Comparison of Prevalence, Presentation, and Prognosis of Acute Coronary Syndromes in ≤35 years, 36 − 54 years, and ≥ 55 years Patients

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Whether very young patients (≤35-year-old) differ in the prevalence, presentation and prognosis of ACS is not well known. Of 43,446 patients who were referred to a tertiary care cardiac catheterization laboratory between January 1, 2006 and June 30, 2017, 26,545 patients were ACS (defined as ST Elevation MI, Non-ST Elevation MI or unstable angina pectoris). Detailed chart review was performed and characteristics at baseline were compared for ages ≤35 years, ages 36 to 54 years and ages ≥55 years. A total of 291 (1.1%) were ≤35-year-old, 7,649 (28.8) were 36 to 54-year-old and 18,605 (70.1%) were ≥55-year-old. ACS patients aged ≤35-year-old, were more likely to be men, Caucasian white, smoker, obese, and have family history of coronary artery disease and less likely to have comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia compared with older patients. They were also more likely to present with elevated troponin levels than other groups. They also tended to present with late ST elevation myocardial infarction and were more likely to receive bare metal stents than older patients. The prevalence of 2- and 3-vessel disease was lower compared with older patients. They also had higher prevalence of cardiogenic shock. Compared with 36 to 54-year-old patients, ≤35-year-old were at significant higher risk of 30-day mortality in a multivariable adjusted regression model (Odds ratio 5.65, 95% confidence interval 2.49 to 12.82, p <0.001). Very young patients comprised ~1% of all ACS cases but had much more prevalence of modifiable risk factors and significantly worse mortality. Modifying these risk factors may mitigate the risk in these patients and should be studied in the future. **(Am J Cardiol 2021;140:1−6)**

With major advances in treatment of cardiovascular disease, there is a steady decline in the incidence of acute myocardial infarction (AMI) over the past several years.[1] However, a similar decline has not been observed in young and very young patients and the AMI hospitalization rates have remained consistent from <55 years of age.[2,3]. Multiple small retrospective studies investigated risk factors and epidemiology for acute coronary syndromes (ACS) in young adults (<45 years old).[4-8] While, only two studies including data from Switzerland [9] and USA[10] examined very young adults (≤35-year-old), none of the studies have examined the very young adults in the contemporary drug eluting stent era. Therefore, we sought to review cardiac risk factors profile, clinical presentation, angiographic findings and prognosis of very young adults (≤35-year-old) presenting with ACS, and compare them with young adult patients (aged 36 to 54 years) and older patients (aged ≥55 years).

Methods

We collected and reviewed data from consecutive patients who were referred to the cardiac catheterization laboratory at University of Massachusetts Medical Center between January 1, 2005 and June 30, 2014 with a diagnosis of presumptive ACS. ACS was defined as either ST Elevation MI (STEMI), non-ST Elevation MI (NSTEMI) or unstable angina pectoris according to the American College of Cardiology Foundation/American Heart Association 2013 guidelines.[11] All the patients had electrocardiographic changes and/or elevation in cardiac enzymes (troponin T or I ≥3 times upper limit of normal), in addition to symptoms of chest pain. Patients were excluded if they were <18 years old. The study protocol was approved by the University of Massachusetts school of medicine institutional board review and informed consent was waived due to the retrospective nature of the study.

Data for all patients was abstracted from the Centricity cardiology data management system (General Electric Healthcare, United Kingdom) using automatic queries from the University of Massachusetts cardiac catheterization laboratory registry. For each patient, we reviewed the following: demographic data including age, gender, race/ethnicity and body mass index at the time of presentation; and traditional cardiac risk factors, including hypertension, diabetes, hyperlipidemia, smoking history ,and positive family history for coronary artery disease, all defined as following:

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hypertension was defined as having a history of hypertension and/or treatment with any hypertensive drug, diabetes was defined as having a history of reported diabetes and treatment with insulin, oral antidiabetics or diet controlled, hyperlipidemia was defined as carrying the diagnosis of dyslipidemia, treatment with antihyperlipidemic medication, or elevated lipid levels based on the adult treatment panel III guidelines.[12] Patient was considered to have an active smoking history if he reported smoking in the last 30 days. Family history was considered positive if there is a documented history of coronary event in first degree relatives (male <55 years old or females<65 years old). In addition, we collected the following: mode of presentation of ACS (STEMI versus NSTEMI versus unstable angina pectoris), angiographic data including number of diseased arteries (with significant obstructive disease defined as ≥50% of vessel diameter if left main or ≥70% if left anterior descending artery, left circumflex artery, ramus intermedius, or right coronary artery); type of revascularization (primary percutaneous revascularization vs coronary artery bypass surgery); presence of heart failure and/or cardiogenic shock on presentation, use of mechanical support devices (such as intra-aortic balloon pump, Impella device, extracorporeal membrane oxygenation, and Tandem heart), 30 day mortality, and length of hospitalization. Angiographic data including use of thrombectomy, coronary physiology assessment, lesion length, intracoronary imaging use was also obtained from cardiac catheterization reports. The primary outcome was 30-day mortality. The echocardiographic left ventricular functions before and after the ACS was also obtained. Information about major bleeding was also obtained which was based on definition by international society on thrombosis and haemostasis.[13]

Patient groups were stratified into 3 groups: ≤35 years, 36 to 54 years, and ≥55-year-old for comparison. Continuous data were presented as mean ± standard deviation if the data were not skewed and as median (25thto 75th percentile) if the data were skewed. Continuous variables were compared in 3 groups using analysis of covariance. Categorical variables were presented as frequencies (percentages) and compared in groups by the chi-square test. Multivariable adjusted logistic regression model was used to compute odds ratio and 95% confidence intervals for the association of ≤35-year-old and ≥55-year-old compared with 36 to 54 years with 30-day mortality. The model was adjusted for age groups, men, race, hypertension, hyperlipidemia, diabetes mellitus, smoker, peripheral vascular disease, congestive heart failure, cerebrovascular disease, family history of coronary artery disease, body mass index, type of ACS, coronary physiological assessment, thrombectomy use, intracoronary imaging, and mechanical support device. A p-value of <0.05 was considered significant. The SPSS Version 27.0 (SPSS Inc. Chicago) and STATA 14.2 software (StataCorp, College Station, Texas) software were used for statistical analyses.

Results

A total of 43,446 patients were referred to the cardiac catheterization at the University of Massachusetts Medical Center had a presumptive diagnosis of ACS before cardiac catheterization. Of those, 504 (1.2%) patients were ≤35-year-old, 12,391 (28.5%) were 36 to 54-year-old and 30,544 (70.3%) were ≥55-year-old. Of these 504 patients, only 291/504 (57.8%) had confirmed ACS in ≤35-year-old, 7,649/12,391 (61.7%) were 36 to 54-year-old and 18,605/30,544 (60.9%) were ≥55-year-old (Supplemental figure 1). NSTEMI was the commonest diagnosis 118/291 (40.5%) followed by unstable angina pectoris 111/291 (38.1%), while unstable angina pectoris was the most common diagnosis in the older groups (Table 1).

ACS patients that were ≤35-year-old were more likely to be men, Caucasian white, smoker, obese (higher body mass index), positive family history of coronary artery disease, and had higher troponin levels on presentation than older ACS patients. They were less likely to have comorbidities such as hypertensin, diabetes mellites, hyperlipidemia, previous revascularization or coronary artery disease, peripheral vascular disease, and congestive heart failure. They were also more likely to present with NSTEMI and STEMI than older ACS patients.

Thrombectomy was employed more often in ≤35-year-old while mechanical cardiac support was used more commonly in the older groups. Bare metal stents were more commonly used in the ≤35-year-old and they were more likely to present late and therefore were more likely to be managed conservatively. Understandably, the prevalence of 1 vessel disease was higher in ≤35-year-old than older ACS patients (Table 2).

In multivariable adjusted logistic regression model, the odds of dying within first 30 days were approximately 5 times more than 36 to 54-year-old ACS patients (Figure 1). Kaplan-Meier's survival curves for all 3 age groups are shown in Figure 2. The mortality rate was highest for STEMI presentation in the 36 to 54-year-old group (26 [54.2%]) compared with ≤35-year-old (2 [25%]) and ≥55-year-old (155 [38.9%]). While the mortality rate for NSTEMI presentation was highest in the ≤35-year-old (5 [62.5%]) compared with 36 to 54-year-old (15 [31.3%]) and ≥55-year-old (194 [48.7%]). Table 3 shows that ≤35-year-old were more likely to have cardiogenic shock, 30-day mortality, shorter length of stay, and less likely to suffer from major bleeding, lower ejection fraction before discharge, and coronary artery bypass grafting.

Discussion

To the best of our knowledge, this is the first largest analysis that has examined the cardiovascular risk factors, patterns of coronary disease involvement, mode of presentation and outcomes of ACS of very young adults (≤35-year-old) and compared them with the young (36 to 54-year-old) and older (≥55-year-old) ACS patients. We showed that very young adults that presented with ACS were not only more likely to have higher burden of certain modifiable cardiac risk factors such as smoking and obesity but also had worse outcomes compared with the older patients.

The first report of AMI in 21 very young patients (<30 years of age) was published in 1978.[14] Subsequently the epidemiological data came from Framingham cohort that suggested an incidence rate of 1.3 per 1,000 person

Table 1
Baseline characteristics

Characteristics	Total (n = 26,545)	Age groups ≤35 years (n = 291)	36-54 years (n = 7,649)	≥55 years (n = 18,605)	p Value
Mean age ± standard deviation (years)	63.2 ±15.2	31.0 ± 3.7	48.6 ± 4.8	69.6 ± 9.1	<0.001
Men	17,675 (66.6%)	223 (76.6%)	5,609 (73.3%)	11,843 (63.7%)	<0.001
Race/ethnicity					<0.001
Caucasian white	18,280 (68.9%)	220 (75.6%)	5,341 (69.8%)	12,719 (68.4%)	
African American	393 (1.5%)	11 (3.8%)	152 (2.0%)	230 (1.2%)	
Others	7,872 (29.7%)	60 (20.6%)	2,156 (28.2%)	5,656 (30.4%)	
Smoker	10,310 (38.8%)	154 (52.9%)	4,051 (53.0%)	6,105 (32.8%)	<0.001
Hypertension	20,638 (77.8%)	134 (46.0%)	5,011 (65.5%)	15,493 (83.3%)	<0.001
Diabetes mellitus	8,996 (33.9%)	52 (17.9%)	2,136 (27.9%)	6,808 (36.6%)	<0.001
Hyperlipidemia	20,672 (77.9%)	133 (45.7%)	5,347 (69.9%)	15,192 (81.7%)	<0.001
Family history of coronary artery disease	11,813 (44.5%)	142 (48.8%)	4,169 (54.5%)	7,498 (40.3%)	<0.001
Prior revascularization	2,748 (13.3%)	30 (11.7%)	817 (13.3%)	1,901 (13.4%)	<0.001
Peripheral vascular disease	6,166 (29.9%)	64 (24.9%)	1,737 (28.3%)	4,365 (30.7%)	<0.001
Congestive heart failure	2,681 (10.1%)	12 (4.1%)	390 (5.1%)	2270 (12.2%)	<0.001
ST elevation myocardial infarction	4,407 (16.6%)	62 (21.3%)	1,628 (21.3%)	2,717 (14.6%)	<0.001
Non-ST elevation myocardial infarction	9,285 (35%)	118 (40.5%)	2,312 (30.2%)	6,855 (36.8%)	<0.001
Unstable angina pectoris	12,853 (48.4%)	111 (38.1%)	3,709 (48.5%)	9,033 (48.6%)	<0.001
Body mass index ± standard deviation (kg/m^2)	29.9 ± 7.8	31.2 ± 7.1	31.2 ± 8.8	29.3 ± 7.3	<0.001
Initial troponin (25th − 75th percentile) (ng/dl)	0.42 (0.05 − 3.45)	0.31 (0.04 − 4.16)	0.35 (0.04 − 3.14)	0.48 (0.05 − 3.64)	0.005
Peak troponin (25th − 75th percentile) (ng/dl)	14.09 (2.16 − 56.14)	21.69 (6.07 − 70.00)	16.20 (2.67 − 59.57)	12.74 (2.0 − 53.85)	<0.001
Serum creatinine (mg/dl)	1.0 (0.8 − 1.2)	1.0 (0.8 − 1.2)	1.0 (0.8 − 1.2)	1.0 (0.8 − 1.2)	0.16
Left ventricular ejection fraction	57.9% ± 13.0%	57.0% ± 13.9%	57.9% ± 12.8%	57.9% ± 13.0%	0.63

years of unrecognized ACS in adults aged 30 to 34 years.[15] Later on, several studies attempted to evaluate AMI in young adults however due to small number of patients the studies limited the cut-off of 45 years.[3-7,16-18] Only a couple of studies, including a large study of 28,778 adults from Switzerland that enrolled patients from 1997 to 2008 reported an incidence of 0.7% of AMI in very young adults (≤35-year-old) however this study was limited by use of ICD codes to identify the diagnoses, lacked use of newer drug eluting stents, and did not have granularity to identify the angiographic characteristics of the patients. A 2011 US based study of 124 very young adults showed a prevalence of 0.95% ACS but failed to compare the patient characteristics, angiographic features and clinical outcomes with the older age groups. In our cohort, we also reported a prevalence of 1.1% ACS however we did look into the actual etiology of these ACS and found that only half of these patients had true ACS with obstructive coronary artery disease. In comparison with older patients the incidence of ACS with unidentifiable culprit was commoner. This could be either due to use of troponin assay rather than myocardial creatinine kinase type B that has a much higher sensitivity to minimal myocardial damage and could have increased the prevalence of ACS in this group. In addition, it is possible that younger adults might have higher prevalence of atherosclerotic precursor lesions that might predispose them to develop thrombus as evidenced by intravascular ultrasound study in women with nonobstructive

Table 2
Angiographic findings and procedural characteristics

Variables	Total	Age groups ≤35 years	36-54 years	≥55 years	p Value
Thrombectomy use	1,476 (5.6%)	18 (6.2%)	474 (6.2%)	984 (5.3%)	0.01
Intracoronary imaging use	792 (3.0%)	12 (4.1%)	248 (3.2%)	532 (2.9%)	0.13
Mechanical support use	1,168 (4.4%)	11 (3.8%)	271 (3.5%)	886 (4.8%)	<0.001
Lesion length (mm) mean ± standard deviation	16.5 ± 9.0	16.8 ± 8.1	16.6 ± 9.0	16.5 ± 9.0	0.89
Bare metal stents	1,746 (6.6%)	22 (7.6%)	530 (6.9%)	1,194 (6.4%)	<0.001
Drug eluting stent use	16,106 (60.7%)	143 (49.1%)	4,791 (62.6%)	11,172 (60.0%)	<0.001
Balloon angioplasty only	490 (1.8%)	4 (1.4%)	150 (2.0%)	336 (1.8%)	<0.001
Thrombectomy only	391 (1.5%)	2 (0.7%)	68 (0.9%)	321 (1.7%)	<0.001
Late presentation/chronic total occlusion	5,739 (21.6%)	108 (37.1%)	1,670 (21.8%)	3,961 (21.3%)	<0.001
Death in catheterization laboratory without percutaneous coronary intervention	44 (0.2%)	1 (0.3%)	3 (0.0%)	40 (0.2%)	0.005
Non obstructive disease with myocardial infarction	6,270 (23.6%)	158 (54.3%)	2,376 (31.1%)	3,736 (20.1%)	<0.001
1 vessel obstructive disease	9,053 (34.1%)	106 (36.4%)	3,010 (39.4%)	5,937 (31.9%)	<0.001
2 vessel obstructive disease	5,210 (19.6%)	17 (5.8%)	1,330 (17.4%)	3,863 (20.8%)	<0.001
3 vessel obstructive disease	6,012 (22.6%)	10 (3.4%)	933 (12.2%)	5,069 (27.2%)	<0.001

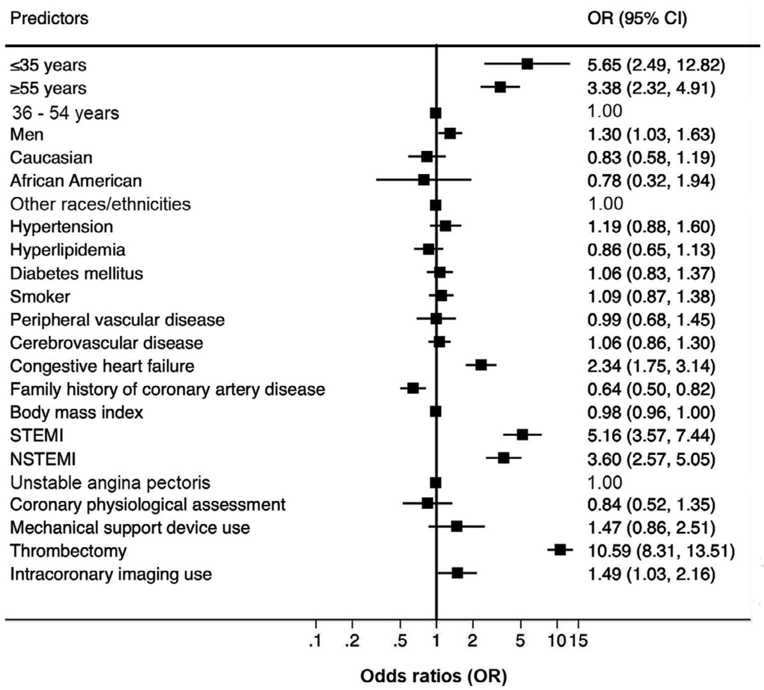

Figure 1. Predictors of 30-day mortality in multivariable logistic regression model.

coronary artery disease.[19] Another explanation could be that some of these patients had a thrombo-embolic events or de novo thrombus causing the ACS presentation that has resolved at the time of the catheterization resulting in "clean coronaries," and therefore all these presentations should be treated as coronary-equivalent, until proven otherwise. It is interesting to note that this very young adult group has a phenotype of a male obese and smoker. The prevalence of these specific cardiac risk factors was significantly higher than older adults, who were more likely to be diabetic, hypertensive and hyperlipidemic. These findings were similar to previously reported studies.[7,10−12,20-23] Finally, about 4% of this very young population self-reported use of either a prescription drug overdose or illicit

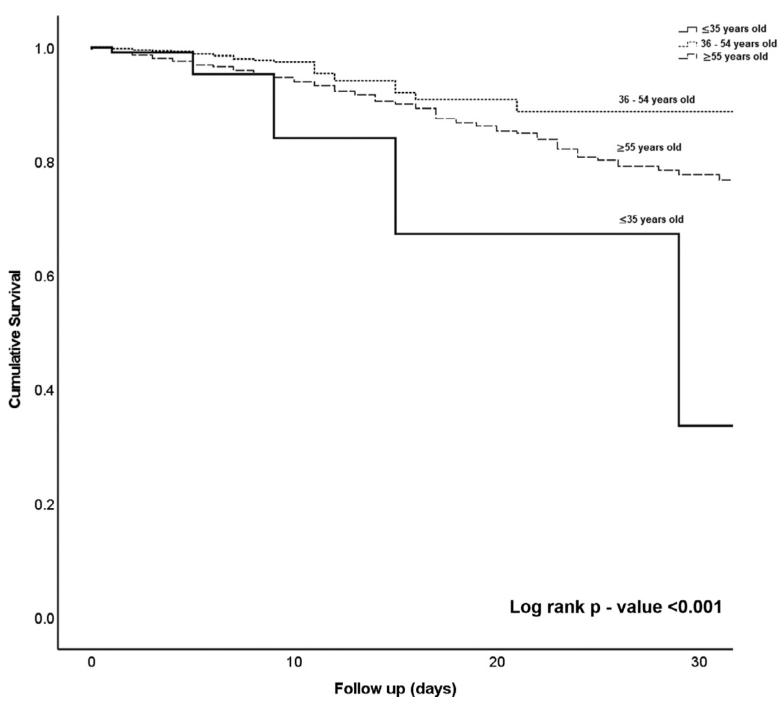

Figure 2. Kaplan-Meier's survival curve for 30-day mortality by age groups.

Table 3
Complications and outcomes

	Total	≤35 years	Age groups 36-54 years	≥55 years	p Value
Post catheterization left ventricular ejection fraction	51.4% ±12.8%	52.7%±12.0%	52.8%±11.9%	50.8%±13.2%	<0.001
Cardiogenic shock	336 (1.9%)	5 (3.0%)	73 (1.4%)	258 (2.1%)	<0.001
Coronary artery bypass grafting	2,405 (9.1%)	6 (2.1%)	409 (5.4%)	1,990 (10.7%)	<0.001
Major bleeding	1,168 (4.4%)	9 (3.1%)	275 (3.6%)	893 (4.8%)	<0.001
Length of stay (days)	1 (1 − 3)	1 (0 − 2)	1 (0 − 2)	1 (1 − 3)	<0.001
30-day mortality	454 (1.7%)	8 (2.8%)	48 (0.6%)	398 (2.1%)	<0.001

drug abuse, a well-known risk factor of ACS through atherosclerosis acceleration and acute coronary spasm.[24]

There are several implications of this study. One of the important finding of the study is that almost half of very young patient presented with STEMI, as similar finding as observed in Dresden myocardial infarction registry.[25] Secondly, due to low SYNTAX score of this group these patients are likely to undergo percutaneous coronary intervention. This demographic has much changed from the prestent era, coronary artery surgery study registry comprising 8,839 patients, when younger men ≤35-year-old and women ≤45 years old presenting with ACS underwent coronary artery bypass grafting and had significantly improved 7-years survival rate when compared with older men and women (84% vs 75% and 90% vs 77% respectively, $p < 0.01$).[21] These patients that underwent percutaneous coronary intervention at a very young age will eventually develop stent restenosis that is now emerging as a complex and difficult interventional cardiology problem. It is important to use all possible measures to prevent early stent restenosis especially the use of intravascular ultrasound or optical coherence tomography should be considered more frequently as these modalities have shown to prevent earlier restenosis and ACS.[26-29] We observed a higher mortality rate in very young patients which is contrary to previous studies that showed better survival in young patients.[25] A national inpatient sample study from 2010 to 2014 showed that there were no gender differences in mortality, however there were lower odds of getting revascularized in young women compared with men.[30]

There are several limitations to our study. This was a single center, retrospective study, and its findings may not reflect the situations in other institutions or countries. Complete data was not available for all the patients. The relatively low number of patients may create a potential for sampling bias, although our results were grossly in par with similar previous studies. The discharge diagnosis of myocarditis or other given to young patients ≤35-year-old presenting with ACS and no coronary disease on angiography was left up to the admitting cardiologist discretion and not always confirmed with additional diagnostic or imaging studies. These data were not available for comparison with older population. Specific testing for hypercoagulable states in the young population was not performed, and it remains unclear whether this may be contributing to the high prevalence of acute thrombus formation.

Compared with the older ACS patients, very young ACS patients were more likely to be smokers with a higher body mass index. The initial presentation was more likely to be STEMI. The use of bare metal stents was higher in this group as compared with older patients. There is further need to study the various reasons that could have led to observed higher 30-day mortality in this group.

Authors contribution

Waqas T. Qureshi − writing original draft, formal statistical analysis, critical revision, revision of the manuscript. Nikolaos Kakouros − critical revision of the manuscript, initial statistical analyses, preparation of manuscript, provision of dataset. Joe Fahed − conceptualization, preparation of original manuscript, initial statistical analyses. Jeffrey Rade − conceptualization and idea of the original manuscript, design of methodology, oversight and supervision of the manuscript, provision of dataset.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.054.

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