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The influence of serum sodium concentration on prognosis in patients with urothelial carcinoma treated by radical cystectomy

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Abstract

Serum sodium concentration has been found to be associated with poor survival in many solid tumors. This study investigated the effect of basal serum sodium concentration on prognostic in patients with muscle-invasive bladder cancer (MIBC) undergoing radical cystectomy (RC). MIBC patients with histologically proven urothelial carcinoma treated by RC were retrospectively reviewed. According to the optimal cutoff value, we divided the patients into 2 groups: high-serum sodium concentration group (≥140 mmol/L, n = 39) and low-serum sodium concentration group (<140 mmol/L, n = 32). Overall survival (OS) was estimated with the Kaplan–Meier method and the significance was examined by the log-rank test. Multivariable Cox regression for OS was performed for lymphatic metastasis, hypertension, diabetes mellitus, and tumor size. A total of 71 MIBC patients (60 males and 11 females) were included who underwent cystectomy between 2014 and 2018. The patients' ages at the time of operation ranged from 44 to 86 years (mean, 66.66 years). Patients' serum sodium concentration <140 mmol/L had shorter median OS (1224 days (HR: 2.454 [95% CI, 1.083–5.561; *P* = .031]). In multivariate analysis, lower serum sodium concentration was significantly associated with worse OS after adjusted (adjusted HR: 2.422 [95% CI, 1.055–5.561; *P* = .037]). Serum sodium concentration <140 mmol/L was independently associated with a poorer prognosis in patients with MIBC used who underwent RC.

Abbreviations: ALB = albumin, BC = bladder cancer, HLB = hemoglobin, MIBC = muscle-invasive bladder cancer, Na = serum sodium, OS = overall survival, PFS = progression-free survival, RC = radical cystectomy, ROC = receiver operating curve.

Keywords: cystectomy, prognostic factors, serum sodium concentration, urothelial carcinoma

1. Introduction

Bladder cancer (BC) is not a rare disease, as it is the eleventh most common worldwide.[1] And there are approximately 430,000 new cases and 165,000 deaths each year worldwide. At primary diagnosis, 30% of patients have muscle-invasive bladder cancer (MIBC) and 10% to 15% of patients with non-MIBC will progress to muscle-invasive disease.[2–4] Radical cystectomy (RC) in nonmetastatic MIBC was considered the standard treatment for localized MIBC.[5] Meanwhile, approximately 35% of local invasive BC patients who undergo RC developed distant metastasis and eventually died.[6,7] However, surgery was associated with perioperative mortality and complications, impaired quality of life related to urinary diversion. And hospital stays were extended even in patients operated by high-volume surgeons.[8–10]

A local or pelvic recurrence is detected in 5% to 15% of patients, usually within 24 months after surgery. Predictive factors are higher stage or lymph node metastasis, positive margins, and perioperative chemotherapy.[11] Hyponatremia has recently been identified as a complication of several inflammatory diseases associated with inflammatory cytokines such as interleukin-6.[12] Nakata et al reported that preoperative serum sodium levels ≤139 mEq/L were related to a poor prognosis in patients with invasive BC without metastasis after RC.[13] Recently, serum sodium concentration was reported to be associated with prognosis in localized cancers (N0M0), such as non-small cell lung cancer,[14] upper urinary tract cancer[15] and renal cell carcinoma,[16] even if it is within the normal range. However, there are few reports on MIBC patients.

Identification of poor prognostic factors is a major concern for doctors. The role of baseline serum sodium in MIBC patients treated with RC is not clear. In this study, the aim was to investigate the association of serum sodium with prognosis MIBC patients diagnosed with histologically proven urothelial cell carcinoma.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of General Hospital of Northern Theater Command and followed the principles outlined in the Declaration of Helsinki. The requirement for patient informed consent was waived because of the retrospective nature of this study.

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Table 1

The clinicopathological characteristics of patients.

		Serum sodium concentration		
	Total (n = 71)	**Na < 140 mmol/L (n = 32)**	**Na ≥ 140 mmol/L (n = 39)**	***P* value**
Age (yr)	66.66 ± 10.46	67.9 ± 12.18	65.64 ± 1.55	.368
Sex (male/female)	60/11	28/4	32/7	.528
BMI (kg/m^2)	23.27 ± 3.04	22.92 ± 2.84	23.55 ± 3.20	.383
Smoking index	419.72 ± 624.22	465.63 ± 516.30	382.05 ± 705.04	.163
Tumor size (cm)	4.46 ± 2.42	5.01 ± 2.58	4.01 ± 2.21	.056
Tumor morphology (cauliflower-like/protuberant/other) (n)	31/34/6	13/17/2	18/17/4	.673
Lymphatic metastasis	7	6	1	.023
Surgery (open/laparoscopic/robotic, n)	37/21/13	14/11/7	23/10/6	.441
Diversions (n)				
Ureterocutaneostomy	51	28	23	.739
Orthotopic neobladder	15	9	6	
Other	5	2	3	
TNM staging (II/III/IV, n)	54/7/10	21/4/7	33/3/3	.153
Pathological grade (High/Low, n)	53/18	25/7	28/11	.594
Alcohol (n)	21	8	13	.444
Diabetes mellitus (n)	10	2	8	.086
Family history of cancer (n)	4	3	1	.216
Hypertension (n)	25	16	9	.018
Hematuria time (d)	96.04 ± 174.04	111.41 ± 205.45	83.43 ± 144.91	.417
Preoperative blood laboratory data				
WBC (10^9/L)	6.77 ± 1.85	6.89 ± 2.18	6.671 ± 0.55	.615
HLB (g/L)	131.70 ± 19.50	127.38 ± 18.09	135.26 ± 20.11	.891
ALB (g/L)	37.03 ± 6.54	36.82 ± 6.04	37.2 ± 7.00	.361
CREA (μmol/L)	99.41 ± 112.56	111.33 ± 142.76	89.63 ± 80.60	.460
Glu (mmol/L)	6.24 ± 2.66	5.81 ± 0.86	6.58 ± 3.48	.876

ALB = albumin, BMI = body mass index, Clu = serum glucose, CREA = creatinine, HLB = haemoglobin, Na = serum sodium concentration, WBC = white blood cell.

2. Material and methods

2.1. Patient population

Patients who underwent cystectomy due to MIBC at General Hospital of Northern Theater Command from 2014 to 2018 were retrospectively included. Inclusion criteria were as follows: only patients diagnosed with MIBC after RC; histologically proven urothelial carcinoma of the bladder. Exclusion criteria were as follows: patients who were treated with partial cystectomy, or if they received adjuvant chemotherapy.

This study was approved by the Ethics Committee of General Hospital of Northern Theater Command and followed the principles outlined in the Declaration of Helsinki. The requirement for patients' informed consent was waived because of the retrospective nature of this study.

Data from 71 patients, including baseline demographic, clinical, and laboratory data, pathology, surgery reports and medical records, were fully anonymized and obtained from the hospital's database. The baseline demographic characters included age, sex, body mass index, tumor history, hematuria time, smoking, alcohol, accompanied diseases, and values of laboratory data including serum sodium (Na), hemoglobin (HLB), creatinine, blood glucose, albumin (ALB). The histopathological characteristics, including histology, TNM, size, number, tumor grade, were also analyzed. Histopathological classification was performed according to the abbreviated 3-grade Fuhrman scale, and the tumors were staged according to the TNM classification (2010) of malignant tumors.[17]

2.2. Statistical analysis

Overall survival (OS) was defined as time between the time of admission to the hospital and the date of death from any cause, or it was censored at the date of the last follow-up visit. Progression-free survival (PFS) was defined as the time of admission to the hospital to disease progression (locoregional and/or metastatic) or death from any cause. In selecting the optimal cutoff value for determining the effect of serum sodium concentration on survival, the receiver operating curve (ROC) analysis was performed. Then the patients were divided into 2 groups according to the optimal cutoff value to investigate the association with clinicopathological factors.

OS and PFS were estimated by the Kaplan–Meier method and differences between groups were examined by the log-rank test. Univariate and multivariate Cox proportional hazard models were used to assess the prognostic impact of serum sodium on OS and PFS. All variables with *P* value of .1 or less were included in the multivariate model. Variables included in the univariate analysis were tumor size, T stage and N stage. Correlation between variables was tested. All *P* values were two-sided, and $P < .05$ was considered statistically significant.

3. Results

3.1. Patients' characteristics

A total of 71 MIBC patients (60 males and 11 females) underwent cystectomy were included between 2014 and 2018. The patients' ages at the time of operation ranged from 44 to 86 years (mean, 66.66 years). Among the patients, 51 (71.83%) patients received ureterocutaneostomy diversions, 15 (21.13%) received orthotopic neobladder, and 5 patients (7.04%) were uremia patients with regular dialysis treatment. The median follow-up time was 27 months (range 1–66 months). At last follow-up, 24 patients were dead (Metastasis, n = 15; cachexia, n = 4; unknown, n = 5), 47 patients (66.19%) alive. The clinicopathological characteristics of patients were summarized in Table 1.

3.2. Optimal cutoff value of serum sodium concentration

The ROC curve of serum sodium was shown in Figure 1. The AUC value was 0.6126 (95% CI, 0.4695–0.7557). It was suggested that serum sodium concentration could be used as

a predictor of long-term prognosis. Further, n the ROC analysis of predicting death factors in patients with total BC, the critical value of serum sodium was 140, with a sensitivity of 62.5% and a specificity of 63.84%, the values of absolute and relative presenteeism that maximized the Youden index (sensitivity + specificity −1) were 26.33. The 140 mmol/L was considered as optimal cutoff value, the patients were divided into 2 groups according to serum sodium concentration for further study: Na ≥ 140 mmol/L (n = 32) and Na < 140 mmol/L (n = 39). Lymph-node involvement in the hyponatremia group and larger tumors tend to indicate a greater likelihood of subsequent metastasis or recurrence. Our COX regression analysis showed that the probability of death in patients was 3.08 times higher than that in the unaffected group, but the difference was not statistically significant (Adjusted HR = 3.08, *P* = .078).

3.3. Overall survival and progression-free survival

Kaplan–Meier survivals described that the median OS and PFS was showed in Table 2. OS (HR: 2.397 [95% CI, (1.063–5.407; *P* = .031]) and PFS (HR: 2.248 [95% CI, 1.001–5.049; *P* = .047]) in baseline serum Na < 140 mmol/L was significantly shorter than that of patients with normal serum sodium levels ≥140 mmol/L (Figs. 2 and 3).

3.4. Univariable and multivariate analysis

The relationships between the serum sodium concentration and clinical factors were shown in Table 1. There were no significant differences in baseline demographic like age, sex, body mass index, smoking index or alcohol history between 2 groups. In laboratory data, Na < 140 mmol/L had lower HLB, ALB, and longer hematuria time, while it showed no significant difference. As to comorbidity and history, patients with hypertension were more frequent in the Na < 140 mmol/L group than in the Na ≥ 140 mmol/L group (*P* = .018). Further, there were significant differences in the number of lymphatic metastases between 2 groups (*P* = .023). All the above indicated patients with low sodium were more likely to have a history of hypertension and more likely to have lymphatic metastasis in pathology.

All variables with a *P* value of .1 or less, including lymphatic metastasis, hypertension, diabetes mellitus, tumor size, were included in the multivariate model. After adjusting for the risk factors on multivariate analysis, there was statistically significant in Na ≥ 140 mmol/L (adjusted HR: 2.422 [95% CI, 1.055–5.561; *P* = .037]), and worse PFS after adjusted (adjusted HR: 2.266 [95% CI,0.988–5.200; *P* = .054]) (Table 2), which might indicate serum sodium concentration as an independent predictor for OS and PFS.

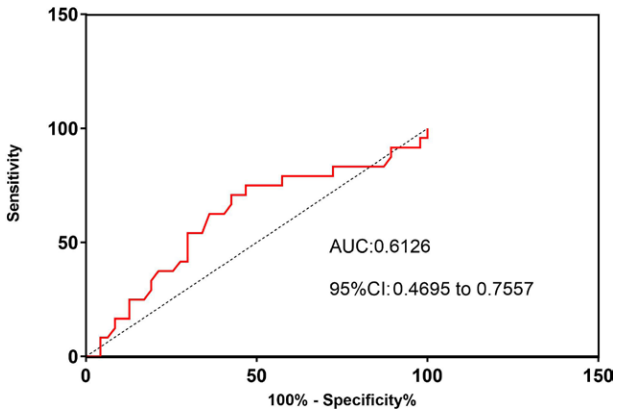

Figure 1. Receiver operating curve (ROC) curve of serum sodium concentration.

4. Discussion

There are few studies concerning serum sodium levels in MIBC. This is the first report to investigate the association of serum sodium on treatment outcomes in MIBC patients after RC. Patients who had relative lower preoperative serum sodium concentration at initiation (<140 mmol/L) more likely had hypertension, lymphatic metastasis, and related to poor prognosis after RC. Lower preoperative serum sodium (<140 mmol/L) was found to be associated with a significant lower OS in MIBC patients receiving cystectomy compared with those patients had relative higher preoperative serum sodium concentration (≥140 mmol/L). It remained statistically significant even after adjusting factors, including lymphatic metastasis, hypertension, diabetes mellitus, tumor size.

Sodium is essential for fluid balance and cellular homeostasis. Recently, the predictive and prognostic role of low serum sodium has been recognized. It is known that hyponatremia was associated with poor outcomes in several medical conditions like liver cirrhosis, congestive heart failure, and infectious diseases as pneumonia, childhood meningitis, and necrotizing soft-tissue infection.[18] Previously, hyponatremia has been reported as a poor prognostic factor for hepatocellular carcinoma,[19] gastric carcinoma[20] and renal cell carcinoma.[16,21] Recently, high immune response was reported to lead to the development of hyponatremia because of pro-inflammatory cytokines.[22] In renal cell cancer, preoperative hyponatremia was an unfavorable prognostic factor in the treatment of renal cell carcinoma.[23] The cause of hyponatremia in patients with BC is not fully understood.

It was demonstrated that even within the normal range lower serum sodium in MIBC patients treated with cystectomy had poor prognosis compared to patients with baseline higher serum sodium levels in this study. These results were similar with the report of Nakata et al They found that serum sodium concentration and CRP level was significantly correlated with the cancer-specific survival of patients with invasive BC without metastasis treated by cystectomy, in which serum sodium concentration (Na ≤ 139 mEq/L) was also an independent risk factor for cancer-specific survival.[13]

Nearly all BC patients have chronic hematuria, which led to hypovolemia and decreased in the true circulating blood

Table 2

Survival analysis and Hazard ratio (HR) for OS and PFS with 95% confidence intervals (CI).

		Na < 140 mmol/L (n = 32)	Na ≥ 140mmol/L (n = 39)	*P* value	HR (95% CI)
OS	Mean, mo	48.43 (40.900–55.781)	37.087 (27.193–40.980)	.031	2.397 (1.063–5.407)
	Median, mo	–	40.800 (11.215–70.385)		
PFS	Mean, mo	48.33 (40.900–55.762)	36.678 (26.431–46.926)	.047	2.248 (1.001–5.049)
	Median, mo	–	35.13 (10.769–59.491)		

CI = confidence interval, HR = hazard ratio, Na = serum sodium, OS = overall survival, PFS = progression-free survival.

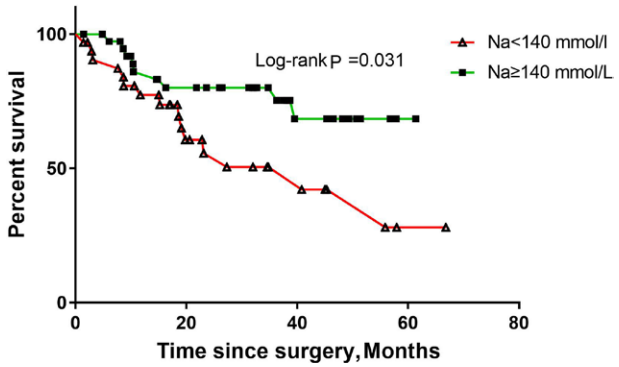

Figure 2. Kaplan–Meier plots of overall survival.

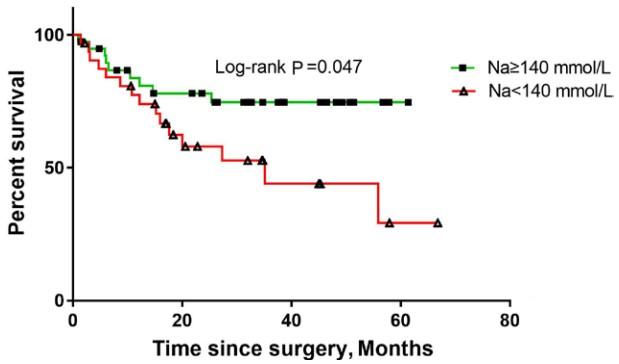

Figure 3. Kaplan–Meier plots of progression-free survival.

volume. In an attempt to restore the perfusion pressure to the tissues of the body, these baroreceptors signal the posterior pituitary to release antidiuretic hormone resulting in free water reabsorption and hyponatremia, even if the plasma is already dilute.[24] In laboratory data, this study found that lower sodium had longer hematuria time, and lower HLB, ALB. This decreased the osmotic threshold and then antidiuretic hormone was secreted and caused a series of changes. There were no statistical differences in HLB indicators (P = .891); however, the mean value of hemoglobin in hyponatremia group (127.38 ± 18.09) was lower than that in normal sodium group (135.26 ± 20.11). How the lower serum sodium relates to poor prognosis still needs further study, especially the mechanisms underlying the development of hyponatremia in MIBC patients. Several other comorbidities or factors may impair sodium homeostasis such as ethnicity, CHF, hypertension, diabetes, cirrhosis, adrenal insufficiency, hypothyroidism, diuretics, steroids, antiepileptics, selective serotonin reuptake inhibitors, or alcohol use.[25]

There were several limitations in this study, which include the retrospective nature of our study and the lack of evaluation of serum sodium after RC. It was unknown if aggressive treatment of sodium supplement could eventually alter the outcome of RC patients. Although lower Na was prognostic, we could not determine if it was a predictive biomarker since it was within the normal range.

5. Conclusion

In conclusion, preoperative serum sodium concentration <140 mmol/L was independently associated with a worse outcome in MIBC patients treated with RC. Preoperative serum sodium levels were found to be independent risk factors. Serum sodium level may be useful for estimating OS and PFS. However, since the present retrospective study only included a small number of cases from a single institution, the results still need to be validated in further studies that are preferably prospective, with larger numbers of patients.

Author contributions

Yan Zhang and Long He: project development, data collection and management, manuscript writing and revising; Zuojun Wang, Xue Yang: data collection, data analysis; Qing-chun Zhao, Wei-hong Meng: project design and development, data interpretation, manuscript editing and revising. All authors read and approved the final manuscript.
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