



Preoperative serum albumin as a prognostic factor in patients with upper urinary tract urothelial carcinoma

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ABSTRACT

Purpose: The study evaluated whether preoperative measures of the C-reactive protein-based systemic inflammatory response may predict cancer survival independent of tumor stage in patients with upper urinary tract urothelial carcinoma (UTUC).

Materials and Methods: Between September 1999 and October 2010, 181 patients submitted to radical nephroureterectomy were available for evaluation. Multivariate survival analyses were performed using Cox's proportional hazards model and the coefficient for each factor was divided by the highest coefficient, multiplied by 4, and rounded to the nearest integer.

Results: Multivariate analyses showed that tumor location, pathologic T stage, lymphovascular invasion, margin status, and albumin level were independent contributors. The bootstrap-corrected C statistics of the model were 0.813 for disease-specific survival and 0.755 for overall survival, respectively. For time to disease-specific and overall mortality for patients, integrated area under the curve values were 0.792 and 0.739, respectively. When patients were clustered into three groups according to their model-predicted survival, the 5-year disease-specific survival in the low-, intermediate- and high-risk group was 95.4%, 76.2%, and 36.9%, respectively ($p < 0.001$), and were 87.8%, 54.4%, and 31.8%, respectively, for overall survival ($p < 0.001$). Decision curve analysis revealed that the use of model was associated with net benefit gains relative to the treat-all strategy.

Conclusions: Pretreatment albumin is a simple biomarker based on routinely available well-standardized measures, and is not an expensive and time-consuming process. Hypoalbuminemia is an independent marker of poor prognosis in patients with upper urinary tract urothelial carcinoma.

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INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is a relatively rare malignancy, accounting for 5% of all urothelial carcinomas (1). Since these tumors often behave aggressively and local failure rates are high, even after radical surgical treatment, the outcome of patients with UTUC is still generally poor (1). Although tumor stage and histologic grade are the most significant prognos-

tic factors for UTUC, the significance of other relevant factors, such as lymphovascular invasion, tumor necrosis, tumor architecture, and concomitant carcinoma in situ, are unclear (2).

Disease outcome in cancer patients is not solely determined by the local characteristics of the tumor. The host systemic inflammatory response (SIR) is also involved (3). As a state of chronic inflammation plays a role in the initiation, promotion, and progression of malignant disease

(4), host SIR may be an important tumor stage-independent predictor of outcome in cancer. Previous studies have established the prognostic importance of the SIR in patients with localized tumor undergoing curative surgery (5) as well as advanced tumors (6). Based on a previous study, C-reactive protein (CRP) level >10 mg/l (7), albumin level <35 g/l (7), and white cell count $>11 \times 10^9/l$ (8) were considered to indicate the presence of a SIR. In particular, CRP-based SIR have been explored and these prognostic scores have been associated with survival in patients with cancer: the combination of serum CRP and albumin as the original Glasgow prognostic score (9) and modified Glasgow prognostic score (10), and a combination of CRP and white cell count in the prognostic index (11).

To our knowledge, a few studies have evaluated the prognostic value of CRP-based SIR in patients with UTUC (12). The aim of this study was to evaluate whether preoperative measures of CRP-based SIR may predict cancer survival, independent of tumor stage, in patients with UTUC.

MATERIALS AND METHODS

Patient selection and data collection

The study protocol was approved by our Institutional Review Board. We retrospectively reviewed our database of the 303 patients who underwent radical nephroureterectomy for primary UTUC between September 1999 and October 2010. Exclusion criteria were: 1) no available laboratory data for inflammation, such as CRP, albumin, and white cell count; 2) clinical evidence of infection or inflammatory conditions, such as pneumonia, inflammatory bowel disease, or rheumatoid arthritis; 3) history of bladder tumor at a higher stage than the upper tract disease; 4) preoperative chemotherapy or irradiation; and 5) distant metastatic disease at the time of surgery. In total, 181 patients (median age 65.7 years, range 34.2-90.0 years) were available for evaluation. Median follow-up period of those patients was 56.4 months (range 0.1 to 158.0). The clinical and histologic criteria for these 181 patients are shown in Table-1.

Table 1 - Patient characteristics.

Variables	
Total	181
Gender (male/female)	144 (79.6)/37 (20.4)
Age, year (median, interquartile range)	65.7, 59.4-72.6
Body mass index, cm/kg ² (median, interquartile range)	24.1, 22.2-25.8
Tumor location (renal pelvis/ureter/both)	86 (47.5)/67 (37.0)/28 (15.5)
Pathologic T stage (pTa/is/1/2/3/4)	22 (12.2)/1 (0.6)/43 (23.8)/35 (19.3)/76 (42.0)/4 (2.2)
Tumor grade (G1/2/3)	8 (4.4)/113 (62.4)/60 (33.1)
Lymph node stage (Nx/0/+)	147 (81.2)/26 (14.4)/8 (4.4)
Concomitant carcinoma in situ (absent/present)	164 (90.6)/17 (9.4)
Lymphovascular invasion (absent/present)	150 (82.9)/31 (17.1)
Margin status (negative/positive)	170 (93.9)/11 (6.1)
C-reactive protein, mg/l (≤ 10 / >10)	137 (75.7)/44 (24.3)
Albumin, g/l (≥ 35 / <35)	165 (91.2)/16 (8.8)
White Cell Count, $10^9/l$ (≤ 11 / >11)	168 (92.8)/13 (7.2)
Glasgow Prognostic Score (0/1/2)	130 (71.8)/42 (23.2)/9 (5.0)
Modified Glasgow Prognostic Score (0/1/2)	137 (75.7)/35 (19.3)/9 (5.0)
Prognostic Index (0/1/2)	134 (74.0)/37 (20.4)/10 (5.5)

Data presented are number (%) or median (interquartile range).

The kidney, ureter, and bladder cuff were excised en bloc. A regional lymphadenectomy was performed when nodal involvement was suspected from the preoperative workup or was discovered during the procedure. Adjuvant cisplatin-based combination chemotherapy was administered in most patients with disease pT3 or pT4, and/or nodal involvement, but the decision for conducting adjuvant chemotherapy was left to the treating urologists.

Laboratory measurements

CRP, albumin, and white cell count were measured a few days prior to surgery as part of the routine examination. Routine laboratory measurements including the serum level of CRP, albumin, and white cell count were performed preoperatively. The coefficient of variation for these methods over the range of measurement was <5% as established by routine quality control procedures. The prognostic subdivisions used for each described prognostic score are consistent with the previously published literature (Table-2) (7-11).

Pathologic analysis

All surgical specimens were examined by a dedicated genitourinary pathologist and processed according to standardized procedures. The TNM stage was determined according to the Union Internationale Contre le Cancer/American Joint Cancer Committee 2004 classification. The tumor grade was determined according to the World Health Organization 1973 and 2004 classifications (13). Lymphovascular invasion was defined as the presence of tumor cells in an endothelium-lined space but not in the underlying muscular walls. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any upper urinary tract location. Positive margin status was defined as tumor presence at linked areas of soft tissue on the surgical specimen.

Postoperative follow-up

Patients were generally followed every 3-4 months for the first 2 years, every 6 months in years 3 and 4, and annually thereafter. Follow-up examinations included a history, physical examination, blood laboratory tests, urine cyto-

Table 2 - Systemic inflammation-based prognostic scores.

Prognostic scores	Score
C-reactive protein⁷	
≤10 mg/l	0
>10 mg/l	1
Albumin⁷	
≥35 g/l	0
<35 g/l	1
White cell count⁸	
≤11 (10 ⁹ /l)	0
>11 (10 ⁹ /l)	1
Glasgow Prognostic Score⁹	
C-reactive protein ≤10 mg/l and albumin ≥35 g/l	0
C-reactive protein ≤10 mg/l and albumin <35 g/l	1
C-reactive protein >10 mg/l	1
C-reactive protein >10 mg/l and albumin <35 g/l	2
Modified Glasgow Prognostic Score¹⁰	
C-reactive protein ≤10 mg/l and albumin ≥35 g/l	0
C-reactive protein ≤10 mg/l and albumin <35 g/l	0
C-reactive protein >10 mg/l	1
C-reactive protein >10 mg/l and albumin <35 g/l	2
Prognostic Index¹¹	
C-reactive protein ≤10 mg/l and white cell count ≤11 (10 ⁹ /l)	0
C-reactive protein ≤10 mg/l and white cell count >11 (10 ⁹ /l)	1
C-reactive protein >10 mg/l and white cell count ≤11 (10 ⁹ /l)	1
C-reactive protein >10 mg/l and white cell count >11 (10 ⁹ /l)	2

logy, cystoscopic evaluation, chest radiography, and abdomino-pelvic computed tomography (CT). Oncological outcome analyses focused on disease-specific survival (DSS). Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Patient data were censored at

the last follow-up or death if the event of interest had not been attained. All patients who were identified as having died of UTUC had progressive and widely disseminated metastases at the time of death. Patients who died in the perioperative period within 30 days of surgery were censored at time of death for DSS analyses.

Statistical analysis

Data are presented as median and interquartile range. Several variables were chosen, including gender, patient age, body mass index, pathologic T stage, tumor grade, lymph node stage, concomitant carcinoma in situ, lymphovascular invasion, margin status, CRP, albumin, white cell count, Glasgow prognostic score, modified Glasgow prognostic score, and prognostic index. Multivariate survival analysis with calculation of hazard ratio (HR) with 95% confidence interval (CI) was performed using the Cox proportional hazards model including all covariates that were significant on univariate analysis. We applied a weighting method to each variable (14); the coefficient for each factor was divided by the highest coefficient, multiplied by 4, and rounded to the nearest integer (15). Precision of the reported coefficients was assessed by creating 1,000 bootstrap samples from the entire data set and replicating the estimation process. CIs were obtained using this bootstrap method of the corresponding sampling distributions.

To evaluate the performance of the models, we assessed these models in terms of both discrimination and calibration (16). The discriminative ability of the model was measured quantitatively using the C statistic (17) and time-dependent receiver operating characteristics curve (18). A score was calculated for each patient by adding together the points corresponding to his or her factors, and the patients were divided into three groups on the basis of the score. The survival stratified by risk groups was calculated using the Kaplan-Meier method. Calibration was also assessed by the calibration plot. To determine the net benefit, we relied on decision curve analysis (19).

For all statistical analyses, two-sided $p < 0.05$ was regarded as significant. Analysis was

performed using SPSS software (SPSS, Chicago, IL) and R 2.13.0 (R Development Core Team, Vienna, Austria, <http://www.R-project.org>).

RESULTS

Table-3 shows the results of the multivariate Cox regression analyses in the cohort related to survival. Univariate analysis revealed that tumor location, pathologic T stage, tumor grade, lymph node stage, lymphovascular invasion, margin status, and albumin level were significant predictors of disease-specific survival. Multivariate analysis with these variables as covariates showed that tumor location, pathologic T stage, lymphovascular invasion, margin status, and albumin level were independent contributors. The score for DSS was calculated as 2 (if tumors located in both renal pelvis and ureter) + 3 (if pT2) or 4 (if \geq pT3) + 3 (if lymphovascular invasion) + 4 (if positive margin) + 2 (if albumin < 35 g/l) and 0 (otherwise). In univariate analysis, tumor location, pathologic T stage, tumor grade, lymph node stage, lymphovascular invasion, margin status, CRP, and albumin level were significantly associated with overall survival (OS). Tumor location, pathologic T stage, lymphovascular invasion, margin status, and albumin level were independent contributors in the Cox regression model for OS. The score for OS was calculated as 2 (if tumors located in both renal pelvis and ureter) + 3 (if \geq pT3) + 3 (if lymphovascular invasion) + 4 (if positive margin) + 3 (if albumin < 35 g/l) and 0 (otherwise) (Table-3).

Model discrimination was good for both models. The bootstrap-corrected C statistics of the multivariate Cox regression model were 0.813 (95% CI, 0.761–0.865) for DSS and 0.755 (95% CI, 0.702–0.807) for OS, respectively. To determine the accuracy of DSS and OS by the Cox regression model over the course of a follow-up period, we completed a concordance summary (integrated area under the curve). For time to disease-specific and overall mortality for patients, integrated area under the curve values were 0.792 and 0.739, respectively (Figure-1). Figure-2 illustrates the Kaplan-Meier curves for patients stratified into three groups from the models. Patients were clustered into three groups according to their model-

Table 3 - Multivariate Cox proportional hazard regression analysis of survival and scoring system based on regression coefficient.

	Disease-specific survival				Overall survival			
	p	HR (95% CI)	Coefficient (95% CI)*	Score†	p	HR (95% CI)	Coefficient (95% CI)*	Score†
Tumor location								
renal pelvis		reference				reference		
ureter	0.163	1.66 (0.82-3.36)			0.317	1.34 (0.75-2.39)		
both	0.006	3.06 (1.38-6.79)	1.12 (0.16-2.63)	2	0.009	2.29 (1.23-4.25)	0.83 (0.12-1.90)	2
Pathologic T stage								
pTa/is/1		reference				reference		
pT2	0.008	4.37 (1.47-13.02)	1.48 (0.49-3.32)	3	0.114	1.92 (0.86-4.31)		
pT3/4	<0.001	6.21 (2.38-16.21)	1.83 (1.07-3.39)	4	<0.001	3.27 (1.72-6.24)	1.19 (0.62-2.03)	3
Grade								
G1/2		reference				reference		
G3	0.239	1.44 (0.79-2.68)			0.515	1.18 (0.71-1.97)		
Lymph node stage								
Nx/0		reference				reference		
N+	0.790	0.85 (0.27-2.75)			0.668	0.79 (0.26-2.37)		
LVI								
Absent		reference				reference		
Present	<0.001	4.68 (2.41-9.10)	1.54 (0.88-2.46)	3	<0.001	3.46 (1.96-6.11)	1.24 (0.74-2.04)	3
Margin status								
negative		reference				reference		
positive	<0.001	5.24 (2.09-13.14)	1.66 (0.39-2.92)	4	<0.001	4.25 (1.98-9.09)	1.45 (0.56-2.35)	4
CRP, mg/l								
≤10		reference				reference		
>10					0.470	1.24 (0.69-2.22)		
Albumin, g/l								
≥35		reference				reference		
<35	0.013	2.97 (1.25-7.03)	1.09 (-0.08-2.34)	2	0.016	2.48 (1.18-5.21)	0.91 (-0.09-1.89)	3

HR: hazard ratio, CI: confidence interval, LVI: lymphovascular invasion, CRP: C-reactive protein.

*Bootstrap results are based on 1,000 bootstrap samples.

†Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by the highest coefficient, multiplied by 4, and rounded to the nearest integer.

Figure 1 - Time-dependent receiver operating characteristics curve analysis of the Cox regression model. Curve plots the area under the curve over time. (A) Disease-specific survival. Integrated AUC value was 0.792. (B) Overall survival. Integrated AUC value was 0.739.

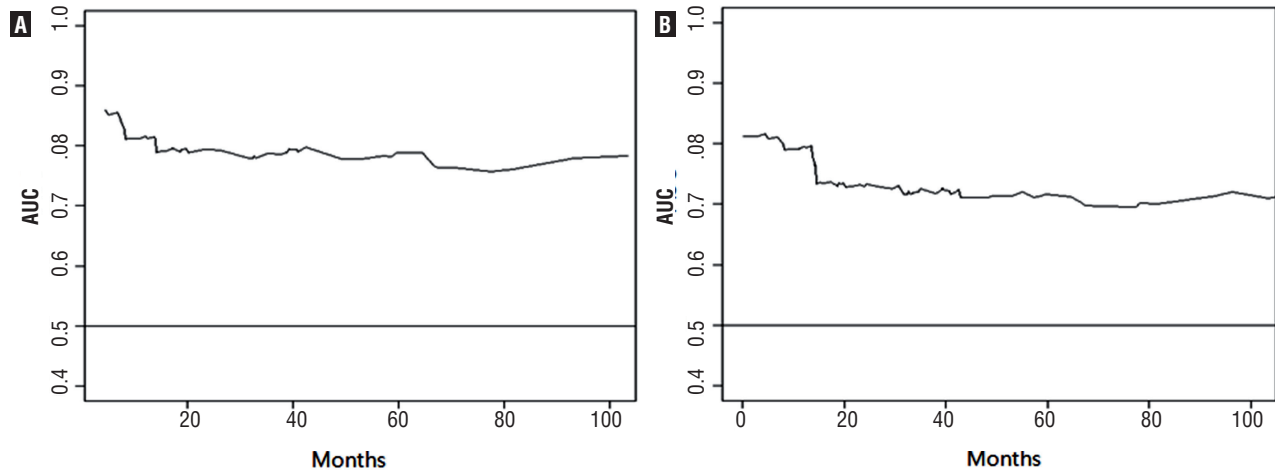
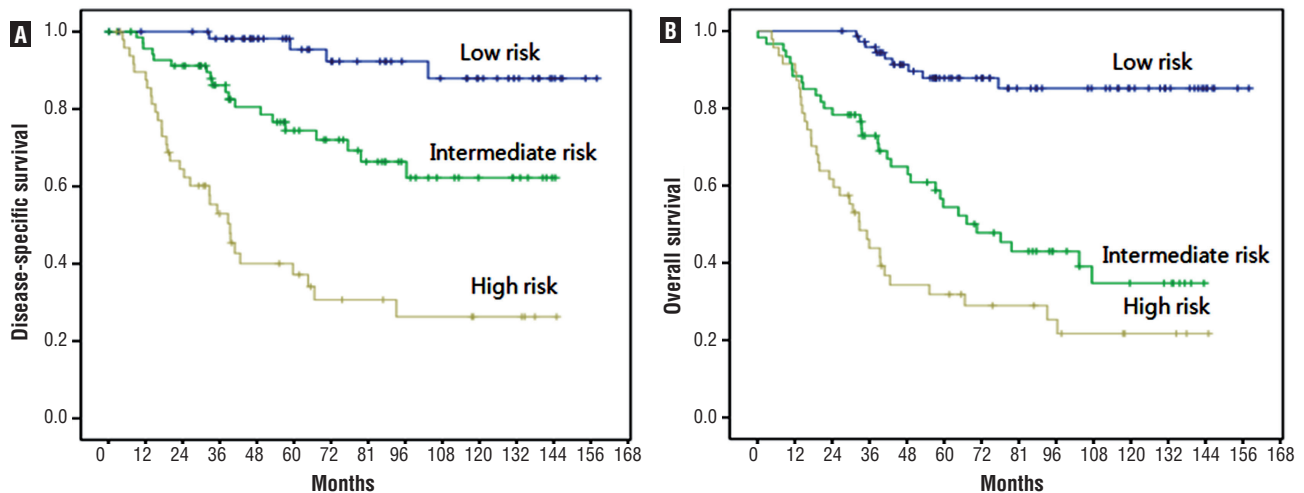


Figure 2 - (A) Kaplan-Meier plots of disease-specific survival of the Cox regression mode ($p < 0.0001$). (B) Kaplan-Meier plots of overall survival of the Cox regression mode ($p < 0.0001$).



-predicted survival (first quartile, <33%; second quartile, 33% to 66%; third quartile, >66%). As depicted, models discriminated well and log-rank test were all highly significant ($p < 0.001$). According to the models, the 5-year DSS in the low-, intermediate-, and high-risk group was 95.4%, 76.2%, and 36.9%, respectively (Figure-2A), and 87.8%, 54.4%, and 31.8%, respectively, for OS (Figure-2B). To assess the agreement between the predicted and actual outcomes, we generated calibration curves. The dashed line represents the performance of an ideal model, where the pre-

dicted outcome would correspond perfectly with the actual outcome. The performance of model is plotted as the solid line. The models were reasonably calibrated (Figure-3). Figure-4 presents the results of the decision curve analysis at 5 years. In our cohort, the predictions resulted in good net benefit across the range of risk thresholds. Decision curve analysis revealed that the use of model was associated with net benefit gains relative to the treat-all strategy. The models performed well across a wide range of threshold probabilities using decision curve analysis.

Figure 3 - (A) Calibration curves for 5-year disease-specific survival predictions. (B)

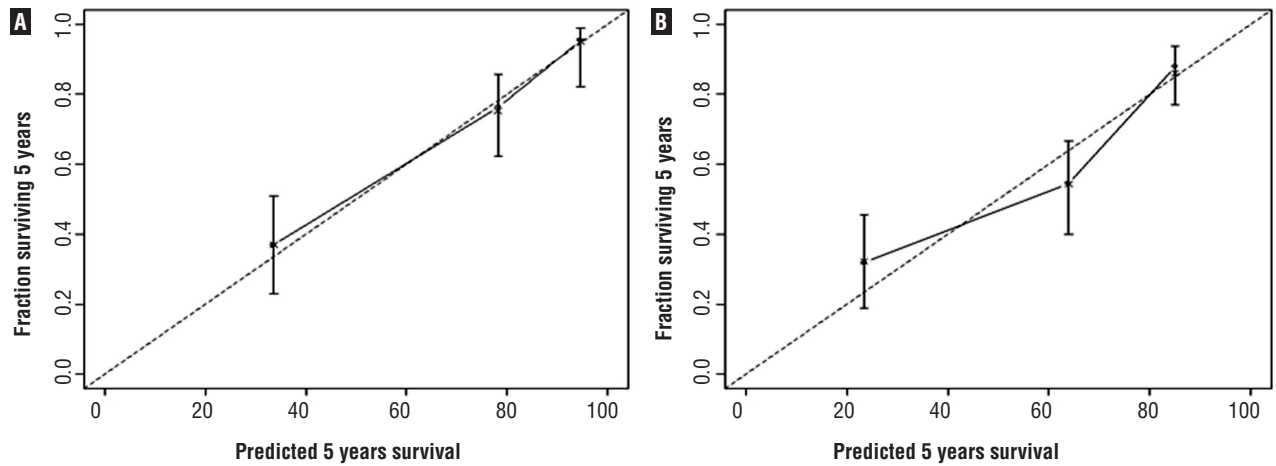
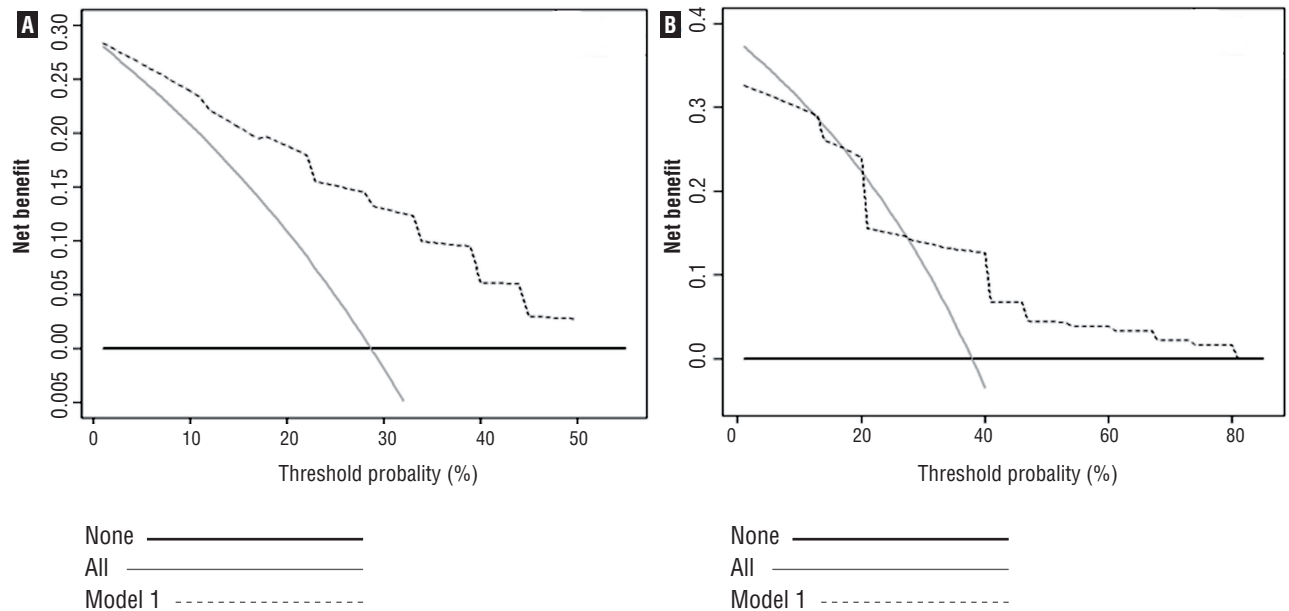


Figure 4 - Decision curve analysis for 5-year survival predictions. (A) Disease-specific survival. (B) Overall survival. In decision curve analysis, the y-axis measures net benefit, calculated by summing the benefits (true positives) and subtracting the harms (false positives). The straight line represents the assumption that all patients will die and the horizontal line represents the assumption that no patients will die. The dotted line indicates the net benefit of using the new model.



DISCUSSION

The prognosis of patients with UTUC remains unsatisfactory because it is one of the most aggressive carcinomas. Knowledge about prognosis is essential for patients and clinicians whenever

multimodal treatment is considered. At present, no biomarker has been applicable for predicting the outcomes in patients with UTUC. There is increasing evidence that the presence of SIR is associated with poor outcome in patients undergoing resection for a variety of common solid tumors.

It has been proposed that there are intrinsic pathways involved in cancer-related inflammation, such as the induction of genetic instability by inflammatory mediators. A recent review proposed that cancer-related inflammation is the seventh hallmark of cancer (3). Inflammation in the tumor microenvironment plays an important role in tumor proliferation and the survival of malignant cells, and promotes tumor angiogenesis, invasion, and metastasis (4).

Recent definitions of cancer cachexia include elevation of CRP and hypoalbuminemia (20). CRP is an acute phase reactant that acts as a surveillance molecule for the activation of the adaptive immune system. It is considered a nonspecific but sensitive marker of systemic inflammation and has been related to most of the signs of nutritional depletion (21). Albumin represents a negative acute phase protein and its level decreases as CRP rises (22). Albumin is no longer considered as a nutritional marker, but rather is considered an inflammatory response marker (23). Increased catabolism, chronic malnutrition, and a chronic inflammatory reaction due to cancer eventually lead to hypoalbuminemia. Hypoalbuminemia may be due to the production of cytokines, such as interleukin-6, which modulates the production of albumin by hepatocytes (24). Alternatively, tumor necrosis factor may increase the permeability of the microvasculature, allowing an increased transcapillary passage of albumin (25). Also, the presence of micrometastatic tumor cells in liver may induce Kupffer cells to produce a variety of cytokines, which may modulate albumin synthesis by hepatocytes (24,26).

Hypoalbuminemia provides additional prognostic information for patients with cancer in various organs. Hypoalbuminemia is predictive of increased 90-day mortality and poor overall survival after radical cystectomy in patients with bladder cancer (27). In patients with hepatocellular carcinoma, hypoalbuminemia is an independent poor prognostic factor (28). Separate studies reported that preoperative hypoalbuminemia is associated with earlier tumor recurrence and death following potentially curative resection for colon and rectal cancer (24,29). Hypoalbuminemia as a marker of the SIR and not CRP is a significant and

independent predictor of survival in patients with primary operable breast cancer (30).

It is not yet established if any specific component of SIR is a better predictor of cancer survival. This study is the first to show hypoalbuminemia to be superior to other CRP-based SIR prognostic scores for the prediction of prognosis in patients with UTUC. Presently, among the inflammation-based prognostic scores, only albumin was significantly associated with disease-specific survival and had prognostic value independent of TNM stage. This would suggest that albumin has superior prognostic value than other scores based on CRP (Glasgow prognostic score, modified Glasgow prognostic score, and prognostic index) in terms of outcome and should be used in preference to cellular markers of the SIR. Therefore, any further development of prognostic scores based on the SIR should include albumin. However, since the basis of the relationship between the SIR and poorer DSS in patients with UTUC is not clear, the cause-effect relationship between a SIR and DSS is questionable.

We used a wide array of tools to evaluate our multivariate Cox regression model including discrimination as well as calibration analyses. In addition, we used decision curve analysis to show the clinical net benefit. Our study results support the view that hypoalbuminemia has significant prognostic value. We observed a good prediction of clinical outcome by the model. The accuracy of the model for DSS and OS disease-specific and overall survival was 81.3% and 75.5%, respectively. The Kaplan-Meier curve was within the boundaries of predictions for each of the three strata. Using decision curve analysis, the model demonstrated net benefit gains for predictions of the examined end points at 5 years after radical nephroureterectomy.

The present cohort has a number of limitations. Despite the retrospective nature of the data collection, not all patients in our database had preoperative data on CRP-based SIR. Therefore, the patients were not necessarily representative of all patients with UTUC in general. A large-scale prospective validation study is needed to confirm the results.

However, despite the retrospective nature of the study and a relatively small number of pa-

tients in a single center, a homogeneous patient population was sufficient to indicate the significance of hypoalbuminemia as a postoperative prognostication of patients with UTUC.

CONCLUSIONS

In the present study, hypoalbuminemia predicted DSS as well as OS independent of stage in patients with UTUC. Pretreatment albumin is a simple biomarker based on routinely available well-standardized measures, is not expensive, and does not involve a time-consuming process. Our study demonstrates that hypoalbuminemia is an independent marker of poor prognosis in patients with UTUC and is superior to other CRP-based SIR protocols in terms of prognostic ability.

ABBREVIATIONS

CI = confidence interval
 CRP = C-reactive protein
 CT = computed tomography
 DSS = disease-specific survival
 HR = hazard ratio
 OS = overall survival
 SIR = systemic inflammatory response
 UTUC = upper urinary tract urothelial carcinoma

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