UNIVERSITI TEKNOLOGI MARA

DETECTION RATE AND DIAGNOSTIC ACCURACY OF FAMILIAL HYPERCHOLESTEROLAEMIA TOOLS (FAMCAT, SB, DLCC) VS. GENETIC DIAGNOSIS IN THE MALAYSIAN PRIMARY CARE SETTING

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Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science
(Medicine)

Faculty of Medicine

December 2024

ABSTRACT

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that increases low-density lipoprotein cholesterol (LDL-c) levels, raising the risk of premature coronary artery disease. This study aimed to assess the detection rate and diagnostic accuracy of the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT), Simon Broome (SB) criteria, and Dutch Lipid Clinic Criteria (DLCC) against genetic diagnosis in the Malaysian primary care settings. The study was conducted at 11 public primary care clinics in Klang Valley from September 2020 to December 2022, involving 3085 patients aged ≥18 years with LDL-c ≥4.0 mmol/L. Of these, 429 (13.9%) were eligible, and 310 (72.3%) met criteria for genetic testing. Of this, 86 patients were genetically confirmed to have FH. Detection rates for SB criteria, DLCC and FAMCAT were 25.2%, 21.6%, and 16.8%, respectively. FAMCAT demonstrated a high specificity (57.6%) among the tools. Its positive predictive value (PPV) was also the highest at 35.4%, indicating that it is effective in identifying patients with FH who are more likely to have the condition. The area under the curve (AUC) for FAMCAT was 0.59, showing decent overall performance. In comparison, SB criteria had the highest sensitivity (90.7%) but lower specificity (18.8%), while DLCC had moderate sensitivity (77.9%) and specificity (40.2%). Additionally, FAMCAT exhibited the highest overall diagnostic accuracy at 58.4%, outperforming both DLCC (50.6%) and SB criteria (38.7%), further validating its utility for FH screening in primary care. In conclusion, FAMCAT's high specificity, PPV and the overall diagnostic accuracy makes it a valuable screening tool for FH in primary care. Those who are identified to have high probability of FH using FAMCAT should then be assessed with the clinical diagnostic criteria (SB and DLCC). Patients who are clinically diagnosed can then be referred for genetic testing if it is available.

ACKNOWLEDGEMENT

First and foremost, I am deeply grateful to God for the opportunity to embark on this Master's journey and for guiding me through its challenges and rewards.

My sincerest appreciation goes to my esteemed supervisor, Prof. Dr. Anis Safura Ramli, whose unwavering guidance, patience, and encouragement brought out the best in me. I am equally thankful to my co-supervisors, Assoc. Prof. Dr. Mohamed Syarif Bin Mohamed Kassim and Assoc. Prof. Dr. Noorhida Baharudin, for their invaluable support and unwavering commitment throughout this process.

I am also indebted to for their generous sharing of knowledge and expertise. To my colleagues, friends, and special one,

your unwavering support, both mental and physical, has been invaluable. I wish you all the best in your future endeavours.

My heartfelt thanks extend to the dedicated staff members of the Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM), the compassionate nurses and phlebotomists from 11 MOH Primary Care Clinics and UiTM Specialist Clinic, and all the patients who generously participated in this study. Your contributions have been instrumental in advancing scientific knowledge.

Finally, my deepest gratitude goes to my beloved parents,
for their unconditional love and unwavering support throughout my life. I would also like to express my heartfelt thanks to my sister, for her constant encouragement and love. I am also grateful to my extended family and friends for their constant belief in me. This thesis is dedicated to all my loved ones.

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CHAPTER 1
INTRODUCTION

1.1 Research Background

Familial hypercholesterolemia (FH) is the most common inherited form of hyperlipidaemia, with an autosomal dominant inheritance pattern (Najam & Ray, 2015). It is caused by pathogenic variants (PVs) in genes encoding proteins involved in LDL cholesterol (LDL-c) metabolism, primarily the *LDL receptor* (*LDLR*). These PVs lead to markedly increased serum LDL-c levels, which can accelerate the development of atherosclerosis and premature coronary artery disease (PCAD) (Marks et al., 2003). Mutations in *Apolipoprotein B-100* (*APOB100)* and *Proprotein Convertase Subtilisin/Kexin Type 9* (*PCSK9)* genes are also associated with autosomal dominant form of FH (Al-Khateeb et al., 2011; Austin et al., 2004). On the other hand, mutations in the *low-density lipoprotein receptor adaptor protein 1* (*LDLRAP1*) genes have been associated with autosomal recessive form of FH (Tada et al., 2015). *LDLR* mutations are the most common genetic cause of FH (90-95%), followed by *APOB-100* (5-10%), *PCSK9* (<3%) and *LDLRAP1* is quite rare and not reported yet (Bruikman et al., 2017; Sun et al., 2018). Over 2000 *LDLR* variants have been reported to date in the Human Gene Mutation Database (Miroshnikova et al., 2021), which suggests that these mutations are the most common cause of FH. *LDLR* mutations impair LDL-c uptake, while *APOB-100* mutations affect LDL-c binding to *LDLR* which may cause FH (Gidding et al., 2015; Sarraju & Knowles, 2019). However, individuals with PV in *APOB-100*, generally have less severe phenotype compared to FH individuals with PV in *LDLR* (Iacocca & Hegele, 2017). With regards to *PCSK9* gene, a gain-of-function (GOF) mutation increases *PCSK9* activity, which degrades *LDLR* and elevates LDL-c (Gidding et al., 2015). *LDLRAP1* encodes a protein that serves as an adaptor for LDL receptor endocytosis in the liver cells causing an increase in the LDL-c level (Tada et al., 2015).

There are several established diagnostic criteria for FH diagnosis, such as the DLCC (Watts et al., 2011), SB (Steering & Register, 1999), United States Make Early Diagnosis to Prevent Early Deaths (US MEDPED)(Williams et al., 1993) and the Japanese FH management criteria (JFHMC)(Harada-Shiba et al., 2012). DLCC is the