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STUDY OF RELATIONSHIP BETWEEN ACUTE CORONARY SYNDROME AND TOTAL BILIRUBIN LEVEL.

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INTRODUCTION:

The most common cause of mortality in the developed nations is cardiovascular disease (CVD) which accounts for up to one-third of all deaths in the world.[1] Vascular pathology is responsible for more morbidity and mortality than any other class of human disease.[2] It has been predicted that greater than one half the worldwide CVD risk burden will be borne by the Indian subcontinent in the next decade according to the current epidemiological studies.[3] The expeditious diagnosis of acute coronary syndrome (ACS) is lifesaving.[4] Prompt identification of the evolution of heart disease is limited by two vital factors. Firstly, it is often latent. Coronary artery disease (CAD) can progress to an advanced stage before the patient perceives any symptoms. Secondly, the symptoms attributable to heart disease is limited, so various pathologies may commonly present with similar symptoms.[5]ACS may present as ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI).

In spite of the fact that patients with STEMI or NSTEMI share similar cardiovascular risk factors, patients with STEMI have poor short-term mortality in comparison to patients with NSTEMI.[6] Acute myocardial infarction (AMI) is defined as death or necrosis of myocytes, characterized by a typical clinical presentation consisting of chest pain, dyspnoea, with rise in troponin or creatine kinase-MB(CK-MB). Occlusion of the coronary artery deprives the myocardium of oxygen and causes reduced fatty acid utilization with free radical formation which further damages the myocardium.[7] Majority of the ACS cases are caused due to rupture of an atherosclerotic plaque in a coronary artery, leading to the formation of a thrombus. Atherosclerosis results from an excess of radical generating as compared to radical scavenging systems.[3]

The role of inflammation in CVD is substantiated. Oxidative stress plays a vital role in atherosclerosis, which is a chronic inflammatory process catalyzed by a variety of factors aiding in inflammatory cell entry and activation.[8] Bilirubin was considered to be a toxic waste product of the heme oxygenase action, but now among various boons, it is found to have a strong relation with CAD.[3] Bilirubin has been recognized as an important endogenous anti- oxidant and anti-inflammatory molecule in the recent decades and is postulated to be protective against atherosclerosis.[8] It has been demonstrated to play an essential role in maintaining the body's redox equilibrium. Disturbances of this equilibrium is considered as one of the major risk factors for the development of non-communicable diseases.[9]

Despite the astounding therapeutic advances and considerable improvements in reperfusion therapy, myocardial infarction (MI) can yield major complications, including heart failure (HF), which results in an increase in morbidity and mortality.[10,11] Hence, strategies that enhance risk stratification and warrant early personalized treatment modalities and follow-up programs are essential.[11] Only a handful of studies are conducted in India to prove the relationship between serum bilirubin levels and CAD.[12] Hence, the present study was undertaken to evaluate the association between these two variables by comparing it with a control group. We strive to elucidate this intricate relationship between bilirubin and CAD as a guide for physicians and other healthcare workers.

MATERIAL AND METHODS:

The present cross-sectional study was conducted at M.S. Ramaiah hospital by including the patients presenting with ACS in the casualty and admitted in coronary care unit (CCU) of M.S. Ramaiah hospital for a period of two years.

We had included all the patients of wither gender aged more than18 years diagnosed with Non ST–segment elevation MI, ST segment elevation MI and unstable angina are selected on the basis of history, examination and relevant investigation. Known cases of hepatitis, who are on hepatotoxic drugs, non-cardiac chest pain, Cirrhosis of liver, Bile duct obstruction and the Hemolytic jaundice had been excluded from our clinical study.

Method Of Collection Of Data

Institutional ethical clearance was obtained prior to the beginning of the study and informed consent was obtained from patients. A detailed history, general physical examination, systemic examination and investigations were performed on all patients who fulfilled the inclusion criterion. Controls were selected and matched with gender and other co-morbid conditions.

The investigations include: CBC RBS Liver Function test Lipid profile ECG 2D ECHO Troponin CHD was defined as definite myocardial infarction confirmed by electrocardiogram and/or enzyme changes or any angina diagnosis that required intervention after confirmation of coronary artery stenosis by coronary angiography. (1) DM was defined as a fasting plasma glucose concentration ≥126 mg/dl or current treatment with hypoglycemic agents. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive drugs. (2)

Laboratory Principle: Serum was separated from venous blood of fasting subjects and analyzed within two hours of collection.

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Sample: - Serum/plasma (free of haemolysis) Procedure: - Total bilirubin reagent-1000µL, Serum-50µL Mix well and incubate for 5minutes. Measure the absorbance of the sample against the respective sample blank at 546 or 532nm. Calculation for semi auto with factor: Total bilirubin = OD of test-OD of sample blank × Factor with artificial standard: Total bilirubin concentration = OD of test-OD of sample blank/OD of standard Sulfanilic acid reacts with sodium nitrite to form diazotized sulfanilic acid. Total Bilirubin reacts with diazotized sulfanilic acid in the presence of DMSO (Di Methyl Sulf Oxide) to form azobilirubin. Normal range of Total bilirubin: 0.2 to 1.0 mg/dl, Mean 0.6 mg/dl. (3)

Statistical Analysis: The data was analyzed using SPSS version 22. Mean was derived for all the parametric variables and the parametric variables between the cases and controls were compared using unpaired student T test and comparison between the frequencies was done by using chi-square test considering $p < 0.05$ as statistically significant. Descriptive statistics such as mean and percentage were used to present the data. SAMPLE SIZE The prevalence of CAD in India is 8%. The sample size is 192 using the statistical formula: $n = (1.96)2 \times p \times q/d2$ p= prevalence of acute coronary syndrome q= (100-p) d= Margin error ± 5

RESULTS:

A total of 196 patients were included in the study from September 2018 to August 2020. Age group between 51 to 60 predominated in study group. Male predominated in the study group. Patient with T2DM had more incidence of ACS. People with HTN had more incidence of ACS.

Table 1: Distribution of Study Subject Based on Age

Age (yrs.)	Experimental		Control		Total
	Number	percent	Number	percent	
31 - 40	2	2.04	12	12.24	14
41 - 50	15	15.31	23	23.47	38
51 - 60	37	37.76	27	27.55	64
61 - 70	28	28.57	24	24.49	52
71 - 80	12	12.24	11	11.22	23
> 80	4	4.08	1	1.02	5
Total	98	100.00	98	100.00	196

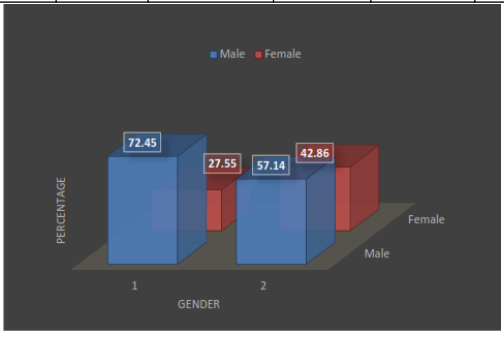

Figure 1: Distribution of Study Subjects Based on Gender

Majority of our study population were aged between 51 to 60 years with no significant difference. Also, Male predominated in the study group in either group with no statistically significant difference.

TABLE 2: Distribution of Study Subjects Based on history of HTN, T2DM and family history of CAD

DM	Experimental		Control		Total
	Number	%	Number	%	
HTN	30	30.61	30	30.61	60
DM	25	25.51	24	24.49	49
Family history of CAD	19	19.39	19	19.39	38

We could observe that the patients with HTN and T2DM had more incidence of ACS. Whereas the family history of CAD also been equally distributed between both groups.

Table 3: Distribution of Study Subjects Based on Smoking

Smoking	Experimental		Control		Total
	Number	percent	Number	percent	
No	76	77.55	75	76.53	151
Yes	22	22.45	23	23.47	45
Total	98	100.00	98	100.00	196

Table 7: Distribution of ACS in Study Subjects

ACS	Experimental	
	Number	Percent
STEMI	60	61.22
NSTEMI	26	26.53
Unstable	12	12.24
Total	98	100.00

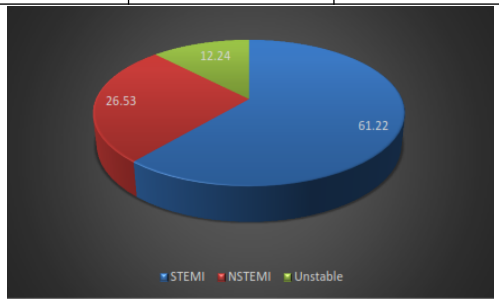

Figure 2: Type of ACS

Table 4: Association between Serum Bilirubin and ACS

Serum bilirubin - T	Mean	SD	F-value	P-value
STEMI	0.43	0.10	7.829	0.001
NSTEMI	0.54	0.05		
Unstable	1.08	1.52		
Total	0.54	0.56		

Showed inverse co relation with significant p value

Table 5: Multiple Comparisons Bonferroni

(I) ACS		Mean Difference (I-J)	P-value
STEMI - NSTEMI	NSTEMI	0.114	1.000
STEMI - Unstable	Unstable	0.655*	0.000
NSTEMI - Unstable	Unstable	0.541*	0.012

Table 6: Correlation between Lipid Profile and ACS

	Experimental		Control		t-value	P-value
	Mean	SD	Mean	SD		
Lipid Profile– T. Cholesterol	177.91	139.95	153.60	20.40	1.701	0.090
Lipid Profile – LDL	129.04	21.97	105.74	22.43	7.346	0.000
Lipid Profile – HDL	45.93	12.12	51.68	10.81	3.508	0.001

Table 7: Correlation between Liver Enzymes and ACS

	Experimental		Control		t- value	P-value
	Mean	SD	Mean	SD		
Liver - AST	12.45	5.06	12.98	5.55	0.699	0.485
Enzymes - ALT	12.66	5.55	12.46	3.92	0.297	0.767

Table 8: Association between Total Bilirubin and Direct Bilirubin

	Experimental		Control		t- value	P-value
	Mean	SD	Mean	SD		
Serum bilirubin - T	0.54	0.56	0.75	0.25	3.395	0.001
Serum bilirubin - D	0.09	0.09	0.09	0.08	0.230	0.818

DISCUSSION:

The prompt diagnosis of ACS is lifesaving. ACS is diagnosed by evaluation of typical symptoms with ischemic ECG changes and/or

cardiac biomarker elevation. The role of oxidative stress and inflammation in the pathophysiology of ACS is well known. This study was conducted on 196 patients admitted with acute coronary syndrome (ACS) at M.S. Ramaiah hospital, Bangalore. Age distribution was in comparison with other studies. The age ranged from 30 to >80 years in the present study. The mean age of the ACS group was 59.3+13.19 SD years which is similar to a study by Huang et al in 2017 which showed the mean age to be 64.2 ± 11.9 years.[13] The patients in the age group of 51 to 60 years had the highest incidence of ACS which is in concordance with the study by Purushotham et al (2018)[3].

This elucidates the fact that the incidence of ACS increases with age. Percentage of males and females in different studies of the study group, 72.45 were males and 27.55 were females in the present study which is similar to a study by Sahin O et al in which 66% of participants were male and 34% were female.[14] A study by Hopkins et al had 75.6% males and 24.4% females.[15] However, a study by Huang et al in 2017 showed a higher percentage of males comprising of 82.8%.[13] Comparison of the presentation of ACS with other studies In the present study, the percentage of ACS patients presenting with STEMI were 61.22%, NSTEMI were 26.53% and unstable angina were 12.24%.

These findings were in concordance with a study by Purushotham et al in 2018 where the percentages of STEMI were 72.5%, NSTEMI were 18.5% and unstable angina were 8.8%.[3] Comparison of serum bilirubin with other studies the mean total bilirubin in the present study was 0.54±0.55 SD mg/dl. This is in concordance with other study by Huang (2017) which showed the mean total bilirubin to be 0.42 mg/dl and 0.45 mg/dl respectively.[13] Serum levels of total bilirubin in the ACS group were significantly lower than those in the control group ($p < 0.0001$). This finding is similar to a study by Ke-Fu Zhu et al in 2016.[16] Similar negative association between serum bilirubin and ACS was also noted in study by Oda et al in 2016.[17]

The mean total bilirubin in patients of STEMI, NSTEMI and unstable angina were 0.43+0.10 SD, 0.54+0.05 SD and 1.08+1.52 SD mg/dl in the present study, which is similar to a study by Purushotham et al in 2018.[3] Mean direct bilirubin and direct bilirubin were 0.09mg/dl and 0.09 mg/dl respectively in the present study. These findings were similar to a study by Carine Ghem et al in 2010 showing 0.08 mg/dl and 0.29 mg/dl as values of direct and indirect bilirubin respectively.[18] while many studies have rendered evidence regarding the benefits of bilirubin against CVD, there are a number of studies providing evidence for the contrary.

A study conducted by Ozturk et al in 2016 on 782 patients of non-ST-elevation acute coronary syndrome, reported a significantly higher bilirubin level in such patients.[4] Study of risk factors showed that in the present study, 25.51% of ACS patients had underlying DM, 30.61% had hypertension, 19.39% had family history of ACS, and 22.45% had history of smoking. The most common underlying risk factor in CAD patients was hypertension, constituting 35.7%, which is in concordance with a study by Gul et al in 2013.[19] Comparison of total leucocyte count among different studies showed that the mean TLC in the present study was 12,325.87 cells/microliter in the CAD patients, which is in concordance with a study by Purushottam et al 2018, with mean WBC count of 13,785.7 cells/microliter.[3] Similar findings were also noted in a study by Salehi N et al.[20]

CONCLUSION:

Total bilirubin a potential risk factor marker to predict in-hospital major adverse cardiac events and cardiac death. Serum bilirubin levels can be used in screening individuals at high risk for ACS and preventive strategies can be applied before the onset of overt CVD. Total bilirubin is an inexpensive, non-invasive, immediately obtainable and easily measured biomarker which is frequently included in routine laboratory panels. It has a potential to provides further prognostic information in addition to standard clinical risk factors for recognizing CAD

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