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**Polygenic Risk Score Significantly Predicted Coronary Heart Disease Death among those
with Type 2 Diabetes in The Malaysian Cohort**

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ABSTRACT

Polygenic risk scores (PRS) have been widely researched to measure the risk of coronary heart disease (CHD), however, they are mainly optimised for the Caucasian population. There is a lack of PRS specifically targeting the Malaysian population. This study was aimed at developing a PRS to predict CHD death risk among type 2 diabetes (T2D) participants in The Malaysian Cohort project (TMC). In Phase I, T2D TMC participants (224 “T2DM+CHD” as cases, 625 “T2DM” as controls) were genotyped using genomic microarray followed by genetic imputations using GenomeAsia reference panel to identify single nucleotide polymorphisms (SNP) associated with CHD death and to construct the PRS. In Phase II, T2D participants without known CHD during recruitment (n=806) and followed-up until their deaths, were analysed based on their PRS risk categories. The outcome of interest was CHD deaths in both phases. From the 56 CHD-related SNPs with suggestive genome-wide significance identified in Phase I ($P < 5.00 \times 10^{-5}$), PRS was constructed using 15 SNPs genotyped from the microarray. Compared to “T2DM”, the “T2DM+CHD” had higher PRS scores across ethnicities while the area under the receiver operating curve (AUC) showed the ability of PRS to classify CHD death. Using the cut-off point of 0.8493 (AUC=0.762, sensitivity=64.7%, specificity=73.1%), the odds of CHD death in the high-risk category were 6.96, 7.90, and 22.58 for Malay, Chinese, and Indian, respectively. In Phase II, survival analysis showed that mean survival years were shorter in high-risk than the low-risk category among Malays (6.60 vs 8.92 years), Chinese (6.20 vs 8.66 years), and Indians (7.21 vs 8.60 years). Meanwhile, among high-risk participants, the CHD death risk was 3.32, 3.36, and 12.72 times higher among Malays, Chinese, and Indians, respectively. The potential use of PRS to predict CHD death among T2D patients could assist in the long-term management and risk identification, subsequently enhancing the precision medicine practice in Malaysia.

Keywords: CHD death; coronary heart disease; type 2 diabetes mellitus; single nucleotide polymorphism; polygenic risk score; The Malaysian Cohort Project