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ORIGINAL ARTICLE

The prognostic impact of ABO blood groups and Rhesus factor in patients with upper tract urothelial carcinoma

Djordje Radisavcevic[1], Zoran Dzamic[1,2], Emre Cico[1], Sandra Sipetic Grujicic[3], Bogomir Milojevic[1,2]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia. [2]Clinic of Urology, Clinical Center of Serbia, Belgrade, Serbia. [3]Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Summary

Purpose: *To evaluate the prognostic impact of ABO blood groups and Rhesus factor in patients with upper tract urothelial cancer (UTUC).*

Methods: *The study included 78 consecutive patients who were treated with RNU. Demographic and clinicopathologic factors were analyzed using x^2 or an unpaired t-test. Recurrence-free probabilities and cancer-specific (CSS) were estimated by the Kaplan-Meier method, and the log-rank test was used for the statistical differences. Univariate and multivariate Cox proportional hazard regression models were used to evaluate the association between various clinicopathologic factors with disease recurrence and CSS.*

Results: *ABO blood groups antigen and Rhesus factor were not significantly associated with any clinicopathologic and patient characteristics. At a median follow up of 25.2 months, 42.3% of the patients experienced disease recurrence and 15.4% died of UTUC. History of bladder tumor (HR 1.34; 95% CI, 0.76-2.34; p=0.3) was associated with disease recurrence. ABO blood group (p=0.3) and Rhesus factor (HR 6.7; 95% CI, 0.76-59.2; p=0.08) were not independently associated with disease recurrence. There was no difference in CSS when we compared ABO blood groups and Rhesus factor. ABO blood group and Rhesus factor were not significantly associated with worse disease recurrence-free survival (p=0.4, log rank), (p=0.8, log rank) respectively. In addition, ABO blood group was not significantly associated with CSS (p=0.55), as well as Rhesus factor (p=0.3).*

Conclusions: *ABO blood group antigens and Rhesus factor expression were unable to predict outcomes in a single-center series of consecutive patients who were treated with radical nephroureterectomy (RNU).*

Key words: *ABO blood group, radical nephroureterectomy, recurrence, Rhesus factor, upper tract urothelial carcinoma*

Introduction

Upper urinary tract carcinomas (UTUC) are uncommon and account for only 5–10% of urothelial carcinomas [1,2]. Pyelocaliceal tumors are approximately twice as common as ureteral tumors [3]. For UTUC, radical nephroureterectomy represents the gold standard [4], although kidney-sparing surgery, typically performed endoscopically, may be offered in carefully selected cases for low-risk tumors or in a solitary kidney [5].

ABO blood types are associated with a substantial number of malignant diseases [6-9]. Association of ABO blood types and clinicopathologic features of ureteral transitional cell carcinoma in a single-center in China showed that patients with ureteral transitional cell carcinoma (TCC) who have A or AB blood types was shown less likely to suffer from muscle invasive ureteral TCC as compared with individuals who had B or O blood types [10].

Corresponding author: Djordje Radisavcevic, MD. Faculty of Medicine, University of Belgrade, Belgrade, Serbia; Dr Subotica 8, 11000 Belgrade, Serbia.
Tel: +381 694700470, Email: djordjeradisavcevic@gmail.com
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Franchini et al have noted a relationship between ABO blood types and the risk and prognostic value of neoplastic diseases [11]. This study showed the prognostic impact of ABO blood groups in patients with bladder cancer and renal cell carcinoma, but the results were inconsistent [11].

To date, associations between blood type and histopathologic results or survival of patients with UTUC have not been well developed.

The purpose of this study was to investigate the prognostic impact of ABO blood groups and Rhesus factor in patients with upper tract urothelial carcinoma after radical nephroureterectomy.

Methods

Patient selection

With the approval of our institutional review board, hospital medical records of patients with UTUC were retrospectively reviewed to assess the significance of several clinicopathologic factors stratified by ABO and Rhesus factor (Table 1).

The present study cohort included 78 patients who were surgically treated for UTUC with nephroureterectomy between January 2016 and July 2020. Patients with a history of bladder tumor at a higher stage than the upper tract disease, preoperative chemotherapy, or previous contralateral UTUC were excluded. None of the

Table 1. The demographic, clinical and pathological profiles of 60 patients with UTUC managed by RNU stratified by AB0 blood groups system and Rh factor

Variable	*Number of patients (%)*	*ABO blood group antigen*				*p*	*Rhesus factor*		*p*
		A0	*B0*	*AB*	*00*		*Positive*	*Negative*	
All	60 (100)	25 (41.7)	13 (21.7)	7 (11.6)	15 (25.0)	-	51 (85)	9 (15)	-
Age (year), mean ± SD	68.3 ±7.6	67.8 ±7.9	68.5 ±7.2	65.8 ±8.6	70.2 ±7.0	0.21	67.7 ±7.5	71.2 ±7.2	0.13
Tumor side						0.83			0.50
Left	30 (50)	13 (43.3)	7 (23.3)	4 (13.3)	6 (20)		26 (86.7)	4 (13.3)	
Right	30 (50)	12 (40)	6 (20)	3 (10)	9 (30)		25 (83.3)	5 (16.7)	
Previous NMIBC						0.92			0.60
Yes	15 (25)	6 (40)	4 (26.7)	2 (13.3)	3 (20)		13 (86.7)	2 (13.3)	
No	45 (75)	19 (42.2)	9 (20)	5 (11.1)	12 (26.7)		38 (84.4)	7 (15.6)	
Anemia						0.66			0.43
Yes	38 (63.3)	17 (44.7)	8 (21)	3 (7.9)	10 (26.3)		33 (86.8)	5 (13.2)	
No	22 (36.7)	8 (36.4)	5 (22.7)	4 (18.2)	5 (22.7)		18 (81.8)	4 (18.2)	
Tumor location						0.18			0.15
Renal pelvis	34 (56.7)	10 (29.4)	9 (26.5)	5 (14.7)	10 (29.4)		27 (79.4)	7 (20.6)	
Ureter	26 (43.3)	15 (57.7)	4 (15.4)	2 (7.7)	5 (19.2)		24 (92.3)	2 (7.7)	
Tumor focality						0.18			0.71
Unifocal	42 (70)	16 (38.1)	7 (16.7)	6 (14.3)	13 (30.9)		35 (83.3)	7 (16.7)	
Multifocal	18 (30)	9 (50)	6 (33.3)	1 (5.6)	2 (11.1)		16 (88.9)	2 (11.1)	
Tumor size , cm						0.46			0.29
≤3	31 (51.7)	12 (38.7)	8 (25.8)	2 (6.5)	9 (29)		28 (90.3)	3 (9.7)	
>3	29 (48.3)	13 (44.8)	5 (17.2)	5 (17.2)	6 (20.7)		23 (79.3)	6 (20.7)	
Tumor grade						0.39			0.63
G1 or G2	33 (55)	13 (39.4)	6 (18.2)	3 (9.1)	11 (33.3)		28 (84.85)	5 (15.15)	
G3	27 (45)	12 (44.4)	7 (25.9)	4 (14.8)	4 (14.8)		23 (85.2)	4 (14.8)	
Tumor stage						0.72			0.52
pT2 or less	36 (60)	13 (36.1)	8 (22.2)	5 (13.9)	10 (27.8)		31 (86.1)	5 (13.9)	
pT3 or greater	24 (40)	12 (50)	5 (20.8)	2 (8.3)	5 (20.8)		20 (83.3)	4 (16.7)	
Lymph node metastasis						0.41			0.72
pNx / pN0	58 (96.7)	23 (39.7)	13 (22.4)	7 (12.1)	15 (25.9)		49 (84.5)	9 (15.5)	
pN+	2 (3.3)	2 (100)	0 (0)	0 (0)	0 (0)		2 (100)	0 (0)	
Lymphovascular invasion						0.21			0.58
Absent	32 (53.3)	15 (46.9)	4 (12.5)	3 (9.4)	10 (31.2)		27 (84.4)	5 (15.6)	
Present	28 (46.7)	10 (35.7)	9 (32.1)	4 (14.3)	5 (17.9)		24 (85.7)	4 (14.3)	

patients included in this study had distant metastasis at diagnosis of UTUC. Patients with concomitant bladder cancer and those with incomplete medical data were also excluded. In total, 60 patients (mean age ± SD, 68.3 ± 7.6) were then available for evaluation.

Information on ABO blood types and Rhesus factor were gathered from the preoperative blood type analysis in the medical charts. Serological testing was performed preoperatively as a routine testing.

The diagnosis of UTUC was established by computed tomography, excretory urography, a retrograde ureteropyelogram, and/or ureteroscopy with tissue biopsies. The initial treatment of all patients was open RNU. Whether lymph node dissection (LND) would be performed or not as well as the extent of LND when performed were determined by each surgeon and not by strict prospective criteria. The extent of LND ranged from just the ipsilateral hilar lymph nodes (LNs) to all LNs around the ipsilateral great vessels with or without interaortocaval LNs.

Pathologic evaluation

Tumors were staged according to the TNM system [10] and graded using the 1998 World Health Organization classification [11]. Tumor location was defined as either renal pelvic or ureteral on the basis of the location of the dominant tumor. The dominant lesion was defined as that with the highest pathologic tumor stage (pT). For multifocal tumors at the same stage, the higher grade was selected for main tumor location. Tumor multifocality was defined as the synchronous presence of 2 or more pathologically confirmed tumors in any upper urinary tract location. No immunohistochemistry techniques were used to determine the presence of lymphovascular invasion (LVI).

Follow-up program

Routine follow-up consisted of physical examination and cystoscopy every 3 months during the first year and every 6 to 12 months thereafter. Chest radiography, abdominal ultrasonography, computed tomography, and excretory urography were performed annually, depending on the clinical stage of the cancer in the upper urinary tract. Most patients who were identified as having died from UTUC had progressive, widely disseminated metastases at the time of death.

Statistics

Demographic and clinicopathologic factors were analyzed using x^2 or an unpaired t-test. Recurrence-free probabilities and CSS were estimated by the Kaplan-Meier method, and the log-rank test was used to assess statistical differences. We defined the time of surgery as time 0.

Univariate and multivariate Cox proportional hazard regression models were used to evaluate the association between various clinicopathologic factors with cancer recurrence and CSS after surgery. Only the significant factors were entered into multivariate Cox proportional hazard regression models. Hazard ratios (HRs) were estimated from the Cox analyses and are reported as relative risk with corresponding 95% confidence interval. In all tests, $p<0.05$ (2-sided) was considered statistically significant.

Results

The patient clinical and pathologic profiles are listed in Table 1. The median follow-up after surgery was 25.2 months (range 4-55). The distribution of ABO blood group antigens was 41.7, 21.7,

Table 2. Univariate and multivariate Cox regression models predicting disease recurrence and CSS in 60 patients after radical nephroureterectomy for UTUC

Variable	*Disease recurrence free survival*						*Cancer specific survival*					
	Univariate			*Multivariate*			*Univariate*			Multivariate		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*	HR	95% CI	P
Rhesus factor (+ vs –)	6.70	0.76-59.3	0.08				0.42	0.08-2.19	0.30			
AB0 blood group antigen	1.34	0.76-2.34	0.30				1.85	0.39-1.80	0.67			
Age (years) (≤60 vs. >60)	0.66	0.15-2.93	0.58				0.69	0.13-3.76	0.67			
Anemia (No vs. Yes)	0.89	0.28-2.77	0.84				4.65	0.88-24.38	0.07			
History of BC (No vs. Yes)	2.14	1.02-5.27	0.04	3.67	1.06-12.68	0.03	1.52	0.29-7.91	0.62	0.73	0.44-1.22	0.23
Renal pelvis vs. Ureter	0.80	0.28-2.29	0.68				1.34	0.29-6.05	0.71			
Unifocal vs. Multifocal	0.48	0.16-1.44	0.18				1.51	0.35-6.50	0.58			
Tumor size (≤3cm vs. >3cm)	1.19	0.38-3.68	0.76				1.47	0.33-6.62	0.61			
G1 or G2 vs. G3	1.63	0.51-5.19	0.41				4.21	0.81-21.80	0.08			
≤ pT2 vs. ≥ pT3	1.07	0.25-4.63	0.92				2.86	0.62-13.08	0.17			
pNx vs. pN+	2.82	0.35-22.47	0.33				26.5	3.69-191.1	0.001	26.5	3.69-191.1	0.001
LVI (absent vs. present)	0.73	0.19-2.68	0.63				1.15	0.25-5.22	0.85			

P values assessed by log-rank test, CI: confidence interval, HR: hazard ratio, BC: bladder cancer, LVI: lymphovascular invasion.

11.6, and 25.0% for AO, BO, AB and OO, respectively. Rhesus factor was positive in 85.0% and negative in 15.0% of the patients. ABO blood groups antigen and Rhesus factor were not significantly associated with any clinicopathologic and patient characteristics (Table 1).

At a median follow-up of 25.2 months, 42.3% of the patients experienced disease recurrence and 15.4% died of UTUC. Using univariate analysis, history of bladder tumor (HR 2.14; 95% confidence interval, CI 1.02-5.27; p=0.03) was associated with disease recurrence. Using multivariate analysis, history of bladder tumor (HR 3.67; 95% CI 1.06-12.68; p=0.03) was associated with disease recurrence (Table 2). ABO blood group and Rhesus factor were not independently associated with disease recurrence (hazard ratio, HR 1.34; 95% confidence interval, CI 0.76-2.34; p= 0.3); (HR 6.7; 95% confidence interval, CI 0.76-59.2; p= 0.08), respectively. Multivariate analysis of lymph node status (HR 26.5; 95% CI 3.69-191.1; p= 0.001) showed that it was associated with CSS (Table 2). There was no difference in CSS when we compared ABO blood groups and Rhesus factor.

Kaplan-Meier analysis showed that ABO blood group and Rhesus factor were not significantly associated with worse disease recurrence-free survival (log rank p=0.4 and log rank p=0.8, respectively). Also, the Kaplan-Meier analysis showed that ABO blood group was not significantly associated with CSS (log rank p=0.55), as well as Rhesus factor (log rank p=0.3, log rank mean disease RFS for patients with Rh positive factor 48.1 ± 2.9 months versus mean disease RFS for patients Rh negative factor 36.6 ± 5.8 months).

Discussion

ABO antigens were reported to be expressed on the cell surface of a number of epithelial cell types, including the urogenital epithelium and not only on the surface of red blood cells [12-14]. Connection between ABO blood types and different malignant diseases have been reported. Such as association was observed in renal cell carcinoma [12] ovarian, endometrial and cervical cancer [8], oral cancer [7], esophageal squamous cell carcinoma [6], urothelial cancer of urinary bladder [9] and gastric cancer [15].

Association of ABO blood types and clinicopathologic features of ureteral transitional cell carcinoma in a single-center in China revealed that patients with ureteral TCC who had A or AB blood types were less likely to suffer from muscle invasive ureteral TCC as compared with individuals who had B or O blood types [10]. Also, Lippert and colleagues had demonstrated that those ureteral TCC patients who retained ABO antigens in the surface of TCC were associated with lower tumor grade and longer disease-free interval [16]. In the present study, we failed to detect differences in disease recurrence and survival, when stratifying patients by ABO blood group system and Rhesus factor.

Engel et al [17] showed the impact of ABO and the Rhesus blood group system on outcomes in bladder cancer patients treated with radical cystectomy. Also, Rink et al [18] found significant association between ABO and Rhesus blood grouping systems on the oncologic outcome in UTUC after radical nephroureterectomy which confronts our results. ABO blood group antigen expression showed a significant association with sessile tumor architecture and tumor grading, specifically G1 [18]. We showed no correlation between ABO blood group system and Rhesus factor with pathologic tumor stage, grade, and lymphovascular invasion. That is why ABO blood groups system and Rhesus factor were unable to be strong prognostic marker that might guide the decision making process during the postoperative clinical management of patients with UTUC after surgery with curative intent.

Engel et al showed that ABO blood group antigen expression was associated with a higher tumor grade in patients with bladder cancer [17]. We found that history of bladder tumor was independetly associated with disease recurrence in patients treated with radical nephroureterectomy for UTUC. However, ABO blood groups antigen and Rhesus factor were not significantly associated with history of bladder tumor in our study.

In this study, lymph node metastasis was the strongest predictor of survival in UTUC cases which is in accordance with our previous studies [19, 20]. However, our results showed that ABO blood group system and Rhesus factor were not independetly associated with disease recurrence and CSS.

This study is inherently limited by biases associated with its retrospective design. In addition, our results are subject to the inherent biases associated with high-volume tertiary care centres. In this cohort of patients, none had received neoadjuvant chemotherapy, which can be a limitation of the study. This analysis excluded patients for whom we could not obtain complete information, possibly creating a selection bias. Despite these limitations, our study has strengths, such as a centralized pathologic review and standardized follow-up.

Conclusions

In our study, the ABO blood group antigens and Rhesus factor expression were unable to predict outcomes in a single-center series of consecutive patients who were treated with radical nephroureterectomy for UTUC. Anyway, due to the low number of patients in this study, we suggest that further studies with a larger cohort of different patient populations are necessary to confirm the prognostic role of ABO types and Rhesus factor in patients with UTUC.

Acknowledgment

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the insitutional and/or National Research Committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflict of interests

The authors declare no conflict of interests.

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