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Title: Predicting therapy-induced cardiomyopathy in long-term survivors of childhood cancer: a report from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS).

Background: Cancer-therapy-induced cardiomyopathy (CCM) is the leading noncancer cause of mortality among long-term survivors of childhood cancer, the prevalence of which increases with age. Early identification of survivors at risk provides opportunities for targeted prevention strategies. Here, we developed and validated a clinically applicable CCM prediction model based on survivor characteristics, treatment exposures and inherited genetic variation among long-term survivors of childhood cancer.

Methods: Long-term survivors from SJLIFE (training cohort; n=3,350; median age 34 years, range 8-72 years) and CCSS (validation cohort; n=7,008; median age 36 years, range 11-64 years) were assessed by the five different general population polygenic risk scores (multiPRS) for dilated cardiomyopathy, hypertrophic cardiomyopathy, heart failure, ejection fraction and left ventricular end systolic volume. Multivariable logistic regression was used to predict 15-year risk of the CCM (defined as CTCAE grade ≥3 cardiomyopathy requiring heart failure medications or heart transplantation or leading to death). Model performance was assessed by the area under the receiver operating characteristic curve (AUC).

Results: CCM was clinically identified in 150 (4.5%) SJLIFE and self-reported in 156 (2.1%) CCSS survivors, respectively. AUC of clinical models with attained age, sex, age at primary cancer diagnosis, cumulative anthracycline dose, mean heart radiation dose (heart RT), and genetic ancestry was 0.81 (95% CI, 0.78-0.85) in SJLIFE and 0.78 (95% CI, 0.74-0.81) in CCSS. Inclusion of cardiovascular risk factors (hypertension, dyslipidemia, and diabetes) significantly increased AUC to 0.83 (95% CI, 0.80-0.87; P=0.011; SJLIFE) and 0.84 (95% CI, 0.80-0.87; P<0.001; CCSS). The addition of the multiPRS further provided significant but modest increases in AUC in SJLIFE (0.84; 95% CI, 0.81-0.87; P=0.022) and CCSS (0.85; 95% CI, 0.81-0.88; P=0.031). In low-risk survivors (exposed to <100 mg/m² anthracyclines and <15 Gray heart RT), we observed a possibly larger magnitude AUC increase after adding multiPRS, 0.73 (95% CI, 0.65-0.82) to 0.76 (95% CI, 0.68-0.83; P=0.11) in SJLIFE and 0.77 (95% CI, 0.65-0.90) to 0.82 (95% CI, 0.69-0.94; P=0.073) in CCSS.
Conclusions: Inherited polygenic factors contributed significantly to improve CCM prediction over available clinical risk factors and may be of benefit to low-risk survivors for whom routine cardiac surveillance is not currently recommended.