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ORIGINAL RESEARCH

A surge in prevalence and factors affecting early onset acute coronary syndrome

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Abstract

Acute coronary syndrome (ACS) with early onset of age (especially in <30 years) is an infrequent (up to 0.05 to 0.4%) but serious entity, with modest available data. A rise in incidence has been witnessed, especially in South Asia. The aim was to ascertain the proportion of very young patients (≤35 years) among all adult patients with ACS and important factors associated with it. Patients presenting with ACS during September 2020 to January 2021 were incorporated in this cross-sectional single-center study and were analyzed by age: Group I (20–35 years), Group II (36–45 years), and Group III (>45 years). Demographic characteristics, angiographic findings, co-morbidities and treatment strategies were recorded. 1314 patients with ACS in the study period were examined. Patients in Group I accounted for 6.2% (81) of the study cohort. Of these, 2.1% (28) were aged 20 to 30 years and 4.03% (53) were aged 30 to 35 years. Analysis of age groups by ACS risk factors revealed that male gender, overweight, smoking, using smokeless tobacco (especially gutka), were significantly higher in Group I. Other conventional risk factors were more prevalent in Group III. In Group 1, anterior wall myocardial infarction, single vessel coronary artery disease (SVCAD) and re-canalized vessels were significantly more frequent. Significantly higher proportion of patients were treated with conservative management alone in Group I. In our crossectional study we report an inclining shift in the frequency of early onset ACS than previously observed. In this recent cohort, ACS in the youngest adult patients was significantly associated with being overweight, smoking, and smokeless tobacco use, especially gutka. Moreover, these patients' higher rates of SVCAD and re-canalized vessels due to hypercoagulable milieu, could be better responsive to aggressive pharmacologic treatment noted in these young patients.

Keywords

ACS; Premature CAD; Frequency; Risk factors; Young adult

1. Introduction

Acute coronary syndrome (ACS) is a constellation of problems caused by abrupt partial or complete cessation of the heart muscle's blood supply that may results from a potentially dynamic state of unstable angina pectoris (USAP) to irreparable cell damage of myocardial infarction (MI). Coronary atherosclerosis is the cardinal problem for ACS, with very few exceptions. Other less common causes of ACS include coronary dissection, thromboembolism, arteritis, myocardial bridging and coronary spasm without apparent coronary artery disease (CAD) [1]. ACS is currently a prime cause of deaths globally. For example, in the US, over one million Americans have a diagnosis of ACS, and more than 400,000 die of CAD annually [2].

South Asian countries have witnessed a rapid transformation in lifestyle and dietary behavior, and tobacco use in particular is widespread. This change in behavior has likely contributed to the steep increase in prevalence of coronary heart disease (CHD). Globally, the incidence of CHD is rising [3]. One study from China on cardiovascular disease (CVD) in 2014 concluded that CVD worldwide inflicted around 290 million individuals. Due to this fact, the proportion of CVD is increasing and has established publicly as a significant health issue [4].

While occurring less frequently in young adults, ACS nonetheless carries detrimental effects. There is an increase in incidence of very young patients with ACS. Urbanization, obesity, overweight and drug abuse are principal risk factors for this group. The manifestation of ACS in younger population is distinct from the elder subset as a result of their more thrombogenic milieu, which might be more amenable to aggressive pharmacological measures [5]. Given there are

patients with significant thrombus loads but angiographically almost imperceptible atherosclerotic lesions, questions regarding causality are raised [6]. Cheema FM *et al.* [7], demonstrated a male predominance and positive family history as a common predisposing risk factor for ACS in those aged 18 to 40 years. The extent to which a diverse group of factors contribute to the onset and propagation of CAD appears to vary by age. Smoking has been demonstrated to be an important cause of early onset CAD. Multiple studies have reported the association between CAD and hyperuricemia in older people [8]. Dyslipidemia is recognized as a major and modifiable contributor to cardiovascular diseases (CVDs) worldwide. Cumulative burdens of low density lipoprotein cholesterol (LDL-C) exposure over one's lifetime highlight the value of early identification and interventions to achieve optimal cholesterol levels during young adulthood [9]. Higher baseline total cholesterol, triglycerides levels, LDL-C and lower high density lipoprotein cholesterol levels are linked with higher risks of subsequent atherosclerotic cardiovascular disease (ASCVD), especially MI [10]. Similarly, in late adolescence raised body mass index (BMI), even within the presently acceptable normal limit, is firmly connected with cardiovascular death in younger subset [11].

ACS in the very young adults is an infrequent but concerning entity, with limited data thus far from South Asia. While Batra MK *et al.* [12] report in a patients up to 40 years old a frequency of patients with premature MI of 12%, this does not reflect the very youngest adults group. There is paucity of data focusing the very young age group with ACS locally; however, around the globe incidence of ACS in patients up to the age of 30 years has been reported as less than 1% (0.05% in 2013 in a Swiss study by S. Puricel [13]; 0.4% in 2003 by Gotsman *et al.* [14]; 0.32% in 2018 by Chhabra ST *et al.* [5]) (Fig. 1).

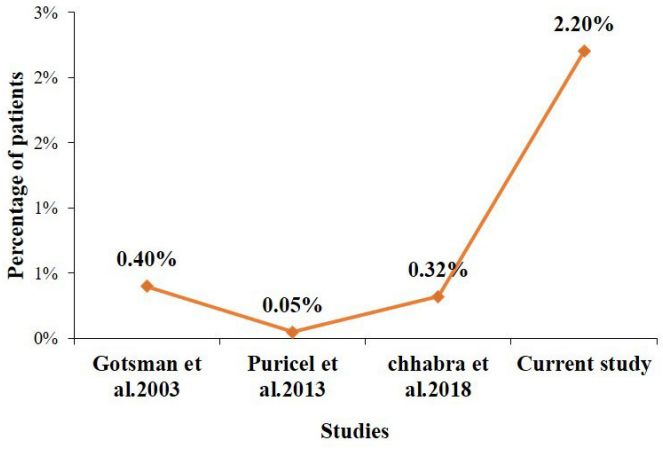

FIGURE 1. Rising trend of frequency of very young age (20–30 years) ACS in comparison with other studies. STEMI, ST elevation myocardial infarction; NSTEMI, non-STEMI; MI, myocardial infarction; USAP, unstable angina pectoris; SVCAD, single vessel coronary artery disease; 2VCAD, two vessel coronary artery disease; 3VCAD, three vessel coronary artery disease; PCI, percutaneous coronary intervention.

In recent years a rising trend of ACS in this age group has been suspected in Pakistan, but exact incidence has not been well established. This study sought to examine the proportion of ACS patients requiring angiography in this early age group (20–35 years) better understand potentially actionable risk factors for the disease.

2. Material and methods

This cross-sectional prospective study examined patients managed at a single tertiary care hospital in the southern region of Pakistan. All ACS patients (n = 1314) who underwent coronary angiogram were enrolled from September 2020 to January 2021 and analyzed. Patients were separated into three groups for analysis: Group I (very young age group 20 to 35 years), Group II (young age group, 36 to 45 years) and Group III (older age group, 45 years and older).

Patients satisfying the criteria for diagnosis of ACS were included. The ACS diagnosis was made as unstable angina pectoris (USAP), ST-segment elevation myocardial infarction (STEMI) or Non-STEMI (NSTEMI). Patients of chest discomfort with ST segment elevation or left bundle branch block (LBBB) of presumably new onset in electrocardiographic (ECG) leads were classified as STEMI.

Patients with congenital heart disease, myocarditis and atypical chest pain were excluded.

Sample size was calculated through systematic sampling given the previously-described/wide discrepancy in the number of patients in the very young age group as compared to the older age group [5, 15]. Information on known ACS risk factors were collected. Data pertaining to age, gender, BMI, history of smoking, history of smokeless chewable tobacco and its subtypes (e.g., plain tobacco; gutka—a kind of flavored tobacco mixed with crushed areca nut, catechu and paraffin wax; paan—tobacco combined with areca nut and betel leaf; naswar—moist powdered tobacco), drug abuse, alcohol use, family history of early onset CAD, hypertension, dyslipidemia, diabetes, and history of prior CAD was noted at the time of presentation after written and informed consent. The definition of BMI was established as per classification by World Health Organization (WHO) [16].

Characteristics of ACS were noted, including presence of STEMI, NSTEMI and USAP. The STEMI patients presenting in the appropriate time period were offered primary angioplasty or fibrinolysis with the provision of standard guideline directed medical treatment in emergency room. The fibrinolysed patients or delayed presentation of STEMI patients, USAP/NSTEMI patients underwent cardiac catheterization and treated either by early invasive percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or medical treatment alone. CAD was further stratified as single vessel coronary artery disease (SVCAD), two vessel coronary artery disease (2VCAD) and three vessel coronary artery disease (3VCAD). Non-significant disease described as <50% occlusion of the lumen. Patients found to have recanalized vessels either manifested as non-obstructive CAD or normal were also evaluated. Culprit coronary artery was noted as right coronary artery (RCA), left anterior descending artery (LAD) and left circumflex artery (LCx). Method of

definitive management was described as conservative medical management, early invasive or primary PCI and CABG.

Data analyses were conducted using Social package of statistical sciences of SPSS Inc. (version 21, Chicago, USA) after quality assessment of data was complete. Study variables were summarized with using descriptive statistics such as frequency and percentages and mean ± standard deviation (SD) or median (IQR). Data were stratified into three groups based on age, very young group (20–35 years), young group (36–45 years), and older group (>45 years) of age. Study results in very young group (Group I) were compared independently with those of young group (Group II); similarly, results in Group I were also compared independently with results of older group (Group III). Categorical variables, were compared using Chi-square test or when expected cell count of ≤5, Fisher's exact test. After hypothesis of normality for the continuous response variables was assessed by conducting Kolmogorov-Smirnov (KS) test, independent sample *t*-test and Mann–Whitney U test were used where appropriate. However, no multiple comparison tests were applied in order to focus the emphasis on comparison of very young population group with other counterparts. A two-tailed *p*-value ≤ 0.05 was considered significant.

3. Results

Of the total 1314 patients with ACS included for analysis 6.2% (n = 81) were from the very young age group; among these, 2.1% (n = 28) were found to be between 20 to 30 years, while 4.03% (n = 53) were between 30 to 35 years of age. Outside of this very young age group, 16.1% (n = 211) were from young (Group 2) and 77.8% (n = 1022) from older age group (Group 3).

In group 1, 36 (44.4%) patients were found to be smokers, 13 (16%) patients were using smokeless tobacco [out of which 6 (50%) were using gutka], 23 (28.4%) had hypertension, 9 (11.1%) were diabetics. Sixty-six of the 81 (81.5%) in group I were noted to have BMI >25, of whom 67.9% were noticed to be overweight (BMI: 25–29.9) and 13.6% were obese. Mean BMI was 26.76 ± 2.85 kg/m^2. One patient (1.2%) (n = 1) was underweight while 17.3% (n = 14) had BMI within normal limit. History of premature CAD was present in 8 (9.9%) patients. Only 1.2% patients were alcoholic.

In the ACS spectrum, 74 (91.4%) patients in group 1 presented with STEMI, 6 (7.4%) with NSTEMI, and only 1 (1.2%) with USAP (Fig. 2A). Out of those with STEMI, 51 (68.9%) patients had anterior wall myocardial infarction (AWMI) and 23 (31.1%) had inferior wall myocardial infarction (IWMI).

Of the 74 STEMI patients arriving to the hospital within the time limit of reperfusion, 66 (89.1.5%) underwent primary PCI with stent while eight (10.8%) did not require intervention. Non-intervention reasons for 4 (5.4%) patients were due to recanalized vessels and 4 (5.4%) patients due to severe diffuse disease not amenable for revascularization (Fig. 2B). LAD was culprit in 56 (61.9%) patients, RCA in 15 (18.5%) patients and left circumflex artery in 9 (11.1%) patients. Fifty-nine (72.8%) patients were diagnosed as having SVCAD, while only 11 (13.6%) and 7 (8.6%) were observed to have 2VCAD and 3VCAD respectively (Fig. 2C).

When Group 1 was separately compared to the other two groups, demographic characteristics, distribution of risk factors, and angiographic findings were not statistically different in group I and group II except conventional risk factors such as DM, HTN, and dyslipidemia which observed to be higher in group II. Angiographic findings of normal coronaries and recanalized vessels were relatively higher in group I (Tables 1,2,3).

Male gender accounted for a significantly larger proportion of very young patients, being 86.4% in group I and 76.1% in group III ($p = 0.034$). A relatively higher number of patients (67.9% versus 60.2%) were also observed to be overweight and obese in this group. There was a significantly larger percentage of individuals in group I who used substances: smoking tobacco (44.4% versus 32.6%, $p = 0.029$), smokeless tobacco (especially gutka 50% versus 8.9% (p-value ≤ 0.001) in contrast to group III. Conventional predisposing risk factors like diabetes mellitus (37.9% vs. 11.1%), hypertension (70.2% vs. 28.4%) and dyslipidemia (18.8% vs. 2.5%) were more prominent in group III in contrast to group I ($p \leq 0.001$). STEMI in group I (91.4%) and in group III (88.2%) was the most frequent mode of emergency room (ER) presentation in both groups but AWMI was considerably significant in group I ($p = 0.008$). More patients in group III presented with NSTEMI and USAP (Fig. 2A). SVCAD (72.8% vs. 35.3%) was predominant in group I, whereas 2VCAD (31.3% vs. 13.6%) and 3VCAD (33% vs. 8.6%) were significantly higher in group III ($p \leq 0.001$). A significantly distinct percentage of patients in group I were discovered to have recanalized coronaries either in the form of non-obstructive CAD or normal coronaries (4.9% vs. 0.4%) (Fig. 2D). Primary PCI was the common mode of treatment in both group, but early invasive PCI (9.7% vs. 6.2%) and CABG (2.2% vs. 0%) were relatively more frequent in group III. Conversely, medical treatment alone was significantly more frequent in group I (12.2% vs. 3.7%; $p = 0.001$) (Tables 1,2,3).

4. Discussion

The present study is the biggest observational cross-sectional study focusing on younger age ranging mainly from 20 to 35 years with ACS to date in a high-volume setting in Pakistan. Younger age ACS has been demonstrated in earlier studies and there is an enormous literature but majority in the age range of 35–45 years [8–12]. An earlier study reported an incidence of 0.4% of ACS aged 20–30 years in 2003 [14] and another study, conducted in 2018 found an incidence of 0.32% with 114 patients presenting with ACS in the similar age range [5]. However, in the current study, we specifically looked at the proportion of patients below 30 years, as no other study found locally after thorough review of literature reported this frequency. 2.1% (n = 28) much higher than previously reported number around the world (Fig. 2). This suggests a surge in incidence of ACS in this specified group. However, this frequency increased further to 6.2% (n = 81), when including those up to the age of 35 years.

Overweight and obesity was of paramount importance in the risk factor profile of the study's very young population, 81.5% (n = 66) were found to have BMI ≥25, with 55 being ranged as

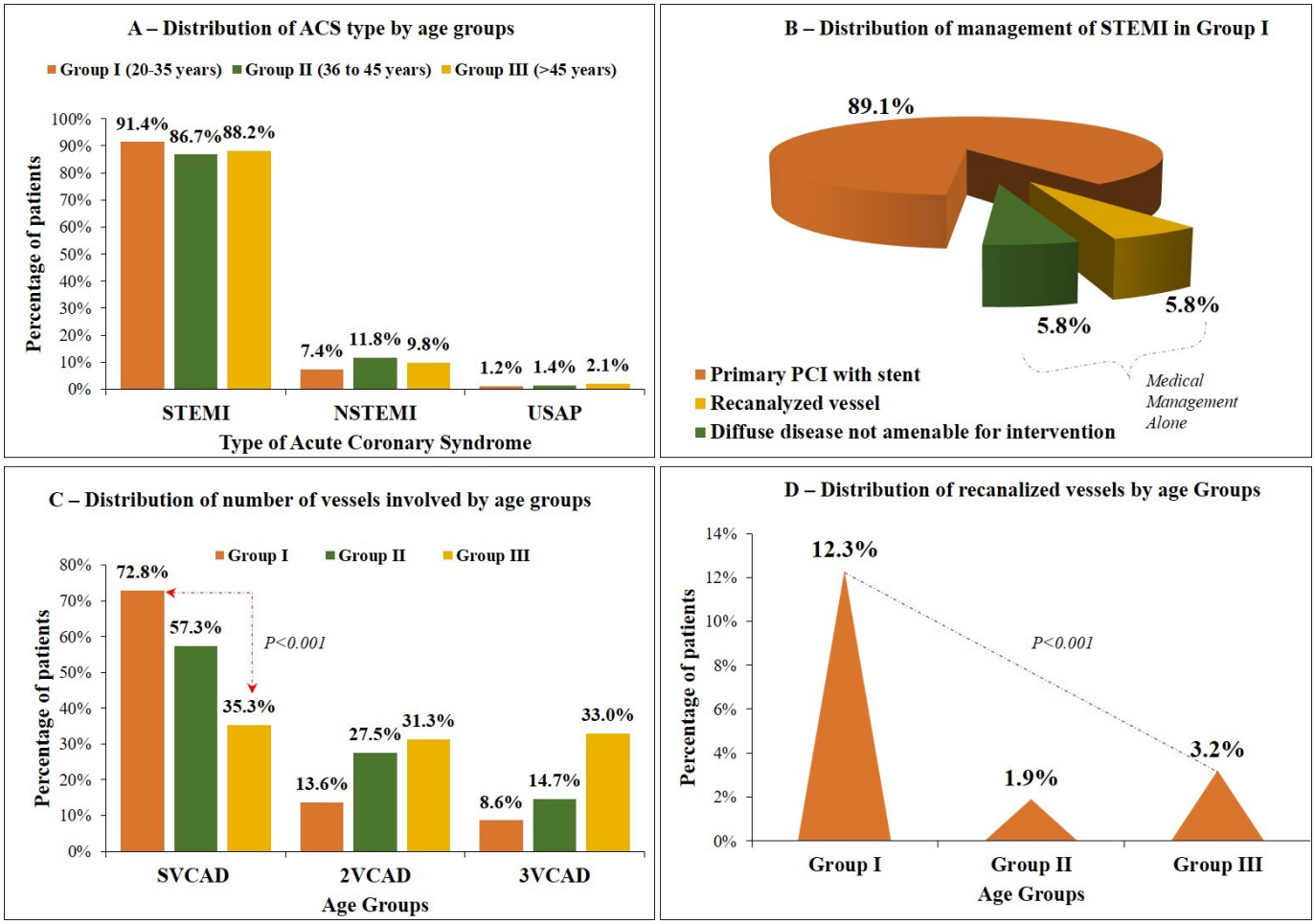

FIGURE 2. Various demographic and angiographic distribution. (A) Distribution of ACS by age groups, (B) distribution of management strategy for STEMI patients in very young age group, (C) distribution of number of vessels involved by age groups, and (D) distribution of recanalized vessels by age groups.

TABLE 1. Distribution of demographic by age groups.

Characteristics	Group I	Group II		Group III	
	20–35 years	36–45 years	*p*-value (vs. I)	>45 years	*p*-value (vs. I)
Total (N)	81	211		1022	
Gender					
Male	86.4% (70)	82% (173)	0.365	76.1% (778)	0.034
Female	13.6% (11)	18% (38)		23.9% (244)	
Mean age (years)	31.99 ± 3.53	42.07 ± 2.56	<0.001	59.08 ± 8.31	<0.001
Body mass index (kg/m^2)	26.76 ± 2.85	27.48 ± 3.88	0.129	26.81 ± 3.43	0.904
Under weight	1.2% (1)	0% (0)	0.277	0.2% (2)	0.205
Normal weight	17.3% (14)	20.9% (44)	0.494	27.5% (281)	0.046
Over weight	67.9% (55)	62.6% (132)	0.394	60.2% (615)	0.171
Obese	13.6% (11)	16.6% (35)	0.528	12.1% (124)	0.702
Heart rate (bpm)	84.95 ± 13.56	87.23 ± 16.27	0.263	83.54 ± 15.66	0.432
Systolic blood pressure (mmHg)	132.04 ± 17.97	137.86 ± 25.82	0.064	135.83 ± 25.03	0.181
Diastolic blood pressure (mmHg)	86.05 ± 13.29	87.48 ± 16.16	0.477	82.59 ± 15.43	0.050

overweight and 11 came out as obese. Twig *et al*. [11] in their study found a correlation between BMI and subsequent cardiovascular mortality, in age of 17.3 ± 0.4 years more prominently in midlife. Their study showed a hazard ratio of 3.0 for BMI in the range of overweight (85th to 94th percentiles) and 4.89 for BMI ≥95th percentile in the obesity range for

TABLE 2. Distribution of risk factors of CAD by age groups.

Characteristics	Group I	Group II		Group III	
	20–35 years	36–45 years	*p*-value (vs. I)	>45 years	*p*-value (vs. I)
Total (N)	81	211		1022	
Smoking	44.4% (36)	41.2% (87)	0.619	32.6% (333)	0.029
Current smokers	86.1% (31)	88.4% (76)	0.729	76.3% (254)	0.181
Ex-smokers	13.9% (5)	11.6% (10)		23.7% (79)	
Smokeless tobacco use	16% (13)	11.8% (25)	0.339	9.2% (94)	0.045
Paan	16.7% (2)	36% (9)	0.733	50% (45)	0.572
Gutka	50% (6)	24% (6)	0.099	8.9% (8)	<0.001
Naswar	8.3% (1)	20% (5)	>0.999	22.2% (20)	>0.999
Chewable tobacco	16.7% (2)	24% (6)	>0.999	21.1% (19)	0.663
Alcohol consumption	1.2% (1)	0.9% (2)	>0.999	0.5% (5)	0.368
Drug addict	0% (0)	0% (0)	-	0.4% (4)	-
Charas or Hashish (Cannabis)	0% (0)	0% (0)	-	75% (3)	-
Sleeping pills	0% (0)	0% (0)		25% (1)	
Diabetes mellitus	11.1% (9)	26.1% (55)	0.006	37.9% (387)	<0.001
NIDDM	88.9% (8)	87.3% (48)	>0.999	96.1% (374)	0.311
IDDM	11.1% (1)	12.7% (7)		3.9% (15)	
Hypertension	28.4% (23)	48.3% (102)	0.002	70.2% (717)	<0.001
Positive family history	9.9% (8)	6.6% (14)	0.347	9.4% (96)	0.886
Dyslipidemia	2.5% (2)	9.5% (20)	0.042	18.8% (192)	<0.001
CKD	0% (0)	0% (0)	-	2.9% (30)	-
Prior CAD	2.5% (2)	7.1% (15)	0.130	14.6% (149)	0.002

IDDM, insulin dependent diabetes; NIDDM, non-insulin dependent diabetes; CKD, chronic kidney disease; CAD, coronary artery disease.

mortality from CHD. Likewise, a higher BMI of about 26.7 ± 4.2 (mean ± SD) with CAD in substrates <40 years of age was also demonstrated by Tsai *et al.* [17]. Hence, obesity is one of the crucial changeable predisposing risk factors in this younger population. Another more important prevailing factor in this patient group is use of chewable smokeless tobacco named locally as gutka, which is a kind of flavored tobacco mixed with crushed areca nut, catechu and paraffin wax as described earlier, being used by 50% (n = 6), perhaps because it is considered a common social gathering symbol of entertainment initially especially in small business community in this region, but consequently result in addiction and same may also true for smoking 44.4% (n = 36). Smoking has always been regarded as crucial but modifiable risk enhancing factor in young patients for development of ACS due to nicotine susceptibility for thrombus formation or spasm [13, 14, 18]. Biery *et al.* [19] demonstrated in a recent cohort study of over one thousand patients, approximately half experiencing an MI at ≤50 years were smokers. Moreover, cessation of smoking after MI within 1 year was associated with >50% lowering of all-cause and cardiovascular mortality in these patients. It seems that there is an immediate need for earlier prevention so as to overcome this threat right at its beginning in younger ages. This could produce a pivotal role in reducing the cardiovascular events in this socioeconomically crucial population. Likewise, as in earlier studies, conventional modifiable risk factors such as hypertension, dyslipidemia and diabetes were observed in a relatively lesser percentage of younger subset [5, 20], but were significantly more prevailing in older group III. However, diastolic blood pressure was found to be significantly higher in the younger group, which itself was a predictor of increased cardiovascular morbidity, signify their presentation as ACS [21]. Interestingly, family history of premature CAD was present in 9.9% (n = 8) patients of group I, though, earlier studies reported the same in almost 15–45% patients in their inhabitants [18, 22]. This disparity is likely the result of variation in genetic makeup, which is why different socioeconomic and ethnic group of people should be analyzed individually for causation and management measures. Four (4.9%) patients were found to have recanalized vessels either normal or milder non-obstructive disease, so subsequently managed with conservative treatment alone.

STEMI 91.4% (n = 74) was the most frequent presentation in the very younger age group, out of which AWMI 68.9 % (n = 51) was predominantly common in this age group. Sixty-six patients presented within the time limit of reperfusion and underwent primary PCI, as our center is a high volume center which can treat multiple primary PCI simultaneously due to multiple functional catheterization labs. SVCAD involvement was distinctly the most frequent (72.8%), with LAD being the

TABLE 3. Distribution of angiographic finding and management by age groups.

Characteristics	Group I	Group II		Group III	
	20–35 years	36–45 years	*p*-value (vs. I)	>45 years	*p*-value (vs. I)
Total (N)	81	211		1022	
Type of acute coronary syndrome					
Unstable angina	1.2% (1)	1.4% (3)	>0.999	2.1% (21)	>0.999
NSTEMI	7.4% (6)	11.8% (25)	0.270	9.8% (100)	0.485
STEMI	91.4% (74)	86.7% (183)	0.276	88.2% (901)	0.387
Anterior wall MI	68.9% (51)	57.4% (105)	0.086	52.9% (477)	0.008
Inferior wall MI	31.1% (23)	42.6% (78)		47.1% (424)	
ST depression/T wave inversion	8.6% (7)	13.3% (28)	0.267	11.5% (118)	0.427
Positive Troponin	95.1% (77)	96.2% (203)	0.659	95.7% (978)	0.788
Number of vessels					
Normal	1.2% (1)	0.5% (1)	0.479	0% (0)	0.073
Single vessel coronary artery disease	72.8% (59)	57.3% (121)	0.015	35.3% (361)	<0.001
Two vessel coronary artery disease	13.6% (11)	27.5% (58)	0.012	31.3% (320)	0.001
Three vessel coronary artery disease	8.6% (7)	14.7% (31)	0.169	33% (337)	<0.001
NOCAD/recanalized vessel	3.7% (3)	0% (0)	0.021	0.4% (4)	0.011
Infarct related artery					
None	1.2% (1)	0.5% (1)	0.479	0% (0)	0.073
LAD	69.1% (56)	57.3% (121)	0.065	53% (542)	0.005
RCA	18.5% (15)	30.3% (64)	0.042	32.9% (336)	0.008
LCx	11.1% (9)	11.4% (24)	0.949	13.7% (140)	0.512
Multiple	0% (0)	0.5% (1)	>0.999	0.4% (4)	>0.999
Management strategy					
Primary PCI	81.5% (66)	84.8% (179)	0.485	84.9% (868)	0.407
Early invasive PCI	6.2% (5)	12.8% (27)	0.105	9.7% (99)	0.298
CABG	0% (0)	0.5% (1)	>0.999	2.2% (22)	0.399
Medical treatment only	12.3% (10)	1.9% (4)	0.001	3.2% (33)	0.001

STEMI, ST elevation myocardial infarction; NSTEMI, non-STEMI; MI, myocardial infarction; NOCAD, non-obstructive coronary artery disease; LAD, left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

commonest vessel found to be culprit (69.1%). Surprisingly, though there was a significantly high proportion of patients 4.9 % (n = 4) in younger individuals who were found to have normal or non-obstructive CAD as a result of recanalization. This percentage is a bit lower compared to other studies like 15.8%, by Iragavarapu T *et al.* [23] and 16.9% by Maroszyńska-Dmoch *et al.* [24]. This may be of note, because the baseline mechanism in very younger individuals is plaque disruption or ulceration with significant clot burden, causing occlusion momentarily, resulting in ischemia or infarction. Consequently, anticoagulant therapy or fibrinolysis may make the lumen patent again. Vasospasm and milder form of atherosclerotic plaque with positive remodulation could be alternative causes in this subset [25]. These kinds of lesions commonly reveal features of propensity like thin fibrous covering and large lipid content, which may make them more vulnerable for plaque disruption. Of consideration, hypercoagulable states might increase the hazardous outcomes of these lesions. Two of the patients from group I who were diagnosed with NSTEMI found to have high thrombus burden (60–70%) in mid RCA and in mid LAD (50–60%), but responded well to aggressive pharmacologic therapy including anticoagulation with enoxaparin. Repeat angiography after almost a week revealed recanalized vessels. Puricel *et al.* [13] showed that in 15% of their young substrates the most frequently encountered atypical cause was hereditary thrombophilia. The very young subset of patients found to have a mechanism (high thrombogenic milieu, plaque vulnerability, and vasospasm) was a bit different from the older age group, who had distinct plaque composition with more underlying fibrosis, necrosis, atherosclerosis and calcification. Therefore, this young group of patients might be more amenable to aggressive pharmacological therapy in terms of anticoagulation/fibrinolysis and other guideline directed treatment. This could suggest that these patients might do better without subjecting them to undergo invasive procedures like stenting or ballooning if they present within the given time

frame and found to have significant thrombus burden. Therefore, aggressive pharmacological therapy with adjourn angioplasty might be the treatment of choice for revascularization in this young subset. Another compelling and noteworthy observation of this study was a tremendous rise in the percentage of ACS up to 2.1% in patients <30 years, and 6.2% up to the age of 35 years as compared to another recent era especially in our region compared to previous prevalence in different regions of the world 0.05% in 2013 in a Swiss study by S. Puricel [13] and 0.4% in 2003 by Gotsman *et al*. [14] and 0.32% in 2018 by Chhabra ST *et al*. [5] (Fig. 1). This should highlight the concern to take the maximum corrective measures for modifiable risk factors that should be begin as earlier as possible from childhood so as to protect these young economically crucial lives. Treating medical staff also required to identify ACS in these patients as early as possible and manage them rigorously.

To the best of our knowledge, this is the largest observational study conducted at one of the largest cardiac care centers in Pakistan. Our findings highlight a tremendous increase in premature CAD affecting productive years of socioeconomically imperative subset of very young population. Nonetheless, this study has certain limitations such as observational nature of the study, single center coverage, and predominantly urban population. Secondly, due to exclusion of non-consenting patients for invasive procedure and for participation in the study may have induced certain selection bias. Also, due to observational nature of the study, no additional clinical and laboratory assessment were performed such as lipid profile and lifestyle (sedentary/active). Finally, due to disproportionate distribution of sample in various age groups, the statistical significance for various differences could not be achieved. Hence, larger studies are warranted with more geographical as well as demographical coverage to evaluate and understand the gravity of subject matter in our population.

5. Conclusions

In conclusion, there is a steep rise in the prevalence of ACS in very young patients in the current era in South Asia, especially in Pakistan. Overweight, current smoking, use of smokeless tobacco especially gutka are the potential risk predisposing factors. Moreover, these patients were distinct with higher incidence of SVCAD and re-canalized vessel due to hypercoagulable milieu, which could be better responsive to aggressive pharmacologic treatment.

AUTHOR CONTRIBUTIONS

KAK, MNK, RK, JAS, and MKB contributed to the concept and design of study. KAK, DK, RK and JAS contributed to the collection, analysis and interpretation of data. KAK, MNK, RK, NK, JS, and MK contributed to the drafting of the manuscript, and JS, TS, and MK critically analyzed for content. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Ethical Review Committee of National Institute of Cardiovascular Diseases (NICVD), Karachi Pakistan, with reference number 47/2020.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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