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Stage and Age Characterize Distinct, Time-Varying Mortality Pathways in Older Adults With Bladder Cancer: A Population-Based Competing-Risk Study

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Research Article

Keywords: Bladder cancer, older adults, competing risks, cause-specific mortality, cumulative incidence, SEER

Posted Date: November 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11180119/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Older adults with bladder cancer face both cancer-related and competing mortality. We examined how tumor stage and age were associated with these outcomes and how their relative hazards changed during follow-up.

Methods

This retrospective cohort included adults aged ≥ 75 years with bladder urothelial carcinoma diagnosed during 2010–2015 in the Surveillance, Epidemiology, and End Results 17 Registries database. We used Aalen–Johansen estimators, adjusted cause-specific Cox models and smoothed monthly hazards. A sustained crossover required other-cause hazard to exceed bladder-cancer hazard for six consecutive monthly points with adequate numbers at risk. Secondary prediction models underwent internal temporal validation.

Results

Among 38,852 patients, stage IV versus stage 0a was associated with a bladder-cancer death hazard ratio of 22.92 (95% confidence interval 21.24–24.72). For other-cause death, the hazard ratio for age ≥ 90 versus 75–79 years was 3.68 (3.49–3.88). Other-cause hazard predominated near diagnosis in stages 0a, 0is and I. Sustained crossovers occurred at approximately 40.5 months in stage II and 56.5 months in stage III; no stable crossover was identified in stage IV within the 84-month observation window. Bladder-cancer death nevertheless remained the more frequent cumulative outcome at 84 months in stages II and III. Temporal-validation areas under the curve at 12, 36 and 60 months were 0.855, 0.822 and 0.800 for bladder-cancer death and 0.629, 0.632 and 0.644 for other-cause death.

Conclusions

Stage showed a steeper gradient for bladder-cancer mortality, whereas age differentiated other-cause mortality more strongly than stage. Their changing balance may inform the timing and focus of survivorship assessment. These population-level patterns do not define treatment thresholds, and age cannot replace an individual geriatric assessment.

Background

Bladder cancer is mainly diagnosed in older adults, but patients with the same tumor stage can have different outcomes and treatment tolerance. Tumor extent describes the cancer burden, while comorbidity, functional impairment, cognitive problems and poor nutrition may affect competing health

risks and the demands of treatment. The International Society of Geriatric Oncology recommends that decisions for older patients with bladder cancer consider health status rather than chronological age alone [1, 2]. The American Society of Clinical Oncology also recommends multidomain geriatric assessment for older adults receiving systemic cancer therapy [3]. Prognostic assessment in this population therefore needs to account for both cancer and competing illness.

Deaths unrelated to the index bladder cancer account for a substantial part of mortality after diagnosis. Population-based studies have described these deaths during early follow-up and long-term survivorship [4–6]. Studies of patients undergoing radical cystectomy have also examined the association of age with other-cause mortality [7, 8]. These reports establish the relevance of competing mortality, but leave less clear how the associations of stage and age differ between the two mortality endpoints across the full stage spectrum.

This distinction matters in older patients with non-muscle-invasive bladder cancer, who may undergo repeated procedures and prolonged surveillance while living with geriatric conditions [9]. Patient priorities may also place independence and quality of life ahead of some conventional oncological outcomes [10]. Recent studies of geriatric assessment and frailty in bladder cancer reinforce the limitations of chronological age as a measure of vulnerability [11–13]. An age gradient in registry-based mortality should consequently prompt individual assessment, rather than be interpreted as a direct measure of frailty.

Prognosis also changes with time survived. Conditional-survival studies after radical cystectomy, trimodal therapy and in broader registry cohorts describe how outcome probabilities evolve during follow-up [14–17]. Competing-risk models and nomograms estimate cancer-specific or all-cause mortality in selected bladder-cancer populations [18–20]. A complementary question is when, among patients still alive, the hazard of other-cause death becomes higher than the hazard of bladder-cancer death. The timing of this change may differ by stage and age, even when cumulative cancer mortality remains high.

We examined adults aged ≥ 75 years with bladder urothelial carcinoma in the SEER 17 Registries database. This threshold focused the analysis on an older population while retaining sufficient patients across stage groups. We assessed whether stage and age showed different associations with bladder-cancer and other-cause mortality, and whether the balance between the two hazards changed during follow-up. Cumulative-incidence estimates, adjusted cause-specific models and a sustained-hazard crossover analysis addressed these questions. As a secondary analysis, we evaluated diagnosis-time prediction of both outcomes in a temporally separated validation cohort. The study describes population-level mortality patterns; it was not designed to select treatments or replace individual geriatric assessment.

Methods

Study design and data source

We conducted a retrospective population-based cohort study using the SEER Research Data, 17 Registries, November 2024 submission, covering diagnoses from 2000 to 2022 [21]. We used the version linked to county-level attributes and accessed the data on 27 August 2026. Diagnoses were restricted to 2010–2015 to use a consistent AJCC seventh-edition staging system [22]. This period also allowed assessment of mortality over an 84-month observation window. Reporting followed the STROBE recommendations [23]; the completed checklist is provided as Additional file 3.

Eligibility and cohort construction

We selected adults aged ≥75 years with bladder urothelial carcinoma, defined by ICD-O-3 site codes C67.0–C67.9 and histology codes 8120 or 8130. No additional restrictions on treatment, survival duration or stage were applied during the SEER*Stat export. Study size was determined by all eligible records in the selected database and diagnosis period.

The export contained 41,526 tumor records. Records with unknown AJCC stage (n = 1,514), unknown survival time (n = 1), or unknown cause of death (n = 335) were excluded. Among the remaining 39,676 eligible records, we retained the earliest diagnosis year for each Patient ID, using SEER sequence number to resolve ties. The primary cohort comprised 38,852 unique patients. Records with unknown cause of death were reintroduced only in separate record-level sensitivity analyses.

Variables and outcomes

The main variables were Derived AJCC Stage Group, seventh edition (0a, 0is, I, II, III and IV), and age group (75–79, 80–84, 85–89 and ≥90 years). Sex, race and diagnosis year were included in the adjusted association models. The secondary prediction models additionally included marital status and tumor grade. All variables were obtained from SEER. Unknown race, marital status and grade were retained as separate categories; no imputation was performed.

Death attributed to the index bladder cancer and death from other causes were treated as mutually exclusive competing events. Outcomes were defined using the SEER cause-specific and other-cause death classification variables [21]. Other-cause death could include another malignancy as well as non-cancer causes and was not interpreted as a specific disease endpoint.

Follow-up

Follow-up began at diagnosis and ended at death, the last recorded follow-up, or 84 months, whichever occurred first. Deaths recorded at 84 months were retained as events; deaths after 84 months were administratively censored at that point. Records with zero months of survival were retained and assigned

0.5 months for the time-to-event analyses, including cumulative incidence, Cox models and hazard smoothing. The primary analyses used one record per patient. Analyses retaining all eligible tumor records were considered supportive sensitivity analyses because their unit of analysis differed from the primary cohort.

Cumulative incidence and adjusted associations

Aalen–Johansen estimators were used to estimate the cumulative incidence of each death endpoint at 12, 36, 60 and 84 months [24]. Stage groups were compared using Gray tests [25]. Cause-specific Cox models were fitted separately for each endpoint, with the competing death censored at its occurrence [26]. Models included stage, age group, sex, race and diagnosis year centered at 2010. Sex, race and diagnosis year accounted for measured demographic differences and calendar time when comparing stage and age associations. Efron's method handled tied event times, and robust variance estimates were clustered by Patient ID.

Robust joint Wald tests assessed the joint associations of the stage and age coefficient blocks with each endpoint. Chi-square statistics divided by their degrees of freedom were reported as descriptive comparisons, not as measures of causal contribution or validated variable-importance rankings. Scaled Schoenfeld residuals with a Kaplan–Meier time transformation assessed proportional hazards globally and by covariate. Where this assumption did not hold, hazard ratios were interpreted as follow-up summary associations rather than constant effects. An exploratory stage-by-age interaction was assessed using a 15-degree-of-freedom robust joint Wald test.

Dynamic hazards and crossover analysis

Cause-specific cumulative-hazard increments were smoothed with a Gaussian kernel using a six-month bandwidth and reflection at the origin and the 84-month boundary. Hazards were evaluated at monthly midpoints from 0.5 to 82.5 months. A sustained crossover was the first grid point at which other-cause hazard exceeded bladder-cancer hazard for six consecutive monthly points. Every point in that six-month sequence required a risk set of at least 100 patients and at least 5% of the stratum's baseline cohort. If this condition held from the first grid point, the stratum was described as other-cause predominant near diagnosis rather than as a later crossover.

Patient-level bootstrap resampling repeated the smoothing and crossover procedure, using 300 replicates for stage-level estimates and 150 for stage-by-age estimates. We reported the proportion of replicates with an eligible crossover. Percentile 95% intervals were calculated from the 2.5th and 97.5th percentiles among replicates with a finite crossover and were therefore conditional on detecting one. A finite point estimate was considered stable when at least 80% of replicates yielded an eligible crossover. Otherwise, no stable crossover was reported. These criteria also prevented late estimates based on an inadequate risk set.

Bandwidth sensitivity analyses used 3-, 6- and 12-month kernels, with 200 patient-level bootstrap replicates per analysis. Separate record-level analyses retained all eligible tumor records and reassigned unknown-cause deaths to bladder-cancer death or other-cause death in two extreme scenarios. These earlier record-level analyses used origin reflection and were interpreted as supportive checks, not exact replications of the patient-level estimator. Details are provided in Additional file 1.

Secondary prediction analysis

The patient-level cohort was divided by diagnosis year into development (2010–2013) and temporal-validation (2014–2015) samples. This was internal temporal validation within the same registry system, not external validation. Two cause-specific Cox models used stage, age group, sex, race, marital status, grade and centered diagnosis year. Treatment variables were excluded. The prediction models used Breslow's method for tied event times. Absolute risks at 12, 36 and 60 months were obtained by combining both cause-specific hazards and the resulting overall survival function [26].

Performance was evaluated using inverse-probability-of-censoring weighting (IPCW), with the marginal censoring distribution estimated by reverse Kaplan–Meier in the validation sample. For each endpoint, cumulative/dynamic AUCs compared patients who died from that cause by the prediction horizon with patients who did not, including competing deaths [27]. Brier scores were calculated as IPCW squared prediction errors normalized by the sum of weights. Patients censored before the horizon did not contribute known outcomes to these comparisons.

Calibration plots compared mean predicted risk with IPCW observed risk within prediction deciles. Calibration intercepts and slopes were estimated by weighted linear regression on the risk scale. They are descriptive summaries and should not be interpreted as conventional logit-scale calibration parameters [28]. Validation-sample bootstrap intervals used 200 resamples, with censoring weights recalculated but the prediction models held fixed. These intervals describe validation-sample uncertainty, not model-development uncertainty or optimism correction. Prediction details are provided in Additional file 2, with reporting informed by TRIPOD [29].

Software and reporting

Analyses were performed in R and Python. Principal libraries included survival, cmprsk and data.table in R, and NumPy, pandas and SciPy in Python. Tests were two-sided, with $P < 0.05$ used as a descriptive significance threshold. Interaction, crossover, sensitivity and prediction analyses were exploratory; no multiplicity adjustment was applied. Findings were interpreted through effect estimates, uncertainty and consistency rather than isolated P values.

OpenAI Codex (OpenAI) assisted with language editing, code review and figure formatting. The authors reviewed the generated material and remained responsible for the analyses and interpretation. Further

details are provided in the Acknowledgements.

Results

Cohort and baseline characteristics

The primary cohort included 38,852 patients (Fig. 1). There were 13,851 patients aged 75–79 years (35.7%), 12,429 aged 80–84 years (32.0%), 8,578 aged 85–89 years (22.1%) and 3,994 aged ≥90 years (10.3%). Men accounted for 76.0% and White patients for 90.6%. Stage 0a was most common (n = 18,198), followed by stage I (n = 9,810), stage II (n = 5,445), stage IV (n = 2,102), stage 0is (n = 1,876) and stage III (n = 1,421). Baseline characteristics are shown in Table 1. Race was unknown for 131 patients (0.3%), marital status for 3,103 (8.0%) and grade for 8,903 (22.9%); these categories were retained.

Within the 84-month window, 10,616 patients died from bladder cancer and 15,440 from other causes; 12,796 were censored, including 452 before 84 months. Total observed analysis time was 1,866,175 patient-months, with a median of 49 months (interquartile range 16–84). These summaries describe time to death or censoring, not a reverse-Kaplan–Meier estimate of potential follow-up.

Cumulative incidence of competing deaths

The cumulative incidence of both endpoints differed across stage groups (Gray tests, both $P < 0.001$; Fig. 2). At 12 months, other-cause mortality exceeded bladder-cancer mortality in stage 0a (7.24% vs 2.12%), stage 0is (7.41% vs 4.21%) and stage I (9.53% vs 9.05%). Bladder-cancer mortality was higher in stage II (32.04% vs 12.63%), stage III (32.70% vs 11.77%) and stage IV (61.50% vs 9.96%).

At 84 months, other-cause mortality remained higher in stage 0a (45.10% vs 11.72%), stage 0is (41.43% vs 18.98%) and stage I (42.34% vs 27.92%). Bladder-cancer mortality remained higher in stages II, III and IV (54.17% vs 31.18%, 56.82% vs 28.29%, and 79.98% vs 14.92%, respectively). Table 2 presents stage-specific estimates; age-stratified estimates are provided in Additional file 1.

Dynamic hazards and crossover

Other-cause hazard predominated near diagnosis in stages 0a, 0is and I (Fig. 3). Sustained crossovers occurred at 40.5 months in stage II (conditional bootstrap 95% interval 36.5–45.5) and 56.5 months in stage III (48.5–62.5). Both crossovers were detected in all 300 stage-level bootstrap replicates. The stage IV point estimate was 77.5 months, but an eligible crossover was detected in only 42% of replicates and was classified as unstable. Stage-by-age estimates are shown in Fig. 4; most early-stage strata were other-cause predominant near diagnosis.

Sensitivity analyses

Alternative bandwidths yielded stage II crossover estimates of 40.5–43.5 months and stage III estimates of 53.5–56.5 months. The stage IV crossover remained unstable. Record-level extreme-case assignments of unknown-cause deaths showed the same broad stage pattern. These results were supportive, given differences in the analysis unit and smoothing implementation. Detailed estimates and bootstrap detection proportions are provided in Additional file 1.

Cause-specific mortality associations

Stage showed a steeper gradient for bladder-cancer death than for other-cause death (Fig. 5). Relative to stage 0a, the bladder-cancer death hazard ratio increased from 1.70 (95% CI 1.52–1.90) in stage 0is to 22.92 (21.24–24.72) in stage IV. The corresponding stage IV hazard ratio for other-cause death was 1.49 (1.32–1.69). Compared with age 75–79 years, other-cause death hazard ratios were 1.52 (1.46–1.59), 2.31 (2.21–2.41) and 3.68 (3.49–3.88) for ages 80–84, 85–89 and ≥90 years. Corresponding bladder-cancer death hazard ratios were 1.36 (1.29–1.44), 1.93 (1.82–2.04) and 2.87 (2.68–3.07).

Joint Wald statistics differed by endpoint. For bladder-cancer death, the stage block had $\chi^2 = 9347.3$ (5 df; $\chi^2/df = 1869.5$), compared with $\chi^2 = 1117.2$ for age (3 df; $\chi^2/df = 372.4$). For other-cause death, the age block had $\chi^2 = 2854.5$ (3 df; $\chi^2/df = 951.5$), compared with $\chi^2 = 192.6$ for stage (5 df; $\chi^2/df = 38.5$). All four tests had $P < 0.001$. These descriptive comparisons were consistent with the endpoint-specific gradients. Exploratory stage-by-age interaction tests yielded $\chi^2 = 48.64$ (15 df; $P = 2.00 \times 10^{-5}$) for bladder-cancer death and $\chi^2 = 18.66$ (15 df; $P = 0.230$) for other-cause death.

Proportional-hazards tests were significant globally for bladder-cancer death ($\chi^2 = 817.14$, 14 df, $P < 0.001$) and other-cause death ($\chi^2 = 166.87$, 14 df, $P < 0.001$). Stage and sex were non-proportional in the bladder-cancer model (both $P < 0.001$). In the other-cause model, stage and age were non-proportional (both $P < 0.001$), as was diagnosis year ($P = 0.023$). Hazard ratios should therefore be read as follow-up summary associations, not effects that remain constant over time.

Secondary prediction analysis

The development and temporal-validation cohorts included 25,912 and 12,940 patients, respectively. In temporal validation, IPCW AUCs at 12, 36 and 60 months were 0.855, 0.822 and 0.800 for bladder-cancer death, compared with 0.629, 0.632 and 0.644 for other-cause death (Fig. 6; Table 3). Other-cause mortality was thus less well discriminated by the recorded variables. Risk-scale calibration slopes ranged from 1.004 to 1.235 for bladder-cancer death and from 0.919 to 1.066 for other-cause death. Intercepts ranged from −0.019 to 0.007 across endpoints and horizons. The bladder-cancer model showed the largest calibration deviation at 12 months. Detailed coefficients, uncertainty intervals and calibration-decile values are provided in Additional file 2.

Discussion

Principal findings

Stage and age showed different associations with mortality in this cohort of adults aged ≥75 years with bladder urothelial carcinoma. The stage gradient was much steeper for bladder-cancer death, whereas age differentiated other-cause mortality more strongly than stage. These patterns support a descriptive stage–age framework, but do not establish independent biological mechanisms. Age was also associated with bladder-cancer death, and stage was associated with other-cause death. The two dimensions therefore overlap rather than form separate or interchangeable measures of prognosis.

The balance between the two hazards changed during follow-up. Other-cause hazard predominated near diagnosis in stages 0a, 0is and I. In stages II and III, it overtook bladder-cancer hazard later among surviving patients, although cumulative bladder-cancer mortality remained higher at 84 months. No stable stage IV crossover was identified. This distinction between accumulated deaths and the current hazard among survivors is central to the clinical interpretation.

Interpreting the stage and age gradients

The stage gradient is consistent with the importance of anatomic disease extent for bladder-cancer mortality. The stage IV versus stage 0a hazard ratio was approximately 23, substantially larger than the oldest-versus-youngest age-group contrast for this endpoint. Cause-of-death studies have described the burden of cancer and competing deaths [4–6], while cystectomy cohorts have examined mortality in treatment-selected populations [7,8]. Our analysis places both outcomes within the same stage-stratified cohort. The block-level Wald results support this descriptive comparison, but depend on variable coding, category frequencies and precision. They should not be taken as a causal decomposition or universal ranking of prognostic importance.

Stage IV included patients with different disease patterns and should not be equated with metastatic disease alone. Its high early cancer mortality left a small late risk set, making the crossover estimate sensitive to smoothing and resampling. Failure to identify a stable crossover does not establish that other-cause hazard could never predominate. It indicates that the available data did not support a reliable transition within the observation window. Competing illness may remain clinically important even when cancer accounts for most deaths.

Age showed a stronger gradient for other-cause mortality, consistent with studies linking older age to competing death after cystectomy [7,8]. However, the observed age association cannot identify whether an individual patient has frailty, comorbidity or impaired function. SEER lacks these measures. SIOG and ASCO guidance emphasizes direct assessment of health status [1,3], and bladder-cancer studies show the relevance of geriatric conditions, patient priorities and frailty [9–13]. The age gradient is therefore a reason to investigate vulnerability, not a justification for withholding treatment based on age. The exploratory interaction for bladder-cancer death also suggests that the age association varies across stages, although this finding requires confirmation.

What the hazard crossover adds

Conditional-survival analyses estimate future outcome probabilities given survival to a specified time [14–17]. Our crossover analysis instead compares the two cause-specific hazards among patients still alive. These are complementary descriptions. A hazard crossover can occur while cumulative cancer mortality remains higher because the cumulative incidence retains deaths that occurred earlier. In stages II and III, the crossovers at approximately 40.5 and 56.5 months therefore do not mean that the prior cancer burden has disappeared or that cancer surveillance is no longer needed.

The changing hazard balance may help frame survivorship assessment. Patients who survive the period of highest cancer mortality may increasingly face competing health problems. Follow-up can then address comorbidity, function and patient priorities alongside continued cancer surveillance. This interpretation is consistent with geriatric oncology guidance [1,3], but was not tested as a care intervention. The estimated months are descriptive features of this cohort, not thresholds for reducing treatment or changing surveillance schedules. Survival selection, unmeasured health differences and treatment history may all contribute to the observed curves.

In stages 0a, 0is and I, early other-cause predominance does not imply that bladder cancer creates little burden. Repeated cystoscopy, transurethral procedures and intravesical treatment can be demanding for older adults [9]. Decisions still need to consider recurrence and progression, which were not evaluated here, as well as life expectancy and the outcomes patients value [10]. The mortality results provide one part of that assessment rather than a complete account of the benefits and harms of care.

Meaning of the prediction analysis

The secondary models provided better discrimination for bladder-cancer death than for other-cause death. This difference is compatible with the detailed tumor information available in SEER and the absence of direct geriatric measures, although the study cannot show which missing variables would improve prediction. Calibration summaries were reasonably close to their reference values at several horizons, but the 12-month bladder-cancer slope showed a departure from one. Calibration should therefore be assessed by endpoint and horizon rather than summarized as uniformly good.

Previous competing-risk models have estimated outcomes in older adults and non-muscle-invasive bladder-cancer populations [18–20]. The purpose of the present models was to quantify the two mortality endpoints using a common set of diagnosis-time variables, not to establish superiority over those models. AUCs of 0.629–0.644 for other-cause death indicate limited individual discrimination. Acceptable average calibration would not overcome that limitation [28]. The temporal split tests performance in later diagnosis years within SEER; external validation and evaluation in cohorts with geriatric measures are needed before clinical use.

Strengths and limitations

Strengths include a large population-based cohort, competing-risk estimation and one eligible record per patient. Cumulative incidence and smoothed hazards address different aspects of mortality, and sustained-crossover and risk-set criteria reduce reliance on isolated late fluctuations. Patient-level resampling quantified crossover reproducibility. The results were broadly consistent across smoothing bandwidths, while record-level analyses offered supportive checks under different assumptions.

Several limitations remain. Comorbidity, frailty, functional status, cognition, nutrition, renal function, medication burden and treatment intent were unavailable. Residual confounding limits interpretation of the adjusted associations, and an age category cannot substitute for these clinical measures. Other-cause death is a heterogeneous outcome, including deaths from other malignancies, and registry cause-of-death classification may be imperfect. Excluding unknown stage, survival and cause of death may introduce selection bias. Retaining unknown categories for other covariates preserves patients but does not eliminate bias from incomplete measurement.

The earliest eligible record may not represent the clinically dominant cancer in patients with multiple primaries. The supportive record-level sensitivity analyses use a different analysis unit and smoothing implementation, so they do not isolate the effect of record selection. The 2010–2015 diagnosis period ensures consistent AJCC seventh-edition staging but limits transport to contemporary treatment and staging. The cause-specific Cox models violated proportional hazards, restricting their hazard ratios to summary associations. The prediction models also retained proportional-hazards structures; temporal performance does not establish that their risks transport to other settings or later follow-up.

Crossover estimates depend on smoothing, the six-month persistence rule and the risk-set thresholds. Their bootstrap intervals are conditional on detecting a crossover and do not incorporate the probability of no crossover. Detection proportions are therefore essential, particularly for stage IV. The number of bootstrap replicates also limits the precision of interval endpoints. None of these analyses estimates treatment effects, and neither the crossover times nor the prediction models establish the value of changing care. Contemporary external cohorts with direct geriatric measurements are needed to test that clinical relevance.

Conclusions

Among adults aged ≥ 75 years with bladder urothelial carcinoma, stage and age described overlapping but different mortality patterns. Stage showed a pronounced gradient for bladder-cancer death, while age was more strongly associated with other-cause mortality than stage. Other-cause hazard predominated near diagnosis in early-stage disease and later overtook cancer hazard in stages II and III; no stable transition was identified in stage IV. These patterns may help clinicians discuss changing survivorship priorities, but they do not define treatment thresholds. Individual decisions still require assessment of health status, treatment burden and patient preferences.

Abbreviations

AJCC: American Joint Committee on Cancer; AUC: area under the receiver operating characteristic curve; CI: confidence interval; CIF: cumulative incidence function; df: degrees of freedom; HR: hazard ratio; ICD-O-3: International Classification of Diseases for Oncology, third edition; IPCW: inverse-probability-of-censoring weighting; SEER: Surveillance, Epidemiology, and End Results; SIOG: International Society of Geriatric Oncology; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TRIPOD: Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis.

Declarations

Ethics approval and consent to participate

This study was a secondary analysis of de-identified SEER Research Data accessed under the SEER data-use agreement. Under the institutional requirements applicable to this study, ethics committee review was not required. No participants were contacted, and the investigators had no access to direct identifiers. Individual informed consent was not obtained for this secondary analysis.

Consent for publication

Not applicable. No identifiable individual-level information or participant images are reported.

Clinical trial number

Clinical trial number: not applicable.

Availability of data and materials

The data analyzed in this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program through SEER*Stat. Access to the underlying individual-level registry data is subject to SEER data-use and registration requirements. Derived aggregate results and analysis code are available from the corresponding author on reasonable request, subject to SEER redistribution restrictions. The SEER data portal is available at https://seer.cancer.gov/data/.

Code availability

The R and Python scripts used for data cleaning, competing-risk estimation, cause-specific Cox modeling and figure generation are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no relevant financial or non-financial interests to disclose.

Funding

This work was supported by the Baoji Municipal Health Commission (Project No. 2026-026). The funder had no role in the study design, data collection, analysis or interpretation, manuscript preparation, or the decision to submit for publication.

Authors' contributions

Yu Dai: Conceptualization, methodology, data curation, formal analysis, visualization, and writing—original draft preparation. Yaqiang Feng: Data interpretation and writing—review and editing. Helin Zhang: Data interpretation, methodology review, and writing—review and editing. Cheng Wang: Data interpretation and writing—review and editing. Shuaipeng He: Data interpretation and writing—review and editing. Kangjie Wang: Data interpretation and writing—review and editing. Xiaobao Chen: Data interpretation and writing—review and editing. Qiao Du: Methodology review, supervision, and writing—review and editing. Panfeng Shang: Supervision, project administration, writing—review and editing, and final approval of the manuscript. All authors approved the final version and agree to be accountable for all aspects of the work.

Acknowledgements

We gratefully acknowledge the Surveillance, Epidemiology, and End Results (SEER) Program and the National Cancer Institute for collecting and maintaining the registry data used in this study. We also thank the SEER registries for their contribution to data quality and availability and the Free Statistics team (Beijing, China) for technical assistance with statistical analysis. During manuscript preparation, the authors used OpenAI Codex (GPT-5; OpenAI, https://openai.com/codex/; accessed 15 September 2026) for language organization, code review, and figure-format review. The authors critically reviewed and edited all generated material and independently verified the analyses, results, interpretations, and references. The tool was not used to create or alter the underlying SEER data, and the authors take full responsibility for the manuscript.

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Tables

Table 1. Baseline demographic and tumor characteristics by AJCC stage

Characteristic	Overall N = 38852	Stage 0a n = 18198	Stage 0is n = 1876	Stage I n = 9810	Stage II n = 5445	Stage III n = 1421	Stage IV n = 2102
Age group, years							
75–79	13851 (35.7)	6959 (38.2)	699 (37.3)	3270 (33.3)	1565 (28.7)	512 (36.0)	846 (40.2)
80–84	12429 (32.0)	5895 (32.4)	632 (33.7)	3091 (31.5)	1625 (29.8)	488 (34.3)	698 (33.2)
85–89	8578 (22.1)	3825 (21.0)	389 (20.7)	2229 (22.7)	1441 (26.5)	295 (20.8)	399 (19.0)
≥90	3994 (10.3)	1519 (8.3)	156 (8.3)	1220 (12.4)	814 (14.9)	126 (8.9)	159 (7.6)
Sex							
Male	29532 (76.0)	14013 (77.0)	1505 (80.2)	7557 (77.0)	3887 (71.4)	1093 (76.9)	1477 (70.3)
Female	9320 (24.0)	4185 (23.0)	371 (19.8)	2253 (23.0)	1558 (28.6)	328 (23.1)	625 (29.7)
Race							
White	35185 (90.6)	16595 (91.2)	1722 (91.8)	8870 (90.4)	4882 (89.7)	1264 (89.0)	1852 (88.1)
Black	1646 (4.2)	644 (3.5)	74 (3.9)	441 (4.5)	277 (5.1)	83 (5.8)	127 (6.0)
Asian or Pacific Islander	1787 (4.6)	816 (4.5)	67 (3.6)	461 (4.7)	259 (4.8)	71 (5.0)	113 (5.4)
American Indian/Alaska Native	103 (0.3)	47 (0.3)	6 (0.3)	18 (0.2)	20 (0.4)	2 (0.1)	10 (0.5)
Unknown	131 (0.3)	96 (0.5)	7 (0.4)	20 (0.2)	7 (0.1)	1 (0.1)	0 (0.0)
Year of diagnosis							
2010	6492 (16.7)	3040 (16.7)	357 (19.0)	1600 (16.3)	923 (17.0)	231 (16.3)	341 (16.2)
2011	6435 (16.6)	2978 (16.4)	311 (16.6)	1603 (16.3)	927 (17.0)	250 (17.6)	366 (17.4)
2012	6549 (16.9)	3043 (16.7)	322 (17.2)	1673 (17.1)	937 (17.2)	246 (17.3)	328 (15.6)
2013	6436 (16.6)	3085 (17.0)	280 (14.9)	1632 (16.6)	867 (15.9)	219 (15.4)	353 (16.8)

Characteristic	Overall N = 38852	Stage 0a n = 18198	Stage 0is n = 1876	Stage I n = 9810	Stage II n = 5445	Stage III n = 1421	Stage IV n = 2102
2014	6447 (16.6)	2986 (16.4)	305 (16.3)	1722 (17.6)	885 (16.3)	212 (14.9)	337 (16.0)
2015	6493 (16.7)	3066 (16.8)	301 (16.0)	1580 (16.1)	906 (16.6)	263 (18.5)	377 (17.9)
Marital status at diagnosis							
Married/common law	21442 (55.2)	10279 (56.5)	1115 (59.4)	5436 (55.4)	2725 (50.0)	799 (56.2)	1088 (51.8)
Widowed	9591 (24.7)	4134 (22.7)	372 (19.8)	2422 (24.7)	1705 (31.3)	375 (26.4)	583 (27.7)
Single/never married	2578 (6.6)	1092 (6.0)	112 (6.0)	692 (7.1)	414 (7.6)	93 (6.5)	175 (8.3)
Divorced	1940 (5.0)	883 (4.9)	83 (4.4)	449 (4.6)	297 (5.5)	85 (6.0)	143 (6.8)
Separated	142 (0.4)	65 (0.4)	5 (0.3)	33 (0.3)	18 (0.3)	8 (0.6)	13 (0.6)
Unmarried or Domestic Partner	56 (0.1)	26 (0.1)	0 (0.0)	15 (0.2)	10 (0.2)	2 (0.1)	3 (0.1)
Unknown	3103 (8.0)	1719 (9.4)	189 (10.1)	763 (7.8)	276 (5.1)	59 (4.2)	97 (4.6)
Tumor grade							
Grade I, well differentiated	3392 (8.7)	2881 (15.8)	131 (7.0)	322 (3.3)	38 (0.7)	11 (0.8)	9 (0.4)
Grade II, moderately differentiated	6969 (17.9)	5391 (29.6)	291 (15.5)	1049 (10.7)	138 (2.5)	46 (3.2)	54 (2.6)
Grade III, poorly differentiated	5652 (14.5)	1539 (8.5)	199 (10.6)	1848 (18.8)	1270 (23.3)	314 (22.1)	482 (22.9)
Grade IV, undifferentiated/anaplastic	13936 (35.9)	2600 (14.3)	305 (16.3)	5371 (54.8)	3535 (64.9)	914 (64.3)	1211 (57.6)
Unknown	8903 (22.9)	5787 (31.8)	950 (50.6)	1220 (12.4)	464 (8.5)	136 (9.6)	346 (16.5)

Values are n (column %) unless otherwise indicated. The unit of analysis is the patient; only the earliest eligible record per Patient ID was retained (N = 38852). Unknown categories were retained for race, marital status and grade. Percentages may not total 100 because of rounding.

Table 2. Cumulative incidence estimates at selected time points

AJCC stage	Outcome	12 months	36 months	60 months	84 months
Stage 0a	Bladder-cancer death	2.12%	6.00%	9.10%	11.72%
Stage 0a	Other-cause death	7.24%	20.57%	33.45%	45.10%
Stage 0is	Bladder-cancer death	4.21%	10.84%	15.94%	18.98%
Stage 0is	Other-cause death	7.41%	20.40%	31.25%	41.43%
Stage I	Bladder-cancer death	9.05%	19.60%	24.95%	27.92%
Stage I	Other-cause death	9.53%	22.45%	33.38%	42.34%
Stage II	Bladder-cancer death	32.04%	48.06%	52.32%	54.17%
Stage II	Other-cause death	12.63%	21.72%	27.21%	31.18%
Stage III	Bladder-cancer death	32.70%	49.69%	54.87%	56.82%
Stage III	Other-cause death	11.77%	19.20%	23.54%	28.29%
Stage IV	Bladder-cancer death	61.50%	75.77%	78.67%	79.98%
Stage IV	Other-cause death	9.96%	12.45%	13.95%	14.92%

Values are Aalen–Johansen cumulative incidence estimates. Bladder-cancer death and other-cause death were treated as competing events. Follow-up was truncated at 84 months.

Table 3. Temporal validation performance of the dual-endpoint prediction models

Outcome	Horizon (months)	IPCW AUC (95% CI)	IPCW Brier	Calibration intercept	Calibration slope
Bladder-cancer death	12	0.855 (0.845–0.866)	0.086	-0.019	1.235
Bladder-cancer death	36	0.822 (0.813–0.831)	0.124	-0.010	1.069
Bladder-cancer death	60	0.800 (0.792–0.808)	0.143	0.002	1.004
Other-cause death	12	0.629 (0.615–0.646)	0.077	0.007	0.919
Other-cause death	36	0.632 (0.621–0.643)	0.154	-0.001	1.017
Other-cause death	60	0.644 (0.633–0.653)	0.199	-0.013	1.066

IPCW, inverse-probability-of-censoring weighted; AUC, area under the receiver operating characteristic curve; CI, confidence interval. AUC intervals use 200 validation-sample bootstrap resamples without model refitting and do not represent optimism correction. Brier scores are normalized IPCW squared

errors. Calibration intercept and slope are descriptive weighted risk-scale summaries, not logit-scale parameters.

Figures

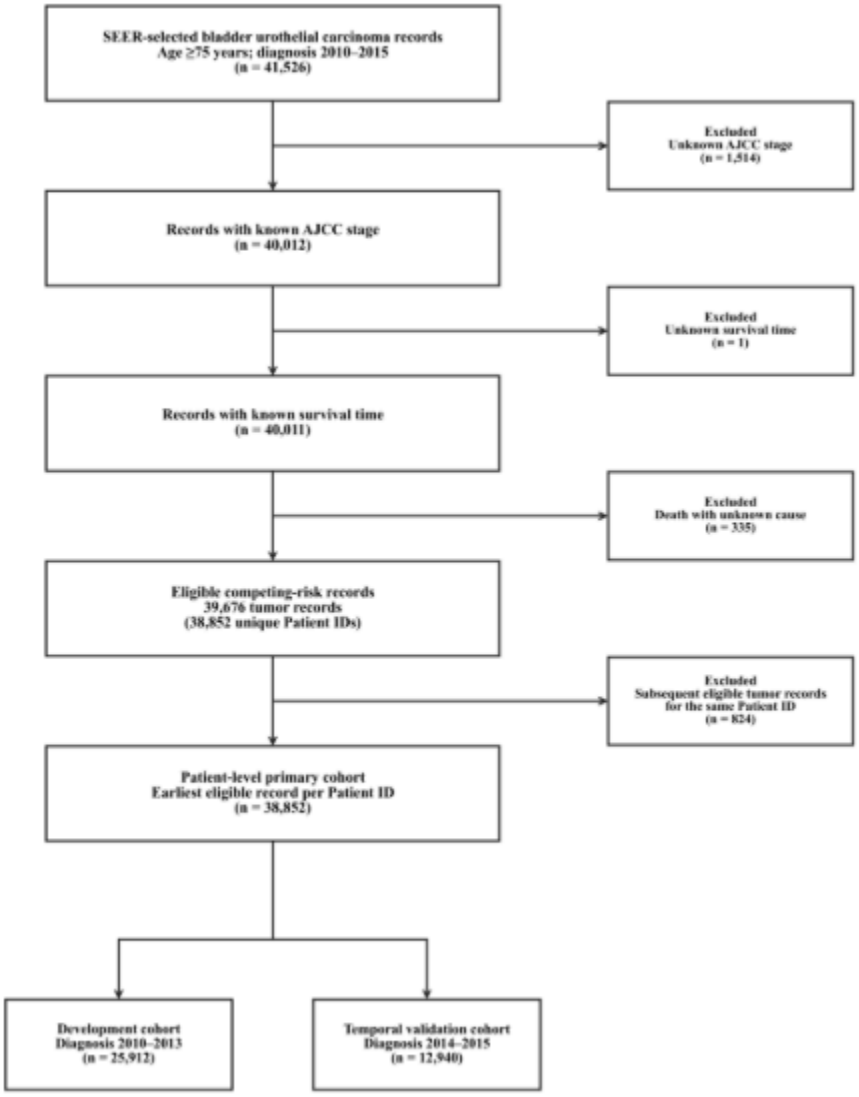


Figure 1

Cohort selection

Selection of adults aged ≥75 years with bladder urothelial carcinoma diagnosed during 2010–2015 in SEER 17 Registries. Exclusions were applied to tumor records before the earliest eligible record per Patient ID was retained. The primary cohort contained 38852 patients, with 25912 in development and 12940 in temporal validation.

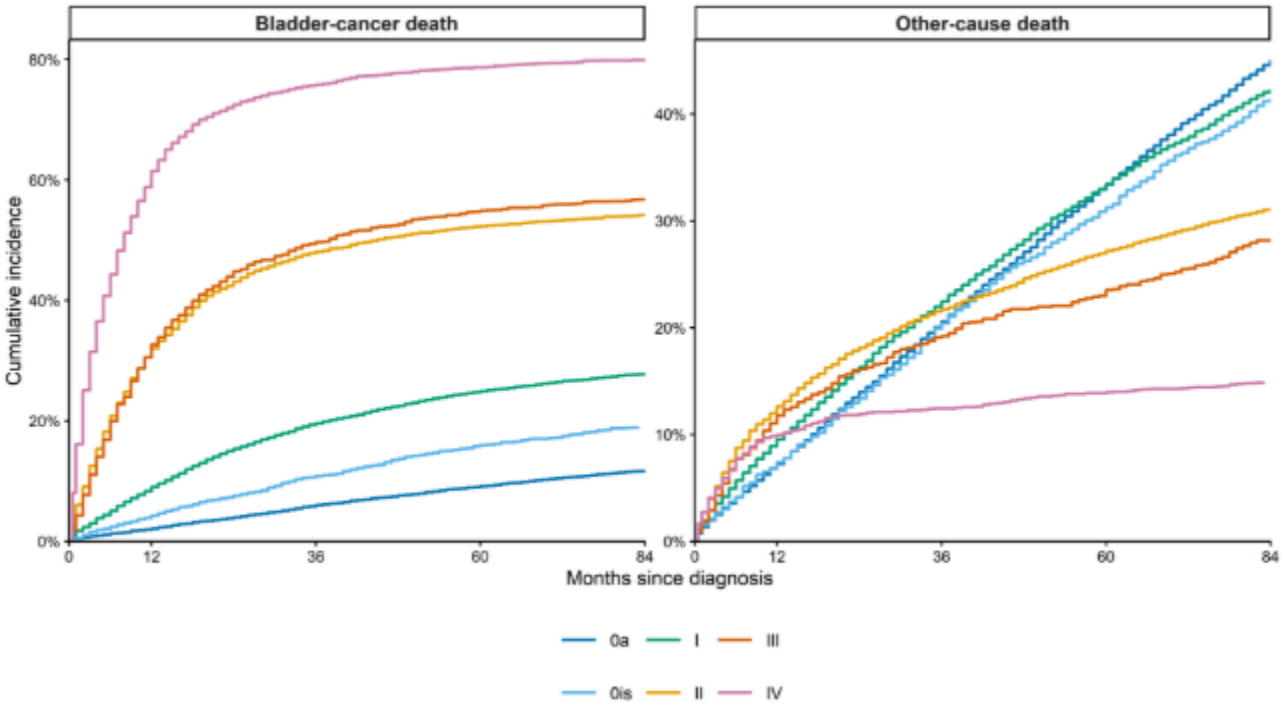


Figure 2

Cumulative incidence of competing deaths by AJCC stage

Aalen–Johansen cumulative incidence functions for bladder-cancer death and other-cause death in stages 0a, 0is, I, II, III and IV. Death from the alternate cause was treated as a competing event. Cumulative incidence describes the accumulated probability of each outcome from diagnosis and is distinct from the instantaneous hazards in Figure 3.

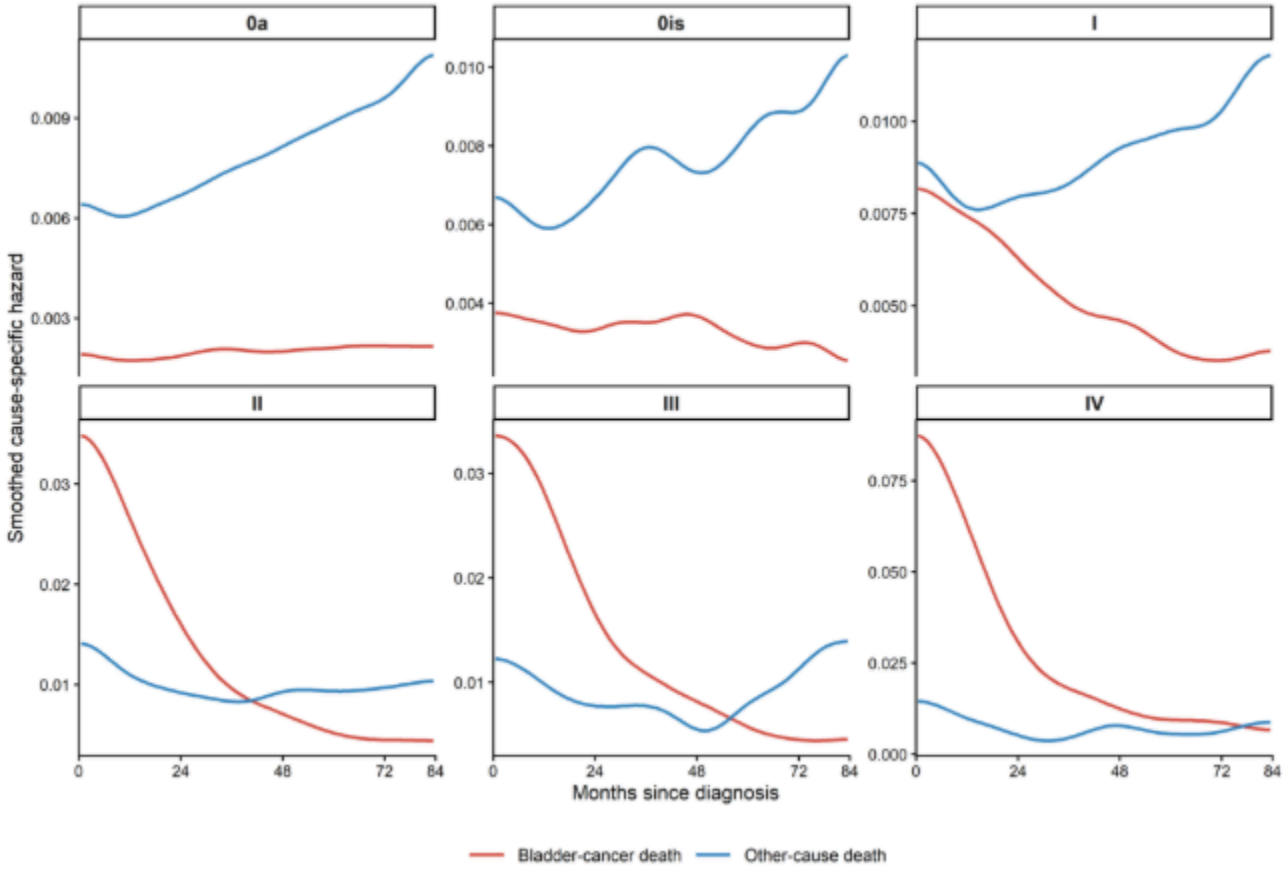


Figure 3

Dynamic cause-specific hazards by AJCC stage

Cause-specific hazard increments were smoothed using a six-month Gaussian kernel with reflection at 0 and 84 months. Curves were evaluated at monthly midpoints from 0.5 to 82.5 months within an 84-month observation window. Hazards describe mortality among patients still alive and at risk, not cumulative incidence.

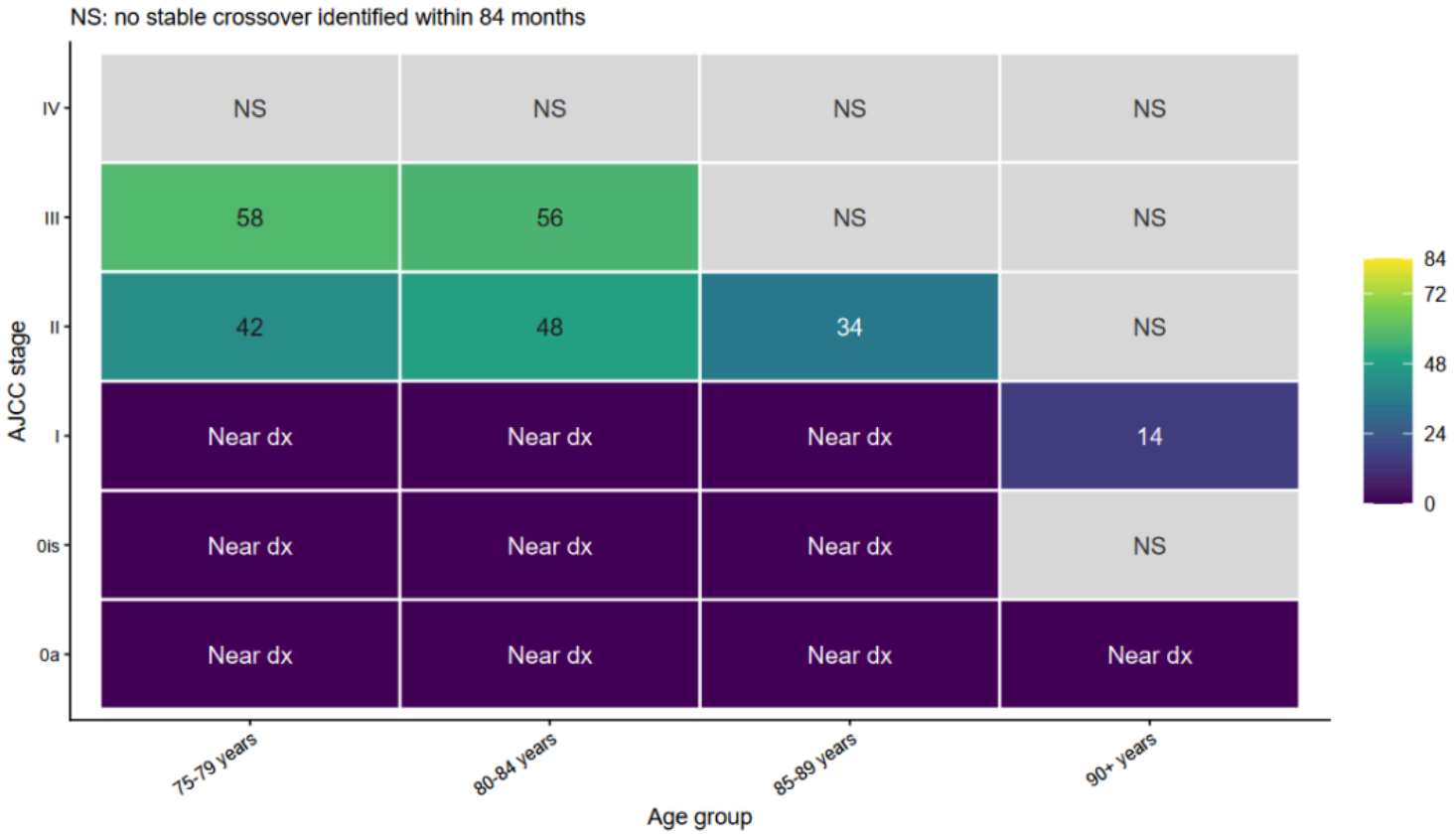


Figure 4

Stage- and age-specific hazard crossover

The heatmap shows the first monthly midpoint at which smoothed other-cause hazard exceeded bladder-cancer hazard for six consecutive eligible points. At each point, the risk set had to contain at least 100 patients and 5% of the baseline stratum. Near dx indicates predominance from the first grid point. NS indicates no stable eligible crossover, including insufficient risk-set support, no finite estimate, or detection in fewer than 80% of patient-level bootstrap replicates. Gray cells should not be interpreted as proof that crossover never occurs.

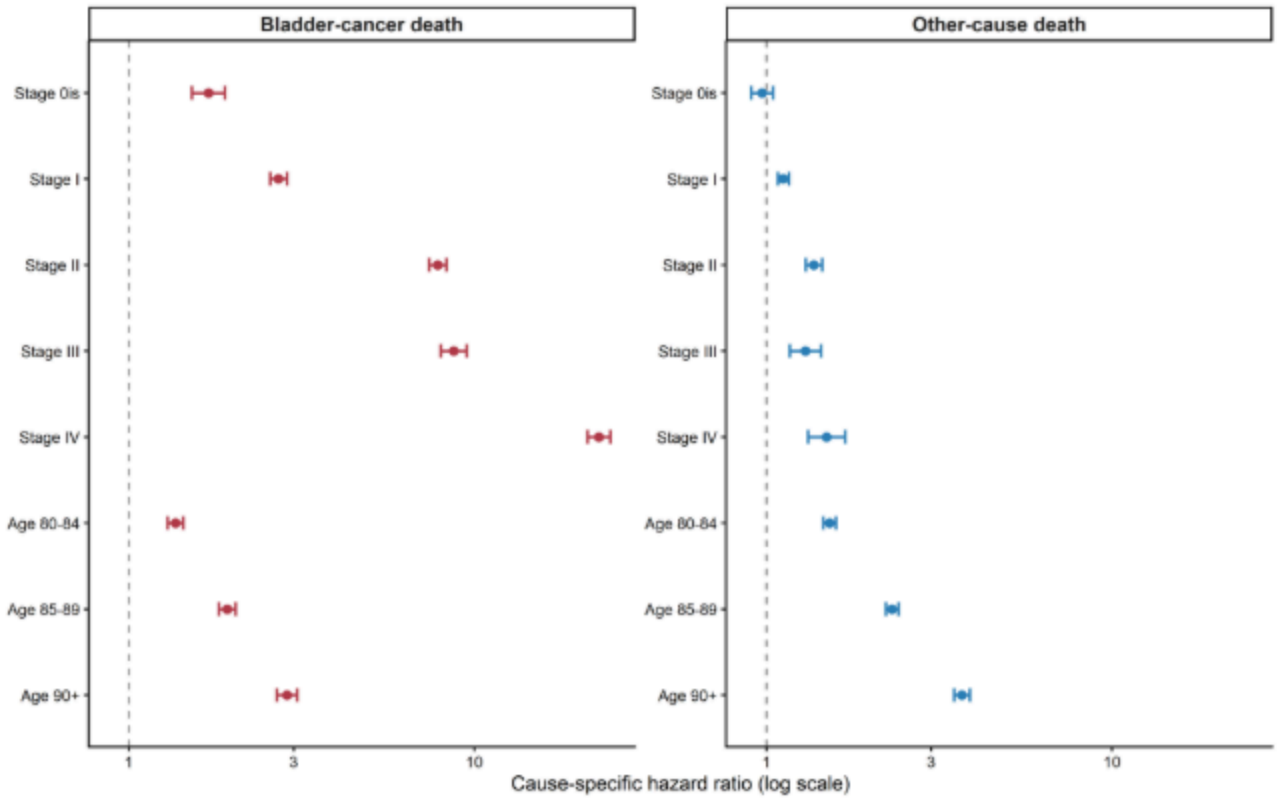


Figure 5

Adjusted cause-specific mortality associations

Stage contrasts use stage 0a as reference; age contrasts use 75–79 years. Separate cause-specific Cox models adjusted for stage, age group, sex, race and centered diagnosis year, with Patient ID-clustered robust variance. Points show hazard ratios and bars show 95% confidence intervals. Significant global proportional-hazards diagnostics mean these are follow-up summary associations, not constant or causal treatment effects.

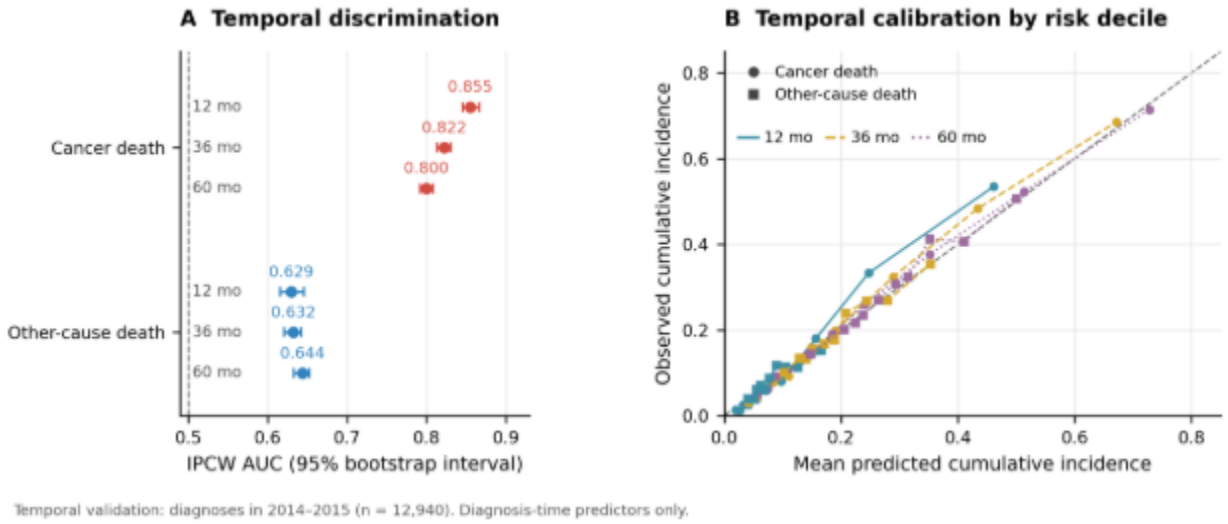


Figure 6

Temporal validation of the dual-endpoint prediction models

Panel A shows IPCW AUCs with percentile 95% intervals from 200 validation-sample bootstrap resamples at 12, 36 and 60 months. Panel B compares mean predicted risks with IPCW observed risks by prediction decile, excluding patients censored before the horizon from the observed-risk denominator. Competing deaths contribute non-target outcomes. The diagonal indicates equal predicted and observed risks. Validation used 12940 patients diagnosed in 2014–2015 and is internal temporal validation within SEER. Calibration intercepts and slopes in Table 3 are descriptive risk-scale summaries.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1agestratifiedandsensitivity.docx
- Additionalfile2predictionmodeldetails.docx
- Additionalfile3STROBEchecklist.docx