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CLINICAL CHARACTERISTICS AND ONE-YEAR TREATMENT OUTCOMES IN A COHORT OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA IN SINGAPORE: FHCARE REGISTRY

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INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant condition characterized by high low-density lipoprotein cholesterol (LDL-C), increasing the risk for premature cardiovascular disease (CVD). The gold standard for diagnosis is the identification of the pathogenic mutation (*LDLR, APOB* and *PCSK9*). We aim to compare clinical characteristics and treatment outcomes in patients with different FH-causing variants.

METHODOLOGY

Patients with possible and definite FH using the Simon-Broome criteria were recruited from acute hospitals and specialist centers in Singapore. Biochemical indices including total cholesterol (TC) and LDL-C were measured in CAP-accredited clinical laboratories. Genetic analysis of peripheral blood cells was performed in the same research laboratory using next-generation sequencing on lipid-related genes, including *LDLR, APOB* and *PCSK9*. CVD was defined as myocardial infarction, ischemic stroke and peripheral arterial disease.

RESULTS

From June 2015 to July 2023, 965 probands were recruited. The median age at entry was 39.7 years (range 29.6 to 53.4), BMI of 25.2 ± 4.68 kg/m^2 with a predominance of males (65%). In those with heterozygous FH, pathogenic and likely pathogenic variants were predominantly *LDLR* (n = 207), followed by *APOB* (n = 22) and *PCSK9* (n = 2). Comparing heterozygous *LDLR* versus no variants and *APOB* variants, those with *LDLR* variants were significantly younger, had significantly higher TC and LDL-C levels (mmol/l): (8.43 ± 1.89) and (6.70 ± 1.87) versus (7.47 ± 1.53) and (5.65 ± 1.21) vs (7.05 ± 1.41) and (5.45 ± 1.28), p <0.0001, higher prevalence of xanthomas, n = 55(23.0%) vs 50(7.5%) and 2 (9.1%), p <0.0001, lower prevalence of hypertension 21(8.8%), 115(18.2%), p = 0.036. (17.2%) and lower prevalence of type 2 diabetes: 14(6.0%) vs 75(11.2%) and 2(9.1%), p = 0.038. There were no statistical differences in the prevalence of CVD and corneal arcus.

At recruitment, a significantly higher proportion of those with LDLR variants vs no variants and APOB variants were on high-intensity statins: 94 (41.2%), 149 (23.4%) and 4 (20.0%), p = 0.001, a significantly higher proportion of patients with *LDLR* and *APOB* variants were on ezetimibe: 74 (37.0%), 5(31.3%) vs 91(16.3%), p <0.0001 After treatment for 12 months. Those with *LDLR* variants vs no variant vs *APOB* variants: TC (mmol/l): (5.34 ± 1.82) vs (5.40 ± 1.79) and (5.13 ± 1.09), p = 0.457. LDL-C: (3.64 ± 1.65) vs (3.47 ± 1.53) and (3.45 ± 1.00), p = 0.067. In those with *LDLR* variant vs no variants and *APOB* variants: 39(57.4%) were on high-intensity statins, p = 0.270. Those with *LDLR* variants vs no variant vs *APOB* variants: Those who achieved 50% LDL-lowering from baseline and target LDL-C<1.8 mmol/l: 15(5.3%), vs 53(8.0%) vs 1(4.8%), p = 0.705.

CONCLUSION
Our data showed that, despite being younger, patients with *LDLR* variants had significantly higher TC and LDL-C levels at baseline, lower prevalence of diabetes and hypertension, and similar prevalence of CVD. While TC and LDL-C levels were significantly lower in all groups after 12 months, not all patients were on high-intensity statins. Probands attaining LDL-C goals were low, suggesting undertreatment. Increased awareness for treatment in these patients should be emphasized.

KEYWORDS
familial hypercholesterolemia, statins, ezetimibe, *LDLR*, *APOB*

OBESITY

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THE ASSOCIATIONS OF ALBUMINURIA AND METABOLIC SYNDROME WITH ALL-CAUSE MORTALITY IN PATIENTS WITHOUT SIGNIFICANT CORONARY ARTERY DISEASE

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INTRODUCTION
Metabolic syndrome is a constellation of cardiovascular risk factors associated with a higher risk of mortality. Albuminuria was previously part of the criteria for metabolic syndrome. We investigated the associations of albuminuria and metabolic syndrome with all-cause mortality among patients without significant coronary artery disease.

METHODOLOGY
We enrolled 1,394 patients who had coronary angiography-proven coronary artery disease but no history of diabetes between 2009 and 2013. All patients underwent an oral glucose tolerance test to determine their glucose regulation state. Metabolic syndrome was determined using the criteria of the National Cholesterol Education Program Adult Treatment Panel III. A spot urine sample was collected to determine the urinary albumin to creatinine ratio (UACR). Information on all-cause mortality was confirmed until March 2023. Cox-proportional hazard models were conducted to examine the associations of metabolic syndrome and albuminuria with all-cause mortality.

RESULTS
A total of 551 patients without significant coronary artery disease were analyzed. After a median follow-up period of 8.94 years, there was no significant difference in all-cause mortality in patients with and without metabolic syndrome (adjusted HR 0.989, 95% CI: 0.530-1.846, $p = 0.971$). In contrast, the presence of albuminuria was associated with an increase in the risk of mortality in both unadjusted (HR 3.683, 95% CI: 2.105- 6.445, $p < 0.001$) and adjusted (HR 2.763, 95% CI: 1.559-4.894, $p < 0.001$) HR models, respectively. Further classification depending on the level of albuminuria showed that the presence of microalbuminuria is associated with a trend towards increased mortality (HR 1.950, 95% CI: 0.971-3.916, $p = 0.061$) while the presence of macroalbuminuria is associated with an almost eight-fold increase in mortality (HR 7.901, 95% CI: 3.272-19.079, $p < 0.001$).

CONCLUSION
We found albuminuria to be an independent predictor of long-term all-cause mortality even in patients without significant coronary artery disease and no history of diabetes. The presence of metabolic syndrome was not associated with increased mortality. Our findings suggest that albuminuria should be screened and monitored even amongst patients without significant coronary artery disease.

KEYWORDS
albuminuria, non-significant coronary artery disease, metabolic syndrome, mortality