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ORIGINAL RESEARCH

TO STUDY THE PREVALENCE OF HYPERFERRITINEMIA IN PATIENTS DIAGNOSED WITH ACUTE CORONARY SYNDROME

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Abstract

Introduction: Cardiovascular diseases (CVDs) are one of the leading cause of mortality in India. One in 4 death in India are now because of CVDs with ischemic heart disease.Chronic inflammation may be a contributory factor in the growing prevalence of Coronary Artery Disease (CAD). Ferritin has been labeled as new marker for evaluation of chronic inflammation and its course in coronary artery disease.

Aims and Objectives: To study the prevalence of Hyperferritinemia in patients diagnosed with Acute Coronary Syndrome.

Materials and Methods: This was a prospective observational study started from 1st December 2020 to 31st May 2022, was conducted on patients admitted to Intensive Coronary Care Unit(ICCU) with a diagnosis of Acute Coronary Syndrome(ACS). Total of 120 cases of Acute Coronary Syndrome of age >18years were included in the study.The reference range for serum ferritin was taken as >400ug/L in males and >150ug/L in females. The prevalence of increased ferritin was studied .

Results : The mean age of studied population was 55.6 ± 13 years. Majority of patients were males (78.33%).Chest pain was the most common presenting symptom (94.17%). Most of the patients (75.83%) presented with STEMI. The prevalence of hyperferritinemia was (25.83%)

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and all these patients had STEMI.The proportion of patients with hyperferritinemia was significantly higher in TVD patients(46.15%).

Conclusions: The ferritin levels need not be considered as an independent risk factor but it can be used as poor prognostic factor in patients with Acute Coronary Syndrome.

Key words: Acute Coronary Syndrome(ACS), Hyperferritinemia, Coronary Artery Score(CAS).

Introduction

At the turn of century, cardiovascular diseases (CVDs) became the leading cause of mortality in India. This epidemiological transition is largely because of increase in the prevalence of CVDs and cardiovascular risk factors in India. In 2016; the estimated prevalence of CVDs in India was estimated to be 54.5 million. One in 4 death in India are now because of CVDs with ischemic heart disease.[1]There are two facets of coronary artery disease: Stable CAD and Unstable CAD which includes patients with Acute Coronary Syndrome(ACS) [Unstable angina(UA) ,Non-ST elevation myocardial infarction(NSTEMI), ST elevation myocardial infarction(STEMI)].[2] Its wide range of risk factors include smoking, hypertension, obesity and dyslipidemia which have been established as useful predictors of acute myocardial infarction.[3] In addition to these classical risk factors, obesity, fatigue ,insufficient sleep, are also risk factors of acute myocardial infarction.[4] Over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for the atherothrombotic vascular diseases.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 triglycerides and number of genetic polymorphism are of particular interest.[5] Ferritin is a large protein having a molecular weight 450KDa comprised 24 subunits, covering an iron core containing up to 4000 atoms of iron. Ferritin acts as the soluble storage form of iron in tissue. Ferritin beyond its function as an iron storage marker ,is a multi-functional protein with possible roles not only in iron delivery , but in proliferation, angiogenesis, and immunosuppression.[6] Excess iron is capable of stimulating the progression of atherosclerotic lesions to catalyze the production of free radicals, and to promote lipid peroxidation by reducing the levels of anti-oxidants in plasma, therefore, it can be associated with the progression of atherosclerosis and increases the risk of ischemic cardiovascular events.Epidemiological studies have provided contradictory results regarding iron stores and

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subsequent atherosclerosis and coronary artery disease (CAD).[7]For example, Klipstein-Grobusch et al. observed an independent relationship between serum ferritin levels and carotid atherosclerosis.[8] However, Knuiman et al., with a 17-year follow-up study in Australia, evaluated the association between serum ferritin level and coronary heart disease (CHD) and stroke events. The results of their study did not show any evidence in relation to ferritin level as a risk factor for CVD.[9]So in this study, we assessed the prevalence of increased ferritin in myocardial infarction and to look for any association between them. Serum ferritin concentrations are directly proportional to intracellular ferritin concentration and considered to be the best clinical measure of body iron stores and most feasible to use in epidemiological studies.

Aims and objectives

Primary Objective- To study the prevalence of hyperferritinemia in patients diagnosed with Acute Coronary Syndrome.

Secondary Objective-1. To study the correlation of ferritin level with in-hospital cardiac complications in patients with Acute Coronary Syndrome.

2. To compare the levels of ferritin amongst those who present with STEMI And NSTEMI/Unstable Angina.

3. To study the association of ferritin levels with the angiographic severity in those who undergo the coronary angiography.

Material and methods

Study design -The prospective observational study.

Study duration- 18 Months (1stdecember 2020 to 31st may 2022).

Study population-120 diagnosed cases of Acute Coronary Syndrome.

Inclusion Criteria- All patients aged >18yrs admitted in ICCU with a diagnosis of acute coronary syndrome were included in the study in accordance with the exclusion criteria .

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Exclusion Criteria- 1. Chronic Renal disease: As per KDIGO classification, G5 stage were excluded.

2. Hereditary hemochromatosis, Non alcoholic fatty liver disease (NAFLD) and virus related chronic liver disease.

3. Hematological disorders (anemia, Hb 16.5gm/dL and Hematocrit >49% in males and Hb>16gm/dL and Hematocrit >48% in females.

4. History of cancers in the past or present.

5. Recent infection in last 7 days(bacterial and viral infections).

6.Severe bleeding that required a blood transfusion.

7. Sepsis/Septic shock.

Sample Size- The sample size was calculated to be n=120 by using the formula n =Za/22 p*(1-p)/d2 ,where Z1-α/2 =1.96, is standard normal deviate at type 1 error α =0.05, p=74% and d=8% margin of error.

Methodology- This was a prospective observational study started from 1st December 2020 to 31st May 2022 at Christian Medical College and Hospital, Ludhiana, were conducted on patients admitted to ICCU with a diagnosis of acute coronary syndrome who gave consent to be a part of the study.Clinical Assessment was done on admission including detailed history regarding the duration, frequency and severity of chest pain ,exercise intolerance ,presence of coronary risk factors and history of previous myocardial infarction .A detailed cardiovascular and systemic examination were carried out for the presence or absence of cardiac failure and presence of associated cardiac lesions .A standard 12 lead ECG recording was done and blood samples were drawn for relevant investigations ,including cardiac markers and ferritin was taken at the time of admission to the hospital.The diagnosis of ACS was made. The serum ferritin levels at time of admission was measured by using Roche cobas 6000 automated machine in biochemistry lab based on electrochemical luminescence technique. The reference range of serum ferritin was taken as >400ug/L in males and >150ug/L in females.Repeat serum ferritin level were done in event of any complications like recurrent angina, post prandial angina ,cardiac failure, arrhythmias-ventricular tacycahrdia and ventricular fibrillation,progression to acute STEMI in patients with NSTEMI/Unstable angina during

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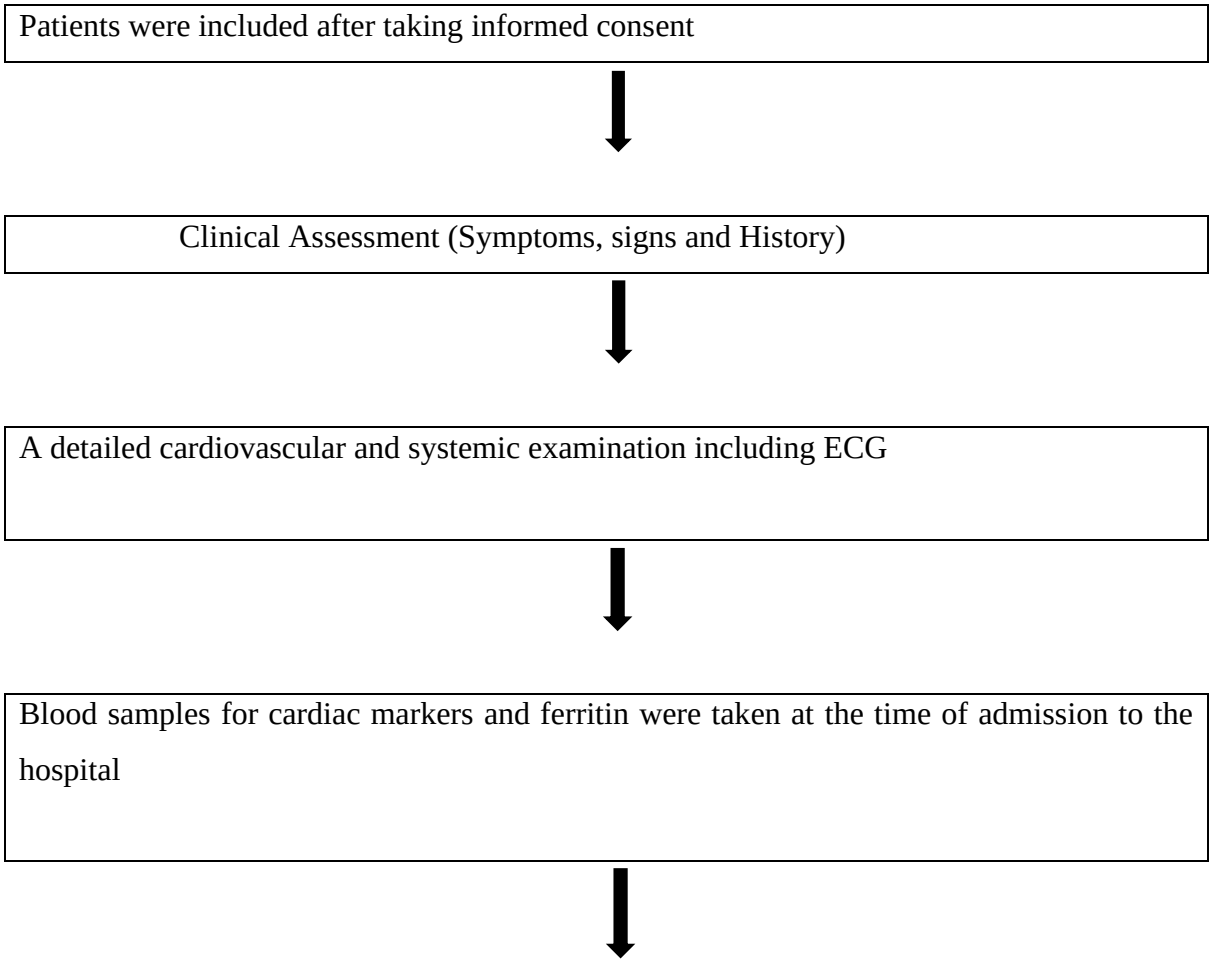
hospital stay. The association of ferritin levels with the angiographic severity was studied in those who underwent the coronary angiography and coronary artery score was calculated as per Dortimer et al coronary artery score according to which the severity of lesions are graded as: Grade 0-no disease, Grade 1-intimal disease to less than 50% stenosis, Grade2-50 to 69% stenosis, Grade3-70 to 95% stenosis ,Grade4-96-99% stenosis or sub total stenosis,Grade5-totally occluded. The maximum score of any vessel shall be the sum of all disease segments. Stenosis existing 50% of major epicardial coronary artery diameter was considered significant.

Statistical Analysis- The data was entered into Microsoft excel sheet. Data was summarized using frequency distribution and descriptive analysis. Chi square test was used to find the association of categorical variables between the groups. The P value <0.05 was considered significant. All statistical analysis were performed using SPSS (Statistical Packages for Social Sciences, version 26.0. Armonk, NY: IBM corp.)

Flow Chart Of The Study



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Repeat serum ferritin levels was done in patient developing any in hospital event

The association of ferritin levels with the angiographic severity and Coronary Artery Score was calculated.

Results

In this study which included 120 patients , majority of patients belonged to age group of 46-55 years(29.17%) followed by 56-65 years (25.83%). The mean age of studied population was 55.6 ± 13 years(fig 1). Majority of patient were males (78.33%) (fig 2). Chest pain was the most common presenting symptom (94.17%)followed by dysponea (20.83%). Most of the patients presented within 1-6hrs of chest pain (63.72%) with mean duration of 7.53 ±9.3hrs.(fig 3).

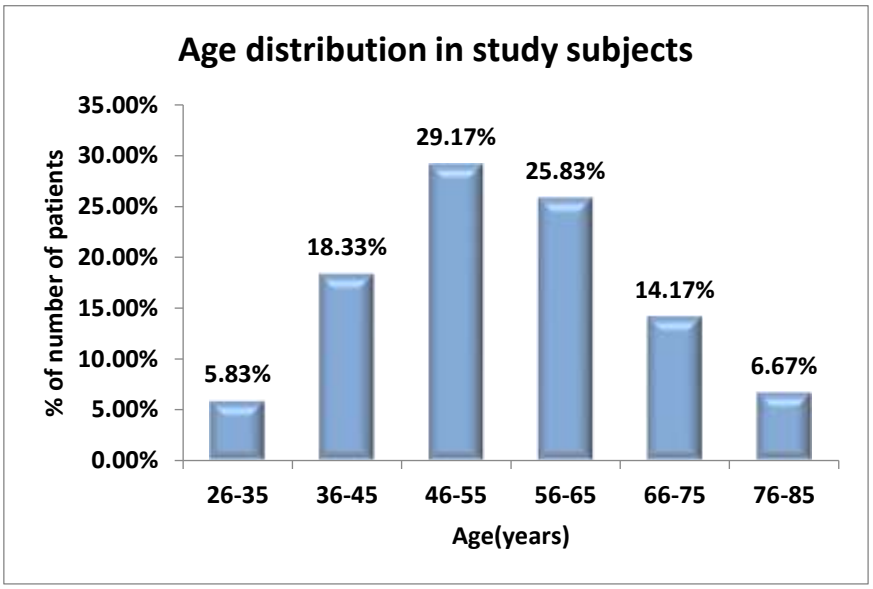

Fig 1:-Age distribution in study subjects.

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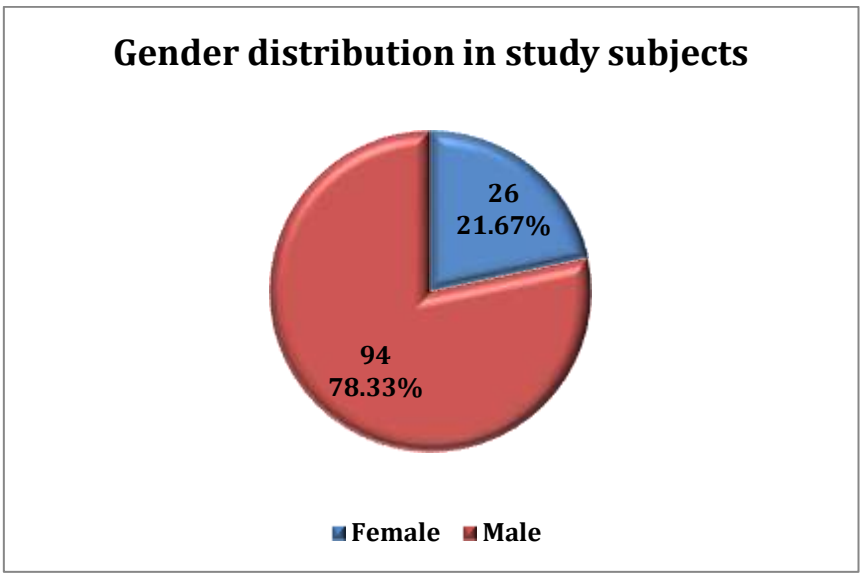

Fig 2:- Gender Distribution in study subjects.

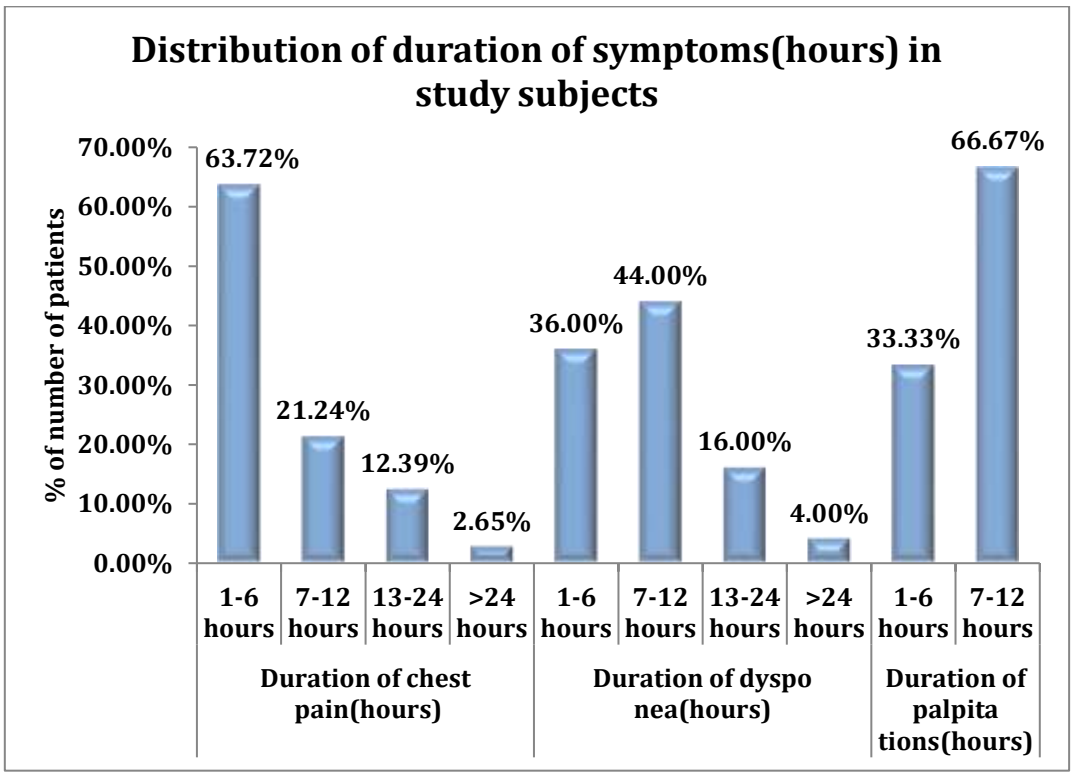

Fig 3:- Descriptive statistics of duration of chest pain(hours), duration of dysponea(hours) and duration of dysponea(hours) in study subjects.

Only 35 out of 120 patients (29.17%) were diabetics and 49 out of 120 patients (40.83%) were hypertensives.(fig 4A and 4B)

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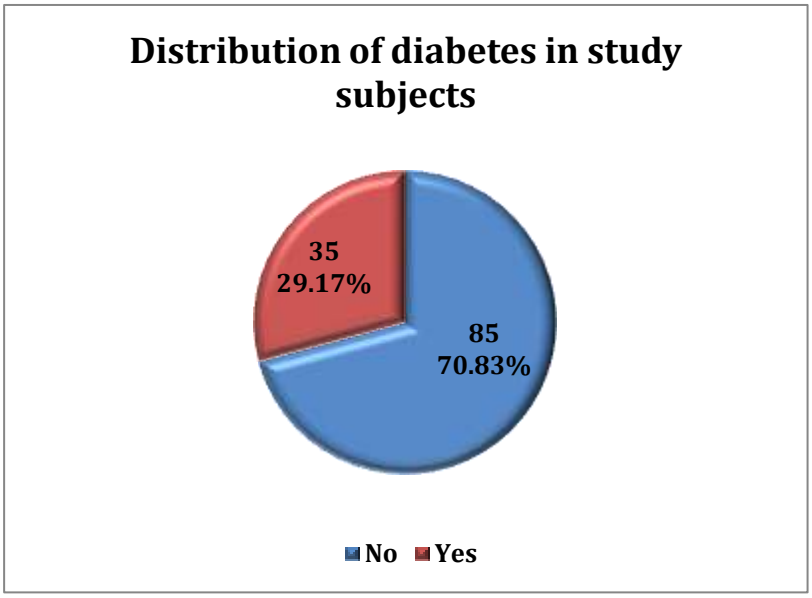

Fig 4A:- Distribution of diabetes in study subjects

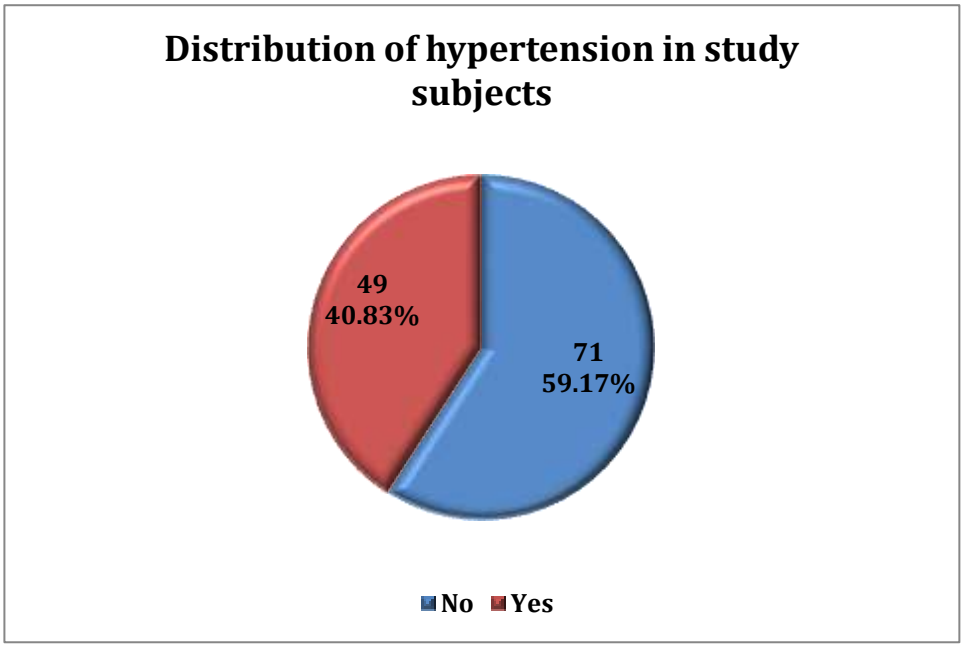

Fig 4B:- Distribution of hypertension in study subjects

Table 1:- Distribution of ECG and Echo changes among study subjects-

Variables	Category	Frequency

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ECG Changes	ST Elevation ST Depression T wave Inversion Qwaves Arrythmias	93(77.50%) 11(9.17%) 14(11.67%) 2(1.67%) 3(2.50%)
ECG Changes	Anterior/anteroseptal Anterolateral Inferior Lateral Posterior	40(33.33%) 25(20.83%) 42(35.00%) 18(15.00%) 4(3.33%)
Echo Findings	Regional wall motion abnormality Reduced left ventricle ejection fraction Valvular abnormality	97(80.83%) 63(52.50%) 85(70.83%)
Type of ACS	STEMI UNSTEMI Unstable Angina	91(75.83%) 6(5.00%) 23(19.17%)

Majority [93(77.50%)] of patients had ST elevation followed by T wave inversion [14(11.67%)], ST depression [11(9.17%)] and arrhythmias [3(2.50%)]. Q waves were seen in only 2 out of 120 patients (1.67%). In majority [42(35.00%)] of patients, ECG showed changes in inferior followed by anterior/anteroseptal [40(33.33%)], anterolateral [25(20.83%)] and lateral [18(15.00%)]. ECG showed changes in posterior in only 4 out of 120 patients (3.33%). In majority [97(80.83%)] of patients, wall motion abnormality was present followed by valvular abnormality [85(70.83%)].Reduced Left ventricular ejection fraction was present in only 63 out of 120 patients (52.50%). In majority [91(75.83%)] of patients, diagnosis was STEMI followed by UA [23(19.17%)]. Diagnosis was NSTEMI in only 6 out of 120 patients (5.00%).

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Table 2:- Hyperferritinemia in Study subjects

Ferritin(ug/L)	**Frequency**	**Percentage**
Hyperferritinemia		
No	89	74.17%
Yes	31	25.83%
Ferritin(ug/L)		
Mean ± SD	253.48 ± 236.31	
Median	184	
Range	10.56-1340	

Hyperferritinemia was present in only 31 out of 120 patients (25.83%).Mean value of Ferritin(ug/L) of study subjects was 253.48 ± 236.31 with median of 184.

Table 3:- Angiographic distribution of site and extent of lesion and distribution of intervention done in study subjects

Variables	**Category**	**Frequency**
Site of lesion	Left Main	2(6.67%)
	Left Anterior Descending	22(73.33%)
	Left Circumflex	18(60.00%)
	Right Coronary	16(53.33%)
Extent of disease	Single vessel disease	3(10.00%)
	Double vessel disease	8(26.67%)
	Triple vessel disease	13(43.33%)
	Normal coronaries	1(3.33%)
	Others(ectatic)	5(16.67%)
Intervention Done	Medical Management	7(23.33%)

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	Coronary Artery Bypass grafting	14(46.67%)
	Percutaneous Coronary Intervention	9(30.00%)

Angiography was done in only 30 out of 120 patients. In majority [22(73.33%)] of patients, site of lesion was left anterior descending followed by left circumflex [18(60.00%)] and right coronary [16(53.33%)]. Site of lesion was left main in only 2 out of 30 patients (6.67%). In majority [13(43.33%)] of patients, extent of disease was triple vessel disease followed by double vessel disease [8(26.67%)], others{Ectatic} [5(16.67%)] and single vessel disease [3(10.00%)]. Only 1 out of 30 patients (3.33%) had normal coronaries. In majority [14(46.67%)] of patients, intervention done was CABG followed by PCI [9(30.00%)]. 7 out of 30 patients (23.33%) were managed conservatively with dual antiplatelets.

Table 4A:- Correlation Of Hyperferritinemia with Different Parameters

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31(25.83%) patients had hyperferritenemia and they all had ST elevation myocardial infarction

PARAMETER	Total	WITH HYPERFERRITINEMIA	WITHOUT HYPERFERRITINEMIA	P VALUE
Type of ACS				
STEMI	91	31 (34.07%)	60(65.93%)	
NSTEMI	6	0	6(100%)	0.0004
Unstable Angina	23	0	23(100%)	
ECHO				
1.Wall Motion abnormality	97	31(31.96%)	66(68.04%)	0.0009
2. Reduced EF	63	22(28.42%)	41(65.08%)	0.017
3.Valvular Abnormality	85	24(28.24%)	61(71.76%)	0.349
Diabetes	35	13(37.14%)	22(62.86%)	0.069
Hypertension	49	26(53.06%)	23(46.94%)	<0.0001
Cardiac Enzymes				
On admission	60	22(36.67%)	38(63.33%)	0.007
CPK (>167u/l)	84	25(29.76%)	59(70.24%)	0.133
CK MB(>25u/l)	61	25(40.98%)	36(59.02%)	0.0001
TroponinT (>0.1ng/ml)				
At 6 hours	87	27(31.03%)	60(68.97%)	0.007
CPK(>167u/l)	98	26(26.53%)	72(73.47%)	0.395
CKMB(>25u/l)	95	27(28.42%)	68(71.58%)	0.023
Troponin T (>0.1ng/ml)				

with p value 0.0004. Proportion of patients with hyperferritinemia was significantly higher in wall motion abnormality. 13 patients with diabetes had hyperferritenemia(37.14%) .No

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significant correlation was seen(p value 0.069). Among hypertensives, 26(53.06%) had hyperferritenemia with p value <0.001. Significant association was seen in CPK(U/L), TROPT (ng/mL) with hyperferritinemia.(p value <.05)

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Table 4B:-Correlation Of Hyperferritinemia with Different Parameters

PARAMETERS		WITH HYPERFERRITINEMIA	WITHOUT HYPERFERRITINEMIA	P VALUE
Angiography Severity-				
Single vessel disease	3	0(0%)	3(100%)	
Double vessel disease	8	0(0%)	8(100%)	0.032
Triple Vessel disease	13	6(46.15%)	7(53.85%)	
Normal	6	0	6(100%)	
Intervention Done				
Medical Management	7	0	7(100%)	0.022
CABG	14	6(42.86%)	8(57.14%)	
PCI	9	0	(100%)	
Cardiac complications				
1.Recurrent Angina	22	14(63.64%)	8(36.36%)	<0.0001
2.Arrythmias	16	9(56.25%)	7(43.75%)	0.003
3.Post prandial Angina	4	2(50%)	2(50%)	0.274
4.Cardiac Failure	5	2(40%)	3(60%)	0.603
5. Progression to acute STEMI from NSTEMI/Unstable Angina	0	0	0	-
Outcome				
Mortality	5	3(60%)	2(40%)	0.108
Discharge	115	28(24.35%)	87(75.65%)	

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Angiography was done in total of 30 patients. Proportion of patients with hyperferritinemia was significantly higher in triple vessel disease(46.15%) as compared to normal, single vessel disease with p value of 0.032. Proportion of patients with hyperferritinemia was significantly higher in CABG intervention(42.86%) as compared to medical(0%), PCI(0%)(p value=0.022).

Proportion of patients with hyperferritinemia was significantly higher in recurrent angina (63.64%) as compared to without recurrent angina (17.35%). (p value <.0001).Distribution of hyperferritinemia was comparable with post prandial angina, cardiac failure, other cardiac complications. Proportion of patients with hyperferritinemia was significantly higher in arrhythmias (56.25%) as compared to without arrhythmias (21.15%). (p value=0.003).

Distribution of hyperferritinemia was comparable with outcome. (Death(60%) vs Discharge(24.35%)). (p value=0.108)

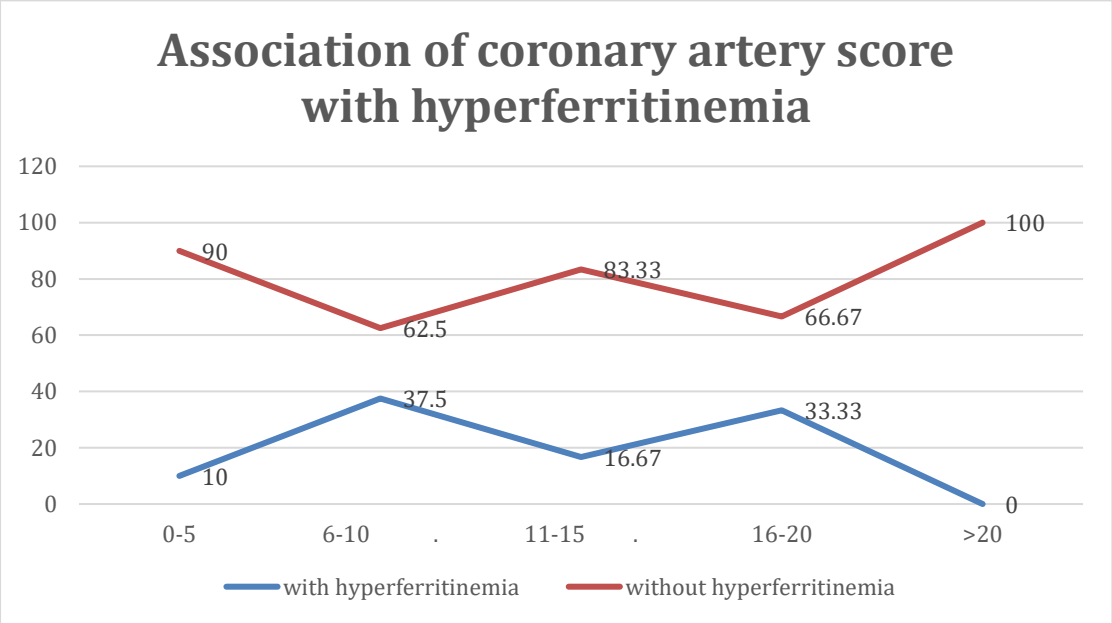

Fig 5:-Association of coronary artery score with hyperferritinemia.

Distribution of hyperferritinemia was comparable with coronary artery score. (0-5(10%) vs 6-10(37.50%) vs 11-15(16.67%) vs 16-20(33.33%) vs >20(0%)). (p value=0.557)

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Discussion

In our study 31(25.83%) patients had hyperferritenemia with mean value of 253.48 +/- 236.31.The results are comparable with the study done by Singh S et al.[10] However in the study conducted by Hoque et al(65 patients),46.2% patients had hyperferritenemia[11] and in the study conducted by Holay MP et al(75 patients), 62.66% patients had high serum ferritin levels.[5] Total 91 patients(75.83%) presented with STEMI, 23 (19.17%) had Unstable Angina and 6(5.00%) patients had NSTEMI.This was in contrast to many studies as conducted by Tsegaye et al [12]and Ralapanawa et al[13]. The difference could be attributed to small sample size. However ,Battula et al in their study on clinical presentation and outcome in ACS found STEMI to be the most common presentation (67%).[14] In our study 31(25.83%) patients had hyperferritenemia and they had ST elevation myocardial infarction with p value 0.0004.The results are comparable with the studies done by Lokary et al[15] and by Singh S.[10] Therefore serum ferritin levels are significantly associated with STEMI group. In our study ,among 13 patients who had TVD, 10 patients (76.92%) had STEMI and 3 patients(23.08%) had NSTEMI which was comparable to the study done by Puymirat et al on STEMI patients found out that 53.7% patients had multivessel disease.[16] However in the study conducted by Agarwal et al,in which patients with NSTEMI were associated with more severe disease.[17] Proportion of patients with hyperferritinemia was significantly higher in triple vessel disease(46.15%) with p value of 0.03.The results are comparable with the study done by Priyank Udagani el al.[18] In present study, 22(18.33%) patients had recurrent angina followed by arrhythmias [16(13.33%)], cardiac failure [5(4.17%)] and post prandial angina [4(3.33%)]. None of the patient progressed to acute STEMI in patients with NSTEMI/Unstable angina.Majority [114(95.00%)] of patients did not have other cardiac complications. This was in contrast to many studies conducted by Sarkari M[19] and by Tabatabi S et al[20],who found cardiac failure to be the most common in-hospital cardiac complication.

Conclusion

This studies showed that the prevalence of hyperferritinemia was 25.83% only but all these patients had STEMI.The repeat ferritin levels were high in patients who had cardiac complications.Ferritin levels were significantly high in patients with triple vessel disease.The patients who died had significantly high levels of ferritin.The hypertensive patients had

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significant high ferritin levels.Thus, the high ferritin levels can be used as poor prognostic factor in patients with Acute Coronary Syndrome.

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