UNIVERSITI TEKNOLOGI MARA

IDENTIFICATION OF CLINICAL AND GENETIC FACTORS OF FAMILIAL HYPERCHOLESTEROLAEMIA AMONG PREMATURE CORONARY ARTERY DISEASE PATIENTS

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ABSTRACT

Coronary artery disease (CAD) is the major cause of death worldwide and highly associated with familial hypercholesterolaemia. Familial hypercholesterolaemia (FH) is an autosomal dominant disorder of lipoprotein metabolism, resulting in an increase in LDL-c levels with subsequent increased risk of premature CAD (PCAD). The prevalence of PCAD and FH among angiogram-proven PCAD (AP-PCAD) patients among Malaysian population is currently under reported. Besides, the genotype of FH-causing gene variants among PCAD patients in Malaysia is not extensively studied yet. Hence, this study aimed to (1) investigate the prevalence of PCAD and their coronary risk factors according to different age cut-offs that define PCAD, (2) determine the prevalence of clinically diagnosed FH in PCAD patients and determine their risk factors and (3) to investigate the spectrum of FH-causing gene variants in clinically diagnosed FH patients among PCAD patients. There were two phases in this study. Phase I was a retrospective study of Malaysians who underwent percutaneous coronary intervention (PCI) from 2007 to 2018 in two Cardiology Specialist Centres. For PCAD prevalence, the patients were grouped into four age groups that commonly defines PCAD based on previous studies. Phase II was a cross-sectional study where AP-PCAD patients (age onset: males: <55 years; females: <60 years) were recruited from Cardiology and Specialist Lipid Clinics. Three-hundred-nineteen AP-PCAD patients were identified and were clinically diagnosed as FH using Dutch Lipid Clinic Network Criteria (DLCC). Targeted next-generation sequencing for identification of FH-candidate genes (FHCG) [*LDLR*, *APOB, PCSK9* and *LDLRAP1*] and hypercholesterolaemia-associated gene (HCAG) [*ABCG5, ABCG8* and *APOE*] was performed among 104 clinically diagnosed FH patients with PCAD who agreed to participate. The prevalence of PCAD was about 9-40%, depending on age cut-off groups. The top three coronary risk factors that mostly influenced PCAD were LDL-c level, TC level and hypertension. The prevalence of clinically diagnosed FH among AP-PCAD was 45.5%; with 16.0% Potential FH (Definite/Probable). Overall, 26.9% (28/104) patients have ≥1 pathogenic variant (PV) in any of the seven genes and 19.2% (20/104) have ≥1 PV in FHCG. Twenty seven percent of Potential FH patients and 17.8% Possible FH patients carry ≥1 PV. Out of 233 variants reported, 11.2% (26/233) were PVs. *LDLR* gene shows the most various types of PVs in this cohort, but *APOB* gene PVs was the most frequently to be reported in this cohort. In conclusion, the prevalence of PCAD was high and nearly half AP-PCAD patients were clinically diagnosed as FH. Almost 27% of the clinically diagnosed FH patients with PCAD were genetically confirmed FH.

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CHAPTER ONE

INTRODUCTION

1.1 Research Background

Cardiovascular disease (CVD), which includes coronary artery disease (CAD), is the leading cause of mortality in Malaysia (Ang & Chan, 2016) and globally (Hata & Kiyohara, 2013), in both genders (Rosamond *et al.*, 2007). Men generally develop CVD at a younger age and have a higher propensity of developing CAD than women; while women are at a higher risk of stroke, which usually arises at older age (Bots *et al.*, 2017).

The occurrence of CAD onset at a young age is called premature CAD (PCAD). Some studies considered the age of onset of PCAD at ≤ 45 years (Patel *et al.*, 2008), another study defined the occurrence of PCAD at <45 years in males and < 55 years in females (Mohammad *et al.*, 2015). According to Arnett *et al.* (2019), CAD before the age of 55 years in men and before 65 years in women was considered as PCAD. The mean age of onset of CAD in Southeast Asian population is 53 years, while it is much older in the European population (63 years) (Yusuf *et al.*, 2004). Malaysians are reported to develop acute coronary syndrome (ACS) at a mean age of 58.7 years compared to 63.4 to 68 years in most developed countries (C. Y. Lee *et al.*, 2021; Mandelzweig *et al.*, 2006; National Heart Association of Malaysia (NHAM) and the Ministry of Health Malaysia, 2022). Nevertheless, there is no universally accepted age cut-off that defines PCAD globally.

The main cause of CAD is atherosclerosis (Hansson, 2005), which is a slowly progressing inflammatory disease of the arteries, that results in the formation of fatty and fibrous lesions of the blood vessel wall due to high plasma concentrations of cholesterol, particularly low-density lipoprotein cholesterol [LDL-c] (de Winther *et al.*, 2005). The formation of fatty lesions, or also known as plague, causes the inside of the arteries to become narrower and slows down the flow of blood, which causes CAD. Plaque build-up can start at an early age, caused by a combination of genetic and environmental factors.

Age, smoking, high blood pressure, gender, dyslipidaemia, and diabetes are the main risk factors for CVD (D'Agostino *et al.*, 2008; McKay *et al.*, 2018). Such