ORIGINAL ARTICLE

PREVALENCE AND RISK FACTORS OF PREMATURE CORONARY ARTERY DISEASE: A COMPARATIVE CROSS-SECTIONAL STUDY BETWEEN TWO TIME FRAMES IN MALAYSIA

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ABSTRACT

Limited studies on prevalence and risk factors of Premature Coronary Artery Disease (PCAD) were done in Malaysia, primarily on lipid profile. This cross sectional study aims to identify any changing patterns in prevalence and risk factors of Premature CAD between 2000 and 2012. From 2000 to 2012 we included 21862 patients who underwent the first Percutaneous Coronary Intervention (PCI). Analysis of risk factors was done to 1660 and 2098 patients from year 2007 and 2012 respectively. Age of less than 45 years was taken as PCAD. Data was collected from PCI database of National Heart Institute (NHI), NHI TrakCare System, and patients' medical records. PCAD significantly decreased from 18.8% (2000) to 11.6% (2012). Malay ethnicity showed increasing trend over the years from 55.1% to 66.9%. Multiple logistic regression analysis in 2007 showed that smoking had the higher risk (AOR=2.52), followed by male gender (AOR=2.06), family history of PCAD (AOR=1.96), Indian ethnicity, (AOR=1.65), triglycerides level (AOR=1.20) and BMI (AOR=1.06). In 2012, family history of PCAD had the highest risk (AOR=2.00) followed by smoking (AOR=1.91) and BMI (AOR=1.11). There are changes in risk factors patterns of premature CAD between 2007 and 2012. Most of them are preventable at earlier stage.

Keywords: *Premature Coronary Artery Disease, risk factors, prevalence.*

INTRODUCTION

According to Malaysian NCVD-PCI Registry, 2007-2009, coronary artery disease (CAD) is defined as the presence of any of the following co-morbidities; history of MI, documented CAD with more than 50% of stenosis, chronic angina (more than 2 weeks), or new onset angina (less than 2 weeks).[1] In other words, Coronary Heart Disease (CHD) would be the manifestation of CAD and according to American Heart Association (AHA), the terms 'coronary artery disease' (CAD) and 'coronary heart disease' (CHD) are used interchangeably.[2]

WHO had reported that up to 2002 a decreasing trend of CHD was observed in many developed countries. However, the reverse is true for developing countries[3]. This might be due to demographic and lifestyle changes which has resulted in the epidemiological transition from infectious diseases to non-communicable diseases, such as CAD. In the developing world, CAD mortality and risk factors continue to rise in developing worlds. It is also predicted that CAD will be the leading cause of death in developing countries by the year 2020.[4] Focusing on the prevalence of CVD in Malaysia, Clinical Practice Guidelines (CPG) on Management of Percutaneous Coronary Intervention (PCI) in 2009 has quoted that CVD had accounted for about a fifth of the total burden of disease in Malaysia based on admissions in government hospitals in 2000.[5] Fifty percent (50%) of this quoted figure was accounted by Coronary Artery Disease (CAD). CPG has also quoted that in 2006, CVD was the commonest cause of deaths in government hospitals, which accounted for 24.2% of total deaths.[5] In Malaysia, there is concern whether the age of presentation of CAD patients are getting younger.

Even though many studies were done in Malaysia on identifying the risk factors of CAD, none of them has provided a complete prevalence of biochemical profile of CAD patients, especially in premature CAD. Besides, studies to determine changing patterns of incidence over time and identification of specific risk factors are fairly limited. This study aimed to determine its prevalence in two time frames, specifically between year 2007 and 2012, the risk factors together with biochemical profiling to CAD and to identify any changes in the patterns of risk factors of CAD.

METHODS

This was a retrospective cross-sectional study conducted in National Heart Institute (NHI), Malaysia. The data was collected using NHI TrakCare System, NHI PCI Database and patient's medical records. Malaysian citizen aged 18 and above diagnosed with CAD and underwent first PCI in NHI between year 2000 and 2012 criteria were included in this study.

Twenty-one thousand eight hundred and sixty-two (21,862) subjects were selected from year 2000 to 2012 based on the criteria above to look into their age, gender and races. Throughout this time period, 1,660 patients from year 2007 and 2,098 patients from year 2012 were compared based on their demographics, anthropometrics, and status of co-morbidities before event and biochemical profile. Patients with history of previous PCI or coronary artery bypass graft in NHI between year 2000 and 2012 were excluded. All the included patients were classified into premature and non-premature CAD group. Premature CAD was taken as those individuals that less than or equal to 45 years old. The prevalence of gender and races from year 2000 to 2012 in these two groups was done. Then, these two groups were taken into comparison between year 2007 and 2012 by looking at their demographics, anthropometrics, status of co morbidities before event (diagnosed hypertension, diabetes mellitus and dyslipidemia) and biochemical profile.

Continuous variables were reported as mean± SD. The chi square test was used for categorical variables and t-test for continuous variables. Significant variables found in bivariate analysis were then analyzed using multiple logistic regression analysis. A p value of <0.05 was taken as significant. The data were analyzed using SPSS version 21.0.

RESULTS

A total of 21,862 (2,916 are premature and 18,946 are non-premature) of CAD patients from year 2000 to 2012 was observed for their pattern in prevalence, male, and gender over the 12 years. Overall, the prevalence of premature CAD (PCAD) in proportion to non-premature CAD (non-PCAD) had decreased, from 18.8% to 11.6% (FIGURE 1). However the actual number of PCAD patients in each year was fairly constant contrary to the actual number of non-premature CAD patients which showed an increasing trend throughout the 13 years (FIGURE 2).

Male were found to be predominant over female, both in PCAD and non-PCAD. The prevalence of male PCAD had decreased from 21.4% to 13.5%, while 8.2% to 3.4% in female PCAD (FIGURE 3 and 4). The prevalence of PCAD was predominantly Malay, followed by Indian, Chinese, and other races. However, a decreasing trend was observed in Malay population, as their prevalence of PCAD had decreased by 9.8% from year 2000 to year 2012 (FIGURE 4).

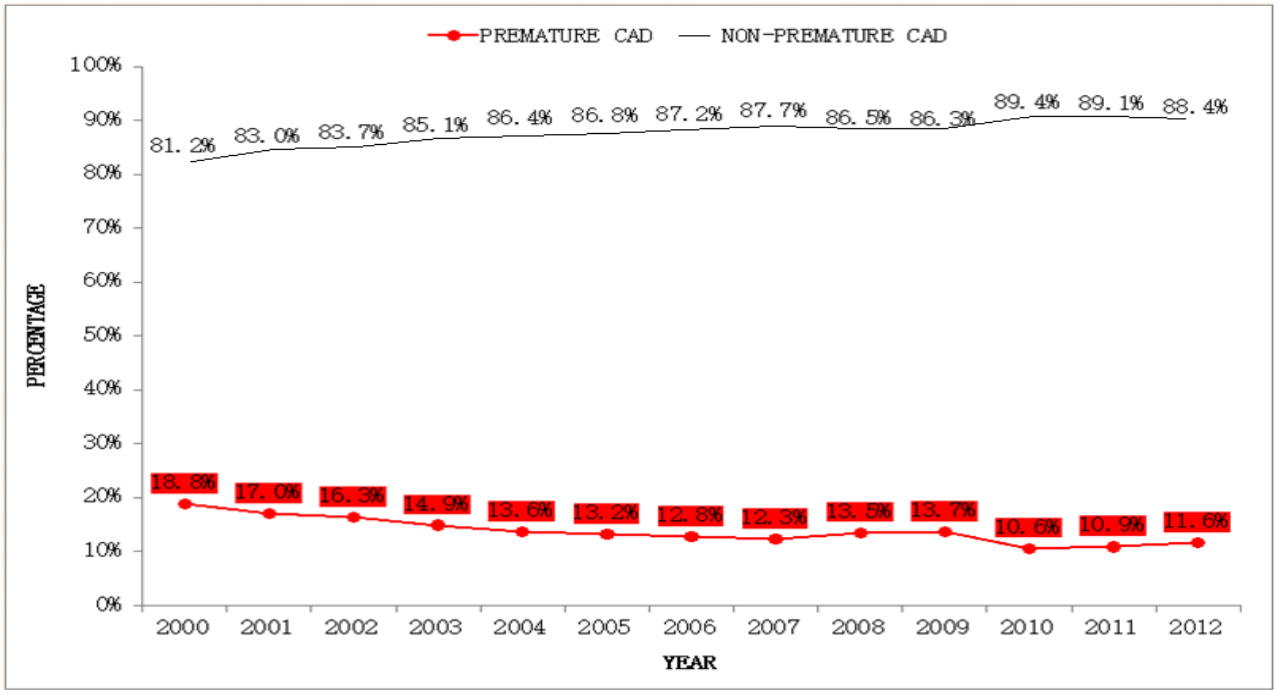

FIGURE 1 Proportion of Premature CAD (PCAD) and Non-Premature CAD from year 2000 until 2012

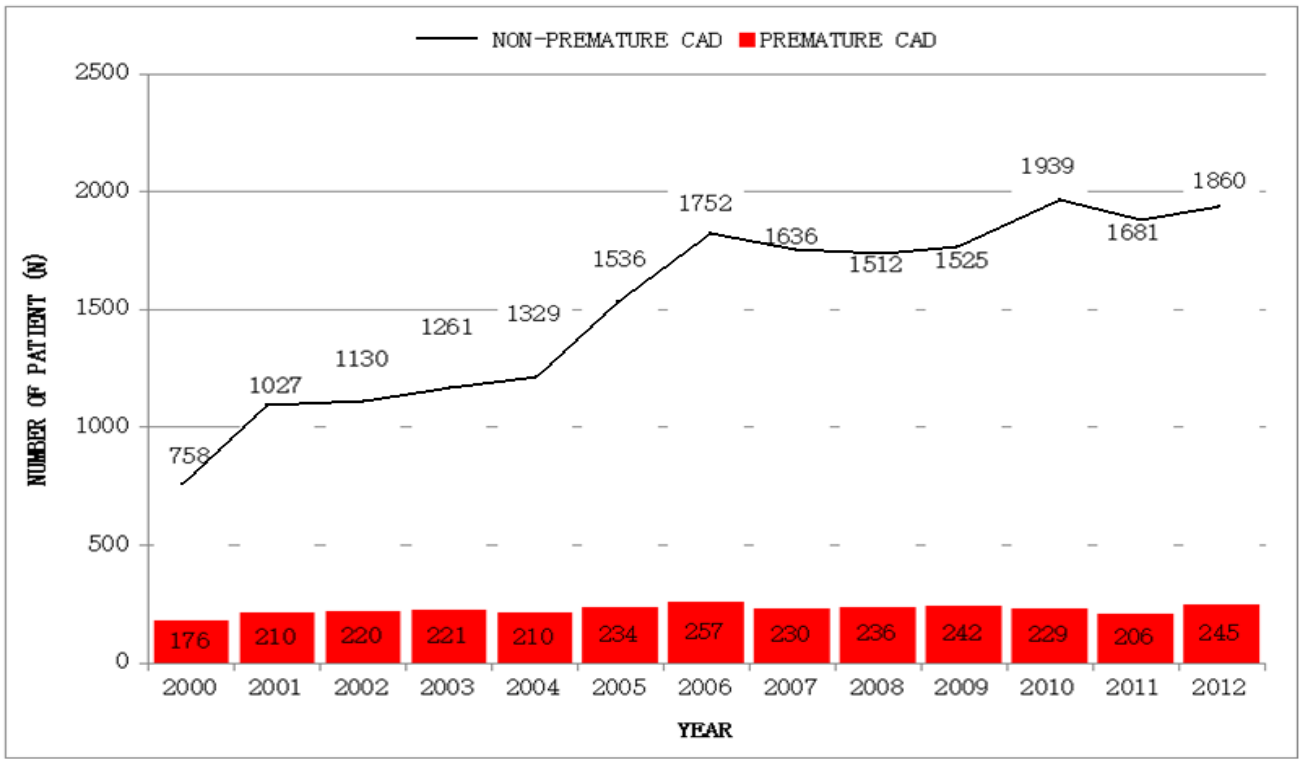

FIGURE 2 Total number of PCAD and non-PCAD from 2000 until 2012

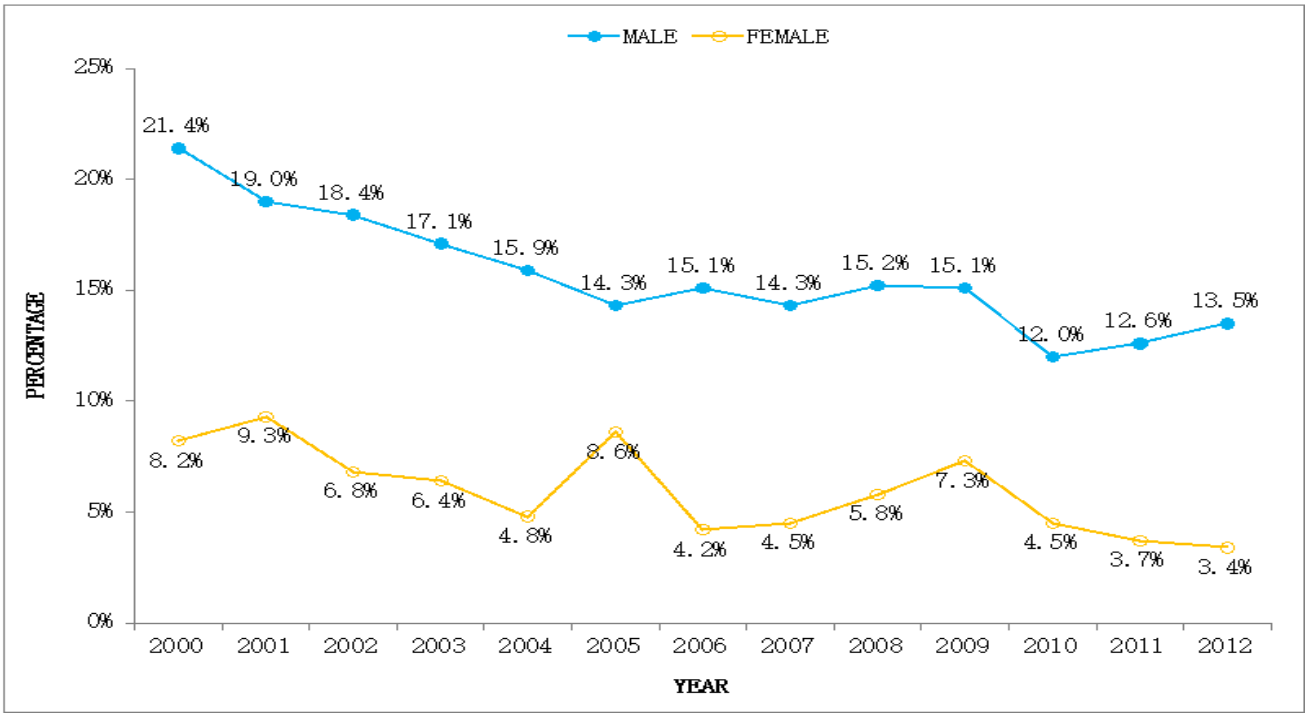

FIGURE 3 Prevalence of PCAD by Gender from 2000 until 2012.

In comparison of PCAD with non-PCAD in year 2007 (1836 cases) and 2012 (2105 cases), bivariate analysis showed that, all conventional risk factors of CAD, which were male, smoking, family history of PCAD, and hypertension, were significant in both 2007 and 2012, except for diabetes mellitus which was only significant in year 2012, and dyslipidemia which was not significant in both years. Male were 3 times higher risk in year 2007, whereas 5 times higher risk in year 2012, in getting PCAD.

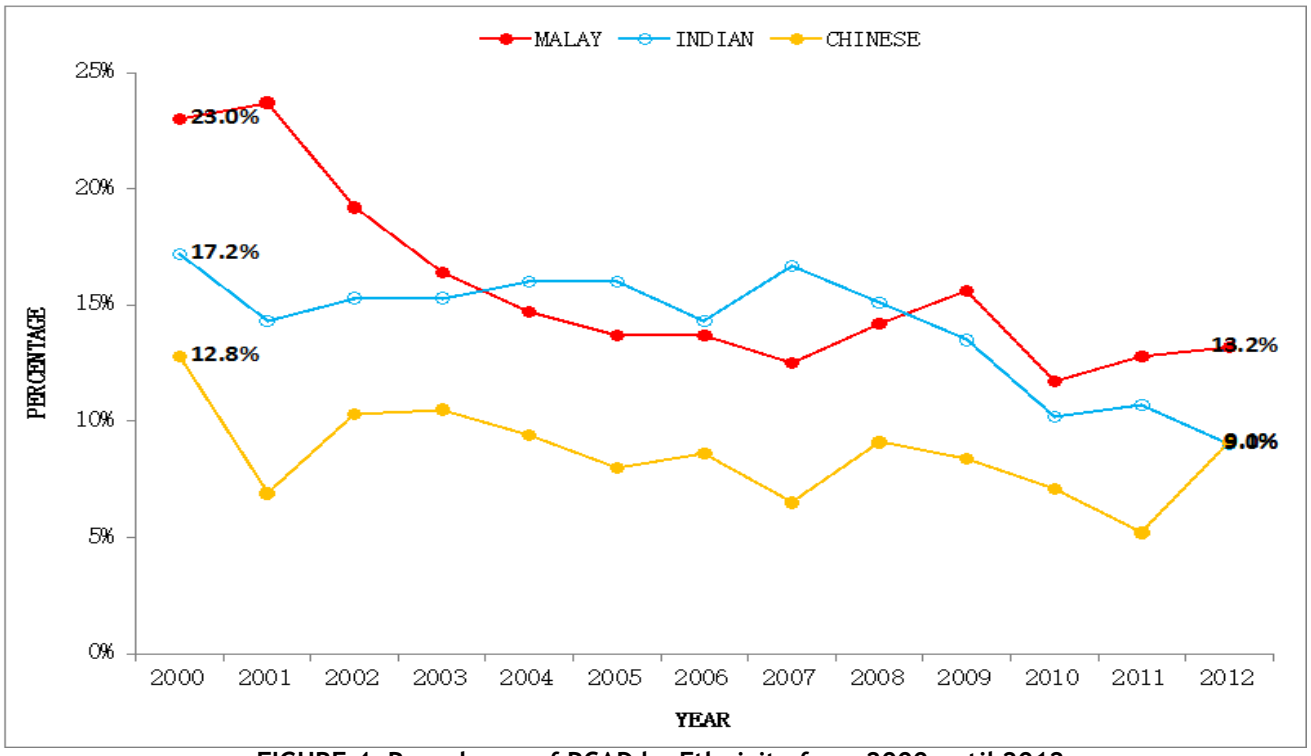

FIGURE 4: Prevalence of PCAD by Ethnicity from 2000 until 2012.

Smoking was 3 times higher, while family history of PCAD was 2 times higher risk for PCAD in both years. By comparing 3 major races in Malaysia, (Malay, Chinese, Indian) in year 2007, Indian had the highest prevalence of PCAD (17.2%), followed by other races (14.3%), Malay (13.2%), and Chinese (8.0%). In year 2012, Malay was predominant among other race (13.0%), followed by Chinese (9.0%), and Indian (8.0%). Diagnosed hypertension was found to be less prevalent in PCAD patients in both years. Diabetes mellitus was less prevalent in PCAD patients in year 2012, but it was not significant in year 2007. History of co-morbidities such as acute angina, heart failure, cerebrovascular disease and peripheral vascular disease had no significant association with PCAD in both years (TABLE 1).

Table 1 Sociodemographic and lifestyle risk factors of PCAD in 2007 and 2012

Categorical Variables	2007		2012	
	N (%)	OR(95%CI)	N (%)	OR(95%CI)
Male	204 (15.5)	3.52(2.11-5.85)	227 (13.26)***	4.76(2.64-8.61)
Smoking	183 (17.0)	2.95(2.05-4.26)	153 (16.54)***	2.71(1.86-3.94)
Family history of PCAD	56 (19.9)	1.76(1.26-2.47)	45 (16.19)**	1.65(1.16-2.35)
Ethnic	Malay: 121(13.2) Indian: 75 (17.2) Chinese: 24(8.0)	Indian vs Chinese 2.37(1.46-3.86)	Malay: 160(12.9) Indian: 46 (8.7) Chinese: 46(8.7)	Malay vs Indian 1.56(1.10-2.20)
Diabetes mellitus	79 (12.7)	0.45(0.68-1.23)	83 (8.08)***	0.44(0.40-0.70)
Hypertension	132 (10.7)	0.45(0.34-0.60)	127 (8.63)***	0.53(0.34-0.59)
Dyslipidemia	174 (13.0)	0.86(0.61-1.22)	141 (11.10)	0.95(0.72-1.25)
Acute Angina	40 (13.5)	0.92(0.64-1.33)	68 (11.9)	1.07(0.79-1.44)
Heart Failure	5 (1.0)	0.64(0.25-1.63)	2 (5.9)	0.48(0.12-2.03)
Cerebrovascular Disease	2 (0.6)	0.39(0.09-1.63)	2 (5.6)	0.46(0.11-1.91)
Peripheral Vascular Disease	2 (10.5)	0.76(0.18-3.33)	2 (11.1)	0.98(0.22-4.27)

The mean value of Body Mass Index (BMI) of PCAD patients showed that they were mostly obese (27.52±4.49 in 2007, 28.11±4.91 in 2012), while non-PCAD patients were mostly overweight (26.34±4.25 in 2007, 26.58±4.48 in 2012) (TABLE 2).

For lipid profile, the mean value of triglyceride level among PCAD patients was significantly higher than non-PCAD patients in both years. HDL level was also significant in both years, with lower mean value in PCAD than non-PCAD (1.08 ± 0.29 in 2007 and 0.99 ± 0.23 in 2012). However, total cholesterol level was only significant in year 2007, which was higher among PCAD patients than non-PCAD patients (4.76 ± 1.22). LDL level was only significant in year 2012, with mean value of 2.80 ± 1.10, which was higher among PCAD patients than non-PCAD patients (TABLE 2).

Sodium level was only significant in year 2007 where it was higher in PCAD (139.33 ± 7.74) than non-PCAD. Urea level was lower among PCAD patients in 2007 (4.91 ± 2.97) compared to non-PCAD, but it was higher among PCAD patients in 2012 (5.86 ± 3.50). In both years, creatinine level was significantly lower among PCAD patients (108.13 ± 100.68 in 2007, 90.75 ± 63.06 in 2012). Aspartate Transaminase (AST) level was significantly higher among PCAD patients in both years (TABLE 2).

TABLE 2: BMI and Biochemical Risk Factors of Premature CAD in 2007 and 2012

BMI and Biochemical parameters	2007			2012		
	Premature (PCAD)	Non-Premature (non-PCAD)	p value	Premature (PCAD)	Non-Premature (non-PCAD)	p value
BMI *kg/m²*	27.52 ± 4.49*	26.34 ± 4.25	0.001	29.11 ± 4.91*	26.58 ± 4.48	<0.001
Triglycerides (TG) *mmol/L*	2.31 ± 1.39*	1.92 ± 1.24	<0.001	2.00 ± 1.07*	1.71 ± 0.90	<0.001
HDL cholesterol *mmol/L*	1.08 ± 0.29**	1.17 ± 0.40	0.003	0.99 ± 0.23**	1.11 ± 0.32	<0.001
Total cholesterol *mmol/L*	4.76 ± 1.22*	4.55 ± 1.19	0.022	5.09 ± 3.95	4.58 ± 3.92	0.073
LDL *mmol/L*	2.64 ± 1.11	2.53 ± 1.23	0.241	2.80 ± 1.10*	2.52 ± 1.47	0.007
Sodium (Na) *mmol/L*	139.33 ± 7.74	140.13 ± 4.18	0.024	138.41±3.28	138.47 ± 3.23	0.784
Urea *mmol/L*	4.91 ± 2.97	6.22 ± 4.56	<0.001	5.86 ± 3.50	4.48 ± 1.89	0.899
Creatinine *mmol/L*	108.13 ± 100.68	127.07 ± 125.18	0.033	90.75 ± 63.06	115.89 ± 118.96	0.001
AST *U/L*	86.47 ± 130.50	65.24 ± 169.48	0.411	94.28 ± 155.07	57.94 ± 92.83	0.003
Fasting Blood Glucose (FBG) *mmol/L*	6.47 ± 2.34	6.82 ± 2.69	0.091	6.60 ± 2.67	6.78 ± 2.68	0.371
HbA1c *%*	8.00 ± 2.19	7.91 ± 1.74	0.836	3.94 ± 4.09	4.58 ± 4.20	0.450
Potassium (K) *mmol/L*	4.44 ± 0.87	4.49 ± 0.63	0.310	4.43 ± 0.50	4.43 ± 0.67	0.899

In the sub analysis of the PCAD group, in both years smoking was high in males whereas diabetes was higher in females. No association was found between hypertension and dyslipidaemia with gender (TABLE 3).

Table 3 Distribution of risk factors in PCAD patients according to gender

Factors	2007 (n=221)			2012 (n=239)		
	Male	Female	OR(95%CI)	Male	Female	95%(CI)
Smoking						
Ever	178(87.3)	5(29.4)	16.43(5.35-50.43)	153(84.5)	0(0.0)	1.32(1.10-1.59)
Never	26(12.7)	12(70.6)		28(15.5)	9(100.0)	*missing value=49
Hypertension						
Yes	120(58.8)	12(70.6)	0.59(0.20-1.75)	121(54.5)	6(54.5)	0.98(0.30-3.37)
No	84(41.2)	5(29.4)		101(45.5)	5(45.5)	*missing value=5
Diabetes						
Yes	67(32.8)	12(70.6)	0.20(0.07-0.60)	75(33.8)	8(66.7)	0.26(0.07-0.88)
No	137(67.2)	5(29.4)		147(66.2)	4(33.3)	*missing value=5
Dyslipidaemia						
Yes	160(78.4)	14(82.4)	0.78(0.21-2.83)	134(60.1)	7(58.3)	1.08(0.33-3.50)
No	44(21.6)	3(17.6)		89(39.9)	5(41.7)	*missing value=4

Multiple logistic regression analysis in 2007 showed that smoking had the higher risk (AOR=2.52), followed by male gender (AOR=2.06), family history of PCAD (AOR=1.96), Indian ethnicity, (AOR=1.65), triglycerides level (AOR=1.20) and BMI (AOR=1.06). In 2012, family history of PCAD had the highest risk (AOR=2.00) followed by smoking (AOR=1.91) and BMI (AOR=1.11). Protective effect was seen in hypertension (AOR=0.37) for 2007. And for 2012 protective effect was also seen in DM (AOR=0.62), hypertension (AOR=0.48) and HDL cholesterol level (AOR=0.20) (TABLE 4).

TABLE 4 Multivariable analysis of factors associated with Premature CAD in 2007 and 2012

Factors	2007	2012
	AOR (95%CI)	AOR (95%CI)
Smoking	2.52 (1.52-4.19)	1.91 (1.14-3.19)
Family history of PCAD	1.96 (1.26-3.03)	2.00 (1.28-3.11)
Body Mass Index (BMI)	1.06 (1.02-1.11)	1.11 (1.07-1.16)
Race: Indian	1.65 (1.07-2.55)	NS
Gender: Male	2.06 (1.01-4.21)	NS
Triglycerides	1.20 (1.00-1.43)	NS
HDL cholesterol level	NS	0.20 (0.09-0.46)
Hypertension	0.37 (0.25-0.56)	0.48 (0.32-0.73)
Diabetes mellitus (DM)	NS	0.62 (0.41-0.94

DISCUSSION

This study has yet again emphasized the presence of conventional risk factors even in the young patients. Many studies had shown the presence of any of the conventional risk factors in most patients suffering from ischemic heart disease.[6-10] Unlike the emerging risk factors for ischemic heart disease[9], these conventional risk factors are modifiable and thus could be prevented or managed so that the risk of developing ischemic heart disease could be reduced remarkably.

The total number of PCAD patients remained rather constant throughout the 12 years and the total number of non-PCAD patients increased across the decade making the proportion of PCAD patients decreasing. This picture might suggest that there are underlying novel risk factors or genetic contribution to the development of PCAD on top of the conventional risk factors. Recent studies had found several more genes that put a person at risk of developing CAD. These genes might be directly associated with blood pressure [11-13], pathway of lipid metabolism [11,12] or even the inflammatory pathway.[12]

Although some studies had query the feasibility and usefulness of screening these factors such as C-reactive protein and lipoprotein (a) [14] the identification of these risk factors might help in active prevention of the disease by intensely advocating the patient to practice protective factors (e.g. regular moderate or high intensity exercise, frequent consumption of fruits and vegetables) into his/her daily life[15]. Our findings are also consistent with several other studies done in the same continent.[7,9,15,16] The findings and advancement of the genetic studies would be able to help in identifying the possible treatment and primary prevention targeted at the possible underlying cause even though the pathogenesis of the disease and its complications are multifactorial. [11-13,17,18]

We have observed that hypertension, dyslipidemia and diabetes mellitus were more prevalent in non-PCAD group. This might be contributed by the fact that these are chronic diseases that often presented at a later stage of life. Similar findings was also noted in several other studies although the cut-off point of age of PCAD and non-PCAD might have some differences.[7-9, 16, 19-21] However, screening of these risk factors should be made available as there were 75% of dyslipidemia cases were undiagnosed. [22] Prevention of ACS in the premature group would benefit a lot to the country in terms of economy as not only the healthcare cost would be reduced but also to prevent the impairment or reduction of productivity of this population.

Lipid profile of the patients showed remarkable changes between the two time-frames but PCAD patients in both years had significantly lower level of HDL and higher level of triglycerides compared to non-PCAD group. In 2007, PCAD patients had significantly higher total cholesterol and in 2012, PCAD patients had significantly higher LDL level. These findings are parallel with the protective factor of HDL and thrombotic factor of raised triglycerides level.[7] The prevalence of dyslipidemia in PCAD patients had remarkably reduced in 2012(60%) compared to 2007(78.7%). This might reflect the underdiagnosed cases of dyslipidemia and thus making it no longer a significant risk factor of PCAD in year 2012.[22]

Male gender was also significantly more prevalent in the non-PCAD group. This could be attributed to the fact that the risk factors are more prevalent in male patients compared to female patients. BMI in PCAD group is obese in contrary to non-PCAD group which was overweight. Obesity has known to be a risk of developing CAD through variable mechanisms, affecting the inflammation and also tissue perfusion.[23,24] Despite of being proven as risk factors of CAD and several mechanisms of CAD acceleration had been proposed[24-26], diabetes mellitus and hypertension was not significantly more prevalent in PCAD patients. This might be due to the fact that more than 50% of diabetes and hypertension were undiagnosed in Malaysia or that the diseases (DM and hypertension) were more prevalent in later age group which peaks at 65-69 year old.[22]

There were several incidental findings in which the sodium was significantly higher in PCAD patients during year 2007 along and the creatinine level was significantly lower among PCAD patients in both 2007 and 2012. The urea level was significantly lower in the PCAD group in year 2007 but interestingly higher in year 2012. The higher sodium level might contribute to higher blood pressure or might reflect poorer control of blood pressure thus leading to ACS which is one of the complications of hypertension. The creatinine level that was significantly higher in the older (non-PCAD) patients might reflect the higher prevalence of patients suffering from underlying kidney disease in older age group. It is known that end stage renal failure was at higher risk of developing cardiovascular disease and have poorer outcome.[27-28] Whether these findings really had significant association with PCAD is still uncertain and warrants further studies.

This study had several limitations. Firstly, this was a retrospective study among the patients. The real odd-risk ratio might be reflected better in a case-control study as long as the biases were kept at minimum. Furthermore, some of other possibly

important risk factors such as abdominal girth, hip girth and abdominal-hip ratio as well as frequency and intensity of exercises were unable to be analyzed. Secondly, this is a single-centered study. Despite of being the referral center from all over the country, the number of samples would still be limited. Multi-centered case-control study would be able to capture more samples and thus could depict a better view regarding the population.

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CONFLICT OF INTEREST

None declared

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