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Prognostic relevance of ABO blood group system in non-metastatic renal cell carcinoma: An analysis of two independent European cohorts with long-term follow-up

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Abstract

Background: The ABO blood group system has been previously discussed as a risk factor to develop, as well as a prognostic factor in non-metastatic renal cell carcinoma (RCC). Controversial findings have been reported in different populations of RCC patients with rather short follow-up periods. In this study, we aimed to clarify the distribution and prognostic role of ABO blood groups upon 15 years of median follow-up in non-metastatic RCC patients.

Materials and methods: We evaluated the distribution and prognostic significance of ABO blood group system in two independent cohorts ($n = 405$ and $n = 1473$) of non-metastatic RCC patients, who underwent curative (partial or total) nephrectomy between 1998 and 2012 at two tertiary academic centers. Cancer-specific survival, metastasis-free survival, as well as overall survival (OS) were assessed using the Kaplan-Meier method, univariable- and multivariable Cox regression models were applied, respectively.

Results: In the two cohorts, blood groups were not associated with any clinical endpoints (for cohort 2: Cancer-specific survival (HR = 1.233; 95%CI 0.998−1.523, $P = 0.052$), metastasis-free survival (HR = 1.161; 95%CI 0.952−1.416, $P = 0.142$) and OS (HR = 1.037; 95%CI 0.890−1.208, $P = 0.641$), respectively). Compared to 250.298 healthy blood-donors of the Styrian state, the distribution of blood groups was (624 (42.4%) versus 106.861 (42.7%) in group A, 191 (13%) vs. 34.164 (13.7%) in group B, 575 (39%) versus 93.579 (37.4%) in group O and 83 (5.6%) vs. 15.694 (6.3%), $P = 0.467$).

Conclusion: In this large study with the longest period of follow-up reported to date, the ABO blood group system could not be validated as a prognostic factor in predicting important clinical endpoints in non-metastatic RCC patients.

Keywords: Renal cell carcinoma; Blood groups; ABO; Prognosis; Surgery

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1. Introduction

Renal cell carcinoma (RCC) is the second most common malignancy of the urinary tract. The worldwide incidence amounts to 403,262 newly diagnosed cases each year, representing 2.2% of all malignancies [1]. Even though a stage migration towards earlier tumor stages within the last decades was observed [2], worldwide kidney cancer-related deaths were estimated at 175,098 according to the GLOBOCAN 2018 database [1].

Surgical tumor resection is the mainstay of treatment for localized RCC and potentially curative tumor stages. Nevertheless 20 to 30% of patients eventually experience systemic recurrence requiring systemic therapies [3]. Accurate outcome prediction beyond traditional and established clinico-pathological factors such as the histological classifications (e.g. clear cell, papillary, chromophobe) or TNM-stages and Tumor-Grade are not widely used in clinical routine [4,5]. In addition to tissue-based and radiological assessment, several blood-based biomarkers have been proposed as potential prognostic factors including parameters of systemic inflammatory response, circulating tumor DNA or non-coding RNAs [5−10].

The ABO blood group system with its different antigens may be involved in cancer progression and has been previously associated with cancer risk of various sites [11]. ABO blood group antigens are usually expressed on erythrocytes and in healthy epithelial tissues and should be carefully considered in solid organ transplantation [12]. They are frequently lost during malignant dedifferentiation and the absence of A and B antigens might be associated with an increased risk of metastatic progression [13]. Furthermore, ABO antigens are associated with coagulation mechanisms and initiation of angiogenesis which are crucial in RCC pathogenesis [13−15]. Thus, the ABO blood group system was repeatedly evaluated for its prognostic value in cancer and was suggested as a prognostic marker in esophageal, pancreatic and gastric cancer [16−18]. In RCC conflicting results about the prognostic value of ABO blood groups have been reported. In more detail, blood group O was first associated with a more favorable outcome as compared to non-O blood type [19], though several subsequent validation studies delivered unequivocal results [20−22].

The present study aims to address this issue and clarify the prognostic value of the ABO blood group system in two large European cohorts of patients with surgically treated non-metastasized RCC. In addition to previous studies, we included all established important clinico-pathological predictors of disease outcome (including sarcomatoid differentiation) and reported the longest follow-up period with a median of fifteen years.

2. Materials and methods

This retrospective analysis included data from 405 patients (screening cohort) with localized RCC who underwent nephrectomy at the Department of Urology at the Medical University of Innsbruck and 1473 consecutive patients with localized RCC who underwent nephrectomy at the Department of Urology at the Medical University of Graz between January 1998 and December 2012 (validation cohort). Last data-cut off for follow-up analysis was December 31, 2020. All clinico-pathological data were retrieved from medical records from the Department of Urology, as well as from pathology reports from the Institute of Pathology at the Medical University of Graz. Routine ABO typing of the patients was performed on the Olympus automated blood grouping testing system (Olympus PK7300, Beckman Coulter, Hamburg) or by standard serologic and gel matrix techniques (MicroTyping System, Bio-Rad) at the Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz [23].

Since the TNM classification system for RCC changed during the observational period, pathologic T-stages were uniformly adjusted according to the 8th edition of the TNM classification system [24]. Other documented clinico-pathological parameters included histological RCC subtype, tumor grade, presence, or absence (not quantitatively assessed) of histologic coagulative tumor necrosis (TN), sarcomatoid differentiation, as well as patients' age and gender. Patients' post-operative surveillance included routine clinical and laboratory examination; regarding imaging methods, X-rays of the chest and abdominal ultrasound were predominantly used, especially in patients with a low relapse risk (pT-1, G1-2), whereas CT or magnetic resonance imaging was performed in all other patients as previously reported [7,25]. Follow-up evaluations were performed every six months for the first five years and annually thereafter for locally advanced tumors. In organ-confined cancers, imaging was performed twice in the first year after surgery and annually thereafter. No neoadjuvant or adjuvant treatment was administered. Dates of death were obtained from the central registry of the Austrian Bureau of Statistics. Cancer-specific survival (CSS) was defined as the time (in months) from date of surgery to a cancer-related death. Metastasis-free survival (MFS) was defined as the time (in months) from date of surgery to the recurrence of radiologically or histologically confirmed distant metastases. OS was defined as the time (in months) from date of surgery to individuals' death of any cause. The study was approved by the local ethical committee (No. 32-225 ex 19/20 and 1202/2018) of the Medical University of Graz/Innsbruck.

2.1. Statistical analyses

The primary study endpoint was CSS. Secondary endpoints included OS and MFS. The proportion of blood types in the studied patients was compared to that of Styrian blood donors ($n = 250.298$ for ABO) by means of Chi-Squared tests. The relationship between the blood groups and clinico-pathological parameters was studied by non-

parametric tests. Patients' clinical endpoints were calculated using the Kaplan-Meier method and compared by the log-rank test. Multivariate Cox proportion analysis was performed to determine the influence of age, gender and all variables with a *P*-value of at least <0.1 in univariable analysis on patients' CSS, MFS and OS. Hazard ratios estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA). A two-sided $P < 0.05$ was considered statistically significant.

3. Results

In our cohort 1 (Innsbruck cohort), we included 405 patients with non-metastatic RCC. Table 1 shows the distribution of clinico-pathological parameters of this cohort. The most prevalent blood group was blood group O (45.7%), followed by blood groups A (41%), B (10.6%) and AB (2.7%), respectively.

No association between blood group O and gender, histology, sarcomatoid differentiation, tumor necrosis, vascular invasion, tumor stage and tumor grading were found ($P > 0.05$ for all parameters, Table 1). As shown in Kaplan Meier Curves in Supplementary Fig. 1, no significant association between blood group O and any of the three selected endpoints CSS, MFS and OS could be detected in cohort 1. As there was a trend for CSS ($P = 0.089$) for decrease in CSS in the group of blood group O carriers, we sought to validate the findings in a much larger validation cohort (cohort 2).

Overall, a total of 1473 patients with non-metastatic RCC were included in cohort 2 (Graz cohort). The minimum follow-up period was 8 years, the maximum 22 years, with a median follow-up period of 15 years. Pathologic T-stage distribution was pT1a in 724 (49.1%), pT1b in 264 (17.9%), pT2a in 78 (5.3%), pT2b in 12 (0.8%), pT3a in 216 (14.6%), pT3b in 170 (11.5%), pT3c in 6 (0.4%) and pT4 in 3 (0.2%) patients. The most prevalent histological type was clear cell RCC, followed by papillary, chromophobe and unclassified RCC (see Table 1). Four patients (0.3%) had collecting (Bellini) duct carcinoma. Tumor grading was G1 in 336 (22.8%), G2 in 894 (60.7%), G3 in 233 (15.8%) and G4 in 10 (0.7%) patients. Presence of sarcomatoid differentiation, tumor necrosis and vascular invasion were observed in 50 (3.4%), 371 (25.2%) and 285 (19.3%) cases, respectively.

Among 1473 patients, 624 (42.4%) carried blood group A, 191 (13%) carried blood group B, 575 (39%) carried blood group O and 83 (5.6%) carried group AB, respectively. In order to clarify significant differences between this RCC cohort, and the whole population in the Styrian state, we compared the distribution to the Styrian-blood donor registry. Of 250.298 blood donors, 106.861 (42.7%) carried blood group A, 34.164 (13.7%) carried blood group B, 93579 (37.4%) carried blood group O and 15.694 (6.3%) carried group AB, respectively. Overall, no significant differences were found in the distribution of ABO blood group types between the patients and the healthy blood donor registry ($P = 0.467$, chi-square test). Regarding the clinical outcome, of the 1473 RCC patients, 381 (25.9%) died due to their advanced disease stage during the follow-up period. Median OS was 188 months (95%CI 176.6−199.4) while it was not reached for CSS and MFS. 188 (30.1%) patients with group A, 58 (30.4%) patients with group B, 152 (26.4%) patients with group O and 25 (30.1%) patients with group AB eventually experienced disease relapse during the whole follow up period. Kaplan-Meier estimation and associated log-rank tests revealed no significant association neither with CSS ($P = 0.052$), nor MFS ($P = 0.141$) nor OS ($P = 0.640$) comparing blood groups O and non-O (Fig. 1), respectively. Likewise, Kaplan-Meier estimators considering each blood group individually using pairwise log-rank comparison could not demonstrate significant differences between the groups regarding CSS, MFS and OS (Fig. 2).

To investigate whether the blood groups were associated with the clinical outcomes of RCC patients, we additionally analyzed parameters in univariable and multivariable analyses for the primary endpoint CSS in cohort 2.

In univariable analysis, blood group O (O vs. non-O) was no significant predictor of CSS (HR = 1.233; 95%CI 0.998−1.523, $P = 0.052$). Histology (clear cell vs. non-clear cell; HR = 0.716, 95%CI 0.541−0.946, $P = 0.019$), sarcomatoid differentiation (HR = 3.965, 95%CI 2.773−5.670, $P < 0.001$), presence of tumor necrosis (HR = 1.884, 95%CI 1.527−2.323, $P < 0.001$), vascular invasion (HR = 2.613, 95%CI 2.114−3.231, $P < 0.001$), higher grade (HR = 1.881; 95%CI 1.611−2.196, $P < 0.001$), T-stage (see Table 2) and higher age (HR = 1.046; 95%CI 1.035−1.056; $P < 0.001$) were identified as significant predictors of CSS in univariable Cox regression and thus included in the multivariable model. Accordingly, there was no significant association of blood group O with OS (HR = 1.037; 95%CI 0.890−1.208, $P = 0.641$) and MFS (HR = 1.161; 95%CI 0.952−1.416, $P = 0.142$) in the univariable analysis (Supplementary Tables 1 and 2).

In the multivariable Cox proportional hazard model, histology (HR = 0.721; 95%CI 0.541−0.961; $P < 0.001$), sarcomatoid differentiation (HR = 2.209; 95%CI 1.462−3.337; $P < 0.001$), tumor necrosis (HR = 1.370; 95%CI 1.091−1.721; $P = 0.007$), T-stage (see Table 2), grading (HR = 1.330; 95%CI 1.119−1.582; $P = 0.001$) and age (HR = 1.040; 95%CI 1.029−1.050; $P < 0.001$) prevailed as independent predictors of CSS. Blood group O was not associated with CSS in the multivariable analysis (HR = 1.198; 95%CI 0.969−1.481; $P = 0.096$).

In addition, blood group O was no significant predictor of the secondary endpoints, OS (HR = 1.043; 95%CI 0.894−1.215, $P = 0.593$) and MFS (HR = 1.121; 95%CI 0.918−1.369, $P = 0.261$) adjusted for age, T-stage, grading, clear cell histology, sarcomatoid differentiation, tumor necrosis

Table 1
Summary table of the study population. *association of clinico-pathological parameters with blood groups (O vs. non-O) compared by Chi-square tests. **clear cell vs. non-clear cell

	Screening cohort (cohort 1) $n = 405$			Validation cohort (cohort 2) $n = 1473$		
	n (%miss.)	Summary measure	*P*-value*	*n* (%miss.)	Summary measure	*P*-value*
Demographic variables						
Sex	405 (0%)		0.406	1473 (0%)		0.814
—female		151 (37.3%)			576 (39.1%)	
—male		254 (62.7%)			897 (60.9%)	
Age (y)	405 (0%)	62 [IQR 52–71]		1473 (0%)	65 [IQR 55.9–72.5]	
Tumor variables						
T-stage	404 (0.3%)		0.232	1473 (0%)		0.087
—pT1		331 (81.7%)			988 (67.1%)	
—pT2		29 (7.2%)			90 (6.1%)	
—pT3		41 (10.1%)			392 (26.6%)	
—pT4		3 (0.7%)			3 (0.2%)	
Tumor grade	403 (0.6%)		0.265	1473 (0%)		0.073
—G1		131 (32.3%)			336 (22.8%)	
—G2		220 (54.3%)			894 (60.7%)	
—G3		41 (10.1%)			233 (15.8%)	
—G4		11 (2.7%)			10 (0.7%)	
Vascular invasion	405 (0%)	117 (28.9%)	0.316	1472 (0.1%)	285 (19.3%)	0.471
Sarcomatoid transformation	405 (0%)	5 (1.2%)	0.121	1473 (0%)	50 (3.4%)	0.299
Tumor necrosis	405 (0%)	108 (26.7%)	0.452	1473 (0%)	371 (25.2%)	0.789
Histology						
RCC subtype	405 (0%)		0.859**	1473 (0%)		0.39**
—clear cell		296 (73.1%)			1182 (80.2%)	
—papillary					185 (12.6%)	
—chromophobe					72 (4.9%)	
—collecting duct					4 (0.3%)	
—unclassified					30 (2%)	
—non-clear cell		109 (26.9%)				
Blood group	405 (0%)			1473 (0%)		
A		166 (41%)			624 (42.4%)	
B		43 (10.6)			191 (13%)	
O		185 (45.7%)			575 (39%)	
AB		11 (2.7%)			83 (5.6%)	

and vascular invasion in the multivariable Cox model, respectively (Supplementary Tables 1 and 2).

4. Discussion

A potential role of ABO blood group antigens in carcinogenesis has already been proposed and investigated for several decades [26]. Proposed pathogenic mechanisms include dysregulated enzymatic activity of ABO glycosyltransferases, thereby altering intercellular adhesion and signaling cascades [27,28]. Other than that, changes in the host inflammatory response to cancer had been linked to polymorphisms in the ABO genes [27]. ABO antigens are expressed on epithelial cells of the digestive system, lung, prostate, bladder and uterine cervix and antigen expression is frequently altered or lost during malignant transformation, which gave rise to the hypothesis of blood groups being associated with the prognosis of cancer patients [13,27]. Indeed, non-O blood groups have recently been confirmed to be associated with increased cancer risk in various malignancies including cancers of the pancreas, breast, bladder, stomach, mouth, and uterus [11]. Moreover, ABO blood groups have been reported to successfully predict for patient outcomes in various solid malignancies [27]. In contrast, evidence in RCC is ambiguous and final conclusions cannot be drawn.

In fact, although A and B antigens are expressed in the renal cortex except for individuals with blood type O, A and B antigen expression was missing or only observed to a limited extent in distal and proximal tubule epithelium and the glomerulus [21,29]. Since most RCCs are thought to arise from these locations [30], Lee et al. [21] argued the biological basis on which blood groups were suggested as reasonable prognostic biomarkers in RCC. Within our present study, we could not externally validate the ABO blood group system as a prognostic factor in two independent cohorts of more than 1800 surgically treated primarily localized RCC patients, yet there was some tendency towards significance in the univariable analysis for CSS. Considering our results, ABO blood groups (O vs. non-O

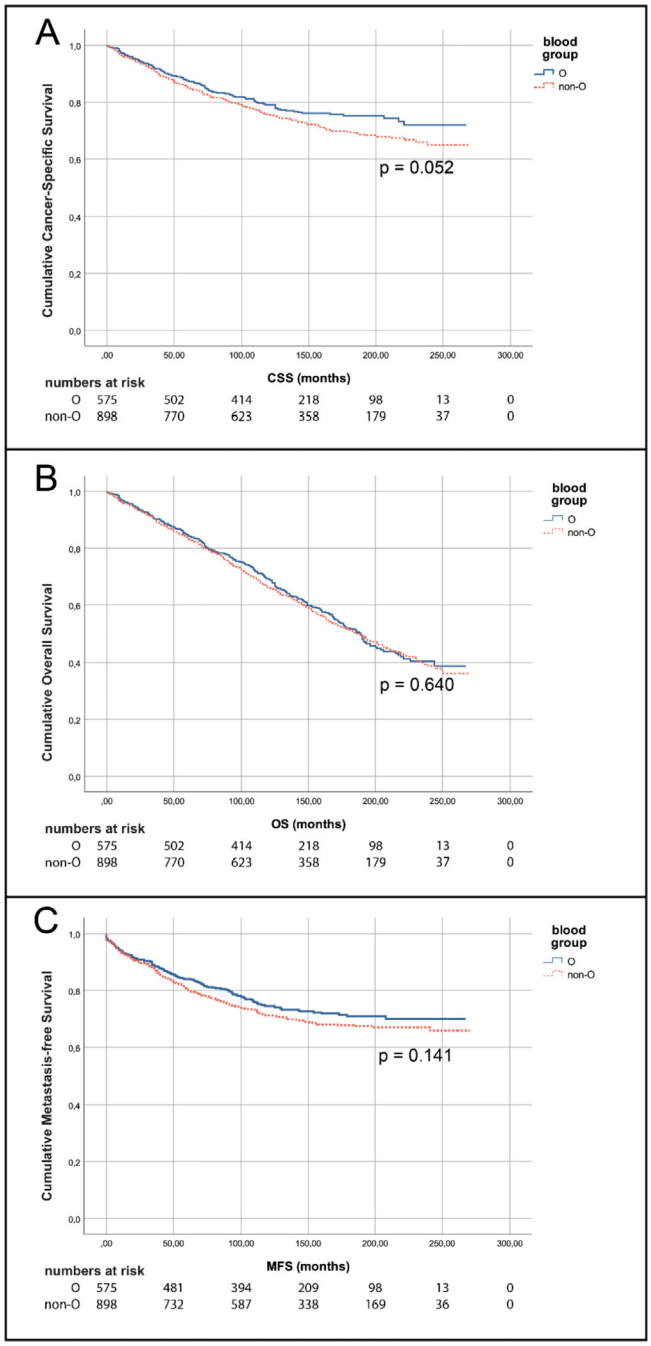

Fig. 1. Kaplan-Meier curves showing cancer-specific survival (CSS) (A), overall survival (OS) (B) for blood group O vs. non-O and metastases-free survival (MFS) (C) in cohort 2.

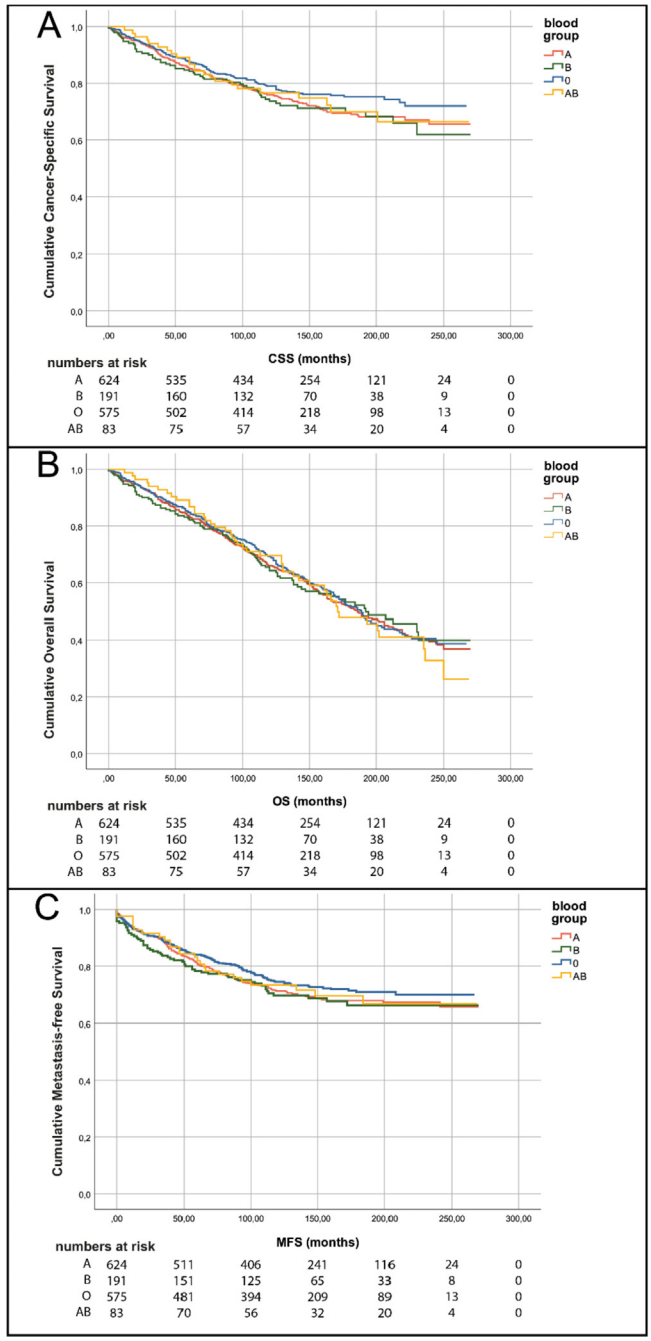

Fig. 2. Kaplan-Meier curves showing pairwise comparisons of survival outcomes in cohort 2: (A) CSS (A vs. B $P = 0.757$; A vs. O $P = 0.077$; A vs. AB $P = 0.842$; B vs. O $P = 0.122$; B vs. AB $P = 0.701$; O vs. AB $P = 0.483$), (B) OS (A vs. B $P = 0.932$; A vs. O $P = 0.677$; A vs. AB $P = 0.789$; B vs. O $P = 0.821$; B vs. AB $P = 0.801$; O vs. AB $P = 0.647$), (C) MFS (A vs. B $P = 0.769$; A vs. O $P = 0.187$; A vs. AB $P = 0.849$; B vs. O $P = 0.226$; B vs. AB $P = 0.744$; O vs. AB $P = 0.626$).

and the four groups by their own) are not significantly associated with three important endpoints including CSS, OS and MFS. In addition, comparing a representative sample of more than 200.000 healthy blood donors of our region with the distribution of blood groups in the large cohort 2, does not indicate any differences in distribution of blood groups (or enrichment of a blood group) in RCC patients.

Our results contrast with a study by Kaffenberger et al [19] who conducted the first large-scaled retrospective study to investigate the prognostic value of ABO blood groups in 900 non-metastatic RCC patients undergoing curative surgery. Before that, only small-sized cohort studies with considerable methodological deficiencies analyzing RCC incidence by ABO blood groups were conducted, yet again with conflicting results [19,31,32].

In their work, Kaffenberger et al. [19] proposed blood group O as a novel favorable prognostic biomarker in RCC

Table 2
Uni- and multivariate Cox regression regarding CSS in cohort 2

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (continuous)	1.046 (1.035–1.056)	**<0.001**	1.040 (1.029–1.050)	**<0.001**
Sex				
Male	1 (reference)			
Female	0.856 (0.694–1.054)	0.143		
T-stage				
pT1	1 (reference)		1 (reference)	
pT2	1.713 (1.135–2.587)	**0.010**	1.312 (0.848–2.031)	0.222
pT3 + pT4	3.098 (2.515–3.816)	**<0.001**	2.065 (1.566–2.723)	**<0.001**
Grading				
G1 + G2	1 (reference)		1 (reference)	
G3 + G4	1.881 (1.611–2.196)	**<0.001**	1.330 (1.119–1.582)	**0.001**
Histology				
Clear cell	1 (reference)		1 (reference)	
Non-clear cell	0.716 (0.541–0.946)	**0.019**	0.721 (0.541–0.961)	**<0.001**
Sarcomatoid transformation				
No	1 (reference)		1 (reference)	
Yes	3.965 (2.773–5.670)	**<0.001**	2.209 (1.462–3.337)	**<0.001**
Tumor necrosis				
No	1 (reference)		1 (reference)	
Yes	1.884 (1.527–2.323)	**<0.001**	1.370 (1.091–1.721)	**0.007**
Vascular invasion				
No	1 (reference)		1 (reference)	
Yes	2.613 (2.114–3.231)	**<0.001**	1.191 (0.900–1.576)	0.222
Blood group (ABO)				
O	1 (reference)	0.052	1 (reference)	
Other blood groups	1.233 (0.998–1.523)		1.198 (0.969–1.481)	0.096

bold values indicate significance (p<0.05)

patients undergoing partial or radical nephrectomy including advanced locoregional disease. Interestingly, blood type O was found to be a significant prognostic factor for OS after numerous statistical adjustments. However, there was no association between blood group and disease specific survival (DSS) in the uni- or multivariate analysis [19]. Considering these partly conflicting results, the authors suggest that blood groups may not be related to RCC prognosis directly, as blood groups might be associated with other conditions influencing patient survival.

Ko et al. [20] included 1750 patients with Asian ancestry and proposed blood group non-O as predictors for PFS, whereas blood group A was significantly and independently associated with decreased CSS [20]. In our present study, the biggest difference in pairwise comparison for CSS was between blood group O and A ($P = 0.077$) hinting in a direction that at least matches the results of Ko et al. [20] in some parts. As opposed to this, Lee et al. [21] included 3172 RCC patients and considered blood groups A, B and AB as individual covariates using type O as a reference. This study comprising the largest sample size so far could not confirm a relationship of blood groups and RCC prognosis (OS, CSS and RFS). In line with our data and the study by Lee and colleagues [21], de Martino et al. [22] could not confirm the prognostic value of blood groups (O vs. non-O) for OS and DSS in 560 consecutive RCC patients.

Several differences between the available studies may impede comparability between them and may account for differences in the results. Apart from differences in the inclusion criteria, as for instance the inclusion of metastatic patients by de Martino et al. [22], blood group distribution varies among different ethnicities and geographic regions [33]. Moreover, multivariate model-building also differs among the studies, which could further explain diverging results. While Lee at al. [21] and Ko et al. [20] included all assessed covariates with potential impact on survival in both the uni- and multivariate model, other studies [20,22] including our present work only considered variables that were already significant predictors of outcome in the univariate analysis for the multivariate Cox model.

Cohort sizes among the previously conducted study significantly vary between 556 [22] and 3172 [21] patients. Similarly, the median follow-up and thus associated survival events range from 28.7 [19] to 60.2 months [21]. Strengths of our present study are the large sample size of more than 1800 patients in two independent cohorts with Caucasian ancestry, which is the largest one in this ethnicity, and the analysis and reporting of three relevant endpoints. Furthermore, with a median follow-up of over 15 years our study has the longest follow-up as compared to other studies investigating blood groups in RCC prognosis [19–22]. Finally, in contrast

to previous studies we also considered tumor necrosis and sarcomatoid differentiatoin, which emerged as two important clinical predictors of RCC prognosis [34,35], in our analysis.

However, some limitations of our study should be noted. Due to the retrospective nature of the study selection bias cannot be entirely excluded, however the use of two independent cohorts of two tertiary academic centers greatly reduce selection bias. Second, our study does not adjust for performance scores or comorbidities of patients undergoing surgery. Third, blood group distribution varies among geographical regions and different ethnicities, which could potentially impede statistical power and the generalizability in other geographic regions. Of note, two studies in Korean populations with consequently similar blood group distributions also showed opposite results [20,21], further underlining the yet undecided utility of ABO blood groups in RCC prognosis. Despite our comparison of blood group distribution in the study cohort 2 (Graz) and the entire population of healthy blood donors did not show significant differences, one should keep in mind that healthy blood donors are usually younger, with varying smoking behavior and less co-morbidities (which we did not adjust for in our study). Another limitation is that though both centers adhere to international risk-adapted follow-up recommendations to detect disease-recurrence, we cannot rule out differences in these protocols.

In conclusion, in this study of two large independent cohorts with a median follow up of 15 years we could not confirm that the phenotype in the blood group system ABO is a valuable prognostic biomarker in RCC patients undergoing curative surgery. In addition, no difference in distribution of blood groups between healthy blood donor and RCC patients could be detected.

Conflict of interest

None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Supplementary materials

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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

[2] Pichler M, Hutterer GC, Chromecki TF, Jesche J, Kampel-Kettner K, Pummer K, et al. Renal cell carcinoma stage migration in a single European centre over 25 years: effects on 5- and 10-year metastasis-free survival. Int Urol Nephrol 2012;44(4):997–1004.

[3] Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. World J Urol 2018;36(12):1943–52.

[4] Zigeuner R, Hutterer G, Chromecki T, Imamovic A, Kampel-Kettner K, Rehak P, et al. External validation of the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score for clear-cell renal cell carcinoma in a single European centre applying routine pathology. Eur Urol 2010;57(1):102–9.

[5] Pichler M, Hutterer GC, Chromecki TF, Jesche J, Kampel-Kettner K, Rehak P, et al. External validation of the Leibovich prognosis score for nonmetastatic clear cell renal cell carcinoma at a single European center applying routine pathology. J Urol 2011;186(5):1773–7.

[6] Hutterer GC, Stoeckigt C, Stojakovic T, Jesche J, Eberhard K, Pummer K, et al. Low preoperative lymphocyte-monocyte ratio (LMR) represents a potentially poor prognostic factor in nonmetastatic clear cell renal cell carcinoma. Urol Oncol 2014;32(7):1041–8.

[7] Bezan A, Mrsic E, Krieger D, Stojakovic T, Pummer K, Zigeuner R, et al. The Preoperative AST/ALT (De Ritis) ratio represents a poor prognostic factor in a cohort of patients with nonmetastatic renal cell carcinoma. J Urol 2015;194(1):30–5.

[8] Dalpiaz O, Luef T, Seles M, Stotz M, Stojakovic T, Pummer K, et al. Critical evaluation of the potential prognostic value of the pretreatment-derived neutrophil-lymphocyte ratio under consideration of C-reactive protein levels in clear cell renal cell carcinoma. Br J Cancer 2017;116(1):85–90.

[9] Barth DA, Drula R, Ott L, Fabris L, Slaby O, Calin GA, et al. Circulating non-coding rnas in renal cell carcinoma—pathogenesis and potential implications as clinical biomarkers. Front Cell Devel Biol 2020;8:828.

[10] Redova M, Poprach A, Nekvindova J, Iliev R, Radova L, Lakomy R, et al. Circulating miR-378 and miR-451 in serum are potential biomarkers for renal cell carcinoma. J Transl Med 2012;10:10–55:2255-5876-.

[11] Vasan SK, Hwang J, Rostgaard K, Nyrén O, Ullum H, Pedersen OBV, et al. ABO blood group and risk of cancer: A register-based cohort study of 1.6 million blood donors. Cancer Epidemiol 2016;44:40–3.

[12] Simmons DP, Savage WJ. Hemolysis from ABO Incompatibility. Hematol Oncol Clin North Am 2015;29(3):429–43.

[13] Ewald DR, Sumner SC. Blood type biochemistry and human disease. Wiley Interdiscip Rev Syst Biol Med 2016;8(6):517–35.

[14] Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers 2017;3:17009.

[15] Teppan J, Barth DA, Prinz F, Jonas K, Pichler M, Klec C. Involvement of long non-coding rnas (lncRNAs) in tumor angiogenesis. non-coding RNA 2020;6(4):42. doi:10.3390/ncrna6040042.

[16] Wang W, Liu L, Wang Z, Wei M, He Q, Ling T, et al. Impact of ABO blood group on the prognosis of patients undergoing surgery for esophageal cancer. BMC Surg 2015;15:106-015-0094-1.

[17] Xu YQ, Jiang TW, Cui YH, Zhao YL, Qiu LQ. Prognostic value of ABO blood group in patients with gastric cancer. J Surg Res 2016;201(1):188–95.

[18] Rahbari NN, Bork U, Hinz U, Leo A, Kirchberg J, Koch M, et al. AB0 blood group and prognosis in patients with pancreatic cancer. BMC Cancer 2012;12:319-2407-12-319.

[19] Kaffenberger SD, Morgan TM, Stratton KL, Boachie AM, Barocas DA, Chang SS, et al. ABO blood group is a predictor of survival in patients undergoing surgery for renal cell carcinoma. BJU Int 2012;110(11 Pt B):E641–6.
[20] Ko K, Park YH, Jeong CW, Ku JH, Kim HH, Kwak C. Prognostic significance of blood type A in patients with renal cell carcinoma. Urol J 2016;13(4):2765–72.
[21] Lee C, You D, Sohn M, Jeong IG, Song C, Kwon T, et al. Prognostic value of ABO blood group in patients with renal cell carcinoma: single-institution results from a large cohort. J Cancer Res Clin Oncol 2015;141(8):1441–7.
[22] de Martino M, Waldert M, Haitel A, Schatzl G, Shariat SF, Klatte T. Evaluation of ABO blood group as a prognostic marker in renal cell carcinoma (RCC). BJU Int 2014;113(5b):E62–6.
[23] Matzhold EM, Drexler C, Wagner A, Bernecker C, Pessentheiner A, Bogner-Strau JG, et al. A 24-base pair deletion in the ABO gene causes a hereditary splice site defect: a novel mechanism underlying ABO blood group O. Transfusion 2020;60(7):1564–72.
[24] Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. Eur Urol 2018;73(4):560–9.
[25] Seles M, Posch F, Pichler GP, Gary T, Pummer K, Zigeuner R, et al. Blood platelet volume represents a novel prognostic factor in patients with nonmetastatic renal cell carcinoma and improves the predictive ability of established prognostic scores. J Urol 2017;198(6):1247–52.
[26] Hakomori S. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. Biochim Biophys Acta 1999;1473(1):247–66.
[27] Franchini M, Liumbruno GM, Lippi G. The prognostic value of ABO blood group in cancer patients. Blood Transfus 2016;14(5):434–40.
[28] Franchini M, Favaloro EJ, Targher G, Lippi G. ABO blood group, hypercoagulability, and cardiovascular and cancer risk. Crit Rev Clin Lab Sci 2012;49(4):137–49.
[29] Breimer ME, Mölne J, Nordén G, Rydberg L, Thiel G, Svalander CT. Blood group A and B antigen expression in human kidneys correlated to A1/A2/B, Lewis, and secretor status. Transplantation 2006;82(4):479–85.
[30] Cairns P. Renal cell carcinoma. Cancer Biomark 2010;9(1-6):461–73.
[31] Giannopoulos A, Kostakopoulos A, Sofras F, Kyriakidis A, Pantazopoulos D. Relation of ABO and RH blood groups with renal cell carcinoma. Acta Urol Belg 1985;53(1):29–31.
[32] Desai M, Brown HE. ABO blood group in relation to hypernephroma. Urology 1976;8(6):596–7.
[33] Garratty G, Glynn SA, McEntire R. Retrovirus Epidemiology Donor Study. ABO and Rh(D) phenotype frequencies of different racial/ethnic groups in the United States. Transfusion 2004;44(5):703–6.
[34] Zhang L, Zha Z, Qu W, Zhao H, Yuan J, Feng Y, et al. Tumor necrosis as a prognostic variable for the clinical outcome in patients with renal cell carcinoma: a systematic review and meta-analysis. BMC Cancer 2018;18(1):870-018-4773-z.
[35] Pichler R, Compérat E, Klatte T, Pichler M, Loidl W, Lusuardi L, et al. Renal cell carcinoma with sarcomatoid features: finally new therapeutic hope? cancers (Basel) 2019;11(3):422. doi:10.3390/cancers11030422.