Risk prediction of dyslipidemia in long-term survivors of childhood cancer: a report from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS)

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Background: Dyslipidemia, a major cardiovascular risk factor, is often underdiagnosed and undertreated among childhood cancer survivors. At present, there are no available calculators to predict dyslipidemia risk in these individuals.

Methods: Childhood cancer survivors participating in the St. Jude Lifetime Cohort (SJLIFE; discovery, n=4,038) and the Childhood Cancer Survivor Study (CCSS; validation, n=7,510) with genotype data were assessed for dyslipidemia (CTCAE grade ≥2 hypercholesterolemia and/or hypertriglyceridemia). Demographic, cancer treatments previously associated with dyslipidemia, comorbidities, and five externally-validated general-population polygenic risk scores (PRSs) for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were evaluated at cohort entry (5 years post-primary cancer diagnosis) as potential predictors for dyslipidemia risk. Cox proportional hazards regression was used to predict the risk of dyslipidemia, with predictors selected by elastic net with a hyperparameter selected by 10-fold

cross-validation. Model performance was evaluated using the time-dependent area under the receiver operating characteristic curve (AUC) at 25 years beginning cohort entry. Based on the predicted hazard ratio (HR) from the final model, survivors were classified into low (predicted HR <1.5), moderate (HR ≥1.5 and <3), and high (HR ≥3) risk groups. The cumulative incidence of dyslipidemia over the next 25 years following cohort entry was then estimated by group.

Results: Dyslipidemia was clinically-identified in 533 (13.2%) SJLIFE and self-reported in 925 (12.3%) CCSS participants. The AUC of a clinical model including demographics (sex, race, age at cancer diagnosis), cancer treatments (cisplatin, carboplatin, brain and abdominal irradiation), and comorbidities at cohort entry (growth hormone deficiency, hypothyroidism) was 0.69 (95% CI: 0.65-0.72) in SJLIFE and 0.65 (95% CI: 0.62-0.67) in CCSS. Adding the five lipid-trait PRSs significantly increased AUC to 0.76 (95% CI: 0.73-0.79, $P=3.2\times10^{-6}$) in SJLIFE and 0.71 (95% CI: 0.69-0.73, $P=5.1\times10^{-8}$) in CCSS. In high-risk group, the cumulative incidence of dyslipidemia with the inclusion of PRSs increased from 22.8% (95% CI: 20.2%-25.3%) to 28.28% (95% CI: 24.9%-31.3%) in SJLIFE, and from 13.9% (95% CI: 12.7%-15.0%) to 17.0% (95% CI: 15.5%-18.5%) in CCSS. The cumulative incidences in the low- and moderate-risk groups were similar regardless of the inclusion of the PRSs.

Conclusions: To our knowledge, this is the first independently validated prediction model estimating dyslipidemia risk among adult survivors of childhood cancer. In addition to clinical and treatment characteristics, the model incorporated genetic predictors, enhancing the accuracy of risk classification and facilitating personalized preventive cardiovascular counselling and screening.