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ORIGINAL PAPER

AB0 blood groups and oncological and functional outcomes in bladder cancer patients treated with radical cystectomy

Alessandro Tafuri [1, 2*], Andrea Panunzio [1,3*], Antonio Soldano [1*], Giovanni Mazzucato [1], Paola Irene Ornaghi [1], Giacomo Di Filippo [4], Alessandra Gozzo [1], Nicola De Maria [1], Francesco Cianflone [1], Aliasger Shakir [5], Zhe Tian [3], Matteo Brunelli [6], Antonio Benito Porcaro [1], Vincenzo Pagliarulo [2], Walter Artibani [1], Pierre I. Karakiewicz [3], Alessandro Antonelli [1], Maria Angela Cerruto [1]

[1] Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy;
[2] Department of Urology, "Vito Fazzi" Hospital, Lecce, Italy;
[3] Cancer and Prognostics Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Quebec, Canada;
[4] Department of General and Hepatobiliary Surgery, University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy;
[5] USC Institute of Urology, Catherine and Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA;
[6] Department of Pathology, University of Verona, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.

[*] *These Authors contributed equally to the manuscript.*

Summary ***Objectives: We investigated AB0 blood groups prevalence according to preoperative and pathological tumor characteristics, and their association with oncological outcomes, and renal function decline in a contemporary large cohort of bladder cancer (BCa) patients, who underwent radical cystectomy (RC) at a tertiary referral center.***
Materials and Methods: We retrospectively evaluated data of patients with histologically confirmed and clinically non metastatic BCa, who underwent RC between 2014 and 2021 at our Institution. Kaplan-Meier (KM) plots and Cox regression (CR) models tested the relationship between AB0 blood groups and local recurrence-, metastasis-, cancer specific mortality-, and overall mortality-free survival. Logistic regression (LR) models tested the association between AB0 blood groups and renal function decline, defined as an estimated Glomerular Filtration Rate (eGFR) < 60 mL/min, at post-operative day 1, discharge and 6-months of follow-up.
Results: Of 301 included patients, 128 (42.5%) had group A, 126 (41.9%) had group 0, 28 (9.3%) had group B, and 19 (6.3%) had group AB. Patients with group 0 developed higher rates of muscle-invasive BCa (p = 0.028) with high-grade features (p = 0.005) at last bladder resection, and less frequently received preoperative immunotherapy with Bacillus of Calmette-Guerin (p = 0.044), than their non-0 counterparts. Additionally, these patients harbored more advanced pathologic tumor stage at RC (p = 0.024). KM plots showed no differences among all tested cancer control outcomes between AB0 blood groups (p > 0.05 in all cases). Patients with group AB presented the lowest median eGFR at each time point. In multivariable LR analyses addressing renal function decline, group AB was independently associated with eGFR< 60 mL/min at discharge (Odds Ratio: 4.28, p = 0.047).
Conclusions: Among AB0 blood groups, patients with group 0 exhibited the most aggressive tumor profile. However, no differences were recorded in recurrence or survival rates. Group AB independently predicted renal function decline at discharge.

KEY WORDS: *AB0 blood groups; Bladder cancer; Radical cystectomy; Outcomes.*

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INTRODUCTION

Bladder cancer (BCa) is the tenth most common cancer among men and women and its mortality varies according to sex, geographic location, race/ethnicity, risk factor exposure, and availability of diagnostic and treatment modalities (1). Currently, BCa is the eighth cause of *cancer specific mortality* (CSM) in the United States, among both sexes (1). *Radical cystectomy* (RC) with bilateral pelvic lymph node dissection and urinary diversion after chemotherapy is the gold-standard treatment for non-metastatic *muscle-invasive bladder cancer* (MIBC) or recurrent high-risk *non-muscle-invasive bladder cancer* (NMIBC) refractory to previous intravesical therapies (2). BCa remains affected by a high rate of local and distant recurrences, which are usually up to 50%, especially in patients with advanced stage and lymph node involvement (3). Several markers and nomograms have been proposed for BCa survival and recurrence prediction (4-6). However, no tool is strongly recommended by international guidelines in disease assessment (2), and pathological tumor features remain the main predictors of oncological outcomes and actually guide decision making regarding use of secondary treatment or follow up schedule (2). Among clinical factors, renal function seems to impact oncological outcomes in NMIBC, MIBC, as well as upper tract urothelial carcinoma. Renal function has a pivotal role in patients' eligibility to chemotherapy (7-9) or different post-operative approaches choice, and in a more adequate follow-up schedule (10, 11).

AB0 blood group is commonly assessed in every patient before RC due to the risk of blood transfusion during and after surgery. The role of AB0 blood group system as a predictor of oncological outcomes has been previously investigated among other malignancies due its implication in cellular dynamics (12). Specifically, many authors have already shown the association between AB0 blood groups and survival in pancreatic (13), breast (14), and gastro-intestinal tumors (15). Few studies investigated the role of AB0 blood group as a predictor of outcome in

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BCa, revealing controversial results (16-19). The aim of this study is to investigate the prevalence of AB0 blood groups and their distribution according to patients' characteristics and pathological tumor features, in addition to determining the association between AB0 blood groups and renal function decline and oncological outcomes in a contemporary cohort of BCa patients, who underwent RC at a high-volume tertiary center.

Materials and methods

Population, data collection and evaluation of parameters

Data collected from patients with histologically confirmed and clinically non metastatic BCa, who were treated with RC at the *Department of Urology at the University of Verona* between September 2014 and February 2021, were retrospectively evaluated. Informed consent was obtained for all subjects. The indication for surgery was given in presence of MIBC or history of high-risk NMIBC refractory to previous intravesical treatment, according to international guidelines (2).

For each patient the AB0 genotype blood group system was assessed preoperatively by the *Department of Transfusion Medicine*. Blood groups were routinely determined on microplates using LIFE reagent and instrumentation (*AstraFormedic, De Mori Group*). Additional personal information such as age, *Body Mass Index* (BMI; kg/m^2), smoking history and *Charlson Comorbidity Index* (CCI) were collected. Preoperative pathological features as NMIBC history, tumor grading and staging after last *trans-urethral bladder resection* (TURB), as well as local immunotherapy administration were reported. Tumor staging was assessed according to the *tumor, node, metastasis* (TNM) classification by the *Union International Contre le Cancer* (UICC, 8th edition) (20), whereas tumor grading was assessed according to the *World Health Organization* (WHO) 2004-2016 classification system (21). Additionally, *estimated glomerular filtration rate* (eGFR) according to *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) equation (22), was assessed preoperatively, at *post-operative day 1* (POD-1), at discharge and at 6 months of follow up. Renal function decline was defined as an eGFR < 60 mL/min at each evaluated timepoint. After RC surgical specimens were evaluated for tumor stage, grade, concomitant presence of *carcinoma in situ* (CIS), *lymph vascular invasion* (LVI), *positive surgical margins* (PSM), number of lymph nodes removed, and number of metastatic lymph nodes, by dedicated uropathologists. Pelvic lymph node dissection was performed according to international recommendations and the template used included the external iliac, obturator, Cloquet and Marcille lymph nodes sites (2). All surgical procedures were performed by five experienced and dedicated surgeons, two of whom were classified as high-volume.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Median and *interquartile ranges* (IQR) were reported for continuously coded variables. Kruskal-Wallis rank sum test, Fisher's exact test and Pearson's Chi-squared test were used to examine the statistical significance of differences in medians and proportions, respectively. *Kaplan-Meier* (KM) plots were utilized to depict *local recurrence-free survival* (LRFS), *metastasis-free survival* (MFS), *CSM-free survival* (CSMFS) and *overall mortality-free survival* (OMFS), according to AB0 blood groups. Univariable and multivariable Cox proportional hazards regression models tested the relationship between AB0 blood groups and oncological outcomes. Covariates consisted of age, sex, pT stage, pN stage, presence of CIS, PSM and LVI. Univariable and multivariable logistic regression models were used to test the association between AB0 blood groups and renal function decline at POD-1, discharge and 6-months follow up. All tests were two-sided with a level of significance set at $p < 0.05$.

Table 1.

Descriptive statistics of 301 bladder cancer patients, who underwent radical cystectomy, according to the AB0-blood group system.

Variable	Overall 301 (100) [1]	0 126 (41.9) [1]	A 128 (42.5) [1]	B 28 (9.3) [1]	AB 19 (6.3%) [1]	p-value [2]
Age at surgery (years)	70 (62, 77)	70 (63, 77)	70 (60, 77)	69 (60, 74)	72 (68, 77)	0.4
Sex						0.1
Female	62 (20.6)	31 (24.6)	22 (17.2)	8 (28.6)	1 (5.3)	
Male	239 (79.4)	95 (75.4)	106 (82.8)	20 (71.4)	18 (94.7)	
Body Mass Index (Kg/m^2)	25.9 (23.8, 28.6)	25.8 (23.4, 28.6)	25.6 (23.8, 28.1)	26.5 (23.9, 29.0)	26.9 (25.6, 29.5)	0.4
Smoking history	226 (75.8)	91 (72.8)	94 (74.6)	24 (85.7)	17 (89.5)	0.3
Diabetes Mellitus	56 (18.6)	20 (15.9)	25 (19.5)	3 (10.7)	8 (42.1)	**0.049**
Charlson Comorbidity Index						0.1
≤ 2	172 (57.1)	76 (60.3)	70 (54.7)	18 (64.3)	8 (42.1)	
> 2	129 (42.9)	50 (39.7)	58 (45.3)	10 (25.7)	11 (57.9)	
Preoperative BCG administration	88 (29.2)	29 (23)	45 (35.1)	9 (33.1)	5 (26.3)	0.2
Clinical tumor stage (TURB)						0.1
NMIBC	137 (45.5)	48 (38.1)	64 (50)	13 (46.4)	12 (63.1)	
MIBC	164 (54.5)	78 (61.9)	64 (50)	15 (53.6)	7 (36.9)	
Grading (TURB)						**0.002**
Low grade	15 (5.2)	1 (0.8)	11 (8.9)	0 (0)	3 (15.8)	
High grade	273 (94.8)	119 (99.2)	113 (91.1)	25 (100)	16 (84.2)	
Pathologic tumor stage						NR*
pT0-T1	119 (39.7)	45 (36)	55 (43)	10 (35.7)	9 (47.4)	
pT2	44 (14.7)	14 (11.2)	20 (15.6)	5 (17.8)	5 (26.3)	
pT3	83 (27.6)	46 (36.8)	28 (21.9)	6 (21.5)	3 (15.8)	
pT4	54 (18)	20 (16)	25 (19.5)	7 (25)	2 (10.5)	
Presence of CIS at final pathology	84 (28)	35 (28)	37 (28.9)	6 (21.4)	6 (31.6)	0.9
Pathologic lymph node involvement	96 (32.2)	45 (36)	36 (28.3)	13 (46.4)	2 (11.1)	**0.047**
Number of lymph nodes removed	22 (15, 30)	22 (15, 28)	21 (14, 30)	26 (20, 30)	21 (14, 30)	0.4
Lymph vascular invasion	149 (56)	68 (60.2)	63 (55.3)	12 (46.1)	6 (46.1)	0.5
Positive surgical margins	34 (11.3)	15 (11.9)	11 (8.6)	5 (17.8)	3 (15.8)	0.4

*[1] Median (IQR); n (%) [2] Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-square test * p-value not estimable.*

BCG, Bacillus Calmette Guerin; TURB, trans urethral bladder resection; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; CIS, carcinoma in situ.

R software environment for statistical computing and graphics (version 4.1.2) was used for all analyses (*R: the R Project for Statistical Computing. https://www.r-project.org*).

Results

Study population

Overall, 301 patients were included of which 128 (42.5%) had group A, 126 (41.9%) had group 0, 28 (9.3%) had group B, and 19 (6.3%) had group AB (Table 1).

The AB0 blood group antigens were only associated with the presence of diabetes mellitus (p = 0.049), tumor grade at last endoscopic procedure (p = 0.002) and pathologic lymph node involvement (p = 0.047). No other statistically significant differences were recorded among demographic and preoperative patients' characteristics or pathological tumor stage distribution. Subgroup analysis showed that patients with group 0 developed higher rates of MIBC (p = 0.028) with concomitant high-grade features (p = 0.005) at last bladder resection, and in consequence received less frequently preoperative immunotherapy with *Bacillus of Calmette-Guerin* (BCG, p = 0.044), compared with their non-0 counterparts. Moreover, these patients harbored more advanced pathological tumor stage (T2-4) at RC compared with non-0 patients (p = 0.024, Table 2).

Impact of AB0 blood groups on oncological outcomes

Median follow up was 22 months (IQR 9-48). Of 248 patients with available follow up data, 43 (17.3%) developed local disease recurrence, 63 (25.4%) experienced metastatic progression, 74 (29.8%) died due to any causes, and 52 (21.0%) died due to BCa. KM plots illustrated the relationship between AB0 blood groups and LRFS, MFS, CSMFS and OMFS, respectively (Figure 1). No statistically significative difference was recorded between the four groups for all tested cancer control outcomes (p > 0.05).

Univariable and multivariable Cox proportional hazards regression models confirmed that AB0 blood group system was not an independent predictor for all tested oncological outcomes, even after adjustment for all covariates (Table 3).

Table 2.
Descriptive statistics of 301 bladder cancer patients, who underwent radical cystectomy, according to AB0-blood group system: 0 vs. non-0.

Variable	0 126 (41.9) [1]	non-0 (A, B, AB) 175 (58.1) [1]	p-value [2]
Age at surgery (years)	70 (63, 77)	70 (60, 77)	0.4
Sex			0.1
Female	31 (24.6)	31 (17.7)	
Male	95 (75.4)	144 (82.3)	
Body Mass Index (Kg/m^2)	25.8 (23.4, 28.6)	26.1 (23.9, 28.6)	0.4
Smoking history	91 (73)	135 (78)	0.3
Diabetes Mellitus	20 (15.9)	36 (20.6)	0.4
Charlson Comorbidity Index			0.3
≤ 2	76 (60.3)	96 (54.9)	
> 2	50 (39.7)	79 (45.1)	
Preoperative BCG administration	29 (23)	59 (34)	**0.044**
Clinical tumor stage (TURB)			**0.028**
NMIBC	48 (38.1)	89 (50.9)	
MIBC	78 (61.9)	86 (49.1)	
Grading (TURB)			**0.005**
Low grade	1 (0.8)	14 (8.3)	
High grade	119 (99.2)	154 (91.7)	
Pathologic tumor stage			**0.024**
pT0-1	45 (36)	74 (42.3)	
pT2	14 (11.2)	30 (17.1)	
pT3	46 (36.8)	37 (21.1)	
pT4	20 (16)	34 (19.5)	
Presence of CIS at final pathology	35 (28)	49 (28)	0.9
Pathologic lymph node involvement	45 (36)	51 (29)	0.2
Number of lymph nodes removed	22 (15, 30)	22 (15, 28)	0.9
Lymph vascular invasion	68 (60)	81 (53)	0.2
Positive surgical margins	15 (12)	19 (11)	0.8

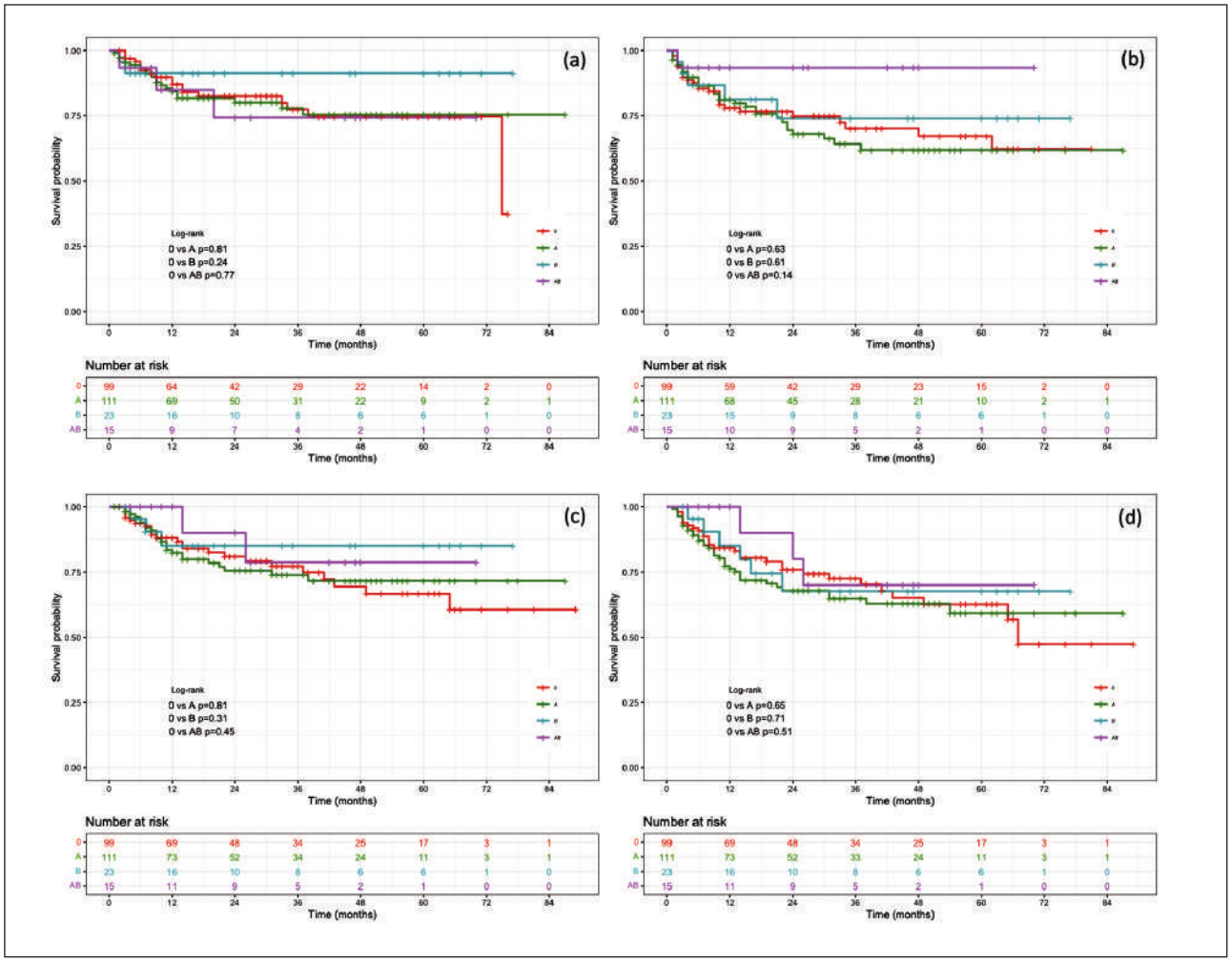
[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-square test.
BCG, Bacillus Calmette Guerin; TURB, trans urethral bladder resection; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; CIS, carcinoma in situ.

Variable	Local Recurrence		Metastatic progression		Cancer Specific Mortality		Overall Mortality	
	HR (95% CI) [1]	p-value	HR (95% CI) [1]	p-value	HR (95% CI) [1]	p-value	HR (95% CI) [1]	p-value
ABO Blood group								
A vs. 0	0.9 (0.45, 1.79)	0.8	1.15 (0.66, 2)	0.6	1.05 (0.57, 1.95)	0.9	1.41 (0.83, 2.39)	0.2
B vs. 0	0.38 (0.08, 1.75)	0.2	0.70 (0.23, 2.11)	0.5	0.8 (0.23, 2.78)	0.7	1.19 (0.47, 3)	0.7
AB vs. 0	3.68 (0.98, 13.84)	0.054	0.56 (0.07, 4.21)	0.6	1.13 (0.26, 4.99)	0.9	1.14 (0.34, 3.85)	0.8
Age at surgery (years)	0.97 (0.94, 1)	0.08	1.05 (1.02, 1.08)	**0.003**	1.05 (1.01, 1.08)	**0.005**	1.06 (1.03, 1.09)	**< 0.001**
Sex								
Male vs. Female	1.02 (0.45, 2.35)	0.9	0.86 (0.44, 1.66)	0.7	1.06 (0.52, 2.15)	0.9	0.9 (0.5, 1.62)	0.7
Pathologic tumor stage								
pT2 vs. pT0-T1	2.70 (0.61, 12.01)	0.2	0.85 (0.25, 2.9)	0.8	1.24 (0.26, 5.84)	0.8	0.91 (0.3, 2.74)	0.9
pT3 vs. pT0-T1	3.89 (0.89, 17.07)	0.07	1.45 (0.49, 4.3)	0.5	1.74 (0.43, 6.98)	0.4	1.46 (0.56, 3.78)	0.4
pT4 vs. pT0-T1	5.64 (1.15, 27.54)	**0.033**	2.62 (0.83, 7.25)	0.1	4.04 (0.97, 16.78)	0.055	3.06 (1.12, 8.35)	**0.029**
Presence of CIS at final pathology								
Yes vs. No	1.94 (0.99, 3.78)	0.053	0.98 (0.54, 1.77)	0.9	1.55 (0.83, 2.86)	0.2	1.52 (0.91, 2.53)	0.1
Pathologic lymph node status								
pN1-2-3 vs pN0	2.30 (1.13, 4.71)	**0.022**	2.16 (1.2, 3.88)	**0.010**	2.31 (1.22, 4.35)	**0.010**	1.72 (1.01, 2.94)	**0.046**
Surgical margins status								
Positive vs. Negative	0.64 (0.22, 1.84)	0.4	1.3 (0.61, 2.76)	0.5	1.05 (0.48, 2.27)	0.9	1.05 (0.53, 2.08)	0.9
Lymph vascular invasion								
Yes vs. No	1.69 (0.54, 5.31)	0.4	1.59 (0.66, 3.85)	0.3	2.5 (0.82, 7.67)	0.1	1.41 (0.65, 3.06)	0.4

[1] 1HR = Hazard Ratio, CI = Confidence Interval.

Table 3.
Multivariable Cox proportional hazards regression models predicting local recurrence, metastatic progression, cancer specific mortality and overall mortality, in 248 bladder cancer patients, who underwent radical cystectomy, with available follow-up data.

Figure 1.
Kaplan-Meier plots illustrating (a) local recurrence free survival, (b) metastasis free survival, (c) cancer specific mortality free survival, (d) overall mortality free survival, in 248 bladder cancer patients, who underwent radical cystectomy with available follow up data, stratified according to the AB0-blood group system.



Association between AB0 blood groups and renal function decline

Patients with group AB exhibited the lowest median eGFR at each specified time point compared to their non-AB counterparts (66.4 vs. 47.8 *vs.* 57.9 *vs.* 52.8 mL/min at preoperative evaluation, POD-1, discharge, and 6-months follow up, respectively). Conversely, patients with group B exhibited the highest median eGFR at the preoperative evaluation (78.6 mL/min), as well as at POD-1 (70.6 mL/min) and at discharge (70.4 mL/min).

Finally, patients with group 0 exhibited the highest median eGFR 6 months after RC (71.2 mL/min). However, a statistically significative difference among median eGFR within AB0 blood groups was recorded only at discharge ($p = 0.030$), as shown in Supplementary Figure 1.

In univariable logistic regression models addressing renal function decline at each specified time point, AB group strongly predicted eGFR < 60 mL/min at discharge (Odds Ratio [OR]: 3.27, $p = 0.025$. Supplementary Table 1). In multivariable logistic regression models AB group remained an independent predictor of renal function decline at discharge even after adjustment for age, preoperative eGFR, CCI, urinary derivation type and postoperative complications (OR: 4.28, $p = 0.047$).

Discussion

The role of AB0 blood group system as a predictor of oncological outcomes in BCa is not well established. The AB0 gene is located in the long arm of chromosome 9 (9q34) (23), and encodes a specific glycosyl transferase, which catalyzes the addition of a monosaccharide to the H antigen, thereby generating surface antigens A and B (23). AB0 blood group antigens are involved in various biological mechanisms. They are expressed on the erythrocytes' surface, as well as on the surface of many types of epithelial cells, including urothelial cells (23). Interestingly, AB0 antigens are mutated or absent in tumor cells in BCa (24). Loss of blood group antigens on the cell surface can affect cell adhesion, cell signaling, and immune surveillance, crucial factors in the development and progression of cancer (25). The main evidence for this effect has been stud-

ied in stomach and pancreatic tumors (13, 15). Two large independent prospective studies showed that compared to patients with group 0, the risk of pancreatic cancer is 1.3 to 1.7-fold higher for patients with non-0 blood type (13). Among urological malignancies, more than 40 years ago, *Cazzola et al.* showed in a small population that AB0 antigens were present on urothelial cells' surface and that their concentration decreased in less differenced urothelial tumors (26). *Joh et al.* reported an increased risk of developing *renal cell carcinoma* (RCC) among female patients with non-0 blood groups. However, no survival differences were recorded between RCC patients according to blood groups (27). In prostate cancer, *Porcaro et al.* found in 1114 patients, who underwent robot-assisted radical prostatectomy that the risk of PSM was increased in group 0-patients independent of other standard preoperative factors as an expression of more aggressive disease (28).

The association between AB0 blood groups and oncological outcomes in BCa was previously studied by other investigators with controversial results. In the current study, we observed that group 0 was associated with a worse pathological tumor stage ($p = 0.028$) and a higher tumor grade ($p = 0.05$) at the time of last TURB before RC, as well as with more advanced pathological tumor stage at the definitive histological examination after RC ($p = 0.024$). However, these findings did not affect prognosis and survival, due to no statistically significative differences noted among LRFS, MFS, CSMFS and OMFS according to AB0 blood groups. A historical report by *Orihuela et al.* showed that AB0 blood group system was not associated with stage at presentation in 494 newly diagnosed BCa patients. However, among patients with NMIBC, those who had group 0 more frequently harbored higher-grade tumors and experienced progression to advanced disease than their non-0 counterparts (29). Similarly, *Klatte et al.* in a retrospective cohort including 931 BCa patients, found that individuals with blood group 0 had higher recurrence and progression rates than those with group A or B (all $p < 0.05$) (30). *Engel et al.* examined a case series of 511 BCa patients, who underwent RC between 1996 and 2011 and found no differences in survival between the four AB0 blood groups (17). Similarly, in a recent single-institution study, *D'Andrea et al.* analyzed data of 463 BCa patients, who underwent RC between 1988 and 2003. These authors observed that AB0 blood group system was not associated with oncological outcomes. Rather, Rhesus-positive patients had an increased risk of relapse-free survival, as well as of CSM and OM, when compared to Resus-negative patients. However, these associations were not confirmed after multivariable adjustment (19). Finally, a large multicenter study involving 7906 BCa patients, demonstrated that blood group B was associated with higher mortality when compared with other blood groups ($p = 0.026$). However, even in this case, statistical significance disappeared in multivariable analysis (16). In contrast, *Gershman et al.* retrospectively evaluated data of 2086 BCa patients, who underwent RC between 1980 and 2008, and observed that non-0 groups, and in particular group A, was associated with higher CSM (HR: 1.23; $p = 0.007$) (18).

In the current study we also tested the association between AB0 blood group system and renal function decline after surgery. Interestingly, we observed that patients with group AB exhibited the lowest median eGFR values at POD-1, discharge and after 6 months follow up, compared to A, B, and 0 blood group patients. However, a statistically significant difference was recorded only at discharge ($p = 0.030$). Similarly, in multivariable logistic regression models, where group 0 was the referent, AB was associated with a 4-fold higher risk of renal function decline at discharge ($p = 0.047$). These results could be partially attributable to a more guarded pre-operative clinical conditions of AB patients. Additionally, most AB patients were diabetic ($p = 0.049$). This study might be in line with studies demonstrated an higher thrombotic risk in AB-patients with non-valvular atrial fibrillation (31), as well as a higher incidence of cardiovascular diseases in non-0 patients (32), which may induces renal failure.

The present study is not devoid of limitations. First, the current investigation is retrospective and suffers of the bias related to these types of studies. Second, despite our data being sourced from a high-volume center for BCa treatment, the overall sample size is limited. In consequence, our observations required interpretations that account for marginal sample sizes and comparisons of small subgroups. In this context, the observed number of BCa patients with group B and AB was very small. However, the prevalence of AB0 blood groups recorded in the current study corresponded to the general AB0 frequency and distribution reported in previous larger historical analyses. Additionally, various surgeons as well as pathologists were involved, and AB0 blood group antigen expression within the tumor as well as Rhesus factor were not assessed. In the future, a combined evaluation of the patient's blood group and the degree of AB0 antigen expression within the tumor is needed in higher level studies.

Conclusions

Among AB0 blood groups, patients with group 0 exhibited the most aggressive tumor profile. However, no differences were recorded in recurrence or survival rates. Patients with group AB presented the lowest median eGFR at each specified time point. Group AB was independently associated with eGFR < 60 mL/min at discharge.

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Correspondence

Alessandro Tafuri, MD (Corresponding Author)
tafuri.alessandro@gmail.com
Vincenzo Pagliarulo, MD - enzopagliarulo@yahoo.com
Department of Urology, "Vito Fazzi" Hospital, Lecce
Piazza Filippo Muratore, 1, 73100 Lecce (Italy)

Andrea Panunzio, MD - panunzioandrea@virgilio.it
Antonio Soldano, MD - soldanoantonio@libero.it
Giovanni Mazzucato, MD - gio.mazzucato@gmail.com
Paola Irene Ornaghi, MD - paolairene.ornaghi@gmail.com
Alessandra Gozzo, MD - la.ale.gozzo@gmail.com
Nicola De Maria, MD - nicola.demaria02@gmail.com
Francesco Cianflone, MD - fra1178@gmail.com
Antonio Benito Porcaro, MD - drporcaro@yahoo.com
Walter Artibani, MD - prof.artibani@gmail.com
Alessandro Antonelli, MD - alessandro_antonelli@me.com
Maria Angela Cerruto, MD - mariaangela.cerruto@univr.it
Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata di Verona, Verona (Italy)

Matteo Brunelli, MD - matteo.brunelli@univr.it
Department of Pathology, University of Verona, Azienda Ospedaliera Universitaria Integrata di Verona, Verona (Italy)

Giacomo Di Filippo, MD - giacomo.difilippo90@gmail.com
Department of General and Hepatobiliary Surgery, University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Verona (Italy)

Aliasger Shakir, MD USC - aliasgershakir@gmail.com
Institute of Urology, Catherine and Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, US

Zhe Tian, MSc - zhe.tian24@gmail.com
Pierre I. Karakiewicz, MD - pierrekarakiewicz@gmail.com
Cancer and Prognostics Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Quebec, Canada