMI especially STEMI. More elaborate studies are required with larger numbers to confirm the correlation.

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