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Familial Hypercholesterolaemia Patients with *LDLR* Mutation Among Asian Population in Southeast Asian Countries: Systematic Review

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ABSTRACT

Familial hypercholesterolaemia (FH) is a genetic disorder associated with premature cardiovascular diseases; however, the majority of patients remain undertreated. This systematic review aimed to determine the prevalence of FH patients with low-density lipoprotein receptor (*LDLR)* gene pathogenic variants (PV) among the Asian population in Southeast Asian countries. Our search yielded 1,120 citations, with 28 deemed possibly suitable based on title and abstract screening. However, only six studies that utilised the Dutch Lipid Clinic Network (DLCN) or Simon Broome (SB) criteria were eligible to be included. These studies provided prevalence figures for clinically diagnosed FH patients, with a total of 17.1% (n=1,005/5,874); this rate was represented by three Malaysian studies, which estimated that 36–76% of clinically diagnosed FH patients had *LDLR* PV. Most patients reported having pre-existing cardiovascular disease, a family history of premature coronary artery disease and tendon xanthomata. This study found that the prevalence of *LDLR* PV among genetically confirmed FH patients in Southeast Asia is 20.5% (n=286/5,874). Genetically confirmed FH patients are at a higher risk of developing premature coronary artery disease, requiring more aggressive lipid-lowering treatment. Therefore, identifying *LDLR* PV among the population is essential for early FH diagnosis and treatment.

KEYWORDS

Arterial disease, autosomal dominant, LDL receptor, *LDLR* prevalence, pathogenic variants, premature CAD, Undertreated

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1. Introduction

Familial hypercholesterolaemia (FH) is an inherited metabolic disorder associated with an elevated level of low-density lipoprotein cholesterol (LDL-C or LDL cholesterol) and a greater risk of developing premature cardiovascular disease (PCAD) in both men and women (Bouhairie and Goldberg, 2015). LDL-C is a type of fat that circulates throughout the body and deposits within artery walls, where it is required for cell repair. Triglycerides and cholesterol, which are insoluble in water, must bind to proteins to pass through the hydrophilic blood (Hevonoja *et al.,* 2000). Early identification of FH, with subsequent effective LDL-C-lowering therapy, will lead to the prevention of coronary heart disease (CHD) and, eventually, early mortality among FH patients (Packard *et al.,* 2021).

FH is an autosomal dominant disorder caused by mutations in the LDL receptor (*LDLR)* or its ligand, apolipoprotein B 100 (*APOB)* (Pejic, 2014). LDL-C receptors are essential for LDL-C absorption from the blood into hepatocytes, while *APOB* is important for LDL-C structure maintenance and serves as a recognition site for the LDL-C receptors, which is required for receptor-mediated endocytosis. Mutations in the *LDLR* were reported to be the most common cause of FH, followed by *APOB* (Iacocca *et al.,* 2018). In rare situations, a gain-of-function variant in the proprotein convertase subtilisin-kexin type 9 gene (*PCSK9*) may be the cause (Vrablik *et al.,* 2020). In 85–90% of individuals with FH, over 1,600 gene variants in the *LDLR* were reported; these were followed by *APOB* mutations, where the most common one (Arg3500⟶Gln) affects approximately 10% of individuals with FH. *PCSK9* gene mutation accounts for less than 5% of FH cases. Furthermore, only severe *PCSK9* mutations cause FH (Pejic, 2014).

LDLR, a glycoprotein found in cell membranes, is involved in the binding and internalisation of lipoprotein particles in the bloodstream that carry cholesterol. *LDLR* is a widely expressed receptor that is essential for cholesterol homeostasis in humans (Goldstein and Brown, 1974). Many studies on how LDLR removes LDL, a significant cholesterol carrier in humans, have been conducted (Goldstein and Brown, 1973; Brown and Goldstein, 1974a; Brown and Goldstein, 1974b; Goldstein and Brown, 1974). Cultured fibroblasts from FH patients cannot remove serum LDL, resulting in higher serum LDL-C levels. Normal fibroblasts have a high cell surface binding affinity for LDL-C via *LDLR* (Brown and Goldstein, 1974a). Individuals with homozygotes for the *LDLR* mutation exhibit extensive deposition of cholesterol-mediated atheromatous plaques in their coronary arteries, aorta and aortic valves, and have blood LDL-C levels as high as 800 mg/dL (Brown and Goldstein, 1974b). Carriers with heterozygote *LDLR* mutations usually had a two-fold increased risk for coronary artery disease and a twice-elevated plasma LDL-C concentration compared to the general population. According to the majority of guidelines, patients with established coronary artery disease should have their LDL-C levels adjusted to below 70 mg/dL and 100 mg/dL, respectively, if they have two or more risk factors for the condition (Goldstein and Brown, 1973).

The exact prevalence of FH in Asian populations remains undetermined. Many studies have determined that the prevalence of FH in the general population ranges from 1:200 to 1:250 (Chua *et al.,* 2021). A meta-analysis of 11 million individuals from 104 studies estimated that the prevalence of heterozygous FH (HeFH) in the general population was 1 in 313 (Beheshti *et al.,* 2020). The European Atherosclerosis Society (EAS) Consensus Panel estimates that the prevalence of HeFH ranges from 1 in 200 to 1 in 500, but it could be as high as 1 in 31 in patients with atherosclerotic cardiovascular disease (ASCVD). Meanwhile, approximately 1:160,000 to 1:300,000 people have homozygous FH (HoFH) (Sun *et al.,* 2023). Both HoFH and HeFH induce a marked increase in LDL-C levelswhich often results in early cardiovascular disease (Marusic *et al.,* 2020). Globally, 90–95% of FH patients remain undiagnosed (EAS, 2018).

Multiple approaches are needed for screening, diagnosing and treating FH (Pang *et al.,* 2020). FH patients can be identified via clinical diagnosis, personal and family history and physical examination, with genetic

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testing used to confirm the diagnosis (Migliara *et al.,* 2017). Physical manifestations of FH, such as tendon xanthomata and corneal arcus in patients under the age of 45, have been used to develop the most utilised diagnostic tools for the clinical diagnosis of FH (Rallidis *et al.,* 2020). For instance, Simon Broome's (SB) criteria are well-known clinical diagnostic measures for FH that are extensively used in the United Kingdom, (Humphries *et al.,* 2018). The Dutch Lipid Clinic Network (DLCN) criteria are commonly used in European nations (Gidding *et al.,* 2022), whereas the Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria are generally used in the United States (Maştaleru *et al.,* 2022). Each of these criteria has distinct features and standards for diagnosing FH. The MEDPED criteria are based solely on age- and family-relative-specific total cholesterol (TC) levels, while the DLCN and SB incorporate a variety of other comparable factors. However, there is no consensus on which diagnostic criteria should be used as standardised international tools for FH identification worldwide (Rallidis *et al.,* 2020).

As FH is an autosomal dominant disorder, a heterozygous individual has a 50% probability of transferring the gene to their offspring. If individuals with identical mutations in both alleles (homozygous), different pathogenic variants (PV) in both alleles of the same gene (compound heterozygotes) or PV in two different genes (double heterozygotes), they will have obligatory heterozygous offspring, as long as their partner does not have FH (McGowan *et al.,* 2019). Thus, cascade screening, which involves genetic testing on family members of a proband who have been previously diagnosed with FH, seems to be an effective strategy for FH screening (Vrablik *et al.,* 2020). Cascade screening is a low-cost method of identifying at-risk individuals that involves systematic family tracing (Migliara *et al.,* 2017).

There are several types of genetic tests, each with different approaches (Futema *et al.,* 2021). Targeted next-generation sequencing (NGS) technologies enabled comprehensive mutation identification, particularly loci of interest and simultaneous sequencing of several genes, resulting in genetic information in FH candidate genes, hypercholesterolaemia-associated genes and other lipid metabolism-related genes (Qin, 2019). However, it is uncertain whether including these additional genes in NGS panels enhances the number of FH patients who could be molecularly identified (Reeskamp *et al.,* 2020). FH, a reasonably common genetic condition, affects an estimated 20 million individuals worldwide, with over 90% of cases remaining untreated (Zubielienė *et al.,* 2022). In Asia Pacific, FH is a common hereditary disorder impacting at least 15 million people (Kalra *et al.,* 2021). The prevalence of FH in Asia was found to be 1:526 in a recent meta-analysis, which included four studies: two from Japan, one from Korea and one from China. In comparison, the FH prevalence in both North America (9 studies) and Europe was 1:313 (19 studies) (Beheshti *et al.,* 2020). Therefore, this systematic review aims to summarise the prevalence of FH patients with *LDLR* PV among the Asian population in Southeast Asian countries.

2. Method

This paper conducted a systematic review of observational studies that were carried out and published per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria but without meta-analysis (Liberati *et al.,* 2009). The Condition, Context and Population (CoCoPop) framework was utilised to formulate the Population, Intervention, Comparator and Outcome (PICO) question (Munn *et al.,* 2015)

2.1. Search Strategy:

To retrieve potentially relevant reviews, we searched PubMed, SCOPUS and Web of Science using the keywords '(((Prevalence) OR (Incidence) OR (Frequency) OR (Occurrence) OR (Burden) OR (Commonness) OR (Frequentness) OR (Chronicity) OR (Continuousness) OR (Regularity) OR (Appearance) OR (Constancy)) AND ((Southeast Asian) OR (Brunei) OR (Cambodia) OR (Indonesia) OR (Laos) OR (Malaysia) OR (Myanmar) OR (Philippines) OR (Singapore) OR (Thailand) OR (Vietnam))) AND ((Familial Hypercholesterolaemia) OR (Familial Hypercholesterolaemia) OR (Hyperlipoproteinaemia) OR (Hyperlipidaemia) OR (HeFH) OR (HoFH) OR (FH))'. English language restrictions were applied to the search.

2.2. Inclusion Criteria:

2.2.1. Study Design

The review includes observational research such as cross-sectional, case-control and case series studies**.**

2.2.2. Scope of Study

The review criteria included studies or articles that: (1) contained information about adult patients (≥18 years old); (2) referred to settings located in Southeast Asia; (3) provided FH disease information; (4) reported on FH disease prevalence; and (5) discussed positive *LDLR* mutations in clinically diagnosed FH patients.

2.3. Outcome:

To determine the prevalence of FH patients with *LDLR* gene PV based on FH diagnostic criteria, study population and demographic profile (age and gender) as well as the frequency of *LDLR* PV in patients with FH within the Asian population in Southeast Asian countries.

2.4. Exclusion Criteria:

This review excluded articles for which full texts could not be obtained from the search; studies that lacked information on FH clinical diagnosis, personal and family history, physical examination or genetic testing; papers that did not include adult patients; or research that did not offer information on the prevalence or incidence of *LDLR* PV among FH patients. Moreover, this review rejected non-English research articles, conference proceedings, abstracts, book chapters and commentaries.

2.5. Study Selection and Data Extraction:

After the articles in the databases were identified, they were imported into the Mendeley version 2.79.0 software (Elsevier, UK). Duplicate articles were then removed. The studies were initially screened based on their titles/abstracts, and irrelevant publications were excluded (Table 1). The qualifying criteria were utilised to conduct the first-level screening of paper titles and abstracts. Systematic reviews and meta-analyses were omitted. Only full-text papers were searched to determine their suitability for additional screening and inclusion in the review. The full texts of the remaining publications were then analysed. A paper was classified as a general population study if the participants involved in the research were selected from the general population, as indicated by the authors. A data extraction form was used to extract the following data: age group of patients (adult or elderly), country of study, total number of FH patients who had *LDLR* mutations and the number of patients with diagnosed FH.

2.6. Strategy for Data Synthesis:

The review focused on narrative synthesis due to the small number of papers included and methodological discrepancies between the studies. Data were summarised using prevalence estimates of FH patients with *LDLR* PV among populations in Southeast Asian countries. If the prevalence was not directly available for data extraction, it was calculated based on the size of the total study cohort and the number of FH individuals with *LDLR* PV. Demographic data

(age, sex) and prevalence are reported as means with percentages (%).

3. Results

3.1. Study Selection:

Our search yielded 1,120 citations, with 28 deemed possibly relevant based on title and abstract screening. Following the application of the inclusion and exclusion criteria, publications were screened at the full-text level, with six papers being included in this review. Figure 1 depicts the flow of the included investigations.

3.2. Characteristics of the Included Studies:

The six included studies were published between 2005 and 2022 (basic details in Table 1). Four studies (Khoo *et al.,* 2000; Al-Khateeb *et al.,* 2011; Lye *et al.,* 2013; Razman *et al.,* 2022) were carried out in Malaysia, while the remaining two (Punzalan *et al.,* 2005; Pek *et al.,* 2018) were conducted in the Philippines and Singapore. All studies in this review used a cross-sectional study design. A total of 5,788 participants were involved in the studies, with the vast majority coming from a single research (Razman *et al.,* 2022). One study (Punzalan *et al.,* 2005) only included 60 participants. All six studies diagnosed FH as definite, probable or possible using either the DLCN or SB criteria.

Figure: 1. PRISMA flow diagram for selecting studies on FH in Southeast Asian countries

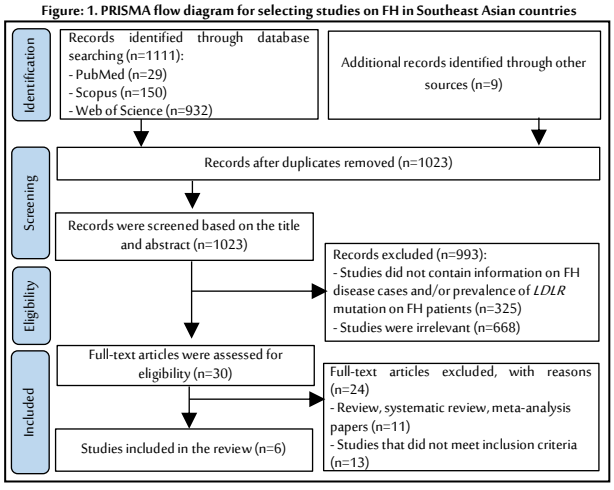

Table: 1. A summary of selected studies on FH in Southeast Asian countries

Study Author (publication year)	Country	Source	Diagnostic Criteria	Analysis Method	Sample Size	Mean Age Years	Sex, N	Outcome		
								Clinical Prevalence (clinically diagnosed FH), N (%)	FH Patients with PV, N (%)	Total *LDLR* PV Confirmed Prevalence, N (%)
Razman *et al.,* (2022)	Malaysia	Patients from hospital-based screening	DLCN	NGS	5,130	51.1	Male: 171 Female: 201	372/5,130 (7.3)	82/372 (22.0)	30/82 (36.6)
Al-Khateeb *et al.,* (2011)	Malaysia	Patients from hospital-based screening	SB	DHPLC	154	44.6	Male: 73 Female: 81	154/154 (100.0)	117/154 (76.0)	117/154 (76.0)
Pek *et al.,* (2018)	Singapore	PS	DLCN	NGS	192	33.5	Male: 77 Female: 115	192/192 (100.0)	54/192 (28.1)	50/192 (26.0)
Punzalan *et al.,* (2005)	Philippines	PS	DLCN	DHPLC	60	55	Male: 21 Female: 39	60/60 (100.0)	60/60 (100.0)	12/60 (20.0)
Lye *et al.,* (2013)	Malaysia	Patients from an outpatient clinic	DLCN	MLPA	252	46.8	Male: 73 Female: 68	141/252 (56.0)	108/141 (76.6)	55/141 (39.0)
Khoo *et al.,* (2000)	Southeast Asia	Patients from a lipid clinic	DLCN	DGGE and DNA-sequencing	86	54	Male: 41 Female: 45	86/86 (100.0)	22/86 (25.6)	22/86 (25.6)

PS: population study; PV: pathogenic variants; DLCN: Dutch Lipid Clinic Network; SB: Simon Broome; NGS: next-generation Sequencing; DHPLC: denaturing high-performance liquid chromatography; MLPA: multiplex-ligation dependent probe amplification; DGGE: denaturing gradient gel electrophoresis.

Table: 2. Publications on *LDLR* pathogenic variants and their associated clinical features and history among FH patients in Southeast Asian countries

Study	Country	Patients with LDLR PV, *n*	*LDLR* Gene Identified			Standard Clinical Presentation
			LDLR Variants	Total *LDLR* Variants, *n*	Total *LDLR* PV, *n* (%)	
Razman *et al.,* (2022)	Malaysia	30	c.241C>T, c.301G>A, c.580A>G, c.811G>A, c.833G>A, c.949G>A, c.1234A>C, c.1284C>G, *c.1289T>G, *c.1571T>G, *c.1774G>T, c.1820A>G, *c.2383C>G, c.2530G>A, c.1217G>A, c.1246C>T, c.1867A>G, c.1187-2A>G	18	18/18 (100.0)	This study found that patients with potential FH had higher proportions of existing personal CVD (13.8%), a family history of PCAD (34.5%), the presence of tendon xanthomata (10.3%) and premature corneal arcus (75.9%) as well as elevated LDL-C levels. Those with possible FH had lower proportions of these factors, with rates of 5.1% for CVD, 13.4% for family history of PCAD and 2.2% for the absence of tendon xanthomata and premature corneal arcus.
Al-Khateeb *et al.,* (2011)	Malaysia	117	c.81C>T, c.190+56G>A, c.190+58C>T, c.300C>T, c.910G>A, c.940+36G>A, c.1060+7T>C, c.1060+10G>C, c.1186+41T>A, c.1194C>T, c.1359-30C>T, c.1411A>G, c.1617C>T, c.1705+56C>T, c.1705+112C>G, c.1706-55A>C, c.1706-69G>T, c.1705+117T>G, c.1773C>T, c.1959T>C, c.2232A>G, *c.190+4A>T, *c.301G>A, *c.415G>C, *c.601G>A, *c.763T>A, *c.1706_1845, *c.2100C>G, *c.1996_2012del17	29	8/29 (27.6)	This study revealed that patients with PV had higher LDL-C levels (1.1%) compared to non-PV patients (0.8%). Also, patients with PV had a higher incidence of tendon xanthomata (66.7%) and CVD (88.1%), while non-PV patients had a lower incidence of tendon xanthomata (31.3%) and CVD (60.7%).
Pek *et al.,* (2018)	Singapore	50	c.232C>T, c.241C>T, c.532G>A, *c.632_634del, c.769C>T, c.985T>G, c.986G>A, c.1009G>A, c.1027G>A, *c.1060G>A, c.1061A>G, *c.1090del, *c.1091G>A, c.1171G>A, c.1217G>A, c.1222G>A, c.1241T>G, c.1247G>A, *c.1292C>T, *c.1420C>T, c.1474G>A, *c.1475A>T, *c.1514G>C, *c.1525A>G, c.1747C>T, c.1765G>A, c.1783C>T, c.1954_1955del, c.1963T>C, c.2054C>T, *c.2093G>A, *c.2108_2114dup, c.2230C>T, c.2291T>C, c.2383C>G, *c.2478del, c.313+1G>A, c.(67+1_68-1)_(2311+1_2312-1)del, c.(1586+1_1587-1)_(2140+1_2141-1)del, c.(2140+1_2141-1)_(2311+1_2312-1)del, c.(940+1_941-1)_1845+1_1846-1)dup	41	26/41 (63.4)	This study found that most patients with pathogenic mutations had a family history of premature CVD. Moreover, 7.4% of them had tendon xanthomata, 7.2% had experienced a CVD event and 6.3% had arcus cornealis.
Punzalan *et al.,* (2005)	Philippines	12	c.268G>A, c.986G>A, c.1747C>T, *p.G50R, *p.D147N, *c.1502C>A, *1602V, *c.190+4A>T, *c.1187-10G>A	9	9/9 (100.0)	This study revealed that patients exhibiting clinical features of FH were relatively young yet already had a high prevalence of CAD and CVD.
Lye et al., (2013)	Malaysia	55	c.940+775G>A	1	1/1 (100.0)	The FH patients recruited in this study were older. Age has been identified as a risk factor for age-related dyslipidaemia. The steady drop in LDL-C clearance as age increases is one of the reasons for age-related disturbance of lipid homeostasis.
Khoo *et al.,* (2000)	Southeast Asia	22	*c.-152G>T, *c.77delG>A, p.D69N, c.313+1G>A, p.R94H, p.R232W, p.E256K, *p.C308Y, *p.Q357X, *p.K372N, *p.L393R, p.I402T, p.N407K, p.G457R, p.D471N, *c.2108ins7bp, *p.A663T, *p.C675Y	18	18/18 (100.0)	This study found that patients with mutations had significantly higher LDL-C levels, a notably higher incidence of xanthomata (65%) and more than double the incidence of CHD (57%), in comparison to patients without the *LDLR* mutation who had xanthomata (41%) and CHD (26%).

LDLR: low-density lipoprotein receptor gene; PV: pathogenic variants; *novel pathogenic variant; CVD: cardiovascular disorder; CAD: coronary artery disease; FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol.

Table 2 presents four studies in which most patients had personal CVD, a family history of PCAD and tendon xanthomata. One study found approximately 41 *LDLR* variants among 50 individuals with FH, of whom 26 had *LDLR* PV (Pek *et al.,* 2018). Moreover, two studies conducted in the same country detected eight *LDLR* PV among 117 patients with FH (Al-Khateeb *et al.,* 2011). Another research found 18 *LDLR* PV among 30 individuals with FH, of which four were novel variants (Razman *et al.,* 2022). In another investigation, nine *LDLR* PVs were discovered, six of which were novel variants identified in 12 patients with FH. Also, a single *LDLR* variant was found in 55 older FH patients, which is considered a rare case (Lye *et al.,* 2013). In a Southeast Asian study, approximately 18

LDLR distinct mutations were found (Khoo *et al.,* 2000); nine of these have been previously detected, while the other nine are novel mutations.

3.3. *LDLR* PV Prevalence Varies by Country:

The results showed that Singapore (Pek *et al.,* 2018), Southeast Asia (Khoo *et al.,* 2000) and the Philippines(Punzalan *et al.,* 2005) had a lower prevalence (26%, 25.6% and 20%, respectively) of *LDLR* mutations among clinically diagnosed FH patients compared to Malaysia (as indicated by three studies), where it was estimated that approximately 36—76% of patients had *LDLR* mutations (Al-Khateeb *et al.,* 2011; Lye *et al.,* 2013; Razman *et al.,* 2022).

3.4. Prevalence Varies Based on the Clinical Diagnostic Criteria:

Five studies (Khoo *et al.,* 2000; Punzalan *et al.,* 2005; Lye *et al.,* 2013; Pek *et al.,* 2018; Razman *et al.,* 2022) utilised DLCN, while only one research (Al-Khateeb *et al.,* 2011) used SB as a diagnostic tool to detect FH patients. The SB study had the highest frequency of *LDLR* PV, reaching 76%. Based on three studies that used DLCN, the prevalence of *LDLR* PV among FH patients was 22% in Malaysia (Razman *et al.,* 2022), 28.1% in Singapore (Pek *et al.,* 2018) and 25.6% in Southeast Asia (Khoo *et al.,* 2000).

3.5. Prevalence Varies Based on the Molecular Detection Technique:

NGS-based studies reported that 26% (Pek *et al.,* 2018) and 36.6% of FH subjects had *LD LR* PV (Razman *et al.,* 2022). Two studies that utilised the DHPLC analysis method found an approximate prevalence of 20% (Punzalan *et al.,* 2005), with Malaysian FH subjects having the highest prevalence of *LDLR* PV at 76% (Al-Khateeb *et al.,* 2011). Moreover, the MLPA method-based research revealed that about 39% of FH patients had *LDLR* PV (Lye *et al.,* 2013). In another study, DGGE and DNA sequencing revealed that around 25.6% of clinically diagnosed FH patients had *LDLR* PV (Khoo *et al.,* 2000).

4. Discussion

This paper is the first systematic review to identify the prevalence of *LDLR* PV among FH patients in Southeast Asian countries. This research included six studies, with a total of 5,788 participants. Approximately 1,005 patients were clinically diagnosed with FH, with 28.5% (n=286/1,005) having *LDLR* mutations; however, the vast majority of FH patients with *LDLR* PV were from a single study (Al-Khateeb *et al.,* 2011). The six studies reported that among the Asian population in Southeast Asian countries, there was a genetically confirmed prevalence of *LDLR* PV in FH patients at approximately 20.5%, with 13 out of 267 cases. In addition, another study discovered that the FH prevalence in the general population was 0.19% in Asia, compared to 0.32% in Europe and North America (Beheshti *et al.,* 2020).

This review found that FH with positive *LDLR* PV affects both men and women equally, and many patients had personal CVD. Over 85% of men and 50% of women with FH are expected to experience coronary events (Woodward, 2019). This increases the likelihood of FH going undetected in female as compared to male patients. However, because CAD usually manifests much later in life among women, most of them may be identified based on clinical criteria as they age (Garcia *et al.,* 2016). Notably, the literature lacks comprehensive investigation into the potential effects of delayed FH diagnosis in women with the presence of PV in the *LDLR*, as opposed to men; it is also uncertain as to whether such delays could lead to sub-optimal health outcomes. Nevertheless, understanding the gender-specific differences in FH with *LDLR* PV manifestation could enable earlier diagnosis of this condition, which is critical from a clinical standpoint.

In most countries, diagnosis is mostly based on DLCN criteria and less commonly on SB or MEDPED (EAS, 2018). The DLCN, SB and MEDPED criteria may yield different diagnostic outcomes even in the same population. This might compromise the accuracy of projected prevalence in various nations and diagnostic reliability in different groups (Hu *et al.,* 2020). Patients with PCAD and increased cholesterol had a greater frequency of *LDLR* PV, as seen in general population research (Beheshti *et al.,* 2020; Hu *et al.,* 2020). Thus, patients with PV require more aggressive lipid-lowering treatment than those without PV. According to a prior study, a significant percentage (>10%) of patients with acute coronary syndrome under the age of 60 were diagnosed with FH (Tanaka *et al.,* 2019). The five non-FH patients who were clinically diagnosed using the DLCN FH criteria were found to have FH. This is because the DLCN FH criteria have several advantages, such as reducing the likelihood of FH denial based on multiple clinical diagnostic elements, particularly the patient's clinical history of premature CAD and genetic diagnosis (Tada *et al.,* 2021). Since the DLCN FH criteria include extra categories (DLCN has four, while SB has three categories), utilising them instead of other criteria may improve sensitivity when accounting for those categories (Tada *et al.,* 2021).

The identification of a disease-causing pathogenic mutation equals a definitive FH diagnosis, making genetic screening the most accurate way to confirm FH (Cuchel *et al.,* 2014). In cascade screening, genetic testing is commonly used to confirm the origin of dyslipidaemia or establish the presence of a disease-causing gene mutation. First-degree relatives should be tested as part of standard clinic screening; it has been hypothesised that a strategy combining index cases and personal contact with family members by medical professionals may increase the number of tested people (Wald and Wald, 2018). According to the NICE recommendations for the diagnosis and treatment of FH, cascade screening, which combines genetic testing with LDL-C concentration measurement, must be used to identify affected relatives of index individuals with a clinical diagnosis of FH. This should include first-, second- and, if feasible, third-degree biological relations (DeMott, *et al.,* 2008; Ned and Sijbrands, 2011). However, genetic screening has its limitations, as it is expensive, time-consuming and needs access to healthcare facilities, making it less useful in less affluent regions of the world (Hu *et al.,* 2020). Furthermore, research utilising genetic screening yields low FH prevalence estimates, probably because not all FH-causing mutations have been found or included in diagnostic testing panels for FH (Medeiros and Bourbon, 2023). Most patients with a polygenic cause of elevated LDL-C are mutation-negative (Mickiewicz *et al.,* 2020). Polygenic hypercholesterolaemia is a common cause of elevated blood cholesterol. It represents the conditions in which serum triglyceride (TG) concentrations are within the recommended range but LDL-C levels are elevated. Polygenic hypercholesterolaemia may coexist with other conditions, such as metabolic syndrome or obesity, in certain people with mixed dyslipidaemias (elevations of both LDL-C and triglycerides). Clinically distinguishing FH from polygenic hypercholesterolaemia can be occasionally challenging.

FH prevalence tends to increase with age. Beheshti *et al.,* (2020) found that the frequency of FH was slightly lower among those aged 0—19 years (1 in 278; 95% CI; 1 in 345 to 1 in 222). Historically, older age has been seen as a risk factor for dyslipidaemia. Both cross-sectional and longitudinal investigations found that TC, LDL-C and TG concentrations were related to age (Cho *et al.,* 2020). Individuals with definite/probable FH who received cholesterol-lowering medication had 193% higher LDL-C levels than those who were unlikely to have FH

but were given cholesterol-lowering medication (Wang *et al.,* 2019). Factors contributing to the age-related disruption of lipid homeostasis and steady decline in LDL-C clearance include a progressively decreasing capacity to remove cholesterol by converting it to bile acids, a decreased activity of the enzyme that controls the rate of bile acid synthesis and a progressively declining growth hormone secretion. Growth hormone influences the expression of hepatic *LDLR*, which is critical for maintaining normal cholesterol levels (Pallottini and Trapani, 2010).

5. Study Limitation

Nevertheless, a multimodal strategy including clinical, biochemical, and genetic parameters is necessary to enhance the detection of FH and reduce CVD and mortality. New information on the prevalence of FH is revealed by these studies. However, certain significant restrictions should be considered. First, even though we used a thorough search approach, we only included peer-reviewed English language studies that were indexed in four online databases. It is still conceivable that other pertinent research was either not published or was indexed in other languages, print repositories, or grey literature. Furthermore, all studies included in this review were conducted on opportunistic samples and drawn from conveniently accessible sources. Thus, these findings could only be generalised to the sub-population from which the samples were collected and may not apply to the entire population.

6. Conclusions

In this systematic review, we concluded that the prevalence of *LDLR* mutations among genetically confirmed FH patients among the general population of Southeast Asians is 13:267 (286/5874), approximately 20.5% which is quite high, emphasising the need for genetic confirmation among index cases, as well as cascade screening from clinically diagnosed FH among Asian populations. There is a need for the identification of the prevalence of FH patients with *LDLR* mutations in Southeast Asian countries individually to determine the potential benefits of intensified FH screening in certain population subgroups and to further investigate potential biases and inequalities in current FH diagnostic criteria and screening programmes.

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