# Symptom-Based Individual Risk Prediction for Late Mortality: A Report from the Childhood Cancer Survivor Study (CCSS)

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**Background:** Survivors of childhood cancer face a higher risk of late mortality than the general population. Yet no prior study has integrated patient-reported symptoms and social determinants of health with treatment exposures to predict late mortality risks.

**Methods:** A total of 9,569 survivors from the CCSS cohort who completed two surveys (baseline [T1], follow-up [T2]) reported 37 symptoms spanning 10 domains (cardiac, pulmonary, sensory, musculoskeletal, nausea, pain, fatigue, memory, anxiety, depression) at T1 and T2. Additional predictors included sociodemographic and lifestyle factors, address-linked Area Deprivation Index, and treatment exposures. Standardized mortality ratios (SMRs) were calculated, stratified by individual symptoms and domains at T2 and T1-T2 change, to compare mortality rates between survivors and the general population five years after T2. Multivariable Cox proportional hazards models with LASSO regularization were used to predict 5-year health-related and cause-specific late mortality (cardiac, pulmonary, subsequent neoplasm) after T1 and T2. The dataset was randomly split into training and test datasets in a 7:3 ratio, and prediction performance was assessed using the area under the receiver operating characteristic curve (AUC).

**Results:** Among 9,569 survivors (52.4% female), the median age at T1 and T2 was 27.1 and 36.9 years; median years from diagnosis to T1 and T2 were 16.6 and 26.3, respectively. Acute lymphoblastic leukemia (31.3%) and Hodgkin lymphoma (15.3%) were the most frequently observed primary diagnoses. Compared with the sex/age/race/calendar year-matched general population, survivors had significantly higher health-related mortality 5 years after T2, with SMR of 4.21 (95%CI 3.76-4.70). Presence of cardiac and pulmonary symptom domains at T2, and their persistence and worsening from T1 to T2, were associated with >10-fold higher SMRs. Presence, persistence, and worsening of individual symptoms, including angina pectoris, chronic cough, and trouble breathing, were also associated with SMRs >10. For 5-year health-related mortality after T2, the symptom-based model yielded an AUC of 0.79 (95%CI 0.75-0.84), surpassing the symptom-agnostic model (AUC 0.76, 95%CI 0.71-0.81) and the T1 model (AUC 0.73, 95%CI 0.67-0.79). Cause-specific models also showed strong prediction performance, with symptom-based AUCs of 0.87 for cardiac, 0.89 for pulmonary, and 0.78 for subsequent neoplasms mortality.

**Conclusion:** Adult survivors of childhood cancer experience elevated SMRs, with the greatest excess late mortality observed in those reporting cardiopulmonary symptoms. Longitudinal symptom-based models yielded the highest predictive performance, outperforming single-time-point and symptom-agnostic models. Incorporating symptom data can strengthen mortality prediction and inform targeted survivorship care.