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Original Article

Internal Medicine Section

AGE-Related Differences of Novel Atherosclerotic Risk Factors and Angiographic Profile Among Gujarati Acute Coronary Syndrome Patients

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ABSTRACT

Context: Although numerous risk factors have been established to predict the development of acute coronary syndrome (ACS), the risk factor profile may be different between the younger and older individuals.

Aim: To analyse the frequency and pattern of atherogenic risk factors and angiographic profiles in age-stratified Gujarati patients with ACS.

Materials and Methods: ACS patients undergoing coronary angiography at U.N. Mehta Institute of Cardiology and Research, Gujarat, India between January 2008 and December 2012 were classified in to two age groups with 40y as cut-off. Patients were assessed for conventional risk factors (diabetes mellitus, dyslipidaemia, hypertension, smoking, obesity), novel risk factors (high sensitivity C-reactive protein, lipoprotein (a), homocysteine), and angiographic profiles.The statistical difference between two age groups was determined by Student's t-test for continuous variables and Chi-square or Fisher's exact test for categorical variables.

Results: A total of 200 patients, 100 patients ≤40 y of age and 100 patients >40 y of age, were evaluated. Older patients had higher frequency of hypertension (32 vs. 16%, p=0.008), while family history of coronary artery disease was more common among younger patients (19 vs. 9%, p=0.041). The incidence of diabetes, dyslipidaemia, smoking and tobacco chewing did not vary significantly between the two groups. Total cholesterol and low-density lipoprotein cholesterol levels were significantly higher in the younger group (p<0.05). Lipoprotein (a), homocysteine and high-sensitivity C reactive protein levels were comparable between two age groups. Multi-vessel coronary artery disease was more common among older group. The most commonly affected coronary artery was the left anterior descending artery among younger patients (44%) and the left circumflex artery among older patients (38.1%).

Conclusion: Young patients with ACS had different atherosclerotic risk profile and less extensive coronary artery disease as compared to older counterparts. Emphasis should be given on diagnosis and management of major modifiable risk factors.

Keywords: Cardiovascular disease Coronary angiography, Coronary artery disease

INTRODUCTION

Acute coronary syndrome (ACS) is a devastating health epidemic worldwide. It may lead to death or disability, without warning, in an otherwise healthy individual in the prime of life [1,2]. The disease is posing a major public health hazard and clinical problem particularly in South Asia. More than half of the worldwide cardiovascular disease risk burden is estimated to be borne by Indian subcontinent by 2020 [3]. Further, it is reported that individuals from Indian subcontinent may develop coronary artery disease (CAD) at a higher rate and at an early age [4]. Onset of CAD before 40 y of age is considered as premature CAD [1,5].Although majority of studies reported that only about 3% of all CAD cases occur in <40 y of age, it should be considered as the 'tip of the iceberg' as young, asymptomatic patients usually do not undergo medical investigations. The incidence of CAD is reported to be 12–16% among young Indian patients, with more than half of death related to cardiovascular disease occurring in patients below the age of 50 y and one-fourth of acute myocardial infarction cases being reported in patients under the age of 40 y [2]. Although numerous risk factors have been established to predict the development of ACS, these risk factor profile, severity of disease and its prognosis may be different between the young and older age groups [5]. Clinical studies have shown that as compared with older patients, patients with early-onset of cardiovascular disease may have preponderance of risk factors such as dyslipidaemia, positive family history, cigarette smoking, with lesser extent and less severe occurrence of CAD [2,6,7]. However, conventional risk-factors may not clearly explain the predisposition to ACS in younger patients. Hence, studies on estimation of novel atherogenic risk factors as well as angiographic studies are emerging in ACS patients [1]. Till date, there is limited information available on conventional and novel risk factors in different age group of patients with ACS from the state of Gujarat, India. In this regard, we conducted a single-centre, observational study with an aim to provide an overview of differences and similarities in characteristics and patterns of risk factors and angiographic details between young Gujarati patients with ACS compared to their older counterparts.

MATERIALS AND METHODS

Study Population

The age-related differences of novel atherosclerotic risk factors and angiographic profile among Gujarati acute coronary syndrome patients (AGE-GAP) was a single-centre, observational study. Patients who presented within one month of chest pain or other symptoms suggestive of ACS and who underwent coronary angiography at the U.N. Mehta Institute of Cardiology and Research, B. J. Medical College & Civil Hospital Campus, Ahmedabad, Gujarat between January 2008 and December 2012 were considered for the enrolment. Patients with valvular heart disease, congenital heart disease, hypertrophic cardiomyopathy, and coronary artery anomalies were excluded from the study as our objective was to analyse the role of atherogenic risk factors in ACS patients exclusively. Selected patients were divided into two age groups (A) those ≤40 years old (Younger Group) and (B) those >40 y (Older Group). In

each age group, 100 consecutive patients who met with inclusion criteria and underwent coronary angiography were enrolled in the study. The study protocol was approved by the Institutional Ethics Committee (UNMICRC/CARDIO/2013/34). The informed consent was obtained from each patient at the time of enrolment. The procedures followed were in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki Declaration.

Presenting symptoms in the enrolled patient ranged from mild chest pain occurring at rest or after mild exertion, lasting for >20 minutes to severe and prolonged chest pain occurring in a crescendo pattern [1]. The ACS was confirmed based on the clinical diagnosis of one of the following criteria: (a) ST segment elevation MI (STEMI), (b) Non-ST segment elevation MI (NSTEMI), (c) Unstable angina with ST-T wave changes. STEMI was diagnosed by increased levels of biochemical markers of MI and abnormal ECG demonstrating either (a) ST-segment elevation ≥ 1 mm in two consecutive leads or (b) left bundle branch block. STEMI patients were further divided into (a) anterior-wall STEMI and (b) posterior-wall STEMI based on their clinical presentation. NSTEMI was diagnosed by increased levels of biochemical markers of MI and non-ST segment elevation or T wave abnormality in ECG. Unstable angina was diagnosed by ischemic symptoms related to ACS and ST segment depression or T wave abnormality in the ECG [8].

Data Collection

Demographic, clinical, and angiographic data were collected from all patients included in the study. Demographic variables included age and gender. Clinical investigations comprised estimation of conventional ACS risk factors including body-mass index (BMI), obesity, hypertension, diabetes mellitus, dyslipidaemia, smoking and tobacco-chewing habits, and family history of premature CAD. In addition, patients were investigated for the levels of novel atherosclerotic risk markers such as homocysteine, high-sensitivity C-reactive protein (Hs-CRP), and lipoprotein (a) {Lp(a)}. To analyse the conventional and novel risk factors, 5 mL blood sample was collected from each patient. All patients underwent coronary angiography through transfemoral route to identify stenosis or occlusion in three major coronary arteries or their branches. Based on the angiographic data, patients were divided into those with (a) normal vessels, (b) single-vessel disease, (c) double-vessel disease, and (d) triple-vessel disease. In addition, frequency of involvement of left anterior descending artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA) was analysed.

BMI was considered to categorize patients into the underweight (<18.5), normal (18.5–25), overweight (25–30), and obese (>30) groups [9]. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90mmHg or self-report of physician diagnosis of hypertension and/or use of antihypertensive medications. Diabetes mellitus was defined as fasting blood glucose levels >125 mg/dL or non-fasting blood glucose >200 mg/dL or self-report of physician diagnosis of diabetes mellitus and/or use of antidiabetic medication. Dyslipidaemia was defined as total cholesterol >200 mg/dL, low-density lipoprotein (LDL) cholesterol >130 mg/dL, high-density lipoproteins (HDL) cholesterol <40 mg/dL or self-report of physician diagnosis of dyslipidaemia and/or use of lipid-lowering medications. Tobacco use and smoking were defined by the habitual use of tobacco and smoking respectively within two years of presentation at our hospital [8].

Total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and glucose concentrations were measured by International Federation of Clinical Chemistry (IFCC) approved enzymatic methods using commercially available kit on auto analyser (ARCHITECH PLUS ci4100, Germany). In addition, lipid ratios of total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol were calculated. Homocysteine was measured using chemiluminescent microparticle immunoassay (CMIA) on ARCHITECT *i* System. Hs-CRP and Lp(a) levels were estimated using commercially available kits (ARCHITECT *c*Systems). To analyse the trend, patients were further sub grouped into normal levels, elevated levels, and highly elevated levels of homocysteine (0–30, 30–89, and ≥90 mg/dL respectively) and lipoproteins (<15, 15–49, and ≥50 µmol/L respectively).

STATISTICAL ANALYSIS

The collected data were analysed using the Statistical Package for Social Sciences (SPSS for Windows version 20.0; Chicago, IL, USA). Categorical variables were presented as frequency and percentage and the groups were compared by using the Chi-square test or the Fisher's exact test. Continuous variables were described as mean value ± standard deviation (SD) and were compared by using the Student's t-test to identify statistical differences between the groups. The p-value <0.05 was considered to indicate statistically significant difference between the groups.

RESULTS

Baseline Demographics

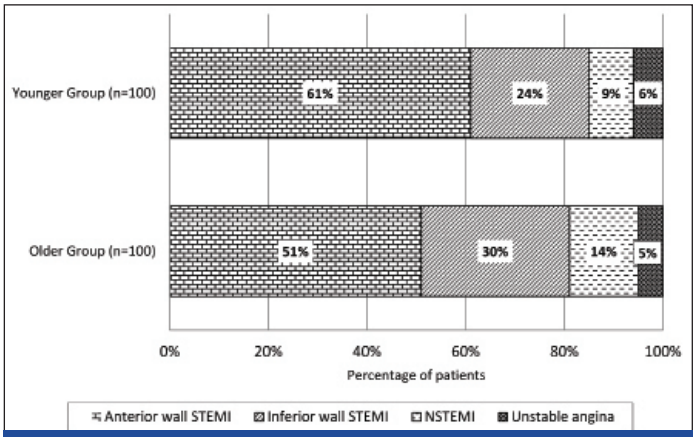
The baseline demographic characteristics of patients with ACS enrolled in our study are presented by age category in [Table/Fig-1].

Variables	Younger Group (≤40 years) n= 100	Older Group (>40 years) n= 100	p-value
Age in years (mean ± SD)	34.69 ± 4.55	56.18 ± 8.72	<0.001
Age range in years	22 to 40	42 to 80	-
Male, n (%)	96 (96.0 %)	89 (89.0%)	0.060
Female, n (%)	4 (4.0 %)	11 (11.0%)	0.060
Male: female ratio	24:1	8.09:1	-

[Table/Fig 1]: Comparison of demographic characteristics between younger and older Gujarati patients with acute coronary syndrome*
Values are expressed as number (%) of patients or mean ± SD; P value was calculated using the Student's t-test for continuous variables and the Chi-square test or the Fisher's exact test for categorical variables

Clinical Presentation

There were no significant differences between the younger and the older groups in terms of frequency of anterior-wall STEMI, inferior-wall STEMI, NSTEMI, or unstable angina presentation [Table/Fig-2]. The mean ejection fraction was 43.48 ± 8.92 in the younger group and 42.99 ± 11.63 in the older group [Table/Fig-3].



[Table/Fig-2]: Distribution of the subjects by clinical diagnosis in younger and older Gujarati patients with acute coronary syndrome*
*STEMI, ST segment elevation myocardial infarction; NSTEMI, Non-ST segment elevation myocardial infarction

Clinical diagnosis	Younger Group (≤40 years) n= 100	Older Group (>40 years) n= 100	p-value
Anterior wall STEMI, n (%)	61 (61.0%)	51 (51.0%)	0.156
Inferior wall STEMI, n (%)	24 (24.0%)	30 (30.0%)	0.337
NSTEMI, n (%)	9 (9.0%)	14 (14.0%)	0.267
Unstable Angina, n (%)	6 (6.0%)	5 (5.0%)	0.756
Ejection Fraction, %(mean ± SD)	43.48 ± 8.92	42.99 ± 11.63	0.738

[Table/Fig 3]: Comparison of clinical diagnosis between younger and older Gujarati patients with acute coronary syndrome*
*Values are expressed as number (%) of patients or mean ± SD; P value was calculated using the Student's t-test for continuous variables and the Chi-square test or the Fisher's exact test for categorical variables; STEMI, ST segment elevation myocardial infarction; NSTEMI, Non-ST segment elevation myocardial infarction

Conventional Atherogenic Risk Factors

The data of conventional atherogenic risk factors for patients with ACS are presented by age category in [Table/Fig-4]. Older Older patients were significantly more likely to have hypertension, while younger patients were more likely to have family history of premature coronary artery disease. The proportions of patients with obesity, dyslipidaemia,diabetes, and active smoking or tobacco chewing habits were statistically comparable between the two groups. A detailed analysis of lipid profile [Table/Fig-5] revealed that the mean total cholesterol, LDL cholesterol, and non-HDL cholesterol levels were significantly higher in the younger group as compared to the older group. Further, the HDL cholesterol levels, VLDL cholesterol levels, and lipid ratios of total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol were non-significantly higher in the younger group.

Variables	Younger Group (≤40 years) n= 100	Older Group (>40 years) n= 100	p-value
Body-mass index, kg/m^2 (mean ± SD)	23.54 ± 3.43	24.08 ± 3.56	0.276
Overweight, n (%)	31 (31.0 %)	36 (36.0%)	0.453
Obese, n (%)	3 (3.0 %)	8 (8.0%)	0.121
Dyslipidaemia, n (%)	47 (47%)	47 (47%)	1.000
Hypertension, n (%)	16 (16.0 %)	32 (32.0%)	0.008
Diabetes mellitus, n (%)	11(11.0 %)	19 (19.0%)	0.114
Family History of premature CAD, n (%)	19 (19.0 %)	9 (9.0%)	0.041
Smoker, n (%)	34 (34.0 %)	45 (45.0%)	0.112
Tobacco chewer, n (%)	19 (19.0 %)	15 (15.0%)	0.453

[Table/Fig-4]: Comparison of conventional risk factors between younger and older Gujarati patients with acute coronary syndrome*
*Values are expressed as n (%) or mean ± SD; p-value was calculated using the Chi-square test or the Fisher's exact test

Variables	Younger Group (≤40 years) n= 100	Older Group (>40 years) n= 100	p-value
Total cholesterol (mg/dL)	156.02 ± 47.74	141.20 ± 36.55	0.015
Triglyceride (mg/dL)	127.58 ±69.81	127.95 ±97.07	0.975
HDL cholesterol (mg/dL)	32.67 ± 7.90	31.80 ± 8.06	0.442
Non-HDL cholesterol (mg/dL)	123.35 ± 46.02	110.83 ± 35.85	0.033
LDL cholesterol (mg/dL)	97.84 ± 42.11	85.24 ± 28.35	0.014
VLDL cholesterol (mg/dL)	25.45±14.07	24.31±10.47	0.516
Ratio oftotal cholesterol to HDL	4.95 ± 1.57	4.65 ± 1.51	0.170
Ratio of LDL to HDL cholesterol	3.11 ± 1.37	2.82 ± 1.15	0.106

[Table/Fig-5]: Comparison of lipid profile between younger and older Gujarati patients with acute coronary syndrome*
*Values are expressed as mean ± SD; P value was calculated using the Student's t-test;LDL, Low-density lipoprotein; HDL, High-density lipoprotein, VLDL, Very-low-density lipoprotein.

Novel Atherogenic Risk Factors

The mean Hs-CRP level was higher among younger patients as compared to the older group, but not statistically significant [Table/Fig-6]. Further, the mean homocysteine and Lp (a) levels were comparable between the two groups. The distribution of patients according to their lipoprotein levels and according to their homocysteine levels showed similar patterns between the younger patients and the older patients [Table/Fig-6].

Variables	Younger Group (≤40 years) n= 100	Older Group (>40 years) n= 100	p-value
Lipoprotein(a)(mg/dL)	34.12 ± 27.10	34.68 ± 29.26	0.888
Normal: 0-30 mg/dL, n (%)	57 (57.0%)	56 (56.0%)	0.889
Elevated: 30–89 mg/dL, n (%)	33 (33.0%)	33 (33.0%)	1.000
Highly elevated: ≥90 mg/dL, n (%)	10 (10.0%)	11 (11.0%)	0.818
Homocysteine (µmol/L)	24.87 ± 15.31	25.17 ± 14.98	0.888
Normal: <15µmol/L, n (%)	30 (30.0%)	35 (35.0%)	0.453
Elevated: 15–49µmol/L, n (%)	51 (51.0%)	47 (47.0%)	0.569
Highly elevated: ≥50µmol/L, n (%)	19 (19.0%)	18 (18.0%)	0.857
Hs-CRP (mg/L)	16.73 ± 22.66	10.28 ± 39.57	0.161

[Table/Fig-6]: Comparison of novel atherosclerotic risk factors between younger and older Gujarati patients with acute coronary syndrome*
*Values are expressed as n (%) or mean ± SD; P value was calculated using the Student's t-test for continuous variables and the Chi-square test or the Fisher's exact test for categorical variables Hs-CRP, High-sensitivity C-reactive protein

Angiographic Findings

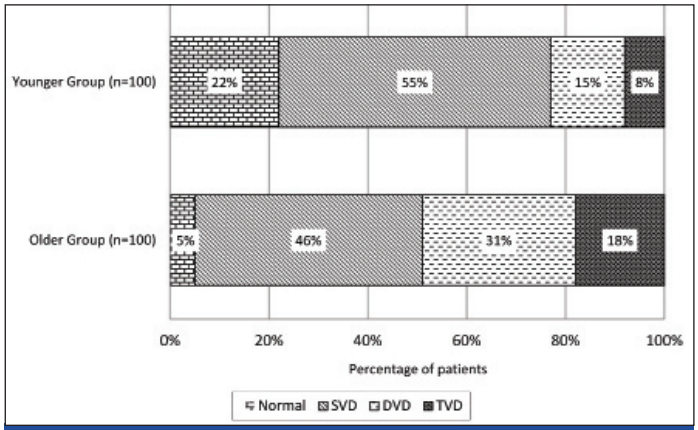
The coronary angiographic profile [Table/Fig-7] revealed that younger patients with ACS were significantly more likely to have normal vessels than that in the older patients. Single-vessel disease was the most common phenomenon in younger patients, while multi-vessel disease was more common in older patients. Distribution of the subjects by the number of coronary artery involvement is depicted in [Table/Fig-8] for in both the groups. LAD was the most common coronary artery involved with angiographic stenosis or occlusion among younger patients, while LCx was the most commonly affected artery among older patients.

	Younger Group (≤40 years) n= 100	Older Group (>40 years) n= 100	p-value
Coronary angiographic evaluation			
Normal Vessels, n (%)	22 (22.0%)	5 (5.0%)	<0.001
Single Vessel Disease, n (%)	55 (55.0%)	46 (46.0%)	0.204
Double Vessel Disease, n (%)	15 (15.0%)	31 (31.0%)	0.007
Triple Vessel Disease, n (%)	8 (8.0%)	18 (18.0%)	0.036
Arteries involved*			
Left anterior descending, n (%)	48 (44.0%)	46 (28.4%)	0.004
Left circumflex, n (%)	29 (26.6%)	62 (38.1%)	0.047
Right coronary artery, n (%)	32 (29.4%)	54 (33.3%)	0.490

[Table/Fig-7]: Comparison of angiographic findings between younger and older Gujarati patients with acute coronary syndrome**
*Total number of arteries involved was 109 in the younger group and 162 in the older group
**Values are expressed as n (%); p-value was calculated using the Chi-square test or the Fisher's exact test.

DISCUSSION

In literature, about 200 risk factors for coronary artery disease have been recognized or hypothesized. Majority of these risk factors are treatable or preventable [10]. Accordingly, these risk factors can be classified into class I (preventable risk factors), class II (requires intervention to lower cardiovascular risk), class III (factors if modified might lower cardiovascular risk) and class IV (unmodifiable risk factors) [10]. In this study, we determined the differences in the



[Table/Fig-8]: Distribution of the subjects by number of the coronary artery involvement in both the groups in younger and older Gujarati patients with acute coronary syndrome*
*SVD, Single Vessel Disease; DVD, Double Vessel Disease; TVD, Triple Vessel Disease

characteristics of class I-IV risk factors and angiographic profile between younger and older patients with ACS. We selected an age cut-off of 40 y to define a premature CAD, based on previous Indian [1,11] and Indian subcontinent studies [2,5-7].

In our study, the youngest patient presented with ACS was 22-year-old, suggesting a very early onset of ACS and requiring an alarming attention. Further, the most obvious finding in our study was a very high prevalence of ACS among men as compared to women. The proportion of males among ACS patients who underwent coronary angiography was 24 times than that of females in the younger group and eight times than that of females in the older group. Although the significant male predominance observed in the present study is in line with other studies [12,13], this should be considered as an indication of the skew in exposure to cardiovascular risk factors that males have been subjected to.

The trend in types of ACS reported in the present study is similar to previously published articles [1,8,13,14]. STEMI was the most frequent presentation in young (85%) and older (81%) patients with ACS. Further, the most common anatomical location of the myocardial infarction was anterior wall (61% and 51% of ACS patients in younger and older groups respectively). These outcomes suggest that the pathophysiology of different types of ACS may be age independent.

Obesity is an alarming concern among young adults [2]. The present study also showed that the mean BMI in younger patients with ACS was comparable to that in older patients with ACS. Further, the proportion of overweight and obese patients was nearly similar between two age groups, suggesting high incidence of obesity at young age. Analysis of other conventional risk factor revealed that dyslipidaemia alone was a significant risk factor in 47% of individuals each in both age groups of patients. Hypertension was two-times more common in older patients than in younger patients with ACS. While diabetes mellitus is a well-known risk factor of ACS, we found no significant difference in the prevalence of diabetes between the two age groups. However, we observed a non-significantly higher prevalence of diabetes mellitus among older patients. On the contrary, family history of premature CAD was more common among young patients.

Smoking and tobacco chewing have also been traditionally recognized as the most common risk factors for heart disease, particular among young patients [2]. In our study, nearly half of the patients in both the age groups were either tobacco chewer or cigarette smoker. While the findings are devastating, it should be emphasized that cigarette smoking and tobacco chewing are reversible risk factors for ACS [12]. Although our study demonstrated a stronger association between smoking, tobacco chewing, hyperlipidemia, and obesity and ACS in younger patients, hypertesnion and positive family history of premature CAD were the only discriminatory risk factors between the two age groups. This is in agreement with other studies of similar nature [5,8,13].

It is widely established that lipid levels are correlated with the extent and the severity of ACS in Asian Indians as in whites, irrespective of age [1]. We found that lipid levels, particularly total cholesterol, LDL cholesterol, and non-HDL cholesterol, were significantly higher among young patients than in their older counterparts. Other lipid parameters were also non-significantly higher among young patients with ACS, suggesting a significant concern about abnormal lipid levels at younger age. We emphasize that such individuals should be treated aggressively.

There is limited data available regarding the comparison of novel atherosclerotic risk factors in patients with premature onset ACS and in older patients with ACS [1]. In this study, we focused on comparing Lp(a), homocysteine, and Hs-CRP levels in our study groups. High Lp(a) levels are highly correlated with the severity of ACS, and the effect of Lp(a) on the atherogenicity is reported to be multiplicative and not additive [1]. In the present study, 43% and 44% patients in the young and the older groups respectively had elevated Lp(a) levels (>30 mg/dL). Similarly, elevated homocysteine levels (>15 μmol/L) were found in 70% and 65% of patients in the young and the older groups. The reason behind the high prevalence of hyperhomocysteinaemia in our patients could be their diet as vegetarians have three times higher risks of hyperhomocysteinaemia as compared to non-vegetarians and considering that majority of people adhere to vegetarian diet in Gujarat. We also found very high Hs-CRP levels, probably due to their estimation in ACS patients which itself is an inflammatory condition. We observed that Hs-CRP levels were non-significantly higher among younger patients with ACS. The findings of our study in terms of novel atherogenic risk factors were comparable to studies reported in literature [15–17].

Analysis of the angiographic pattern revealed that normal or minimal lesion coronary anatomy was more frequent in younger patients with ACS. Further, there was a preponderance of single vessel disease among young (55%) and older group (46%). These findings are in agreement with previously reported literature [8]. In our patients, LAD was the most commonly involved vessel among young patients with ACS, while LCx was the most commonly involved vessel among older patients with ACS. It can be inferred from these data that the distribution of coronary lesion may be age dependent. Our findings are in contrast with other studies, which showed LAD as the most commonly involved vessel in older patients [2,6].

ACS, being an uncommon entity in individuals aged <40 years, constitutes an important challenge for both the patient and the treating physician [2]. Lynch et al., have recently reported that the knowledge of CVD risk factors is extremely low among young adults. In addition to this, the knowledge of CVD risk factors does not appear to influence lifestyle or dietary changes in this population [18]. Hence, we highlight that identification and control of potential risk factors is very crucial in the primary and secondary prevention of cardiovascular disease in young individuals. Emphasis should be given on diagnosis and management of dyslipidaemia, diabetes mellitus, hypertension and cessation of smoking, which have been identified as the major modifiable risk factors in our study. Although the benefit of risk factor reduction is widely reported in older patients, such evidence in younger age group is a significant concern and warrants attention [6].

CONCLUSION

Based on the study findings, it seems reasonable to draw some conclusion about the age-related differences in atherosclerotic risk factors and angiographic profile of the Gujarati patients presenting with ACS. Overall, anterior-wall STEMI was the most common diagnosis in both study groups. Dyslipidaemia and tobacco intake were the most common ACS risk factors in patients of both the groups. Hypertension was more common among older

patients, while family history of CAD was more common among younger patients. Patients had significantly higher levels of total cholesterol, LDL cholesterol, and non-HDL cholesterol at younger age as compared to older patients. Levels and distribution of novel atherogenic risk factors were comparable between the two age groups. Angiographically normal coronary anatomy was more common in the younger patients. LAD was the most commonly affected coronary artery among young patients, while LCx was the most commonly affected coronary artery among older patients. However, a comprehensive, multicentre study is required to offer a better picture of the risk-factor profile and angiographic patterns in young and older patients with ACS.

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