

Young coronary artery disease in patients undergoing percutaneous coronary intervention

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BACKGROUND AND OBJECTIVES: Understanding the nature and pattern of young coronary artery disease (CAD) is important due to the tremendous impact on these patients' socio-economic and physical aspect. Data on young CAD in the southeast Asian region is rather patchy and limited. Hence we utilized our National Cardiovascular Disease Database (NCVD)—Percutaneous Coronary Intervention (PCI) Registry to analyze young patients who underwent PCI in the year 2007 to 2009.

DESIGN AND SETTINGS: This is a retrospective study of all patients who had undergone coronary angioplasty from 2007 to 2009 in 11 hospitals across Malaysia.

METHODS: Data were obtained from the NCVD—PCI Registry, 2007 to 2009. Patients were categorized into 2 groups—young and old, where young was defined as less than 45 years for men and less than 55 years for women and old was defined as more than or equals to 45 years for men and more than or equals to 55 years for women. Patients' baseline characteristics, risk factor profile, extent of coronary disease and outcome on discharge, and 30-day and 1-year follow-up were compared between the 2 groups.

RESULTS: We analyzed 10268 patients, and the prevalence of young CAD was 16% (1595 patients). There was a significantly low prevalence of Chinese patients compared to other major ethnic groups. Active smoking (30.2% vs 17.7%) and obesity (20.9% vs 17.3%) were the 2 risk factors more associated with young CAD. There is a preponderance toward single vessel disease in the young CAD group, and they had a favorable clinical outcome in terms of all-cause mortality at discharge (RR 0.49 [CI 0.26-0.94]) and 1-year follow-up (RR 0.47 [CI 0.19-1.15]).

CONCLUSION: We observed distinctive features of young CAD that would serve as a framework in the primary and secondary prevention of the early onset CAD.

This study utilizes the National Cardiovascular Disease Database (NCVD)—Percutaneous Coronary Intervention (PCI) Registry (Malaysia) to compare the young with the old group of patients who underwent PCI in the year 2007 to 2009. We analyzed 10268 patients and the prevalence of young coronary artery disease (CAD) was 16% (1595 patients). There was a significantly low prevalence of Chinese patients compared to other major ethnic groups. Active smoking (30.2% vs 17.7%) and obesity (20.9% vs 17.3%) were the 2 risk factors more associated with the young CAD group. There is a preponderance toward single vessel disease in the young CAD

group, and they had a favorable clinical outcome in terms of all-cause mortality at discharge (RR 0.49 [CI 0.26-0.94]) and 1-year follow-up (RR 0.47 [CI 0.19-1.15]). We observed distinctive features of young CAD that would serve as a framework in the primary and secondary prevention of the early onset CAD.

CAD predominantly manifests clinically in older patients and was an uncommon clinical entity in young patients until recent years. In general, CAD is thought to be part of our degenerative aging process, accelerated by known conventional atherosclerotic risk factors such as smoking, diabetes, and hypertension. CAD in young adults is now, however, becoming increasingly common,

and it is seen as a worrying trend not only in developing countries but also globally. The incidence of young patients diagnosed to have CAD was reported to vary from 3% to 10%.¹⁻³

Atherosclerotic CAD is notorious for its consequence on clinical morbidity and mortality. Thus, the emergence of an accelerated atherosclerotic process in young adults is of particular concern as it carries a greater impact on their lives. It has many social implications not only to the patients but also to their families because many of them are still in their prime health and physically active. Questions then arise, if this acceleration in atherosclerotic process is associated with a different disease pattern or risk factor profile and also whether it carries an adverse outcome in view of a possible more malignant disease process.

Malaysia has a population of multiple ethnic origins, but our knowledge of CAD in young adults, especially, in the southeast Asian region is scarce due to the limitation of local data. Hence this study was performed to analyze the acute clinical presentation, risk factor profile, coronary angiographic findings, and clinical outcome in young adults who underwent PCI and to compare with that in older patients.

METHODS

Data and follow-up

This cohort study utilizes anonymized patient data obtained from the NCVD—PCI Registry. Patients were those aged more than 18 years who underwent PCI from January 1, 2007, to December 31, 2009. Data was collected by 11 hospitals across the country using a case report form to record patient demographics, status before event, clinical examination and baseline investigation, previous interventions, cardiac status at PCI procedure, catheterization laboratory visit, PCI procedure details, and procedural complication and outcome. Patients were followed up at 30 days and from 6 months to 1 year. For this study, only patients alive at discharge were followed up retrospectively at 30 days and those alive at 30 days were followed up at 1 year. The follow-up period continued till December 31, 2010.

Definition. Patients were categorized into 2 groups—young and old, where young was defined as less than 45 years for men and less than 55 years for women and old was defined as more than or equals to 45 years for men and more than or equals to 55 years for women. The determination of patients' ethnicity was based on self-reporting and their national identity card. The minority ethnic groups (Orang asli, Kadazan Dusun, Melanau, Murut, Bajau, Bidayuh, Iban), those

of Punjabi descent, and foreigners were re-categorized as "Others." Any form of tobacco use (cigarettes, cigars, pipes, tobacco chewing) in the past was identified by smoking status.⁴ Single vessel disease is defined as lesions of >50% in only 1 coronary system, whereas multiple vessel disease is defined as lesions of >50% in 2 or more coronary system (left main system and graft are considered 2 systems). The variables of cardiac status at PCI and procedural complications were defined as per the NCVD data definition document.^{4,5} The outcome of interest was all-cause mortality at discharge, from discharge to 30 days, and from 30 days to 1 year.

Statistical analysis. Data was checked for repeat admissions, and only the initial admission was maintained, resulting to a total of 10 268 patients from the initial total of 11 498. Continuous variables were described in either of the following two ways: (1) if normally distributed, the variables were described as mean (SD) and differences between young and old groups were analyzed using the t test and (2) if skewed, the variables were described as median (IQR) and differences were analyzed using the Wilcoxon rank-sum test. Normality was determined by Stata skewness–kurtosis. Categorical variables were described as numbers (percentages), and differences were analyzed using the chi-square test or the Fisher exact test if totals in the subcategories were less than 5. To avoid biases in the estimates and loss of power, missing data for explanatory variables were assumed to be missing at random and imputed using multiple imputations by chained equations. The body mass index was not imputed directly but calculated from the imputed height and weight variables. A generalized linear model with a log link, binomial distribution, and a robust variance estimator was used to estimate the risk ratios. The risk ratios represent the relative risk for mortality of the old patients compared to that of the young patients. Variables that were statistically significantly different (a 2-sided *P* value of less than .05) between the old and young patients, that were of clinical importance, and that had sufficient outcomes in the respective subcategories were adjusted for in the model. Multicollinearity was assessed by the variance inflation factor. Statistical significance for the risk ratios was considered if the respective 95% confidence intervals excluded the value of 1. All statistical analyses were performed using Stata 11.0 (StataCorp, College Station, Texas, USA).

RESULTS

Patient characteristics

The characteristics and clinical presentation on admis-

Table 1. Patients' baseline characteristics and clinical presentation on admission for young patients compared to older patients.

Demographics	Young (n=1595)	Old (n=8673)	P value
Age (yr) Mean (SD)	42.8 (5.9)	59.6 (8.5)	
Gender, n (%)			
Male	1102 (69.1)	7258 (83.7)	<.001
Female	493 (30.9)	1415 (16.3)	
Ethnicity, n (%)			
Malay	826 (51.8)	4042 (46.6)	<.001
Chinese	257 (16.1)	2219 (25.6)	
Indian	402 (25.2)	1916 (22.1)	
Others	109 (6.8)	493 (5.7)	
Unknown	1 (0.1)	3 (0.0)	
BMI, kg/m², n (%)			
Overweight (≥25 kg/m ² to <30 kg/m ²)	532 (33.4)	2896 (42.6)	<.001
Obese (≥30 kg/m ²)	334 (20.9)	1175 (17.3)	
Risk factors, n (%)			
Smoking			<.001
Former (quit >30 d)	360 (22.6)	2478 (28.6)	
Current (any tobacco use within last 30 d)	481 (30.2)	1539 (17.7)	
Diabetes	669 (41.9)	4018 (46.3)	.001
Hypertension	966 (60.6)	6523 (75.2)	<.001
Dyslipidemia	1157 (72.5)	6348 (73.2)	.55
Premorbid conditions, n (%)			
Cerebrovascular disease	15 (0.9)	145 (1.7)	.03
Peripheral vascular disease	9 (0.6)	93 (1.1)	.06
Chronic renal failure	72 (4.5)	593 (6.8)	<.001
New onset angina (<2 wk)	387 (24.3)	2198 (25.4)	.32
Congestive heart failure	49 (3.1)	374 (4.3)	.02
Myocardial infarction history	732 (45.9)	3473 (40.1)	<.001
Previous intervention, n (%)			
Previous PCI	181 (11.3)	1352 (15.6)	<.001
Previous CABG	9 (0.6)	398 (4.6)	<.001

PCI: Percutaneous coronary intervention, CABG: coronary artery bypass graft, BMI: body mass index.

P values were calculated for comparisons between young and old, comparing all subcategories except the unknown subcategory for all variables; All P values were calculated using the chi-square test unless stated; pPercentages for each variable were calculated from the respective totals that included the unknown category apart from the YES and NO categories.

sion for young compared to older patients are presented in **Table 1**. The patients (n=10 268) were predominantly older (84.5%), male (81.5%), and Malay (47.5%). The higher percentage of males in the old category (83.7%) as opposed to the young (69.1%) was due to the different definition for the cutoffs of young and old for males and females in this study. There was a lower prevalence of Chinese (16.1%) in the young group than in the old (25.6%) group. This difference was statistically significant if compared to the young and old proportion of Malays (P<.01) and Indians (P<.01). However, the proportions were rather similar for the young and old for Malays than for Indians (P=.69). The percentage of Indians in both the young (25.2%) and old groups (22.1%) was more than 3 times the percentage of Indians in the country (6.7%).⁶ However, the proportion of Malays (47.5%) and Chinese (24.1%) patients were not very different from their respective proportion (50.1% and 22.6%) in the population.⁶

Risk factor profile

In terms of smoking, the young group had 12.5% more active smokers than the old group; however the prevalence of former smokers was higher by 6% in the old group. There were 9.2% more overweight patients in the older category of patients compared to the younger category, but there were 3.6% more obese patients among the young compared to the older patients. For clinical history, no statistically significant difference was observed between young and old in terms of new onset angina (less than 2 weeks) (P=.32) and dyslipidemia (P=.55). Myocardial infarction (MI) history was higher among the young (45.9%) compared to the older patients (40.1%). All other clinical history risk factors were higher among the older patients (**Table 1**).

The cardiac status at PCI for young compared to older patients is presented in **Table 2**. The disease severity was more of single vessel for the young (53.9%) but multiple vessels for the old (53.4%).

Medication on discharge

Medications prior to discharge (In addition to aspirin) were presented in **Table 3**. There were slightly more young patients who were on clopidogrel (as part of dual anti-platelet therapy) instead of ticlopidine. Statin therapy was similar in both groups. Beta-blockers and angiotensin-converting enzyme inhibitors were prescribed more in the young group, whereas the old group had more angiotension receptor blockers.

Clinical and mortality outcomes

The procedural complications for young compared to

older patients are shown in **Table 4**. Majority of the patients (>99%), young and old, underwent PCI without any procedural complications. The risks of mortality at discharge, 30 days, and 1 year are presented in **Table 5**. After adjusting for all possible confounding factors, the risk of mortality for young compared to the older patients was found to be significantly lower at discharge (RR=0.49; 95% CI 0.26 to 0.94). The risk of mortality for the young and old patients was rather similar at 30 days (RR=1.14; 95 % CI 0.40 to 3.23). At 1-year follow-up, young patients showed a trend toward a better outcome (RR=0.47; 95% CI 0.19 to 1.15) compared to the older patients, although this was not statistically significant.

DISCUSSION

Atherosclerotic plaque accumulation is a slow process that takes many years before it becomes clinically significant. It was reported that this process may begin at a very early age, as the evidence of atherosclerotic lesions is present in 1 in 6 clinically healthy, asymptomatic teenagers.⁷ Unfortunately for some people, the clinical manifestation of CAD happens early in their lives. The prevalence of young CAD among patients who underwent PCI in our study population was 16%. Comparison with other registries and studies is rather difficult, as there is variation in the cutoff age and definition of “young” patients.⁸ Data from Western registries report a mean age of patients undergoing PCI as around 63 to 65 years old.^{9,10} These mean age figures are still “older” than the mean age of our old CAD group, indicating that our CAD patient population is much younger than the Western population. There has also been a report from an Asian registry on inter-racial variation with Malay and Indian ethics being younger than Chinese.¹¹

We found that male patients were less dominant in the young CAD group compared to the old CAD group. This finding is interestingly contrary to the classical perception of strong male preponderance in young CAD in previous studies.¹²⁻¹⁴ This difference is again due to the different definitions in the cutoff age of young and old for females and males in this study. Otherwise, if the same cutoffs were used for both gender, males would have been more dominant in the young group than in the old group with the following statistics: 92.6% vs 80.0% (if a cut-off of 45 was used) or 88.7% vs 76.1% (if the cutoff of 55 was used).

Our patient population consists of mixed ethnic groups comprising mainly Malay, Chinese, and Indians. From the ethnicity point of view, it has been suggested that the difference in the prevalence rate among the eth-

Table 2. Cardiac status at PCI for young compared to older patients.

Cardiac status	Young (n=1595)	Old (n=8673)	P value
PCI status, n (%)			
Elective	1379 (86.5)	7836 (90.4)	<.001
NSTEMI/UA	92 (5.8)	390 (4.5)	
AMI	120 (7.5)	422 (4.9)	
Disease severity, n (%)			
Single vessel disease	860 (53.9)	3961 (45.7)	<.001
Multiple vessel disease	726 (45.5)	4632 (53.4)	<.001
Graft	1 (0.1)	115 (1.3)	<.001 ^a
Left main stem	12 (0.8)	59 (0.7)	.75

NSTEMI: Non-ST segment myocardial infarction, UA: unstable angina, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention.

P values were calculated for comparisons between young and old comparisons, comparing all subcategories except the unknown subcategory for all variables; All P values were calculated using the chi-square test unless stated.

^aFisher's exact test; Percentages for each variable were calculated from the respective totals, which included the unknown category apart from the YES and NO categories.

Table 3. Medications on discharge in addition to aspirin.

Medication on discharge n (%)	Young (n=1595)	Old (n=8673)	P value
Clopidogrel	1513 (94.9)	8062 (93.0)	.01
Ticlopidine	60 (3.8)	463 (5.3)	.001
Statin	1446 (90.7)	7838 (90.4)	.93
Beta-blocker	1172 (73.5)	6019 (69.4)	.001
ACE-inhibitor	937 (58.8)	4563 (52.6)	<.001
ARB	157 (9.8)	1223 (14.1)	<.001

All P values were calculated using the chi-square. ARB: Angiotensin receptor blocker, ACE: angiotensin-converting enzyme.

nic groups is most marked in young CAD patients.¹⁵ From our analysis, we noted that while the Malays and Indians had a similar composition in both young and old groups, there was a significantly low prevalence of ethnic Chinese in the young CAD group, a difference that was less marked in the old group. This is in consistent with a demographic analysis of young CAD in a neighboring country Singapore, with more or less similar ethnic composition.^{16,17} Although this might be explained by the difference in the risk factor profile for each ethnic group, it is also possible that the higher susceptibility goes beyond the conventional cardiovascular risk factors. The differences between ethnic groups in terms of genetic compositions, dietary intake, psycho-

Table 4. Procedural complications for young patients compared to older patients.

Complications	Young (n=1595)	Old (n=8673)	P value
Local complications, n (%)			
Access site occlusion	2 (0.1)	6 (0.1)	.36 ^b
Loss of distal pulse	0 (0.0)	2 (0.0)	.18 ^b
Dissection	3 (0.2)	24 (0.3)	.79 ^b
Pseudoaneurysm	1 (0.1)	7 (0.1)	1.00 ^b
General complications, n (%)			
Periprocedural MI	7 (0.4)	35 (0.4)	.83
Emergency reintervention/PCI	3 (0.2)	19 (0.2)	1.00 ^b
Bail-out CABG, n (%)	0 (0.0)	6 (0.1)	.60 ^b
Cardiogenic shock, n (%)	8 (0.5)	50 (0.6)	.72
Arrhythmia (VT/VF/Brady), n (%)	9 (0.6)	44 (0.5)	.76
TIA/Stroke, n (%)	0 (0.0)	6 (0.1)	.60 ^b
Tamponade, n (%)	0 (0.0)	4 (0.1)	1.00 ^b
Contrast reaction, n (%)	1 (0.1)	7 (0.1)	1.00 ^b
New renal impairment, n (%)	0 (0.0)	15 (0.2)	.15 ^b

MI: Myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

P values were calculated for comparisons between young and old, comparing all subcategories except the unknown subcategory for all variables; All P values were calculated using the chi-square test unless stated.

^aSkewed, ^bFisher exact test; Percentages for each variable were calculated from the respective totals that included the unknown category apart from the YES and NO categories.

social factors, or socioeconomic status have been implicated to the early predisposition to atherosclerotic formation.^{15,18}

The analysis of conventional risk factors showed that although the rate of hypertension and diabetes were lower in the young CAD, the typically seen pattern in elderly population seems to be emerging in the younger aged group. In fact, the rate of dyslipidemia matched that in the old group. This suggests that the age of onset at which patients typically develop multiple cardiac risk factors has probably shifted to a much earlier age in these recent years. This is also reflected in the physical status of the young CAD patients. Over more than half of the patients in both groups were overweight or obese, but the proportion of obese patients in the young group was more than in the old group. Active smoking was the only risk factor that had a higher prevalence in the young CAD group than in the old CAD group. Cigarette smoking has long been recognized as one of the conventional risk factors in the development of atherosclerotic CAD. It has been persistently reported to be the dominant and most as-

sociated risk factor in young CAD patients.^{2,19,20}

However, according to the National Health and Morbidity Survey of Malaysia's general population in 2006,²¹ the prevalence of overweight and obesity was 33.6%, diabetes 11.6%, smoking 46.5% and hypertension 42.6%. Comparing these figures with our result, it seems that diabetes, hypertension, and obesity were more prevalent in our study patients. Hence, these classical risk factors are still very dominant in both young and old groups. Smoking, although more associated to our young patients in comparison to the old group, was still low in prevalence compared to the general national population.

Our young CAD patients had a comparatively less diffuse disease in terms of the number of diseased coronary vessels. Consistent with other studies,^{1,9,22} there was a tendency toward single coronary vessel disease in the young CAD group in our study, and the clinical presentation was more typically of acute coronary syndrome. As the underlying pathophysiology of acute coronary syndrome is plaque rupture, it is likely that this mechanism plays a more pivotal role in young patients. Thus coronary artery obstruction in young CAD may be more of thrombogenic in nature rather than atherosclerotic per se, and smoking habit—being the most associated risk factor in our young CAD patients—has been linked with atherosclerotic plaque rupture.²³ Therefore the risk reduction strategy in the young population would probably require a slightly different approach than the general population where more emphasis and priority should be given on smoking cessation and obesity-related measures while preventing other risk factors.

The clinical manifestation of CAD at an early age raises concern of a possible underlying malignant atherosclerotic process and consequently an adverse prognosis. With regard to the baseline characteristics, we found that the young CAD group had a lower rate of hypertension, diabetes, and dyslipidemia but a higher prevalence of active smoking. They also had a lower rate of polyvascular disease, i.e. cerebrovascular disease and peripheral vascular disease. All these, along with age as independent predictors of cardiovascular mortality point toward a favorable outcome in the young CAD patients than in the old CAD patients. In fact, although very controversial, a smoking history has been associated with a better outcome in MI, a phenomenon called "smoker paradox."^{24,25} Our analysis on all-cause mortality showed a trend toward a better outcome in the young CAD group at hospital discharge, and 1 year post PCI (after adjusting to relevant confounding factors). However, the only statistically significant favorable outcome for young CAD was in the in-hospital mortal-

Table 5. Risk of mortality for young patients compared to older patients at discharge - 30 days and 1 year.

	Sample size, n (%)		Mortality, n (%)		RR (95% CI)
	Young	Old	Young	Old	
Discharge	1589 (15.5)	8638 (84.5)	11 (0.7)	101 (1.2)	0.49 (0.26, 0.94)
30 d	1067 (15.8)	5682 (84.2)	5 (0.5)	25 (0.4)	1.14 (0.40, 3.23)
1 y	769 (15.9)	4072 (84.1)	5 (0.7)	55 (1.4)	0.47 (0.19, 1.15) ^a

^aAdjusted for gender, race, continuous BMI, smoking status, HPT, DM, myocardial infarction history, history of heart failure, chronic renal failure, extent of coronary disease (single vessel and multiple vessels).

BMI: Body mass index, HPT: hypertension, DM: diabetes mellitus.

ity. The follow-up at 1 year showed a convincing trend toward better outcome in the young group but not at 30 days. The follow-up result of young CAD patients in this study was something of a rather great concern to us. Although they had a clear favorable baseline characteristic, this did not translate into a huge difference in terms of clinical outcome especially in the immediate term post discharge. The possible explanation is that there are significantly more young patients with the previous MI or acute coronary syndrome than with the old patients. Also as prognosis is hugely influenced by the primary diagnosis, we thought that this factor could alter the clinical outcome. A longer and better follow-up rate with subclassification of patients according to the primary diagnoses would certainly improve the result accuracy and clinical implication.

Limitation of the study

This is a retrospective study. Data were collected directly from a registry. Comparison with other studies is rather difficult as there is variation in the definition of "young" CAD. A long-term follow-up might not be accurate as there was significant number of patients who

were lost to follow up.

In conclusion, Young CAD patients made up a significant portion (16%) of those patients undergoing PCI in Malaysia. While the young CAD showed a lower male predominance we observed inter-racial variation in our young patients. Active smoking and obesity were more prevalent in the young CAD patients, but there was an emergence of the other conventional risk factor pattern similar to the old group. We observed a significantly lower all-cause mortality at discharge in the young CAD patient and a trend toward better outcome at 1 year follow-up but no convincing difference at 30 days.

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