

# The Effect of Blood Groups and Rhesus Factor on Prognosis and Survival in Bladder Cancer Patients Underwent Radical Cystectomy

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## Abstract

**Background:** We aimed to investigate the effect of blood groups and Rhesus factor on prognosis and survival in patients who underwent radical cystectomy due to bladder cancer.

**Methods:** Five hundred and twenty four patients who underwent radical cystectomy were enrolled the study between 1992 and 2014. The effect of blood groups and Rhesus factor on prognosis and survival was evaluated.

**Results:** Two hundred and twelve patients (41%) had A blood group, 184 patients (35%) had O blood group, 92 patients (17%) had B blood group, and 36 patients (7%) had AB blood group. Four hundred and fifty-six patients (87%) were Rhesus factor positive and 64 patients (13%) were Rhesus negative. The effect of rhesus factor on prognosis and survival was no statistically significant. Patients with B blood group had higher tumor grade than other blood groups ( $p=0.02$ ). Disease-specific survival were similar in each blood group.

**Conclusion:** We found that B blood group was associated with high grade tumor in patients who underwent radical cystectomy. However there was no statistically significant on survival in multivariate analysis. In addition, blood groups and Rhesus factor were not associated with survival.

## Introduction

In 2014, approximately 75,000 new cases of bladder cancer diagnosed in the USA [1]. Urological cancers account for about 14 % of cancers diagnosed globally and more than a fifth of all cancers in Europe [2]. Bladder cancer is the fourth-most frequent one in males after prostate, lung, and colon cancers [3]. The second most malignancy of genitourinary system is bladder cancer, with male-to-female ratio of 3.8:1 [4,5].

With a wide histological subgroup range, more than 90 % of bladder tumors are urothelial carcinomas in Western countries [6]. The other cancer types are squamous cell carcinoma, adenocarcinoma, sarcomas and rarely bladder pheochromocytomas, melanomas and lymphoepitheliomas, and similar pathological subtypes [4].

Approximately three fourths of patients have non-muscle-invasive bladder cancer and one-fourth present with muscle-invasive disease. For high-risk and recurrent non muscle invasive as well as muscle-invasive bladder cancer, radical cystectomy and pelvic lymphadenectomy are the treatment of choice but mortality rates are high [7].

In the literature, there were established poor prognostic factors for bladder cancer treated with radical cystectomy include pathological T classification, lymph node involvement, grade, lymphovascular invasion, and soft tissue surgical margin status [8-13]. Histologic type is also one of the adverse prognostic factors. Those cancer pathologies different from urothelial carcinoma are more aggressive in nature, and lamina propria involvement or muscle-invasive disease is common at the time of diagnosis [14].

In addition biologic and molecular predictors hold the potential to improve outcome prognostication in bladder cancer [15]. Both the ABO blood group antigen and Rhesus factor expression are routinely determined prior to radical cystectomy, thus representing an optimal biomarker which is nearly universally available and already established in daily clinical practice [16]. The ABO blood group antigens and the Rhesus factor may impact survival by various moleculobiologic mechanisms [17].

In this study, we investigate the effect of ABO blood groups and Rhesus factor on prognosis and survival in patients who underwent radical cystectomy due to bladder cancer.

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**Table 1:** The relationship of blood groups and Rhesus factor with clinical and pathological characteristics.

a	n	Blood Groups				p value	Rhesus factor		
		A	O	B	AB		Positive	Negative	p value
Number of patients(n), (%)	524	212 (41)	184 (35)	92 (17)	36 (7)		456 (87)	68 (13)	
Age (mean -range)		65(46-77)	68 (58-78)	67 (61-71)	66(52-74)	0.565 <sup>a</sup>	69 (46-78)	66 (58-71)	0.869 <sup>b</sup>
<b>Gender</b>									
Male n,(%)	472	190(90)	166 (90)	84 (90)	32 (89)	0.668 <sup>c</sup>	411 (90)	61 (88)	0.667 <sup>c</sup>
Female n,(%)	52	22 (10)	18 (10)	9 (10)	3 (11)		45 (10)	7 (12)	
Lymph node involvement n, (%)	136(26)	57 (27)	46 (25)	25 (28)	8 (23)	0.265 <sup>c</sup>	119 (26)	17 (25)	0.629 <sup>c</sup>
Positive surcigal margin n, (%)	36 (7)	15 (7)	11 (6)	7 (8)	3(8)	0.785 <sup>c</sup>	30 (6)	6 (9)	0.562 <sup>c</sup>
<b>Histologic type</b>									
Urothelial carcinoma (UK)	420 (80)	177 (42)	151 (36)	63 (15)	29 (7)	0.447 <sup>c</sup>	370 (88)	60 (12)	0.788 <sup>c</sup>
Non-UK	104 (20)	42 (40)	37 (35)	17 (16)	8 (8)		88 (85)	16 (15)	

<sup>a</sup> ANOVA; <sup>b</sup> independent sample t test; <sup>c</sup> Chi square test

### Materials and Methods

We retrospectively analyzed 714 patients who underwent radical cystectomy and bilateral pelvic lymphadenectomy, but 190 patients were excluded because of missing data and/or unsuitable follow-up. Five hundred and twenty four patients were enrolled the study between 1992 and 2014. The blood groups were recorded before operation.

Tumors were staged according to the 2009 TNM classification [18]. Tumor grade was assessed according to the 1998 World Health Organization (WHO) grading system [19]. The patients were followed up every 3 months in year 1, every 6 months in year 2, and annually thereafter.

The effect of ABO blood groups and Rhesus factor on prognosis and survival was evaluated.

### Statistics

Impaired student t test, ANOVA was used for numeric values, chi square test was used for nominal values, log rank test and Cox regression analysis were used for survival analysis. p<0.05 was accepted significant.

### Results

Mean age of the patients was 61.92±11.34 years (46-78) and 90% of the patients were male. The mean follow-up time was 66.21±13.4 months. The estimated 5 years disease specific survival 57.7 % and overall survival was 44.6 %, respectively.

Two hundred and twelve patients (41%) had A blood group, 184 patients (35%) had O blood group, 92 patients (17%) had B blood group, and 36 patients (7%) had AB blood group. Four hundred and fifty-six patients (87%) were Rhesus factor positive and 64 patients (13%) were Rhesus negative.

**Table 2:** The association blood groups and Rhesus factor with pathologic stage and grade.

	n	Blood Groups n (%)				p value*	Rhesus factor n (%)		
		A	O	B	AB		positive	negative	p value*
<b>Pathologic stage</b>									
pT0	23	8 (4)	9 (5)	4 (5)	2 (4)	0.758	19 (4)	4 (5)	0.658
CIS	37	17 (8)	11 (6)	5 (6)	4 (11)		33 (8)	4 (7)	
pTa	27	10 (5)	11 (6)	4 (5)	2 (4)		24 (5)	3 (4)	
pT1	78	30 (14)	28 (15)	14 (15)	6 (15)		67 (15)	11 (14)	
pT2	140	56 (26)	52 (28)	22 (23)	10 (29)		124 (27)	16 (26)	
pT3	161	67 (31)	55 (30)	30 (32)	9 (27)		138 (31)	23 (34)	
pT4	58	24 (11)	18 (10)	13 (14)	3 (10)		51 (10)	7 (10)	
Total	524	212	184	92	36	456	68		
<b>Grade</b>									
1	60	26 (14)	24 (15)	6 (8)	4 (15)	0.020	60 (15)	9 (15)	0.548
2	78	34 (18)	30 (18)	10 (12)	4 (15)		77 (19)	7 (16)	
3	326	127 (68)	110 (67)	67 (80)	22 (70)		267 (66)	44 (69)	
Total	464	187	164	83	30	404	60		

\*Chi square test

**Table 3:** Univariate and multivariate analyses of prognostic factors for disease-specific survival.

	Univariate analyses*	Multivariate analyses**	
	p value	p value	HR
Age	0.351		
Gender	0.687		
Pathologic stage	0.016	0.023	1.359
Grade	0.027	0.039	1.542
Lymph node involvement	0.001	0.015	2.259
Positive surgical margin	0.033	0.045	1.150
Blood groups	0.038	0.145	
Rhesus factor	0.042	0.202	
Histologic type	0.121		

\*log rank test; \*\* Cox regression

Age, gender, lymph node involvement, positive surgical margin and histologic type were similar in each blood group and Rhesus factor (Table 1). Pathologic stage had no statistical significance in each blood group and Rhesus factor but patients with B blood group had higher tumor grade than other groups ( $p=0.02$ ) (Table 2).

The estimated 5 years disease specific and overall survival were similar in each blood group and Rhesus factor. The estimated 5 years disease specific survival for A blood group was 58.2%, O blood group was 56.6%, B blood group was 55.9%, AB blood group was 57.3%, rhesus positive was 56.4 %, and rhesus negative was 55.2% respectively ( $p=0.038$ ). The estimated 5 years overall survival for A blood group was 45.2%, O blood group was 46.1%, B blood group was 45.6%, AB blood group was 44.8%, rhesus positive was 45.4 %, and rhesus negative was 44.3 respectively ( $p=0.042$ ) however, in multivariate analysis neither blood groups nor rhesus factor were significant. The most important prognostic factors in multivariate analysis were T stage, grade, lymph node involvement and positive surgical margin (Table 3).

## Discussion

The ABO blood group system was first discovered by Karl Landsteiner in 1900 [20]. Blood group antigens are chemical components on the erythrocyte membrane but they are also expressed on a variety of epithelial cells including urothelium, gastrointestinal, mucosa and lung as well as saliva and body fluids [21,22].

In North America and Europe, 37% to 44% of the population are blood type O, approximately 42% are A, 10% to 14% are B, and 4% to 6.5% are AB [23].

Several mechanisms have been proposed to explain how ABO blood type influences cancer progression, although they are largely unknown. The ABO gene is located on chromosome 9q34.1-34.2, an area which is frequently affected in urothelial carcinoma of the bladder [24,25]. The gene encodes for glycosyltransferases, which catalyze the transfer of sugars to the H antigen [26]. Expression of ABO antigens is lost with progression of disease [27]. It has been suggested the ABO antigens affects cell adhesion, cell signaling, and immune response by TNF alpha [28], but there are no comprehensive investigations in urothelial carcinoma of the bladder or urothelial carcinoma of the bladder cell lines.

Studies show that ABO blood group antigen expression within the bladder cancer decreases with grade [22] and may be linked with outcomes [29,30]. In terms of patients' blood type status, studies conducted several decades ago suggested that blood type O and B are associated with a more unfavorable pathology and possibly worse prognosis, although the differences were clinically small or statistically insignificant [31,32]. In contrast, data from other malignancies indicate that ABO blood type is significantly associated with stage and survival [33-35].

Orihuela et al. [36], ABO blood type was not associated with the stage of the disease. Among patients with non-muscle-invasive, however, patients with blood type O had significantly higher grades and worse progression-free survival than those with blood type other than O. Llopis et al. [37] reported a nonsignificant association of blood type O with higher grades and worse recurrence-free survival compared with blood type A. Comparable results were presented by Srinivas et al [38]. In addition to blood type O, Raitanen et al. [32] showed a similar nonsignificant trend toward higher grades for patients with blood type B.

The majority of evidence on the effect of ABO blood type on the development of malignant tumors is derived from studies on pancreatic cancer. Two large, independent, prospective cohort studies showed that the risk for pancreatic cancer is 1.3- to 1.7-fold increased if a non-O blood type is present [39]. Joh et al. reported that a non-O blood type conveys an increased risk for developing renal cell cancer in women [40]. Among patients with renal cell cancer, however, it appears that ABO blood type is not associated with survival [35]. Studies on ABO blood type as a prognostic marker in nonurological malignancies usually had negative results [41].

The Rhesus factor gene is located on the short arm of chromosome 1, a region of tumor suppressor genes and the proto-oncogene L-Myc, which is down-regulated in urothelial carcinoma of the bladder [42]. The Rhesus factor proteins are expressed on erythrocyte membranes as well as various epithelial tissues, facilitating the oxygenation of tissue and removal of DNA-damaging agents [43]. Thus, the risk of development of various malignancies may be increased in Rhesus factor-negative patients, as shown in skin, esophageal, breast, lung and endometrial cancer [43, 44]. Accordingly, the Rhesus factor expression was not associated with survival in other epithelial malignancies [45].

There are two major limitations in our study. The study is retrospective analysis and small sample size.

Few studies are available assessing the relationship between the survival and prognostic factors and blood groups and Rh factors in patients who underwent radical cystectomy in the literature. This issue is still not clear. In our study group, B blood group was associated with high grade tumor in univariate analysis. This may have resulted from the small number of patients. There was no relationship in multivariate analysis. We did not detect any relation between the rhesus factor and blood groups and prognostic factor and survival.

## Conclusions

We found that B blood group was associated with high grade tumor in patients who underwent radical cystectomy but no significant in multivariate analysis. In addition blood groups and Rhesus factor

are not associated with survival. The association of the blood groups antigens and rhesus factors with survival and prognostic factors should be confirm further validation with prospective randomize studies.

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