Title: Development and validation of diabetes mellitus risk prediction models in survivors of childhood cancer: a St. Jude Lifetime Cohort Study (SJLIFE) and Childhood Cancer Survivor Study (CCSS) report

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Background: Diabetes mellitus (DM) is a prevalent late effect among survivors of childhood cancer. We developed and validated models to predict DM risks in survivors based on clinical characteristics available at the 5-year cancer survival milestone.

Methods: Risk prediction models estimating DM risks by ages 30 and 40 years were trained using data from 5-year survivors in SJLIFE. DM was defined by Common Terminology Criteria for Adverse Events (CTCAE) grades ≥2 for abnormal glucose metabolism or hemoglobin A1c levels ≥6.5%. The XGBoost (eXtreme Gradient Boosting) machine learning algorithm was used to develop models using 3 levels of treatment information: (1) simple model, with treatment exposures without dose; (2) dose model, including delivered cranial, abdominal, and pelvic radiation therapy (RT) and cumulative chemotherapy doses; and (3) pancreatic tail dosimetry model. Other predictors included: sex; race/ethnicity; cancer diagnosis age; total body irradiation (TBI); hematopoietic cell transplantation (HCT). In those with available data, we developed models that also included categorical 5-year survival body mass index (BMI). In SJLIFE, cross-validated age-specific metrics (AUROC/AUPRC: area under the receiver operating characteristic curve/precision-recall curve) evaluated risk prediction performance. Model external validation was conducted in CCSS with self-reported DM (CTCAE grades ≥2). We compared models with Children's Oncology Group Long-Term Follow-Up Guidelines (COG LTFU, v6.0) recommending blood sugar screening following any abdominal RT or TBI.

Results: Among 5086 SJLIFE participants, 147 and 424 developed DM by ages 30 and 40, with incidences of 4% and 12%, respectively. Simple, dose, and pancreatic models featuring treatment characteristics demonstrated modest discrimination (AUROC range: 0.62-0.69) and precision (AUPRC range: 0.09-0.29), with the simple model showing the weakest performance. However, when 5-year survival BMI was added (N=3561), each showed significantly improved discrimination (AUROC: 0.75-0.77, $P<0.001$) and precision (AUPRC: 0.20-0.24, $P<0.01$) in predicting DM risk by age 30. For DM risk prediction by age 40, the performance of models with BMI was sustained (AUROC: 0.74-0.80; AUPRC: 0.32-0.51). After adding 5-year survival BMI, abdominal/pancreatic tail RT and TBI were less influential; cancer diagnosis age, sex, and cranial

RT were more influential. In external validation among CCSS survivors with BMI data (N=5518, incidence by age 30 and 40: 2% and 10%), all models predicting DM risk by age 30 showed good discrimination and precision (AUROC: 0.78-0.79; AUPRC: 0.13-0.14). Small decreases in performance for models predicting DM risk by age 40 were observed (AUROC: 0.73-0.73; AUPRC: 0.14-0.23). In CCSS, COG LTFU guideline-based classification was less predictive (AUROC: 0.56-0.66, P<0.05; AUPRC: 0.03-0.08, P<0.10). Among survivors recommended for screening, the DM incidence was 4% by age 30; the best model with BMI stratified risks by age 30 into low (<5%), medium (5-19%), and high (≥20%) risk groups with corresponding DM incidences of 1%, 6%, and 31%.

Conclusion: Leveraging treatment and 5-year survival BMI information, our newly developed models stratify childhood cancer survivors into distinct DM risk groups by ages 30 and 40 years. Communicating personalized risks can support interventions to prevent DM and reduce cardiovascular disease risk.