

Risk stratification by means of biological age-related factors better predicts cancer-specific survival than chronological age in patients with upper tract urothelial carcinoma: a multi-institutional database study

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Abstract

Background: Chronological age is an important factor in determining the treatment options and clinical response of patients with upper tract urothelial carcinoma (UTUC). Much evidence suggests that chronological age alone is an inadequate indicator to predict the clinical response to radical nephroureterectomy (RNU).

Patients and methods: We retrospectively reviewed the data from 1510 patients with UTUC (Ta-4) treated by surgery. White blood cell (WBC) count, neutrophil-to-lymphocyte ratio, hemoglobin (Hb), platelets, albumin, alkaline phosphatase, lactate dehydrogenase, creatinine, and corrected calcium were tested by the Spearman correlation to indicate the direction of association with chronological age, which yielded significant, negative associations of Hb ($p < 0.001$) and WBC ($p = 0.010$) with chronological age. For scoring, we assigned points for these categories as follows; point '0' for Hb >14 (reference) and 13–13.9 [odds ratio (OR): 1.533], point '1' for 12–12.9 (OR: 2.391), point '2' for 11–11.9 (OR: 3.015), and point '3' for <11 (OR: 3.584). For WBC, point '1' was assigned for >9200 (OR: 2.541) and '0' was assigned for the rest; 9200–8500 (reference), 8499–6000 (OR: 0.873), 5999–4500 (OR: 0.772), 4499–3200 (OR: 0.486), and <3200 (OR: 1.277).

Results: The 10-year cancer-specific survival (CSS) in the higher risk group with scores of 4 or higher in patients age <60 years was worse than a score of 0, or 1 in age >80 years [mean estimated survival 69.7 months, confidence interval (CI): 33.3–106 versus 103.5. CI: 91–115.9]. The concordance index between biological age scoring and chronological age was 0.704 for CSS and 0.798 for recurrence-free survival. The limitation of the present study is the retrospective nature of the cohort included.

Conclusions: The biological age scoring developed for patients with UTUC undergoing RNU. It was applicable to those with localized disease and performed well in diverse age populations.

Keywords: age, prognosis, upper tract urothelial carcinoma

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Introduction

Several studies have evaluated the prognostic value of age in patients with upper tract urothelial carcinoma (UTUC).^{1,2} However, the impact

of chronological age on prognosis is inconclusive. On the other hand, the prognostic impact of biological age has not been reported previously. In most clinical studies, chronological

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age has been used as the aging indicator. Chronological age suggests that the aging processes take place along a continuum with exact distances, across the whole adult lifespan.³ Chronological age measures how much time that has passed since birth, which is not necessarily a good predictor of how well a person is aging. It is necessary to utilize a measure for age that better captures real aging. No solo indicator has been developed to alone reflect the aging processes of the body in a representative manner. Actually, defining the biological age consists of the determination of a number of biological age markers including telomeres, and chromatin.^{4–9} Some of the biological age-related factors are based on routine clinical examinations, which help clinicians to have a general understanding of the study participants, such as sex, body mass index, pulmonary function, blood pressure, urine routine, blood routine, and blood chemistry. Hematologic biomarkers include erythrocyte sedimentation rate,¹⁰ mean corpuscular hemoglobin (Hb),¹¹ red blood cell count,¹² hematocrit,¹³ hemoglobin concentration.¹⁴ White blood cell (WBC) count has been indicated to have prognostic impact in selected conditions. Eizadi-Mood and colleagues reported the prognostic value of routine blood chemistry with the scores of the Acute Physiology and Chronic Health Evaluation (APACHE) II and a modified APACHE II system (MAS) in organophosphate poisoning.¹⁵ They found WBC, potassium, Glasgow coma scale (GCS), age and sodium in APACHE II; GCS and mean arterial pressure in the MAS system as prognostically valuable.¹⁵ In UTUC, Kluth and colleagues evaluated the prognostic value of the Bajorin criteria in a multi-institutional cohort of 242 patients with disease recurrence after surgery.¹⁶ In univariate analyses, a higher pT stage, tumor necrosis, nonadministered salvage chemotherapy, higher age-adjusted Charlson comorbidity index, higher American Society of Anesthesiologists score, lower albumin level and higher WBC count were significantly associated with a shorter time to cancer-specific mortality.¹⁶ So far, no study has related WBC with biological age. We hypothesized that hematologic biomarkers from blood routine testing and blood chemistry testing in patients with UTUC was associated with features of biologically and clinically aggressive phenotypes, thereby potentially helping in the clinical decision-making of UTUC patients. For this purpose, we tested the association of blood routine testing and blood

chemistry testing with chronological age and prognosis in a large multi-institutional cohort of patients treated by radical nephroureterectomy (RNU) for UTUC.

Methods

Study design and population

The present study was a retrospective study of data from academic centers. The study cohort comprised 1510 patients from four academic or cancer-referral centers. Overall, 20 cases were missing the age data and were excluded. There were 10 cases that had unspecified pT stage information and were excluded. A total of 104 cases proven to be pathological node-positive were excluded. Of 1375 cases, 202 cases missed the variables for the risk prediction and were excluded from the analysis. The final cohort for the present study consisted of 1173 cases. Data sharing agreements and institutional review board approval were obtained at each study site. WBC, neutrophil-to-lymphocyte ratio (NLR), Hb, platelets (PLT), albumin (Alb), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatinine (Cr), and corrected calcium (Ca) were tested by the Spearman correlation to indicate the direction of association with chronological age. The test yielded significant, negative associations of Hb ($p < 0.001$) and WBC ($p = 0.010$) with chronological age. Hb (g/dl) and WBC (counts/ μ l) were analyzed to compare the 10-year cancer-specific survival (CSS) by Cox regression analysis as categorical variables (>14, 13–13.9, 12–12.9, 11–11.9, and <11), and (9200–8500, 8499–6000, 5999–4500, 4499–3200, <3200, and >9200), respectively. To establish the scoring system, we assigned points for these categories, and then correlated the total points to predicted probability of the surviving outcome as follows; point ‘0’ for Hb >14 (reference) and 13–13.9 [odds ratio (OR): 1.533], point ‘1’ for 12–12.9 (OR: 2.391), point ‘2’ for 11–11.9 (OR: 3.015), and point ‘3’ for <11 (OR: 3.584). For WBC, point ‘1’ was assigned for >9200 (OR: 2.541) and ‘0’ was assigned for the rest; 9200–8500 (reference), 8499–6000 (OR: 0.873), 5999–4500 (OR: 0.772), 4499–3200 (OR: 0.486), and <3200 (OR: 1.277). All patients had previous, histologically confirmed, urothelial carcinoma with no evidence of distant metastases (anyT, N0, M0) and were followed with office-based cystoscopy and voided urinary cytology. Voided urine cytology was invariably

obtained before cystoscopy. Cytology was considered positive only when malignant cells were present. Patients with UTUC were treated with RNU with a bladder cuff with curative intent. None of the patient included in the present analysis received systemic preoperative chemotherapy or radiotherapy.

Statistical methods

The survival intervals were calculated from the date of RNU to the last available follow up. Patients were followed until death or withdrawal from the study. CSS and overall survival (OS), as functions of age (discrete and continuous) were obtained and evaluated. An event for OS included all deaths within the cohort under investigation. Survival curves were estimated by means of Kaplan–Meier methods. Differences among the survival curves were determined by the log-rank test. Tests of association and correlation were conducted using Pearson's Chi-square test (or Fisher's exact test when appropriate). Differences among numeric variables were evaluated by means of a one-way analysis of variance. Multivariable Cox regression analyses was used to estimate the score to predict biological age that addressed the association among age at diagnosis, Hb, and WBC. Statistical significance was defined as a *p* value <0.05. Statistical analyses were performed using SPSS statistics software, version 24.0 (IBM Corp. Armonk, NY.).

Results

The patient characteristics are shown in Table 1. A total of 1173 patients were identified (70.3% men with a mean age of 71 years). The overall median survival from diagnosis of the whole cohort was 54.3 months [95% confidence interval (CI): 50.7–57.9]. A total of 84.3% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or 0. Among all the patients included in this study, 19.4% had bladder cancer at the diagnosis of UTUC. The pathological diagnosis was pT_a, pT₁, pT₂, pT₃ and pT₄ in 188 (16.0%), 352 (30.0%), 198 (16.9%), 404 (34.4%), and 31 (2.6%) patients, respectively, and half of all patients had muscle-invasive disease (\geq T2N0M0) (Table 1). The results of hematological analyses are reported in Table 2. We analyzed the influence of hematological factors on patient chronological age. The results of the Spearman and

Kendall's correlation analyses for each hematological factor are reported in Table 2. Only hemoglobin value and WBC count were inversely related to chronological age in both analyses (Table 2). Patient survival increased with higher levels of hemoglobin and WBC count. To identify a dose–response effect, hemoglobin and WBC were also assessed according to their categories; both factors remained highly significant in survival function, with a better survival with increasing levels (Table 3).

According to the hazards, we assigned points for these categories as follows; point '0' for Hb >14 (reference) and 13–13.9 (OR: 1.533), point '1' for 12–12.9 (OR: 2.391), point '2' for 11–11.9 (OR: 3.015), and point '3' for <11 (OR: 3.584). For WBC, point '1' was assigned for >9200 (OR: 2.541) and '0' was assigned for the rest; 9200–8500 (reference), 8499–6000 (OR: 0.873), 5999–4500 (OR: 0.772), 4499–3200 (OR: 0.486), and <3200 (OR: 1.277) (Table 3). The 10-year estimated mean CSS was 94.0 months (91.0–97.0) for the whole UTUC cohort (Figure 1). In the risk stratification model, CSS rates were apparently discriminated by the number of adverse biological age-related factors (Figure 1). Kaplan–Meier analyses exhibited the 10-year estimated mean CSS in the group of score 0–1, 2–3, and 4–5 were 103.5 months (99.9–107.2), 90.1 months (84.7–95.5) and 74.0 months (65.6–82.4; *p* < 0.001 for score 0–1 *versus* 2–3 and *p* < 0.001 for score 0–1 *versus* 4–5), respectively (Figure 2). In patients aged <61 years, the estimated mean 10-year CSS for the whole score was 107.3 months and was the longest among any age subgroup (Table 4). Despite the shorter survival time in the elderly group, the difference among biological age-related factors affected actual survival. For the group aged <61 years with scores 4–5, the estimated mean 10-year CSS was 69.7 months, which was apparently shorter than those of the group aged >80 years with scores 0–1 (103.5 months) and scores 2–3 (88.0 months; Table 4).

Discussion

The present study shows that biological age has a higher association with the rate of cancer-related deaths in patients with UTUC than chronological age. In contrast with traditional aging concepts, biological age does not

Table 1. Patient background characteristics.

		Count	%
Age (mean, median, minimum–maximum)		71, 72, 29–96	
Sex	Male	825	70.3%
	Female	348	29.7%
BT at diagnosis	None	938	80.0%
	Yes	227	19.4%
	Unknown	8	0.7%
Cytology	Negative	671	57.2%
	Positive	340	29.0%
	Suspicious	162	13.8%
ECOG PS	0	849	72.4%
	1	140	11.9%
	2	30	2.6%
	3	9	0.8%
	Unknown	145	12.4%
Grade	1	53	4.5%
	2	479	40.8%
	3	588	50.1%
	Unknown	53	4.5%
LVI	No	621	52.9%
	Yes	361	30.8%
	Unknown	191	16.3%
pT classification	pTa	188	16.0%
	pT1	352	30.0%
	pT2	198	16.9%
	pT3	404	34.4%
	pT4	31	2.6%
BT, bladder cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LVI, lymphovascular invasion.			

underline the importance of chronological age, rather using indices of vital organs to represent the senescence of the whole body. The research

for indicators of biological age has been ongoing for over three decades.⁷ For urothelial carcinoma, the role of biological age in physicians' treatment decision-making has not been specified. Yuge and colleagues have reviewed 1252 patients with nonmuscle-invasive bladder cancer (NMIBC) treated with transurethral bladder tumor resection, and 447 patients who were treated with intravesical bacillus Calmette–Guerin (BCG) to evaluate whether patient age influences the treatment success and whether the side effects were tolerable.¹⁷ They found the benefit on recurrence-free survival of a postoperative BCG instillation was preserved across all age groups, with the related side effects in the elderly patients being almost equal to those in the younger, concluding that patient age by itself should not be taken into account in the decision on when to use BCG.¹⁷ Similarly, Evangelos and colleagues evaluated disease recurrence rates associated with one immediate postoperative intravesical instillation of mitomycin C in NMIBC patients using a multicenter retrospective cohort.¹⁸ Patient age did not alter the rate of local recurrence in patients treated with postoperative mitomycin C instillation therapy, suggesting intravesical mitomycin C can be safely managed even in elderly NMIBC patients.¹⁸ For muscle-invasive bladder cancer (MIBC), the curative treatment remains as radical cystectomy and elderly patients should not be withheld a potentially life-saving intervention based only on chronological age.¹⁹ Patients unfit for surgical intervention could be eligible for bladder-sparing techniques.¹⁹ Molecular biology advancements have increased the variety of potential candidate biomarkers that may be considered as biological age predictors.^{3,20} Sun and colleagues characterized the heterogeneity of MIBC using whole genome mRNA expression data from 372 MIBC patients from the Cancer Genome Atlas.²¹ Compared with patients with luminal-type subtypes, patients with basal-like subtypes were more likely to be older, obese, and to start smoking at an early age.²¹ The clinical role of age in UTUC has been discussed in several studies.^{1,2,16,22–25} From the Surveillance, Epidemiology, and End Results database, patients diagnosed with UTUC from 1984 to 2004 were analyzed in relation to age (40–49, 50–59, 60–69, 70–79, and ≥ 80 years), sex, race, disease extent, treatment modalities, and patient death.²⁴ Advancing age was found to be associated with a greater T stage and grade at presentation,

Table 2. The Spearman and Kendall's correlation expected monotonic relationship between age and other continuous variables.

		Hb	WBC	NLR	PLT	Alb	ALP	LDH	Cr	Corrected Ca
Kendall's Tau	Correlation Coefficient	(0.214)	(0.051)	0.027	0.021	(0.005)	(0.023)	(0.019)	0.005	(0.013)
	<i>p</i> value	<0.001	0.009	0.255	0.491	0.878	0.469	0.532	0.879	0.708
Spearman's rank	Correlation coefficient	(0.306)	(0.075)	0.040	0.031	(0.009)	(0.034)	(0.031)	0.007	(0.019)
	<i>p</i> value	<0.001	0.010	0.248	0.494	0.851	0.469	0.504	0.876	0.708

Alb, albumin; ALP, alkaline phosphatase; Ca, calcium; Cr, creatinine; Hb, hemoglobin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; WBC, white blood cell.

Table 3. Risk estimation for 10-year CSS by COX.

	Estimated risk point	<i>p</i> value	OR	95.0% CI	
				Lower	Upper
Hb (g/dl)					
0 = >14	0	Ref			
1 = 13–13.9	0	0.068	1.533	0.968	2.426
2 = 12–12.9	1	0.000	2.391	1.537	3.720
3 = 11–11.9	2	0.000	3.015	1.910	4.757
4 = <11	3	0.000	3.584	2.400	5.352
WBC (counts/mm ³)					
0 = 9200–8500	0	Ref			
1 = 8499–6000	0	0.631	0.873	0.501	1.521
2 = 5999–4500	0	0.372	0.772	0.438	1.361
3 = 4499–3200	0	0.033	0.486	0.250	0.944
4 = <3200	0	0.666	1.277	0.421	3.877
5 = >9200	1	0.002	2.541	1.396	4.625

CI, confidential interval; CSS, cancer-specific survival; Hb, hemoglobin; OR, odds ratio; WBC, while blood cell.

of those 40–49 years old, 41% presented with invasive tumors (T2–T4) compared with 50% of octogenarians.²⁴ Expectedly, octogenarians were less likely to have undergone radical surgical treatment than those 40–49 years old (86% versus 95%).²⁴ Similarly, Shariat and colleagues investigated 1453 UTUC patients and found older age was an independent predictor of poor

CSS.² Our study focused on the classification of peripheral blood WBC count, and Hb density for the biological age estimation. Cheng and colleagues showed that high cell distribution width (RDW) was independently associated with poor OS ($p < 0.001$), and WBC count was a significant prognostic indicator for both OS and CSS (both $p < 0.001$).²² Similar to our cohort

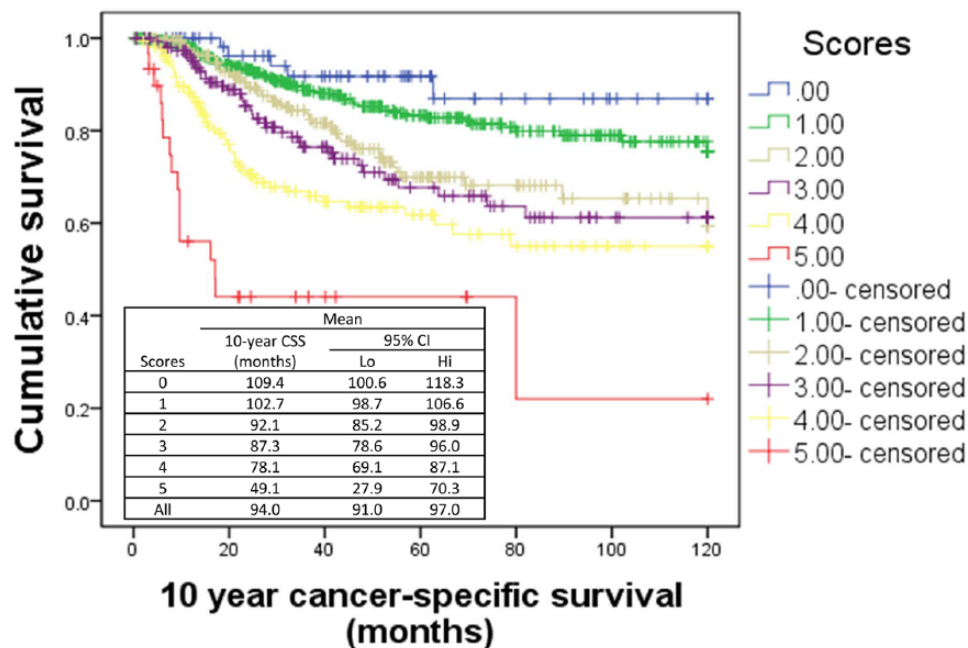


Figure 1. The 10-year CSS of whole UTUC cohorts with stratified biological age predictive score. CSS, cancer-specific survival; UTUC, upper tract urothelial carcinoma.

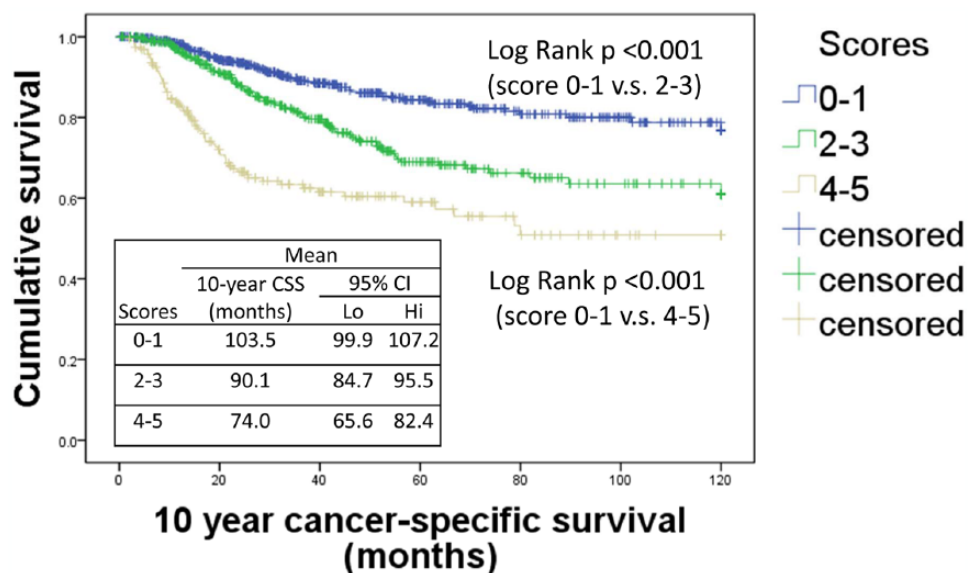


Figure 2. Kaplan–Meier survival curves stratified by three different subgroups. The 10-year CSS in patients with low risk (score 0–1), intermediate risk (score 2–3), and high risk (score 4–5) are indicated. CSS, cancer-specific survival.

managed by RNU, their subgroup analysis exhibited the prognostic significance of RDW for OS was limited in organ-confined disease.²² The present study delineates a significant portion of elderly UTUC patients that could be treated with aggressive treatment including RNU, suggesting advanced age alone should

not be an exclusion criteria for extirpative surgical treatment.

Conclusion

The results of the present study have shown that patients with UTUC managed by RNU can be

Table 4. Estimated mean 10-year CSS of each age group stratified by risk group.

Age	Scores	Survival (months)	SE	95% CI	
				Lo	Hi
<61	0-1	111.5	2.9	105.8	117.1
	2-3	103.7	8.3	87.5	120.0
	4-5	69.7	18.5	33.3	106.0
	All	107.3	3.1	101.3	113.3
61-70	0-1	102.9	3.2	96.7	109.2
	2-3	95.1	4.7	85.9	104.3
	4-5	74.1	8.2	58.0	90.2
	All	96.4	2.6	91.3	101.5
71-75	0-1	97.8	4.8	88.4	107.3
	2-3	91.1	5.4	80.5	101.6
	4-5	69.8	7.8	54.6	85.0
	All	92.5	3.4	85.9	99.1
76-80	0-1	98.1	5.6	87.1	109.0
	2-3	69.9	6.0	58.2	81.6
	4-5	54.8	5.8	43.4	66.1
	All	84.5	4.3	76.1	92.9
>80	0-1	103.5	6.3	91.0	115.9
	2-3	88.0	6.8	74.8	101.3
	4-5	68.9	8.1	52.9	84.8
	All	85.8	4.5	77.0	94.5

CI, confidential interval; CSS, cancer-specific survival; SE, standard error.

stratified according to biological age-related factors. Those with a higher prevalence of biological age-related factors have a greater risk of death from cancer after RNU. These findings could be used as an additional variable by urologists when counseling chronologically-aged patients with UTUC about a more aggressive management strategy.

In terms of clinical practice points, The treatment of UTUC in the elderly has to be patient-oriented and focused on biological age. The curative treatment in UTUC remains RNU and elderly patients should not be withheld a potentially curative surgery only based on chronological age.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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