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ABO Blood Group and Rhesus Factor Are Not Associated with Outcomes After Radical Cystectomy for Non-metastatic Urothelial Carcinoma of the Bladder

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Abstract. *Aim: To investigate the role of ABO blood group and Rhesus factor as a predictor of outcome in patients undergoing radical cystectomy (RC) for non-metastatic urothelial carcinoma of the bladder. Materials and Methods: Data of 463 consecutive patients treated with RC between 1988 and 2003 were retrospectively analyzed. The effect on recurrence-free survival, and cancer-specific and overall mortality were assessed using the Kaplan–Meier and multivariable Cox regression methods. Results: Overall, 185 (41.3%), 190 (42.4%), 46 (10.3%) and 27 (6%) patients expressed O, A, B and AB phenotypes, respectively; 65 (14.5%) were Rhesus-negative. Median follow-up was 14.2 years (interquartile range=10.2-17.1 years). No individual blood group was associated with any clinicopathological characteristics whereas Rhesus-positive patients had a higher rate of pT4 disease (11% vs. 22%; p=0.02). ABO blood groups were not associated with outcomes. Rhesus-positive patients had an increased risk of shorter recurrence-free survival, and of cancer-specific and overall mortality compared to Rhesus-negative patients (all p<0.03). In multivariable analyses that adjusted for the effects of standard characteristics, this association disappeared. Conclusion: The results of our study showed that neither ABO blood group nor Rhesus factor are associated with oncological outcomes. The clinical relevance of blood groups and Rhesus factor in bladder cancer remains questionable.*

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In Europe, bladder cancer is the fourth most common cancer in men and the eight most common cause of cancer-specific mortality (1). Radical cystectomy (RC) with lymph node dissection remains the standard treatment of very high-risk non muscle-invasive and muscle-invasive cancer (2, 3). Despite seemingly adequate surgery, the 5-year overall survival of patients who undergo RC remains below 60% (4-6). Nomograms (7, 8) and markers (9, 10) have been developed for predicting recurrence and survival but they have not changed clinical decision-making to date.

The ABO phenotype has emerged as an inexpensive, readily available marker that is associated with outcomes of various malignancies (11, 12). The association of blood groups with characteristics and outcomes of urothelial carcinoma of the bladder (UCB) remains controversial. For example, while a large cohort study of patients treated with RC showed a higher cancer-specific mortality for those with A blood group (13), another large multicentric study reported a higher mortality for patients mm B blood group (14). While these associations were statistically significant in some cases, they lacked clinical significance testing (15). On the other hand, few data have been reported on the association of Rhesus factor with UCB development and prognosis (16, 17). Limitations of the previous studies (13, 16, 17) were the lack of external validation and the relatively short follow-up. We hypothesized that neither ABO blood group nor the Rhesus factor have a clinically significant

association with clinicopathological characteristics or outcomes for UCB.

To test this hypothesis, we evaluated the association of the ABO blood group and the Rhesus factor with outcomes of patients treated with RC for clinically non-metastatic UCB who had long term follow-up.

Materials and Methods

Study population. After Institutional Review Board approval was obtained (protocol title: Molecular profiling of bladder cancer; protocol number: 1011011386), we evaluated 463 consecutive patients treated with RC and lymphadenectomy for clinically non-metastatic UCB at the Department of Urology of the Cornell University between January 1988 and 2003. The indication for surgery was given in the case of muscle-invasive bladder cancer or high-risk disease, refractory to transurethral resection of the bladder with or without adjuvant intravesical instillation therapy, according to the guidelines at the time. Patients with missing data on blood group and Rhesus factor were excluded. Overall, 15 patients received neoadjuvant chemotherapy and were excluded, leaving 448 patients for final analysis. Due to the retrospective nature of the study, follow-up was not standardized. Patients underwent clinical and radiological follow-up based on final pathology, guidelines at that time and physician discretion. Generally, this comprised physical examination, blood test, urine cytology and imaging such as ultrasonography and computed tomography with urography; bone scan was performed when clinically indicated. Cause of death was attributed through chart or death records reviews (18).

Covariates. The primary endpoint of this retrospective study was to evaluate the association of ABO blood type and Rhesus factor with oncologic l outcomes such as clinicopathological characteristics, recurrence-free survival (RFS), and cancer-specific (CSS) and overall (OS) survival. Pathological T and N stage were coded accordingly to the 2009 TNM classification (19). Tumor grade was assigned according to the 1973 World Health Organization system (20). Lymphovascular invasion was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls (21). A positive soft-tissue surgical margin was defined as presence of tumor at inked areas of soft tissue on the radical cystectomy specimen (22). Variant histology was defined as urothelial carcinoma with any proportion of sarcomatoid, plasmocytoid, micropapillary or neuroendocrine cells (23, 24).

Statistical analyses. Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges (IQR) were reported for continuously coded variables. The Mann–Whitney test and chi-square test were used to compare the statistical significance of differences in medians and proportions, respectively. Kaplan–Meier and multivariable Cox regression analyses were used to evaluate the impact of ABO phenotype and Rhesus factor on disease recurrence, CSS and OS. Statistical significance was considered at $p<0.05$; all tests were two-sided. Statistical analyses were performed using STATA v.14.0 (STATA Corp LLC, College Station, TX, USA) and R statistical package system (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and pathological baseline characteristic and their association with the ABO blood groups and the Rhesus factor are shown in Tables I and II, respectively. Overall, 185 (41.3%), 190 (42.4%), 46 (10.3%) and 27 (6%) patients expressed O, A, B and AB phenotypes, respectively; 65 (14.5%) were Rhesus-negative. The median patient age was 65.2 (IQR=60-71) years. Demographics and pathological stage were equally distributed among the groups (all $p\geq0.1$); ABO blood group was not associated with any of the clinicopathological characteristics. Rhesus-positive patients were more likely to have locally advanced tumor stage ($p=0.02$).

With a median follow-up of 14.2 years (IQR=10.2-17.1 years), 200 patients experienced disease recurrence, 196 died from UCB and 133 died of other causes.

Figures 1 and 2 show the Kaplan–Meier curves assessing the relationship of disease recurrence, CSS and OS for the ABO and the Rhesus groups, respectively.

The 5- and 10-year CSS were 62% and 71% *vs*. 64% and 82% *vs*. 56% and. 62% *vs*. 44% and 62% for patients with O, A, B and AB blood groups, respectively. There was no statistical difference between the four groups (all $p>0.05$) (Figure 1B). Similar results were observed for RFS (Figure 1A) and OS (Figure 1C) (all $p>0.05$).

Regarding the Rhesus factor, the 5- and 10-year CSS were 76% *vs*. 66% and 65% *vs*. 46%, for Rhesus-positive and -negative patients, respectively. Rhesus-positive patients had an increased risk of disease recurrence, and poorer CSS and OS compared to Rhesus-negative patients (Figure 2; all $p<0.03$). On multivariable analyses, adjusting for the effects of standard clinicopathological features Rhesus factor was no longer associated with RFS, CSS, or OS (Table III).

Discussion

Several mechanisms have been proposed to explain the relationship of blood groups and UCB development and progression. Studies published 20 years ago (25-27) described the loss of A and B antigen expression in UCB and an association with cancer aggressiveness. Interestingly, the gene encoding for blood group resides on chromosome 9q34, a locus which is typically deleted in UCB (25, 28). The Rhesus factor gene is located on chromosome 1, a region of tumor-suppressor genes and the proto-oncogene *L-MYC*, which is down-regulated in UCB (29). The loss of blood group antigens on the cell surface can affect cell adhesion, cell signaling, and immune surveillance (30). Based on this immune escape, it could be speculated that blood group phenotype can predispose for UCB progression and poos outcome.

We evaluated the prognostic role of ABO blood group and Rhesus factor in 448 patients treated with RC for

Table I. *Descriptive statistics of 448 patients treated with radical cystectomy for urothelial carcinoma of the bladder stratified according to ABO blood group.*

			Blood group				
Variable		Overall	O	A	B	AB	
Number (%)		(448, 100%)	185 (41.3%)	190 (42.4%)	46,10.3%)	27 (6.0%)	*p*-Value
Age, years	Median (IQR)	65 (60-71)	65 (59-70)	67 (60-73)	67 (63-71)	65 (57-72)	0.1
Gender, n (%)	Male	373 (83.3%)	154 (83.2%)	154 (81.1%)	44 (95.7%)	21 (77.8%)	0.1
	Female	75 (16.7%)	31 (16.8%)	36 (18.9%)	2 (4.3%)	6 (22.2%)	
BMI, kg/m^2	Median (IQR)	25.4 (23.7-28.4)	25.4 (23.5-28.2)	25.4 (23.9-28.7)	26.2 (24.6-28.4)	25.0 (22.2-28.5)	0.8
ASA, n (%)	1	35 (7.8%)	19 (10.3%)	11 (5.8%)	2 (4.3%)	3 (11.1%)	0.1
	2	176 (39.3%)	71 (38.4%)	85 (44.7%)	14 (30.4%)	6 (22.2%)	
	3	115 (25.7%)	43 (23.2%)	45 (23.7%)	16 (34.8%)	11 (40.7%)	
	4	8 (1.8%)	5 (2.7%)	2 (1.1%)	0	1 (3.7%)	
NYHA, n (%)	0	192 (42.9%)	85 (45.9%)	81 (42.6%)	16 (34.8%)	10 (37.0%)	0.2
	1	55 (12.3%)	22 (11.9%)	26 (13.7%)	6 (13.0%)	1 (3.7%)	
	2	78 (17.4%)	29 (15.7%)	30 (15.8%)	9 (19.6%)	10 (37.0%)	
	3	7 (1.6%)	1 (0.5%)	5 (2.6%)	1 (2.2%)	0	
pT stage, n (%)	pT0-T1	74 (16.5%)	28 (15.1%)	34 (17.9%)	6 (13.0%)	6 (22.2%)	0.7
	pT2	86 (19.2%)	43 (23.2%)	33 (17.4%)	6 (13.0%)	4 (14.8%)	
	pT3	196 (43.8%)	78 (42.2%)	81 (42.6%)	25 (54.3%)	12 (44.4%)	
	pT4	92 (20.5%)	36 (19.5%)	42 (22.1%)	9 (19.6%)	5 (18.5%)	
pN stage, n (%)	pN0	277 (61.8%)	111 (60.0%)	121 (63.7%)	28 (60.9%)	17 (63.0%)	0.4
	pN1						
	pN2						
	pN3						
	pN1	59 (13.2%)	19 (10.3%)	25 (13.2%)	9 (19.6%)	6 (22.2%)	
	pN2	104 (23.2%)	52 (28.1%)	41 (21.6%)	8 (17.4%)	3 (11.1%)	
	pN3	8 (1.8%)	3 (1.6%)	3 (1.6%)	1 (2.2%)	1 (3.7%)	
Lymph nodes removed, n	Median (IQR)	14 (10-21)	15 (11-19)	15 (9-22)	14 (9-21)	13 (11-16)	0.7
Grade, n (%)	G1-G2	12 (2.7%)	5 (2.7%)	6 (3.2%)	1 (2.2%)	0	0.8
	G3	436 (97.3%)	180 (97.3%)	184 (96.8%)	45 (97.8%)	27 (100%)	
Histological variant, n (%)*		137 (30.6%)	58 (31.4%)	57 (30.0%)	15 (32.6%)	7 (25.9%)	0.9
LVI, n (%)		185 (41.3%)	76 (41.1%)	77 (40.5%)	23 (50.0%)	9 (33.3%)	0.5
ACT, n (%)		40 (8.9%)	12 (6.5%)	22 (11.6%)	4 (8.7%)	2 (7.4%)	0.4
NCT, n (%)		15 (3.3%)	8 (4.3%)	5 (2.6%)	1 (2.2%)	1 (3.7%)	0.8

IQR: Interquartile range; BMI: body mass index; NYHA: New York Heart Association; ASA: American Association of Anesthesiologists; LVI: lymphovascular invasion; ACT: adjuvant chemotherapy; NCT: neoadjuvant chemotherapy. *Defined as papillary urothelial carcinoma with morphological variants or pure variant features.

clinically non-metastatic UCB with a median follow-up of over 14 years. We found that neither the ABO blood group nor the Rhesus factor were significant prognostic factors for RFS, CSS and OS after RC. These findings are in line with previous publications. For example, in a large multi-institutional series of 3,728 patients, Klatte *et al*. showed that the B blood group was associated with a higher UCB-related mortality when compared to the other blood groups (p=0.026). When adjusting for other prognosticators in multivariable analysis, this association disappeared (14). In contrast, Gershmann *et al*. (13) showed in a retrospective study of 2,086 patients treated with RC for UCB that non-O blood group, specifically blood group A, was associated with higher CSS (hazard ratio=1.23; p=0.007) (13). The overall cohort had lower pN+ disease when compared to our population (14.4% *vs*. 38.2%, respectively) and a 60.5% rate of perioperative blood transfusion. This could have influenced survival rates. Indeed, Moschini *et al*. recently showed that intraoperative transfusion is itself a predictor for poor outcomes after surgery (31). The difference in pathological stage and the high rate of blood transfusion can explain the divergent results from our study. Sadly, data on perioperative blood transfusions were not available in our study.

In a recent study, Engel *et al*. reported on 511 patients treated with RC for UCB. The authors found no difference

Table II. *Association of Rhesus factor with clinicopathological features in 448 patients treated with radical cystectomy for urothelial carcinoma of the bladder.*

Variables		Rhesus-negative	Rhesus-positive	
Number (%)		(65, 14.5%)	(383, 85.5%)	*p*-Value
Age, years	Median (IQR)	65 (60-72)	66 (60-72)	0.9
Gender, n (%)	Male			
Female	53 (81.5%)	320 (83.6%)	0.4	
	Female	12 (18.5%)	63 (16.4%)	
BMI, kg/m2	Median (IQR)	25.3 (22.9-27.6)	25.6 (23.7-28.5)	0.2
ASA, n (%)	1	10 (15.4%)	25 (6.6%)	0.1
	2	23 (35.4%)	153 (39.9%)	
	3	16 (14.6%)	99 (25.8%)	
	4	0	8 (2.1%)	
NYHA, n (%)	0	37 (56.9%)	155 (40.5%)	0.1
	1	6 (9.2%)	49 (12.8%)	
	2	6 (9.2%)	72 (18.8%)	
	3	0	7 (1.8%)	
Pathologic T-stage, n (%)	pT0-T1	18 (27.7%)	56 (14.6%)	0.02
	pT2	12 (18.5%)	74 (19.3%)	
	pT3	28 (43.1%)	168 (43.9%)	
	pT4	7 (10.8%)	85 (22.2%)	
Pathologic N-stage, n (%)	pN0	45 (69.2%)	232 (60.6%)	0.6
	pN1	6 (9.2%)	53 (13.8%)	
	pN2	13 (20.0%)	91 (23.8%)	
	pN3	1 (1.5%)	7 (1.8%)	
Lymph nodes removed, n (%)	Median (IQR)	16 (11-26)	14 (9-20)	0.3
Grade, n (%)	G1-G2	3 (4.6%)	9 (2.3%)	0.4
	G3	62 (95.4%)	374 (97.7%)	
Histological variant, n (%)*		19 (29.2%)	118 (30.8%)	0.5
LVI, n (%)		23 (35.4%)	162 (42.3%)	0.3
ACT, n (%)		7 (10.8%)	33 (8.6%)	0.6
NCT, n (%)		0 (%)	15 (3.7%)	0.2

IQR: Interquartile range; BMI: body mass index; NYHA: New York Heart Association; ASA: American Association of Anesthesiologists; LVI: lymphovascular invasion; ACT: adjuvant chemotherapy; NCT: neoadjuvant chemotherapy. *Defined as papillary urothelial carcinoma with morphological variants or pure variant features.

in RFS, CSS and OS among the four ABO subgroups (all $p>0.14$). Furthermore, the relationship between Rhesus factor and oncological outcomes was evaluated, the authors also found no association with RFS, CSS and OS (all $p>0.5$) (17). Süer *et al*. (16) retrospectively analyzed 290 patients undergoing RC for UCB. The authors concluded that ABO and Rhesus factor are not independent predictors of CSS and OS (16). The results of our study confirm these findings. Nevertheless, there are some differences in the study population that should be considered. In our series, Rhesus-positive patients were more likely to have locally advanced disease, Engel *et al*. found a higher rate of lymph node involvement in their Rhesus-negative group (17). Moreover, the histological type was reported only by Süer *et al*. but they did not report on RFS (16). Substantial histopathological differences could have influenced the slightly divergent results of univariable analyses of previous reports. Propensity score matching has been advocated to estimate the effect of confounders on treatment effect. This method was not used in our analysis, because the number of events per confounder was too high and, in this situation, multivariable analysis is a more powerful tool (32).

There have been several larger studies evaluating blood groups and outcomes after RC (13, 14) but evidence on the role of Rhesus factor is poor. Despite our study not being the largest one, we still provided a relevant population. A strength of our study is certainly the long follow-up of almost 15 years.

In conclusion, based on the results of our study and previous data, we confirm that ABO blood group and Rhesus factor cannot predict the outcome after RC and should therefore not be integrated into prognostic models nor any clinical decision-making.

There are of course various limitations to our study. Firstly, its retrospective nature and the lack of a control

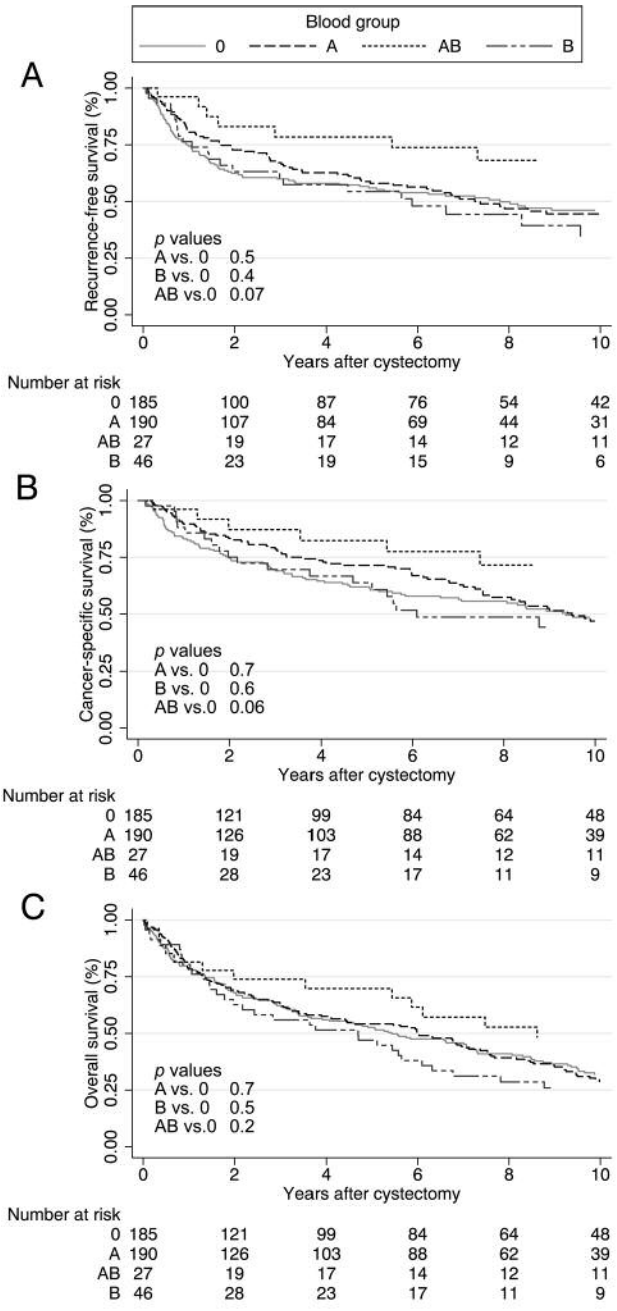

Figure 1. *Kaplan–Meier analysis assessing disease recurrence (A), cancer-specific survival (B) and overall survival (C) rates stratified according to the ABO blood type in 448 patients treated with radical cystectomy for urothelial carcinoma of the bladder.*

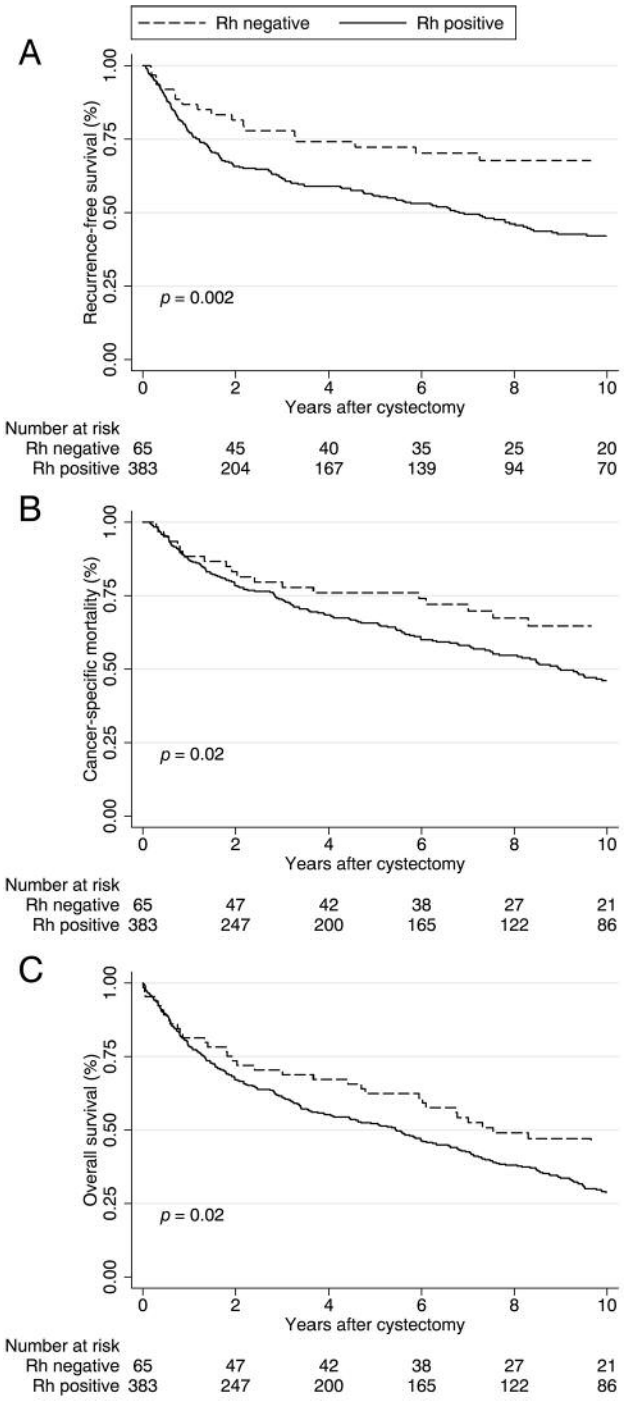

Figure 2. *Kaplan–Meier analysis assessing disease recurrence (A), cancer-specific survival (B), and overall survival (C) rates according to the Rhesus (Rh) factor in 448 patients treated with radical cystectomy for urothelial carcinoma of the bladder.*

group. All patients were treated with RC, producing a relevant selection bias. The timeframe of 15 years during which patients were treated, is of relevance as surgery and investigational techniques for assessing recurrence have evolved during this time. Lastly, this was a single-institutional cohort from a tertiary referral center, and as such, the results may not be generalizable to other populations.

Table III. *Multivariable Cox regression analyses predicting the risk of disease recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) in 448 patients treated with radical cystectomy for urothelial carcinoma of the bladder.*

Variables	RFS		CSS		OS	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	0.9 (0.9-1)	0.07	0.9 (0.9-1)	0.9	1 (1-1)	0.02
Gender, n (%)						
Male	Ref.		Ref.		Ref.	
Female	0.6 (0.3-1.3)	0.2	0.9 (0.6-1.6)	0.8	0.9 (0.6-1.3)	0.5
Blood group, n (%)						
O	Ref.		Ref.		Ref.	
A	1.2 (0.7-2)	0.5	0.9 (0.6-1.5)	0.9	1 (0.8-1.4)	0.6
B	1.8 (0.8.3.8)	0.1	1 (0.6-2)	0.8	1 (0.7-1.7)	0.8
AB	1.1 (0.4-3)	0.8	0.7 (0.3-1.8)	0.5	0.9 (0.5-1.7)	0.9
Positive Rhesus factor, n (%)	1.5 (0.7-3.4)	0.3	1.4 (0.7-2.7)	0.3	1.3 (0.8-1.9)	0.2
Pathologic T-stage, n (%)						
pT0-T1	Ref.		Ref.		Ref.	
pT2	3.7 (1.3-10)	0.01	2.5 (1.1-5.7)	0.03	1.3 (0.8-2)	0.2
pT3	2.5 (0.9-6.8)	0.07	2.4 (1-5.4)	0.03	1.6 (1-2.5)	0.02
pT4	6.9 (2.2-21)	0.001	4.9 (2-11)	0.001	2.8 (1.6-4.8)	<0.001
Positive lymph nodes, n (%)	1.9 (1-3.4)	0.03	1.6 (1-2.5)	0.04	1.5 (1-2.1)	0.02
LVI, n (%)	2.5 (1.5-4.2)	<0.001	2.5 (1.7-3.8)	<0.001	1.4 (1-1.8)	0.03
ACT, n (%)	0.4 (0.1-1.2)	0.09	0.7 (0.3-1.5)	0.4	0.7 (0.4-1.3)	0.3
Histological variant, n (%)	0.8 (0.5-1.5)	0.6	1 (0.6-1.5)	0.9	0.8 (0.6-1.2)	0.3

HR: Hazard ratio, CI: confidence interval, LVI: lymphovascular invasion, ACT: adjuvant chemotherapy.

Conclusion

The results of our study confirm that there is actually no clinically significant association of ABO blood group and Rhesus factor with long-term oncological outcomes after RC for UBC. At this time, the body of evidence suggests no benefit of using ABO or Rhesus groups in determining any clinical decision making.

Conflicts of Interest and Funding

The Authors declare they have no conflict of interest and received no financial support for this study.

The research involved human participants. Due to its retrospective nature and blinded database, no informed consent was needed.

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