Prognostic Significance of Blood Type A in Patients with Renal Cell Carcinoma

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Purpose: In this study, we evaluated the prognostic significance of the ABO blood type in patients with renal cell carcinoma (RCC) who had undergone partial or radical nephrectomy.

Materials and Methods: Information on the ABO blood type was obtained from 1750 patients with RCC. A total of 1243 men and 507 women (mean age, 55.41 ± 12.43 years) with RCC who had undergone partial or radical nephrectomy were enrolled in this study. The median follow-up duration was 35.0 months (interquartile range [IQR], 16.0–67.0). During the follow-up period, 271 patients experienced RCC recurrence, and 137 patients died from RCC.

Results: Type A was the most common blood type (568, 32.5%), followed by type O (525, 30.0%), type B (464, 26.5%), and type AB (193, 11.0%). Generally, blood type was not associated with any clinicopathological factors. Unlike blood type O, the multivariate analysis of progression-free survival (PFS) showed that blood type non-O (A, B, and AB) was an independent prognostic factor for a worse outcome (95% confidence interval [CI]: 1.24–2.37, hazard ratio [HR] = 1.71, P = .001; 95% CI: 1.08–2.13, HR = 1.51, P = .016; 95% CI: 1.03–2.43, HR = 1.58, P = .037, respectively). Cancer-specific survival (CSS) analysis showed that blood type A was an independent factor associated with a worse prognosis for CSS (95% CI: 1.05–2.64, HR 1.66, P = .031, respectively).

Conclusion: The ABO blood type is significantly associated with PFS and CSS in patients with RCC following partial or radical nephrectomy. Blood type non-O (A, B, and AB) is an independent prognostic factor for a worse PFS outcome, and blood type A is an independent factor associated with a worse CSS prognosis.

Key words: ABO blood group; Renal Cell Carcinoma; Prognosis; Prognostic Factor; Nephrectomy

INTRODUCTION

Renal cell carcinoma (RCC) is the most deadly malignancy in urology. Approximately 30–40% of patients die from this disease.[1,2] In 2012, 338,000 patients were newly diagnosed with RCC, and 143,000 patients died from RCC worldwide.[3] Recently, the diagnosis of smaller-sized early-stage renal masses has increased because of the development of radiological diagnostic tools and regular medical examinations. However, the incidence of RCC and the mortality rate per unit population have risen steadily.[4,5] Therefore, more attention is now being paid to RCC prognosis. The TNM Classification of Malignant Tumors stage is a strong prognostic factor in RCC. However, the TNM stage is not completely accurate as a prognostic indicator, as the prognosis of RCC varies widely between patients with same-stage tumors. Many clinicians have been attempting to identify new prognostic factors, such as tumor size and Fuhrman nuclear grade.[6,7] Recently, we reported that body mass index (BMI) and nutritional status also impact prognosis in RCC.[8,9] Other factors, such as hematologic indices, inflammatory markers, and serum calcium level, have also been introduced as next-generation prognostic factors.[6]

The ABO blood type is a classic prognostic factor in several malignant conditions. A correlation between the ABO blood type and gastric cancer was reported sixty years ago.[10] Thereafter, the correlation between the ABO blood type and other malignancies, such as breast cancer, pancreatic cancer, lung cancer, and obstetric cancers, has been continuously reported.[11-14] The ABO gene encodes for glycosyl transferase, which catalyzes the transfer of donor sugar to the H antigen to form the ABO antigen. ABO antigens exist not only on erythrocytes but also in other body tissues, predominantly in the endodermal epithelial lining and in some types of parenchymal cell lines, including those in the kidney.[15,16] Through membrane signaling, mediation of intercellular adhesion, or angiogenic effects, the ABO blood type may affect the progression or survival of patients with RCC. Previous reports have been inconsistent regarding the influence of the ABO blood type on the prognosis of patients with RCC. Because these studies included small sample sizes, direct comparison with the ABO blood type was not evaluated. In this study, we evaluated the prognostic value of the ABO blood type in a relatively large cohort of patients with RCC

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Table 1. Clinicopathological factors

Variables	n = 1750 (100%)
Sex	
male/female	1243 (71.0%) / 507 (29.0%)
Age	56.0 [IQR 47.0 to 65.0] years
BMI	24.20 [22.19 to 26.24] Kg/m2
Tumor diameter	3.65 [IQR, 2.2 to 6.0] cm
Pathology	
Clear cell type	1419 (81.1%)
Chromophobe type	155 (8.9%)
Papillary type	113 (6.5%)
Other	63 (3.2%)
Operation	
Radical/partial	1078 (61.6%)/ 672 (38.4%)
Median follow-up duration	35.0 months [IQR 16.0 to 67.0]
Recurrence of RCC	271 patients (15.5%)
Death of RCC	137 patients (7.8%)

Abbreviations: IQR, Interquartile Range.

who had undergone partial or radical nephrectomy.

MATERIALS AND METHODS

Study Population

We performed a cross-sectional retrospective study of 1763 consecutive patients who had undergone partial (n = 676) or radical nephrectomy (n = 1087) for RCC at a single institution from March 1999 to December 2011. Among the 1763 patients, ABO blood type information was obtained from 1750 patients with RCC. This retrospective analysis of this patient population was approved by an Institutional Review Board.

Evaluations

For the preoperative evaluation, the clinicopathological data of the patients were examined. Clinical data included sex, age, underlying diseases, American Society of Anesthesiologists (ASA) score, BMI, and laboratory tests, including the complete blood cell count, serum chemistry (albumin, creatinine, calcium, and cholesterol), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and the ABO blood type. A preoperative computed tomography exam was performed to evaluate tumor size, tumor location, and distant metastasis.

Procedures

Partial or radical nephrectomy was performed according to standard procedures. When preoperative imaging revealed metastasis, nephrectomy and metastatic tumor excision were performed simultaneously in selected patients. Similarly, when an enlarged lymph node was revealed, lymph node dissection was performed. In patients with completely resected metastasis and staging greater than T3, immunochemotherapy or targeted therapy was administered after radical nephrectomy. However, those with inoperable multiple metastases were excluded from the study.

Assessments

The surgical specimens were evaluated by uropathologists according to the 2010 American Joint Committee on cancer guidelines and the Fuhrman nuclear grading system. Histological subtyping was conducted according to the 2004 World Health Organization classification. Postoperative evaluations consisted of a physical examination, laboratory tests, postero-anterior chest radiography, and computed tomography. According to

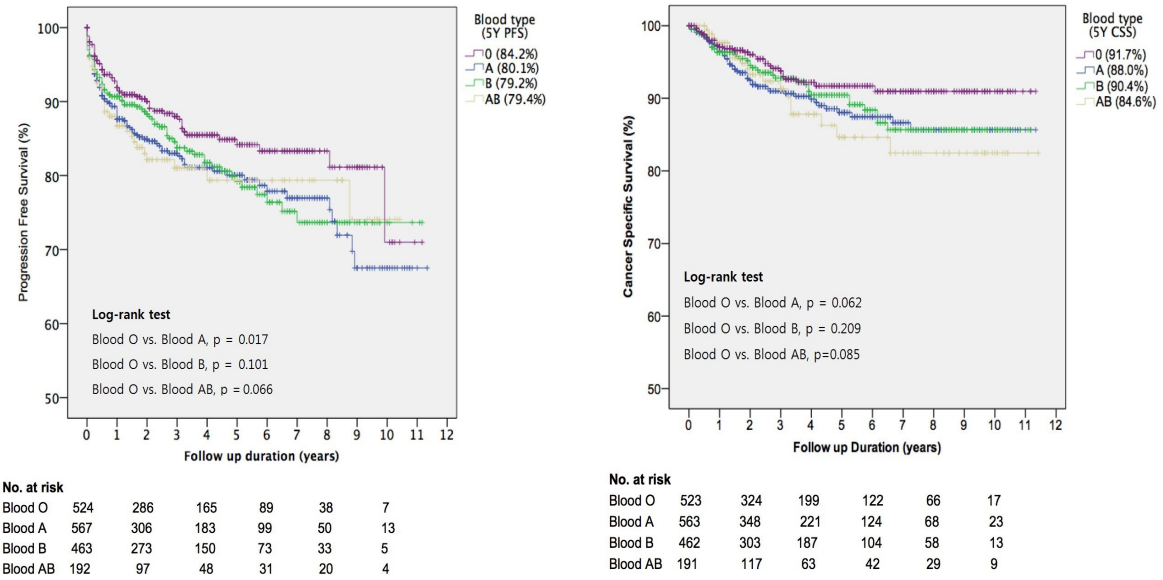

Figure 1. Kaplan-Meier survival analysis. **(A)** Patients with blood type O showed a significantly longer progression-free survival (PFS) than those with blood type A; however, statistical significance was not reached compared with the results of patients with blood types B and AB. **(B)** Patients with blood type O showed a longer Cancer-specific survival (CSS) than those with blood type A; however, the difference did not reach statistical significance.

Table 2. Relationship between ABO blood type and clinical factors

	ABO Blood Type				Total = n (%)	*P* value
	O (n = 525, 30.0%)	A (n = 568, 32.5%)	B (n = 464, 26.5%)	AB (n = 193, 11.0%)	All (n = 1750, 100%)	
Age						.573[b]
≤ 46	125 (23.8%)	139 (24.5%)	108 (23.3%)	42 (21.8%)	414 (23.7%)	
47-55	145 (27.6%)	138 (24.3%)	113 (24.4%)	46 (23.8%)	442 (25.3%)	
56-65	137 (26.1%)	153 (26.9%)	131 (28.2%)	53 (27.5%)	474 (27.1%)	
> 65	118 (22.5%)	138 (24.3%)	112 (24.1%)	56 (26.9%)	420 (24.0%)	
Sex						.526[a]
Male	375 (71.4%)	408 (71.8%)	318 (68.5%)	142 (73.6%)	1243 (71.0%)	
Female	150 (28.6%)	160 (28.2%)	146 (31.5%)	51 (26.4%)	507(29.0%)	
ASA score						.531[b]
1	242 (46.2%)	250 (44.0%)	220 (47.4%)	97 (50.3%)	809 (46.3%)	
2	253 (48.3%)	281 (49.5%)	211 (45.5%)	85 (44.0%)	830 (47.5%)	
3/4	29 (5.5%)	37 (6.5%)	33 (7.1%)	11 (5.7%)	110 (6.3%)	
pT stage						.971[b]
1	394 (75.0%)	422 (74.3%)	351 (75.6%)	146 (75.6%)	1313 (75.0%)	
2	29 (5.5%)	37 (6.5%)	27 (5.8%)	9 (4.7%)	102 (5.8%)	
3	72 (13.7%)	84 (14.8%)	66 (14.2%)	27 (15.0%)	251 (14.3%)	
4	30 (5.7%)	25 (4.4%)	20 (4.3%)	9 (4.7%)	84 (4.8%)	
pN stage						.341[a]
Nx/N0	503 (95.8%)	548 (96.5%)	437 (94.2%)	185 (95.9%)	1673 (95.6%)	
N1	22 (4.2%)	20 (3.5%)	27 (5.8%)	8 (4.2%)	77 (4.4%)	
pM stage						.740[a]
M0	489 (93.1%)	522 (91.9%)	424 (91.4%)	179 (92.7%)	1614 (92.2%)	
M1	36 (6.9%)	46 (8.1%)	40 (8.6%)	14 (7.3%)	136 (7.8%)	
Nuclear grade						.817[a]
1/2	285 (54.6%)	298 (52.6%)	249 (54.2%)	99 (51.3%)	931 (53.5%)	
3/4	237 (45.4%)	269 (47.4%)	210 (45.8%)	94 (48.7%)	810 (46.5%)	
Histology						.051[a]
Clear cell	417 (79.4%)	466 (82.0%)	367 (79.1%)	169 (87.6%)	1419 (81.1%)	
Non clear cell	108 (20.6%)	102 (18.0%)	97 (20.9%)	24 (12.4%)	331 (18.9%)	
Operation						.739[a]
Radical	319 (60.8%)	353 (62.1%)	281 (60.6%)	125 (64.8%)	1078(61.6%)	
Partial	206 (39.2%)	215 (37.9%)	183 (39.4%)	68 (35.2%)	672 (38.4%)	

Abbreviations: ASA, American Society of Anesthesiologists.
a,Chi-square test; b, Kruskal-Wallis test

pathological stage, these examinations were performed trimonthly or semiannually for the first 2 years and annually thereafter. Survival and disease progression data were collected by reviewing medical charts, contacting the family members of patients, or reviewing death certificates. The follow-up duration was from the date of surgery to the last follow-up visit or the date of death.

Statistical Analysis

SPSS version 19 (SPSS, Inc., Chicago, Illinois, USA) was used for the statistical analysis. The chi-square and Mann-Whitney tests were used to assess the correlation between the ABO blood type and clinicopathological variables. Cancer-specific survival (CSS) and progression-free survival (PFS) among the ABO blood groups were estimated by the Kaplan-Meier method and log-rank test. The Cox proportional hazards regression model was used to identify significant factors related to CSS or PFS. The hazard ratios are presented, along with the 95% confidence intervals. For all tests, alpha

Table 3. Progression-free survival and Cox regression analysis.

	Univariate			Multivariate		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Sex (M/F)	0.83	0.63 – 1.09	.181			
Age						
≤ 46	Reference	.001				.258
47-55	1.21	0.83 – 1.77	.330	1.12	0.76 – 1.66	.575
56-65	1.78	1.25 – 2.53	.001	1.42	0.98 – 2.05	.062
> 65	1.85	1.29 – 2.67	.001	1.24	0.84 – 1.81	.281
ASA score						
1	Reference	< .001				.162
2	1.63	1.25 – 2.12	< .001	1.03	0.78 – 1.37	.813
3/4	3.28	2.20 – 4.89	< .001	1.48	0.97 – 2.26	.071
pT stage						
T1	Reference		< .001			< .001
T2	5.11	3.38 – 7.72	< .001	2.99	1.95 – 4.59	< .001
T3	11.67	8.75 – 15.56	< .001	4.67	3.36 – 6.50	< .001
T4	11.32	7.76 – 16.49	< .001	4.00	2.63 – 6.09	< .001
pN stage9.69	7.05 – 13.33	< .001	1.14	0.78 – 1.67		.488
pM stage	23.50	18.12 – 30.48	< .001	8.29	6.00 – 11.47	< .001
Nuclear gr.						
(I-II/III-IV)	4.51	3.39 – 6.01	< .001	1.94	1.42 – 2.64	< .001
Histology						
(clear / non clear)	1.32	0.95 – 1.84	.102			
Operation						
(radical/partial)	6.51	4.21 – 10.08	< .001	2.34	1.47 – 3.72	< .001
Blood Type						
O	Reference		.096			.009
A	1.46	1.07 – 2.00	.018	1.71	1.24 – 2.37	.001
B	1.32	0.95 – 1.85	.102	1.51	1.08 – 2.13	.016
AB	1.48	0.97 – 2.25	.069	1.58	1.03 – 2.43	.037

Abbreviations: ASA, American Society of Anesthesiologists; HR, hazard ratio.

was 0.05, the power was 80%, and *P*-values were 2-sided, with $P < .05$ considered statistically significant.

RESULTS

Clinicopathological data are shown in **Table 1**. A total of 1243 men (71.0%) and 507 women (29.0%) with RCC who had undergone partial or radical nephrectomy were enrolled in this study. The median age was 56.0 (interquartile range (IQR) 47.0 to 65.0) years. The median BMI was 24.20 (IQR, 22.19 to 26.24) kg/m2. The mean ± SD and median tumor diameter were 4.63 ± 3.28 cm and 3.65 (IQR, 2.2 to 6.0) cm, respectively. In all, 1313 (75.0%), 102 (5.8%), 251 (14.3%), and 84 (4.8%) patients had pathological tumor stages of pT1, pT2, pT3, and pT4, respectively. Seventy-seven patients (4.4%) had pathologically confirmed local metastatic lymph nodes, and 136 patients (7.8%) had distant metastases. Clear cell type RCC was the most common subtype (1419, 81.1%), followed by the chromophobe type (155, 8.9%). The median follow-up duration was 35.0 months (IQR, 16.0–67.0). During the follow-up period, 271 patients experienced RCC recurrence, and 137 patients died from RCC. Among the 1750 patients (**Table 2**), the most common blood type was A (568, 32.5%), followed by O (525, 30.0%), B (464, 26.5%), and AB (193, 11.0%). The A and AB blood types were more frequent in patients with clear cell type RCC. However, the histological subtype was not significantly related to the blood type ($P = .051$). In general, blood type was not associated with any of the clinicopathological factors. The results of the Kaplan-Meier survival analysis of PFS and CSS according to ABO blood type are shown

Table 4. Cancer-specific survival and Cox regression analysis

	Univariate			Multivariate		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Sex (M/F)	0.98	0.68 – 1.42	.916			
Age						
≤ 46	Reference		.027			.702
47-55	1.23	0.72 – 2.11	.456	1.28	0.73 – 2.22	.386
56-65	1.95	1.20 – 3.18	.007	1.34	0.80 – 2.26	.267
> 65	1.74	1.04 – 2.93	.037	1.16	0.66 – 2.04	.598
ASA score						
1	Reference		< .001			.204
2	1.76	1.20 – 2.58	.004	1.15	0.77 – 1.72	.499
3/4	4.06	2.37 – 6.95	< .001	1.68	0.95 – 2.99	.076
pT stage						
T1	Reference		< .001			< .001
T2	7.58	4.00 – 14.35	< .001	3.84	2.00 – 7.35	< .001
T3	17.00	10.57 – 27.32	< .001	4.66	2.76 – 7.86	< .001
T4	24.64	14.42 – 42.12	< .001	6.23	3.46 – 11.20	< .001
pN stage11.18	7.41 – 16.88		< .001	1.50	0.93 – 2.41	.095
pM stage	27.20	19.22 – 38.50	< .001	8.12	5.33 – 12.37	< .001
Nuclear gr.						
(I-II/III-IV)	7.14	4.44 – 11.48	< .001	2.58	1.56 – 4.28	< .001
Histology						
(clear / non clear)	1.07	0.69 – 1.67	.750			
Operation						
(radical/partial)	32.91	8.14 – 133.03	< .001	7.55	1.82 – 31.36	.005
Blood Type						
O	Reference		.234			.120
A	1.53	0.98 – 2.39	.064	1.66	1.05 – 2.64	.031
B	1.35	0.84 – 2.17	.213	1.26	0.78 – 2.05	.348
AB	1.65	0.92 – 2.95	.091	1.72	0.95 – 3.14	.075

Abbreviations: ASA, American Society of Anesthesiologists; HR, hazard ratio..

in **Figure 1A and 1B**, respectively. The 5-year PFS in patients with blood type O was 84.2% (95% CI: 80.3–88.1, data not shown). Patients with blood type O had a longer PFS than patients with blood type A (*P* = .017, log-rank test). However, compared with patients with blood types AB and B, the difference did not reach statistical significance (P = .066 and P =.101, respectively; log-rank test). The 5-year CSS in patients with blood type O was 91.7% (95% CI: 88.8 – 94.6, data not shown). CSS was longer in patients with blood type O than in those with blood types A, B, and AB, although the difference did not reach statistical significance (P = .062, *P* =.209, and *P* = .085, respectively; log-rank test). In the univariate analysis, ABO blood type was a significant prognostic factor for PFS. Compared with blood type O, blood type A was associated with PFS (95% CI: 1.07–2.00, HR = 1.46, *P* = .018, respectively; (**Table 3**). Blood types B and AB were not associated with PFS (95% CI: 0.95–1.85, HR = 1.32, *P* =.102; 95% CI: 0.97–2.25, HR = 1.48, *P* = .069, respectively; Table 3). Furthermore, ABO blood type was not related to CSS (95% CI: 0.98–2.39, HR = 1.53, *P* = .064; 95% CI: 0.84 – 2.17, HR = 1.35, *P* = .213; 95% CI: 0.92–2.95, HR = 1.65, *P* = .091, respectively; **Table 4**). In the multivariate analysis of PFS, a non-O blood type (A, B, AB) was a significantly stronger prognostic factor for PFS than blood type O (95% CI: 1.24–2.37, HR = 1.71, P = .001; 95% CI: 1.08–2.13, HR = 1.51, P = .016; 95% CI: 1.03–2.43, HR = 1.58, *P* = .037, respectively; Table 3). In the multivariate analysis of CSS (Table 4), blood type A was found to be an independent factor leading to a worse prognosis for CSS (95% CI: 1.05–2.64, HR = 1.66, *P* = .031, respectively). However, the results for blood types AB and B did not reach

significance (95% CI: 0.95–3.14, HR = 1.72, $P = .075$; 95% CI: 0.78–2.05, HR = 1.26, $P = .348$, respectively).

DISCUSSION

Studies have demonstrated that pathological changes in the ABO antigen are related to RCC. First, ABO antigens exist not only on the surface of erythrocytes but also in other body tissues, including the kidney.(15,16) The normal ABO antigen is lost in RCC, and new tumor antigens are acquired.[13,17,18] Thus, a structural change in the ABO antigen occurs in RCC. The altered ABO antigens in RCC are important mediators of membrane signaling and intercellular adhesion.[15,19] It is therefore possible that a specific blood type may enhance disease progression or survival. Second, the deletion of A or B antigens in non-O blood group patients leads to the up-regulation of precursor H and Lewisy expression, both of which stimulate angiogenesis.[20] In addition, non-O blood group patients have higher levels of von Willebrand factor and factor VIII.[21] Thus, non-O blood group patients have a greater tendency of hypervascularity and hypercoagulability than blood group O patients, which are typical characteristics of RCC. Third, single nucleotide polymorphism studies evaluating the ABO gene locus have uncovered a relationship between the ABO gene and plasma inflammatory markers, such as tumor necrosis factor alpha.[22] Finally, ABO antigens may be related to systemic inflammation, and chronic inflammation is associated with RCC.[23] In this study, ESR levels were not related to ABO blood type (Kruskal-Wallis test, $P = .352$, data not shown), whereas CRP levels were related to ABO blood type (Kruskal-Wallis test, $P = .044$, data not shown). In particular, patients with blood type O had a lower CRP level than those with a non-O blood type (Mann-Whitney test, $P = .007$, data not shown). According to the tumor registry of the European Institute of Oncology, the ABO blood type is generally associated with other cancer types. For example, blood type O patients have a significantly lower incidence of pancreatic cancer.[13] Similar results have been reported in other studies. The Prospective Nurses' Health and Health Professionals Follow-up cohort study revealed that the incidence of RCC is higher in non-O blood type subjects than in blood type O women.[24] A retrospective study in 900 patients with locoregional RCC reported that blood type O is a significant prognostic factor for overall survival but not a prognostic factor for disease-specific survival, and it is not related to lymph node metastasis.[25] Conversely, Martino et al reported that blood type O is not a prognostic factor for survival. Although blood group O was associated with fewer lymph node metastases, the risk of bilateral RCC was increased.[26] The authors suggested that different inclusion criteria, racial variability, and a low event number may have been responsible for the different results in the survival rates between the two reports. In our study, we included both locoregional and advanced cases of RCC. In addition, Korea is a single-race nation. Furthermore, the present study included a relatively larger number of cases and a higher event number than previous studies. Recently, results were published from a large cohort study in Korea that evaluated the prognosis of RCC patients according to ABO blood type.[27] The clinical data from our study and a previous study by Lee et al. are very similar. In particular, the distribution of ABO blood type was the same, which could be explained by the single ethnicity of the Korean population. However, Lee et al. reported that there was no relationship between survival and ABO blood type in patients with RCC. Although both groups conducted large cohort studies, the analysis was retrospective. Our subjects had a higher ASA score and pathological T stage and a short median follow-up duration. Pathological M staging also differed slightly between the two groups. These differences may have contributed to the different results reported in these two studies. In this study, differences according to histological subtype did not reach statistical significance ($P = .051$, **Table 2**). Blood types A and AB were more frequent in patients with clear cell type RCC. However, blood types B and O were more frequent in patients with non-clear cell type RCC, although, in a multivariate analysis, histological subtype, unlike blood type, was not related to PFS and CSS. To our knowledge, the relationship between histological subtype of RCC and blood type A has not been previously studied. First, the A antigen is located on chromosome 9, which contains seven exons that span more than 18 kb of genomic DNA, and it may be related to a tumor suppressor gene or oncogene. Second, the A antigen may be related to chronic inflammation or an alteration in the systemic inflammatory reaction.[13,23] For example, a recent study reported that blood type A was related to nasopharyngeal carcinoma and skin cancer.[28,29] Nevertheless, further studies are warranted. The ABO blood type distribution varies widely according to country, region, and ethnicity.[30] The present data are similar to those reported in Korea (A, 32%; O, 28%; B, 31%; AB, 10%), which is in contrast to the observations that nearly all Bororo and Peruvian Indians have blood type O, eighty-two percent of North American Indians (Blackfoot) have blood type A, and only 9% of Andamanese people have blood type O. However, it is unknown whether CSS or PFS are influenced by the specific blood type. Furthermore, the ABO blood type is inherited and cannot be changed. Regarding this point, our study may be meaningful. Although frequent check-ups are helpful to determine disease progression, more studies on single nucleotide polymorphisms and intracellular signaling of the ABO antigen may be helpful in explaining this genetic variability. Selection bias is one limitation of this retrospective cohort study. However, efforts were made to minimize the missing values, and we were able to collect a nearly complete dataset. This study also had a prospective component because the ABO blood type cannot be changed after birth. Thus, the patients in this cohort were automatically randomized after birth. Second, because the data were obtained from a single Korean institution, our results cannot be generalized to other populations due to the geographic and ethnicity-related differences in the prevalence of ABO blood types. Our results are, however, similar to those reported in studies from Western countries. To the best of our knowledge, this study is the first to analyze the association between ABO blood type, clinicopathological data, and RCC prognosis in an Asian population. Thus, our study provides a clinical basis upon which further research can be expanded.

CONCLUSION

The ABO blood type is significantly associated with PFS and CSS in patients with RCC who have under-

gone radical or partial nephrectomy. A non-O blood type (A, B, and AB) was an independent prognostic factor for a worse PFS, and blood type A was an independent factor associated with a worse prognosis for CSS.

CONFLICT OF INTEREST

There is no conflict of interest

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