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THYROID DYSFUNCTION IN ACUTE CORONARY SYNDROME AND ITS PROGNOSTIC IMPLICATIONS

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ABSTRACT: Background: Thyroid disorders impact the cardiovascular system through direct and indirect mechanisms and are associated with a significantly increased risk of vascular morbidity and mortality. We undertook this study to evaluate the prevalence of thyroid dysfunction in patients with acute coronary syndrome (ACS) and to study the impact of thyroid dysfunction on morbidity and mortality among those patients during 1-year follow-up. **Methods:** We studied 303 consecutive hospitalized patients between March 2018-February 2021 with ACS to determine clinical and sub-clinical features of thyroid dysfunction and their effect on MACE at 1 year follow-up. They were subjected to full history, clinical examination, routine investigations, and estimation of TSH, FT4 and FT3. **Results:** The prevalence of thyroid dysfunction in acute coronary syndrome was19%and the majority had subclinical hypothyroidism 34 (11%), followed by overt hypothyroidism 20 (7%). Hyperthyroidism was uncommon (1.3%). There was a significant preponderance of females in the thyroid dysfunction group. The majority 136 (45%) of patients, had STEMI. MACE rates were higher in the thyroid dysfunction group as compared to euthyroid group (35.6% vs 25.8%). Likewise, the incidence of rehospitalization due to CV causes was significantly higher in the thyroid dysfunction group than in the euthyroid group (32.2% vs 19.7%; p=0.0374). **Conclusion:** Hypothyroidism is an important risk factor in ACS patients, especially women. A clear trend towards higher MACE is seen in thyroid dysfunction patients.

INTRODUCTION: Coronary heart disease (CHD) is the leading cause of death worldwide and in India [1]. More than half of cardiovascular deaths are because of coronary artery disease (CAD); among CAD, acute coronary syndrome (ACS) is the most threatening epitome of CAD [2].

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Acute coronary syndrome (ACS), incorporating unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) continues to be a predominant cause of morbidity and mortality worldwide [3].

Regardless of the significant advances made in recent years to prevent, diagnose, and manage ACS patients, the affliction of recurrent cardiovascular ischemic events and the subsequent mortality continues to be unacceptably high. It would be worthwhile to investigate additional reversible risk factors for the development of ACS.

Strategies to modify these may improve the outcome of patients with ACS [4]. Although not reported among traditional risk factors for coronary artery disease (CAD), changes in circulating concentrations of thyroid hormones which have receptors in both myocardial and vascular endothelial tissues, affect the cardiovascular system. The literature has reported that thyroid dysfunction can be associated with an increased risk of vascular morbidity and mortality up to 20% to 80% [5-8].

Hyperthyroidism has been identified to affect the hemodynamics of the heart. It increases the cardiac output, heart rate, contractility, systolic blood pressure, and left ventricular ejection fraction (LVEF), and decreases peripheral vascular resistance. All together leads to heart failure with higher output [9]. Hypothyroidism affects cardiac contractility, cardiac output, and decreasing heart rate. Due to the associated changes in the renin-angiotensin-aldosterone system, it increases diastolic blood pressure [10]. These changes can accelerate atherosclerosis, leading to coronary artery disease [11].

Subclinical hyperthyroidism and hypothyroidism have been reported as clinical factors that adversely affect the cardiovascular system [12-13]. Subclinical hypothyroidism is associated with an increased risk of coronary heart disease (CHD), heart failure (HF), and mortality in patients with higher TSH levels, mainly those with TSH levels > 10.0 mlU/L. Conversely, subclinical hyperthyroidism is associated with an increased risk of total mortality, CHD mortality, HF, and atrial fibrillation, particularly in those with suppressed TSH levels < 0.10mIU/L [14]. Subclinical hypothyroidism was recognized as an independent risk factor for atherosclerosis and myocardial infarction in elderly women [11].

The data regarding the relationship between thyroid dysfunction and its influence on CVD is not clear and has divergent results. Since most patients with ACS are euthyroid and systematic evaluation of thyroid function is not done, the association between the two needs more studies. There is no prospective study regarding thyroid dysfunction in ACS patients from India. The present study was designed to evaluate the prognosis of thyroid dysfunction in patients with ACS during the follow-up of 1 year.

MATERIALS AND METHODS: This prospective study was conducted in the cardiology department of Batra Hospital & Medical Research Centre, New Delhi. 303 patients diagnosed with ACS above the age of 18 years, presenting within 24 hours of their symptoms to the coronary care unit were enrolled in the study. ACS was defined as unstable angina pectoris, non-ST segment-elevation, or ST-segment-elevation myocardial infarction.

All patients underwent a detailed medical history of cardiac risk factors for developing CAD. The following factors were considered cardiovascular risk factors: smoking status, hypertension, age, gender, diabetes mellitus, obesity, and history of CAD. They also underwent full clinical examination, including heart rate and rhythm, systolic and diastolic blood pressure, including presenting symptoms (chest pain, dyspnea, fatigue, syncope, palpitations). Hypertension was defined as self-reported and the use of antihypertensive medications or as a blood pressure >140/90 mmHg. Diabetes was defined as a fasting glucose >126 mgs or the use of hypoglycemic medication.

Body mass index (BMI) was calculated as body weight (kg)/square of the height (m2), BMI Calculation (WHO criteria for Asian population). A history of myocardial infarction diagnosed CAD or have had revascularization. Patients with angiographic evidence of coronary arterial obstruction with more than 50% stenosis of at least one major coronary artery were also included. Resting standard 12 leads electrocardiogram (ECG) and 2D echocardiography was performed for all the patients at the bedside or in the non-invasive lab using a Philips EPIQ 7C dedicated cardiac machine. Venous blood samples were collected from all the patients within 24 hours of admission to CCU to evaluate Thyroid function Tests - free T3, free T4 and TSH. This was done by an immunoassay method at the hospital's Nuclear Medicine department. The ARCHITECT Free T4 assay is a two-step immunoassay to determine the presence of free thyroxine (Free T4, Free T3 and TSH) in human serum and plasma using CMIA technology with flexible assay protocols, referred

to as Chemiflex. The normal range of free T3, free T4 and TSH are 2.5-5.8 pM/L, 11.5-23 pM/L and 0.2 -5.1 µU/mL, respectively as per our laboratory.

Lab Investigations: Cardiac troponin T/I, kidney functions (including urea, sodium, potassium, creatinine), lipid profile (including total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL-C) and triglycerides (TG), random blood sugar, Brain natriuretic peptide (BNP), hemoglobin and total leucocyte count (TLC). From the creatinine value, an estimated glomerular filtration rate (eGFR) was calculated by using the MDRD study equation.

All patients were treated as per the standard guideline-based treatment of ACS. Associated HT, dyslipidemia, and heart failure were treated per the guideline-based recommendations. Patients with known thyroid disease with or without treatment, Patients receiving any iodinated contrast agent within the previous two weeks, Patients with established disease, such as advanced malignancies, acute decompensated heart failure, Chronic obstructive pulmonary disease, liver cirrhosis, and any conditions that are known to affect thyroid function test were excluded. All patients were divided into two groups according to TSH, T4 and T3 level, a euthyroid group and Thyroid dysfunction group. Thyroid dysfunction group was composed of overt hyper or hypothyroidism and Subclinical hyper or hypothyroidism. Euthyroid status was defined as normal if serum TSH concentration is within (0.2-5.1 µU/mL) range; subclinical hyperthyroidism was defined by low TSH serum levels (<0.2 mU/l), with free T3 and T4 serum levels within the reference range without any clinical features of hyperthyroidism, Subclinical hypothyroidism was defined by serum free T3 and T4 within the reference range, but serum TSH concentrations are elevated (TSH >5.1 mU/l), Overt hypothyroidism was defined by high serum TSH >10 U/mL with an elevated free thyroxin level. The primary endpoint was one year MACE. Secondary endpoints were Heart Failure and Significant Arrhythmia. All patients were followed up for major cardiovascular events (MACE), including recurrent myocardial infarction, coronary revascularization, rehospitalization due to cardiovascular events, cardiovascular death, heart failure and significant arrhythmias at 1 year. The euthyroid group was compared with the thyroid dysfunction group regarding primary and secondary outcomes. The primary and secondary outcomes were also compared with diabetic and non-diabetic patient groups to rule out the impact of diabetes on the cardiovascular outcome.

Ethical Clearance: Written informed consent was taken from all the subjects who participated in this study. The study protocol was approved by the Institutional Ethics Committee on human research vide no. SRERC/2018/TH/11.

Statistical Method: When the sample size is 288 evaluable patients, a two-sided 95% confidence interval for the proportion of patients with MACE using the large sample normal approximation can be estimated at a precision of 5% (i.e. half width of 95% CI for the observed proportion) assuming MACE rate as 25 %. Adjusting for a 5% drop-out rate, a total of 303 patients are expected to be enrolled in the study. A descriptive and exploratory analysis of the variables was conducted, where their distribution, outliers and missing data were evaluated. All the continuous variables were expressed as mean (standard deviation) and between-group analyses were carried out using Student's t-test. Categorical variables were expressed as n (percentage) and compared with the χ^2 test. All tests were two-tailed with a p-value <0.05 was considered significant. All statistical analysis was carried out using the R, and SPSS Statistics 28.0.0.

RESULTS:

TABLE 1: BASELINE CHARACTERISTICS OF EUTHYROID VS THYROID DYSFUNCTION GROUP

Categories	Total (N=303)	Euthyroid (N=244)	Thyroid dysfunction* (N=59)	P value (1)
Demographics				
Age	60.9 (12.32) [59.51 ,62.29]	61.2 (12.46) [59.64,62.76]	59.9 (11.77) [56.90 ,62.90]	0.4755
Gender				
Male	208 (68.65%) [0.2617 ,0.3691]	180 (73.77%)[0.2082,0.3222]	28 (47.46%) [0.3912, 0.6570]	<.0001
Female	95 (31.35%) [0.6309 ,0.7383]	64 (26.23%) [0.6778,0.7918]	31 (52.54%) [0.3430, 0.6088]	
Risk factors				

Smoking	68 (22.44%) [0.1787 ,0.2756]	48 (19.67%) [0.1488, 0.2522]	20 (33.90%) [0.2208 ,0.4739]	**0.0188**
Diabetes Mellitus	146 (48.18%) [0.4244 ,0.5397]	118 (48.36%) [0.4194, 0.5482]	28 (47.46%) [0.3430, 0.6088]	0.9009
Hypertension	204 (67.33%) [0.6173 ,0.7258]	163 (66.80%) [0.6051, 0.7268]	41 (69.49%) [0.5613, 0.8081]	0.6928
History of CAD	156 (51.49%) [0.4570 ,0.5724]	126 (51.64%) [0.4518, 0.5806]	30 (50.85%) [0.3750, 0.6411]	0.9130
BMI	25.0 (4.75) [24.04 ,25.96]	24.9 (4.95) [23.80 ,26.00]	25.4 (3.78) [23.60 ,27.20]	0.6732
Dyslipidemia	46 (15.18%) [0.1133 ,0.1973]	39 (15.98%) [0.1162, 0.2120]	7 (11.86%) [0.0491, 0.2293]	0.4288
Heart Failure	48 (15.84%) [0.1192 ,0.2045]	41 (16.80%) [0.1234, 0.2210]	7 (11.86%) [0.0491, 0.2293]	0.3512
Hemodynamic status				
Pulse Rate	85.0 (18.51)[82.92 ,87.08]	85.1 (19.22) [82.69 ,87.51]	84.5 (15.34) [80.59 ,88.41]	0.8017
Diastolic BP	79.7 (13.96)[78.13 ,81.27]	79.6 (13.95) [77.85 ,81.35]	80.2 (14.14) [76.59 ,83.81]	0.7772
Systolic BP	132.5 (24.98)[129.69 ,135.31]	131.8 (25.04) [128.66, 134.94]	135.5 (24.68) [129.20, 141.80]	0.3024
Primary Diagnosis (Acute Coronary Syndrome)				
UA	83 (27.39%) [0.2245 ,0.3278]	66 (27.05%) [0.2158, 0.3309]	17 (28.81%) [0.1776, 0.4208]	0.5618
NSTEMI	84 (27.72%) [0.2276 ,0.3313]	65 (26.64%) [0.2120, 0.3265]	19 (32.20%) [0.2062, 0.4564]	
STEMI	136 (44.88%) [0.3919 ,0.5068]	113 (46.31%) [0.3993, 0.5279]	23 (38.98%) [0.2655, 0.5256]	
Laboratory data				
Total cholesterol	145.1 (43.62) [139.45 ,150.75]	147.5 (43.97) [141.15, 153.85]	135.5 (41.27) [123.44, 147.56]	0.0993
HDL	36.1 (9.14) [34.92 ,37.28]	36.3 (9.68) [34.90 ,37.70]	35.0 (6.46) [33.11 ,36.89]	0.2814
LDL	102.2 (62.53) [94.15 ,110.25]	106.1 (66.81) [96.52,1 15.68]	86.0 (36.47) [75.34 ,96.66]	0.0071
Triglyceride	136.7 (68.27) [127.80 ,145.60]	132.1 (64.07) [122.79, 141.41]	155.7 (81.51) [131.61, 179.79]	0.0783
KFT _ Urea	37.9 (27.02) [34.85 ,40.95]	39.0 (27.99) [35.47 ,42.53]	33.2 (22.18) [27.54 ,38.86]	0.0875
KFT _ Na	135.5 (6.78) [134.74 ,136.26]	135.6 (7.20) [134.69, 136.51]	135.2 (4.67) [134.01, 136.39]	0.6377
Potassium	4.5 (3.82) [4.07 ,4.93]	4.4 (2.93) [4.03 ,4.77]	5.2 (6.28) [3.60 ,6.80]	0.3574
Creatinine	1.4 (0.96) [1.29 ,1.51]	1.4 (1.04) [1.27 ,1.53]	1.2 (0.47) [1.08 ,1.32]	0.0286
eGFR	65.5 (25.31) [62.65 ,68.35]	65.8 (26.30) [62.50 ,69.10]	64.3 (20.86) [58.98 ,69.62]	0.6460
eGFR ≥ 60				
Blood Sugar Random	177.1 (86.74) [166.13,188.07]	176.3 (86.07) [164.25, 188.35]	181.0 (90.61) [154.23, 207.77]	0.7480
BNP	576.6 (850.19) [461.88 ,691.32]	616.4 (883.96) [483.52, 749.28]	411.6 (677.36)[204.26, 618.94]	0.1071
Hb	12.8 (5.37) [12.19 ,13.41]	12.9 (5.84) [12.16 ,13.64]	12.3 (2.60) [11.64 ,12.96]	0.2389
TLC/DLC	11.1 (5.87)[10.43 ,11.77]	10.9 (6.09)[10.13 ,11.67]	11.8 (4.82) [10.57 ,13.03]	0.1896
Trop T/I	11341.1 (40565.53) [6052.28,16629.92]	11639.8 (44308.07) [5237.59,18042.01]	10032.3 (16302.45) [5101.87, 14962.73]	0.6971
LVEF	47.7 (10.08) [46.48 ,48.92]	47.7 (10.50) [46.27 ,49.13]	47.6 (8.40) [45.38 ,49.82]	0.9580

*Thyroid Dysfunction includes Subclinical Hypothyroidism, Overt Hypothyroidism and Subclinical Hyperthyroidism. P-value (1) = Normal Vs Thyroid Dysfunction.

A total of 303 consecutive patients admitted with ACS were analyzed. The mean age of the patients was 60.9 years. Women were more likely to have thyroid dysfunction than men, achieving high statistical significance compared to euthyroid groups **Table 1**. The prevalence of thyroid dysfunction was significantly more in smokers. But the prevalence of other risk factors for CAD in between the groups was similar **Table 1.**

Thyroid dysfunction groups had numerically elevated triglycerides, potassium, higher blood random sugar and were likely to have lower Estimated Glomerular Filtration rate (eGFR) and higher presentation of non-ST-segment elevation myocardial infarction (NSTEMI). However, none of these differences had statistical significance. Thyroid dysfunction groups did not correlate with total cholesterol, HDL, cardiac enzymes, BNP, random blood sugar, Hb, LVEF, urea, and sodium compared to Euthyroid group. The Most reported symptom at admission was chest pain, followed by dyspnea **Table 1**.

Out of 303 cases, 244 (77 %) had euthyroid, and 59 (19 %) had thyroid dysfunction. Out of 59 patients with abnormal thyroid dysfunction, subclinical hypothyroidism had the highest prevalence (n=34; 11%) followed by overt hypothyroidism (n=20; 7%) and subclinical hyperthyroidism (n=4; 1.3%). Average TSH, T4 and T3 levels were found to be 3.75 µU/mL, 10.11 pM/L and 3.40 pM/L, all within normal limits. Of the 303 patients with ACS, 136 (45%) patients had STEMI, 84 (28%) had NSTEMI and 83 (27%) had Unstable Angina **Table 1**.

TABLE 2: THYROID DYSFUNCTION IN ACUTE CORONARY SYNDROME AND ITS RELATION TO 1 YEAR MACE EVENTS

1 Year MACE	Total (N=303)	Euthyroid (N=244)	Thyroid dysfunction (N=59)	P value (1)
Composite Mace	84 (27.7%) [0.2276, 0.3313]	63 (25.8%) [0.2045,0.3179]	21 (35.6%) [0.2355, 0.4913]	0.1323
Heart Failure	25 (8.3%) [0.0541, 0.1194]	23 (9.4%) [0.0607, 0.1381]	2 (3.4%) [0.0041, 0.1171]	0.1305
Re- MI	19 (6.3%) [0.0382, 0.0962]	17 (7.0%) [0.0411, 0.1092]	2 (3.4%) [0.0041, 0.1171]	0.3091
Rehospitalization	67 (22.1%) [0.1757, 0.2721]	48 (19.7%) [0.1488, 0.2522]	19 (32.2%) [0.2062, 0.4564]	0.0374

Re -revascularization	13 (4.3%) [0.0230, 0.0723]	8 (3.3%) [0.0143, 0.0636]	5 (8.5%) [0.0281, 0.1868]	0.0772
Significant arrhythmia	12 (4.0%) [0.0206, 0.0682]	8 (3.3%) [0.0143,0.0636]	4 (6.8%) [0.0188, 0.1646]	0.2160
CV death	25 (8.3%) [0.0541, 0.1194]	21 (8.6%) [0.0541, 0.1286]	4 (6.8%) [0.0188, 0.1646]	0.6472

*P-value (1) from chi-square/fishers exact test for Normal Vs Thyroid Dysfunction.

Complete follow-up data for cardiovascular outcomes were obtained in 100% of the patients at the end of 1 year. During the long-term follow-up of 1 year, the MACE rate was higher in thyroid dysfunction group as compared to euthyroid group (35.6% vs 25.8%) but did not achieve statistical significance (p= 0.1323). The incidence of rehospitalization for cardiac cause was significantly higher in thyroid dysfunction group 19 (32.2%) compared to euthyroid group 48 (19.7%)(p =0.0374). Similarly, the incidence of coronary revascularization (8.5% vs 3.3%; p = 0.0772) and significant arrhythmias (6.8% vs 3.3%; p = 0.2160) was higher in thyroid dysfunction group as compared to euthyroid group but didn't achieve statistical significance. There was no difference between the groups in terms of recurrent myocardial infarction, cardiovascular death and heart failure **Table 2.**

TABLE 3: DIABETES MELLITUS IN ACUTE CORONARY SYNDROME AND ITS RELATION TO 1-YEAR MACE EVENTS

Parameters	Diabetes Mellitus			p-value
	Total	Yes(N=146)	No(N=157)	
Composite Mace	84 (27.7%) [0.2276 ,0.3313]	42 (28.8%) [0.2158,0.3683]	42 (26.8%) [0.2001,0.3439]	0.6953
Coronary Revascularization	13 (4.3%) [0.0230 ,0.0723]	6 (4.1%) [0.0152,0.0873]	7 (4.5%) [0.0181,0.0897]	0.8809
CV Death	25 (8.3%) [0.0541 ,0.1194]	12 (8.2%) [0.0432,0.1392]	13 (8.3%) [0.0448,0.1374]	0.9846
Recurrent MI	19 (6.3%) [0.0382 ,0.0962]	13 (8.9%) [0.0483,0.1474]	6 (3.8%) [0.0142,0.0813]	0.0682
Rehospitalization due to CV Reason	67 (22.1%) [0.1757 ,0.2721]	33 (22.6%) [0.1610,0.3025]	34 (21.7%) [0.1549,0.2893]	0.8427
Heart Failure	25 (8.3%) [0.0541 ,0.1194]	9 (6.2%) [0.0286,0.1138]	16 (10.2%) [0.0594,0.1602]	0.2030
Significant Arrhythmias	12 (4.0%) [0.0206 ,0.0682]	6 (4.1%) [0.0152,0.0873]	6 (3.8%) [0.0142,0.0813]	0.8978

*P-value (1) from chi-square/fishers exact test for Diabetic Vs Non-Diabetic patients.

We assessed the relationship between Diabetes Mellitus and MACE events at 1-year follow-up. It was observed that the MACE rate was not different in the diabetic patients as compared to the non-diabetic patients during the 1year follow-up (28.8% vs 26.8%). The incidence of Recurrent MI (8.9% vs 3.8%) was towards the higher side in Diabetes Mellitus as compared to non-diabetes group. There was no difference between the groups in terms of rehospitalisation due to cardiac reasons (22.6% vs 21.7%), significant arrhythmias (4.1% vs 3.8%), coronary revascularisation (4.1% vs 4.5%), cardiovascular death (8.2% vs 8.3%) and heart failure (6.2% vs 10.2%) **Table 3.**

TABLE 4: COMPARISON BETWEEN PATIENTS WITH EUTHYROIDISM AND THYROID DYSFUNCTION IN STEMI AND NSTEMI + UA GROUPS WITH REGARD TO MACE

		Stemi patients (N= 136)		p-value
	Total	Euthyroid function (N=113)	Thyroid dysfunction (N=23)	
Coronary Revascularization	6 (4.4%) [0.0164, 0.0936]	5 (4.4%) [0.0145, 0.1002]	1 (4.3%) [0.0011 ,0.2195]	0.9869
Cardiovascular Death	11 (8.1%) [0.0411, 0.1401]	11 (9.7%) [0.0496, 0.1675]	0 (0.0%)	0.1186
Recurrent MI	11 (8.1%) [0.0411, 0.1401]	9 (8.0%) [0.0371, 0.1458]	2 (8.7%) [0.0107 ,0.2804]	0.9067
Rehospitalization due to CV	25(18.4%) [0.1226,0.2593]	19 (16.8%) [0.1044, 0.2501]	6 (26.1%)[0.1023 ,0.4841]	0.2953
Heart Failure	11 (8.1%) [0.0411, 0.1401]	11 (9.7%)[0.0496, 0.1675]	0 (0.0%)	0.1186
Significant Arrhythmia	5 (3.7%) [0.0120, 0.0837]	4 (3.5%) [0.0097, 0.0882]	1 (4.3%) [0.0011 ,0.2195]	0.8511
		NSTEMI & unstable angina patients (N=167)		
	Total	Euthyroid function (N=131)	Thyroid dysfunction (N=36)	
Coronary Revascularization	7 (4.2%) [0.0170, 0.0845]	3 (2.3%) [0.0047, 0.0655]	4 (11.1%) [0.0311, 0.2606]	**0.0193**
Cardiovascular Death	14 (8.4%) [0.0466, 0.1367]	10 (7.6%) [0.0372, 0.1359]	4 (11.1%) [0.0311, 0.2606]	0.5049
Recurrent MI	8 (4.8%) [0.0209, 0.0922]	8 (6.1%) [0.0267, 0.1168]	0 (0.0%)	0.1286
Rehospitalization due to CV	42 (25.1%) [0.1877,0.3244]	29 (22.1%) [0.1535, 0.3022]	13 (36.1%) [0.2082, 0.5378]	0.0870
Heart Failure	14 (8.4%) [0.0466,0.1367]	12 (9.2%) [0.0482, 0.1545]	2 (5.6%) [0.0068, 0.1866]	0.4894
Significant Arrhythmia	7 (4.2%) [0.0170,0.0845]	4 (3.1%) [0.0084, 0.0763]	3 (8.3%) [0.0175, 0.2247]	0.1615

In the STEMI group, the incidence of cardiovascular death and heart failure was higher in the euthyroid group than in the thyroid dysfunction group but not statistically significant. In the NSTEMI & UA group, the study detected a significantly higher incidence of coronary revascularization (11.1 % *vs* 2.3%; p= 0.0193) in patients with thyroid dysfunction as compared to the euthyroid group and it showed statistical significance. The incidence of significant arrhythmias (8.3% vs 3.1%), cardiovascular death (11.1% vs 7.6%) and rehospitalization due to CV reasons (36.1% vs 22.1%) were much higher in the thyroid dysfunction group compared with the euthyroid group but didn't achieve statistical significance **Table 4.**

DISCUSSION: The alterations in thyroid function can cause several derangements of the cardiovascular system leading to hypertension, dyslipidemia, heart rhythm disorders, obesity *etc*. These assume special importance in patients with ACS as reported in many studies [15]. Thyroid dysfunction is more common in females (52%), as seen in our study, and this has been observed in several other studies also [11]. Elderly females with subclinical hypothyroidism had a higher frequency of vascular events [11]. A higher prevalence of hypothyroidism (24%) and increased morbidity and all-cause mortality are attributed to a pro-inflammatory effect of the disease [16]. TSH levels at the upper limits of normal have shown adversities. The HUNT study reported positive and linear associations of thyrotropin levels within the reference range with CHD mortality in Norwegian women but not in men [17].

The present study has demonstrated changes in thyroid hormone profile in 19 % of patients admitted with a diagnosis of ACS (STEMI, NSTEMI, and UA). This data agrees with the study on this subject from India but is lower than other international studies. These studies have reported thyroid dysfunction in around 23% of patients [18, 19]. The prevalence of subclinical hypothyroidism in 11 % of subjects, as seen in our study, is marginally lower than 15 % as reported by Mukherjee *et al.* in a large retrospective study done in 1500 patients in India [20]. Our data of 7% overt hypothyroidism and 1.3% subclinical hyperthyroidism agrees with the findings of Quari FA, who observed overt hypothyroidism in 8% and subclinical hyperthyroidism in 0.5% of patients in their series [19]. A significant relationship between smoking and thyroid dysfunction, which is well-known, was observed in our study [21].

Our study demonstrated that the MACE rate was higher in the thyroid dysfunction group than in the euthyroid group (35.6% vs 25.8%). The incidence of rehospitalization for cardiac disease was significantly higher in the thyroid dysfunction group when compared to euthyroid group. Likewise, the incidence of revascularizations and significant arrhythmias were higher in patients with thyroid dysfunction compared to euthyroid group but did not achieve statistical significance. A similar trend of a higher MACE rate (27%) was seen in Khalil, O. A., *et al.*, in a series of 196 patients of thyroid dysfunction with ACS during a follow-up of 6 months [18].

Our study is consistent with a recent large-scale analysis of 55287 participants from 11 prospective cohorts that showed that subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and mortality, particularly in those with a TSH concentration of ≥ 10mIU/L or greater [22]. In another analysis of 1,898,314 participants from 55 cohort studies, it has been found that SCH is significantly associated with higher risks of cardiac mortality and IHD (TSH level ≥10.0 mIU/L) [23].

This study detected a significantly higher incidence of coronary revascularization (11.1 % vs 2.3%; p= 0.0193) in thyroid dysfunction compared to Euthyroid patients in NSTEMI & UA group. Significant arrhythmia, CV death and rehospitalizations due to CV reasons were also higher in the thyroid dysfunction group as compared to euthyroid group. There was no difference in the incidence of MACE in the STEMI group. These findings are in line with Seo *et al.* [24]. In contrast, Osama et al. showed a significant increase in MCAE in thyroid dysfunction in STEMI group (p<0.001) while there was no significant increase of MCAE in NSTEMI and unstable angina group [18]. Helmy *et al*. compared morbidity and mortality in the euthyroid vs. subclinical hypothyroidism group. There was no statistical significance difference between both

groups. Morbidity was 34.6% in euthyroid vs. 20% in SCH (p = 0.7). Mortality was 2.5% in euthyroid vs. 0% in those with SCH [25]. On the other hand, Bayrak et al. have found no relationship between thyroid hormone levels and sudden cardiac death and major cardiovascular disorders at 3 and 6 months of follow-up [26]. In ACS patients with diabetes mellitus, it was observed that the MACE rate was not different in the diabetic patients as compared to the non-diabetic patients during the 1-year follow-up (28.8% *vs* 26.8%).

The incidence of recurrent MI (8.9% vs 3.8%) was on the higher side in diabetic patients as compared to the non-diabetic group. As diabetes can lead to an increase in MACE, this finding helps us to understand the association of diabetes with MACE. Several possible explanations exist for the link between subclinical hypothyroidism and death caused by CVD. Inadequate thyroid hormone levels affect the relaxation of vascular smooth muscle cells and reduce cardiac contractility by controlling calcium uptake and the expression of several contractile proteins in cardiomyocytes, one of the main regulators of cardiac function and cardiovascular hemodynamics [27, 28]. These biological mechanisms support our findings that CVD partially mediates the linkage of increased TSH concentrations with death, even though the precise underlying mechanisms are still unknown. To our knowledge, this is the first prospective study done on Indian patients to see the clinical impact of thyroid dysfunction in ACS patients with 1-year follow-up. The study shows a clear trend of higher incidence of MACE in thyroid dysfunction group compared to Euthyroid group. Through this study, we would also like to emphasize the potential benefit of testing for abnormal thyroid function during cardiac admissions, and healthcare providers may have a higher index of suspicion for those not yet diagnosed when traditional symptoms are reported.

CONCLUSION: We can conclude that the thyroid dysfunction of 19 % in our cohort of ACS is highly prevalent. The prevalence was much higher in the female population. A higher incidence of MACE rate is seen in the thyroid dysfunction group as compared to euthyroid group at 1 year follow-up. We recommend testing thyroid function during cardiac admissions to see the predictor for risk of morbidity and mortality in those subjects. Larger multicentric studies with sufficient power should be done to see the impact of thyroid dysfunction on the ACS population regarding morbidity and mortality.

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