ORIGINAL RESEARCH

DOI: 10.37047/jos.2022-90679

Predictive and Prognostic Value of ABO Blood Group in Patients Using Immune Checkpoint Inhibitor for Advanced Renal Cell Carcinoma

Yakup ERGÜN[a], Gökhan UÇAR[b], Selin AKTÜRK ESEN[b], Murat BARDAKÇI[b], Ziya KALKAN[c], Zuhat URAKÇI[c], Erdoğan ŞEYRAN[d], Mutlu DOĞAN[d], Gökşen İnanç İMAMOĞLU[e], Ozan YAZICI[f], Seda KAHRAMAN[b], Yusuf AÇIKGÖZ[b], Doğan UNCU[b]

[a]Clinic of Medical Oncology, Batman Training and Research Hospital, Batman, Türkiye
[b]Department of Medical Oncology, University of Health Sciences Ankara City Hospital, Ankara, Türkiye
[c]Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[d]Clinic of Medical Oncology, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Türkiye
[e]Clinic of Medical Oncology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Türkiye
[f]Department of Medical Oncology, Gazi University Faculty of Medicine, Ankara, Türkiye

ABSTRACT Objective: We investigated the prognostic and predictive effects of the ABO blood group system on patients receiving immune checkpoint inhibitors for advanced renal cell carcinoma (RCC). Material and Methods: In this retrospective observational study, the data on the patients with known ABO blood group, who were administered nivolumab for mRCC, were reviewed. The tumor response rates and survival were analyzed based on the ABO blood group. Results: A total of 89 patients were included in the study. The median age of the patients was 57 (range: 24-83 years) years, and 67% (n=60) of the patients were male. Moreover, 43%, 18%, 9%, and 30% of the patients had blood groups A, B, AB, and O, respectively. Our study had a median follow-up time of 11 months. Although the groups did not differ significantly in progression-free survival (PFS) and overall survival (OS) according to the blood groups, patients who had the B blood type survived longer. For patients with blood types A, B, AB, and O, the median PFS was 5.3 months, 8.4 months, 3.7 months, and 7.8 months, respectively (p=0.8), and the median OS was 14.5 months, 20.3 months, 12.0 months, and 16.5 months, respectively (p=0.8). Conclusion: Although the groups did not differ significantly according to the ABO blood group, the patients with the B blood group survived relatively longer. These results suggested that further studies with more patients should be conducted.

Keywords: Immune checkpoint inhibitor; nivolumab; ABO blood-group system; renal cell carcinoma

Renal cell cancer (RCC) is the second most prevalent malignancy of the urinary tract, with 431,288 cases identified each year around the world.[1] While most patients are diagnosed with localized diseases, 30% of the patients are metastatic before diagnosis. Relapse occurs in 50% of the individuals who are diagnosed at the localized stage.[2] Thus, more than half of the RCC patients eventually relapse or exhibit metastasis.

The treatment of metastatic RCC (mRCC) has considerably progressed in recent years. While the median overall survival (OS) was around 1 year in the 1990s, it is almost 5 years with current treatment approaches.[3] Immune checkpoint inhibitors (ICIs) are indispensable for mRCC therapy. In the first-line treatment, either the combination of ICI+ICI or ICI+anti-vascular endothelial growth factor (anti-VEGF) tyrosine kinase inhibitor (TKI) is primarily recommended, while single agents, such as nivolumab and TKI, or their combination is recommended for treatment at later stages.[4] Although ICIs have revolutionized the treatment of mRCC, the re-

Correspondence: Yakup ERGÜN
Clinic of Medical Oncology, Batman Training and Research Hospital, Batman, Türkiye
E-mail: dr.yakupergun@gmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 18 Apr 2022 ***Received in revised form:*** 04 Jun 2022 ***Accepted:*** 10 Jun 2022 ***Available online:*** 29 Jun 2022

sults of the treatment differ among patients. The most commonly used prognostic risk scoring system in mRCC is the International Metastatic RCC Database Consortium (IMDC) risk scoring system. However, the prognostic effect of the IMDC risk scoring system on ICI treatment is not clear. Additionally, no known marker can predict the ICI response in mRCC. The most investigated biomarkers for response to anti-PD1/PDL1 agents were PDL-1 expression, microsatellite instability, tumor mutational burden, and tumor-infiltrating cells. However, no study has shown that these biomarkers can predict the prognosis of mRCC.[5] Therefore, the search for suitable biomarkers is ongoing.

The ABO blood group antigens are expressed on many cell membranes, especially on erythrocytes. Blood group antigens affect the stability and function of other glycans and proteins on the cell surface, and through these interactions, they modulate the binding of antibodies to the cell surface. Blood group antigens/related genes affect the expression of many cell adhesion molecules, cytokines, and chemokines. Thus, they affect the tumor microenvironment.[6] Although ABO antigens and various cancers are related, the prognostic and predictive effects of these antigens remain under-studied.[7] The anti-A and anti-B blood group antibodies are formed naturally by the immune system. When these antibodies encounter A or B antigens, they activate the immune system and lyse the cells containing the antigen. Thus, the immune system and the blood group system are linked. Since ICIs activate the immune system, they might interact with the ABO blood group. The relationship between blood group antigens and conventional chemotherapeutic agents has been investigated in many types of cancers, and the results are debatable.[7] However, the relationship between ICIs and the ABO blood group antigens has received limited attention. The only study on this subject was conducted by us on patients who were diagnosed with melanoma. In that study, the survival and response rates were found to be better with ICI treatment in patients with the B antigen.[8]

In this study, we investigated the predictive and prognostic value of the ABO blood group system in patients who were administered ICIs for treating advanced RCC. This is the first study conducted on patients with RCC.

MATERIAL AND METHODS

PATIENTS

We retrospectively reviewed the data of the patients diagnosed with mRCC, who applied to 6 different oncology centers in Türkiye and were administered nivolumab between January 2018 and June 2021. In Türkiye, a first-line TKI treatment is required before the administration of nivolumab for treating RCC, as per the health policies. Additionally, nivolumab can only be used in Türkiye. Hence, we only studied patients who were administered at least one dose of TKI and nivolumab separately in any of the following lines.

The inclusion criteria were: patients with known ABO blood group, 18 years or older, histopathological diagnosis with clear cell RCC, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and measurable metastatic disease. Patients with non-clear cell histology and brain metastases were excluded from the study.

The ABO blood group, age, gender, smoking status, ECOG-performance status, the IMDC risk score, the number of metastatic sites, metastatic site localization, the line of use of nivolumab, RH blood groups, and laboratory parameters were recorded from the files of the patients.

Nivolumab was administered every 2 weeks at a dosage of 3 mg/kg (maximum dose of 240 mg). All patients underwent a physical examination and basic laboratory tests on the first day of each cycle, once every 2 weeks. The tumor response rates were evaluated by performing computed tomography (CT), magnetic resonance imaging, or positron emission tomography/CT every 3 months following the criteria of iRECIST.

The approval of the ethics committee Ankara City Hospital No. 1 Clinical Research Ethics Committee Presidency was obtained for this study according to the criteria of the Declaration of Helsinki (date: March 23, 2022, no: E1-22-2499).

ANALYSIS OF THE PROGNOSTIC FACTORS

Seven variables that might have a prognostic effect on survival were selected from clinical and laboratory data. The selected variables were divided into 2 or 3 groups; median age (<57 or ≥57 years), gender

(female or male), smoking (no or yes), the IMDC risk score status (low, intermediate, and poor), Rh factor (Rh negative or Rh positive), the ECOG performance score (0/1 or 2), and metastatic site number (1 or ≥2). According to the ABO blood group, the patients were evaluated in a four-arm trial, which included the A, B, AB, and O blood groups. Later, they were evaluated in pairs. Additionally, a different comparison was made as groups containing the A antigen (A/AB) or without the A antigen (B/O) and containing the B antigen (B/AB) or without the B antigen (A/O).

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences Version 22.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. Mann-Whitney U test was performed to compare continuous variables. The median age was used as the cut-off value for age. Pearson's chi-square test or Fisher test was conducted to compare categorical variables. The progression-free survival (PFS) and OS were analyzed using the Kaplan-Meier method by performing the long-rank test. All differences between groups were considered to be statistically significant at $p<0.05$. A multivariate Cox regression test was performed for the variables that were significant in the univariate analysis.

RESULTS

The data from 89 patients who met the inclusion criteria were included. The median age of all patients was 57 (range: 24-83 years) years, and 67% of the patients (n=60) were male. Many patients (65%) were administered sunitinib in the first-line treatment, while nivolumab was administered to 48% of the patients in the 2nd-line treatment, 40% in the tertiary-line treatment, and 12% in the 4th-line treatment. According to the IMDC risk classification, 26% of the patients were in the good class, 48% were in the intermediate class, and 26% were in the poor-risk class. Of the patients, 43%, 18%, 9%, and 30% had blood groups A, B, AB, and O, respectively. The characteristics of the patients are presented in Table 1.

The median follow-up time of our study was 11 months; the median OS was 16.6 months and PFS was 6.0 months for all patients. The PFS and OS of the groups were similar according to the ABO blood groups, but patients in the B blood group survived slightly longer. For the A, B, AB, and O groups, the median PFS was 5.3, 8.4, 3.7, and 7.8 months, respectively (p=0.8), while the median OS was 14.5, 20.3, 12.0, and 16.5 months, respectively (p=0.8). The results of the Cox regression analysis showed no significant difference between any 2 groups. The other analyses performed showed no significant difference between the groups according to the presence of the B antigen (B/AB vs. A/O) and the presence of the A antigen (A/AB vs. B/O). For the patients who received nivolumab only in secondary care (n=43), no significant difference in survival was found between the groups (p=0.7). The survival curves are shown in Figure 1.

Complete response was not obtained in any of the patients. Partial response rates were 33%, 44%, 23%, and 25% for the patients with the A, B, AB, and O blood types, respectively, and the groups did not differ significantly (p=0.3). The survival outcomes and detailed tumor responses are presented in Table 2.

The results of the analysis performed to determine the factors that influence OS showed that only the ECOG performance score was a significant prognostic factor independent of other factors (hazard ratio=0.46, 95% confidence interval=0.1-0.86, p=0.002).

DISCUSSION

The ABO blood types did not have a prognostic or predictive impact on individuals treated with ICI for mRCC. Although patients with the B blood type survived longer, the duration was not significantly different from the survival of patients with other blood types. This could be due to the limited number of patients studied.

The immune system can distinguish between self and non-self.[9] Many cytokines, other molecules, and cells interact with a complex network for the immune system to function efficiently. The relationship between the ABO blood group and an immune response is well-established. Studies have shown that the ABO blood groups are associated with adhesion molecules, such as soluble intercellular adhesion molecule-1, integrins, and selectins.[10] The ABO

TABLE 1: The characteristics of the patients.

	A group (n=38)	B group (n=16)	AB group (n=8)	O group (n=27)	p-value
Age, median (range)	54.0 (32-78)	55.5 (27-68)	64 (48-74)	60 (24-83)	0.1
Sex					
Female	14 (37%)	6 (38%)	3 (38%)	6 (22%)	0.6
Male	24 (63%)	10 (62%)	5 (62%)	21 (78%)	
Smoking					
No	16 (42%)	8 (50%)	5 (62%)	11 (41%)	0.7
Yes	22 (58%)	8 (50%)	3 (38%)	16 (59%)	
ECOG performance status					
0-1	28 (74%)	14 (%87)	6 (75%)	15 (56%)	0.1
0.2	10 (26%)	2 (13%)	2 (2%)	12 (44%)	
IMDC risk score					
Low	9 (24%)	5 (30%)	3 (37%)	7 (26%)	0.9
Intermediate	19 (50%)	8 (50%)	4 (50%)	13 (48%)	
Poor	10 (26%)	3 (20%)	1 (13%)	7 (26%)	
Number of metastatic sites					
Multiple	24 (63%)	11 (69%)	4 (50%)	14 (52%)	0.6
Single	14 (37%)	5 (31%)	4 (50%)	13 (48%)	
Line using nivolumab					
Second line	17 (45%)	7 (43%)	3 (38%)	16 (60%)	0.4
Third line	16 (42%)	6 (38%)	5 (62%)	9 (33%)	
Fourth line	5 (13%)	3 (19%)	0	2 (7%)	
Rh group					
Positive	35 (92%)	14 (88%)	7 (88%)	21 (78%)	0.1
Negative	3 (8%)	2 (12%)	1 (12%)	6 (22%)	

ECOG: Eastern Cooperative Oncology Group; IMDC: International Metastatic RCC Database Consortium.

blood groups are also associated with many cytokines and growth factors, such as tumor necrosis factor alpha. For example, Van Alsten et al. conducted a study with 3,537 patients and found that circulating sVEGFR2 and sVEGFR3 levels were lower in individuals with blood group A.[6] A reduction in the expression of sVEGFR2 is associated with higher metastasis in neuroblastoma and breast cancer.[11,12] Even the differences in the level of angiogenesis are prominent and suggest that the ABO blood group might affect oncological outcomes. Based on the effects of blood groups on the immune system, studies have investigated the relationship between blood groups and cancer formation in many types of cancers and found conflicting results. Based on similar hypotheses, few studies have investigated the effect of blood groups on conventional methods of treatment.[7]

While the interaction between the ABO blood group and the immune system is well-established, the relationship between the ABO blood group and the immunotherapy response is not clear. The first study on this subject was performed in 1981.[13] In that study, the relationship between levamisole, which is used as an immunostimulant in patients with lung cancer, and blood types was investigated. Levamisole was hypothesized to provide this effect by increasing the T-helper (Th) 1-related immune response and decreasing Th2. The results showed that patients with the O blood group had lower survival. After that study, the relationship between immunotherapy and blood type was not sufficiently investigated. Another study, published nearly 35 years later, again showed a relationship between immunotherapy and blood types. Muthana et al. conducted a study in 2015 and investigated the relationship between PROSTVAC-VF, a cancer vaccine, and ABO blood groups in patients (n=80) with prostate cancer.[14] They found that the patients with blood type B had the longest me-

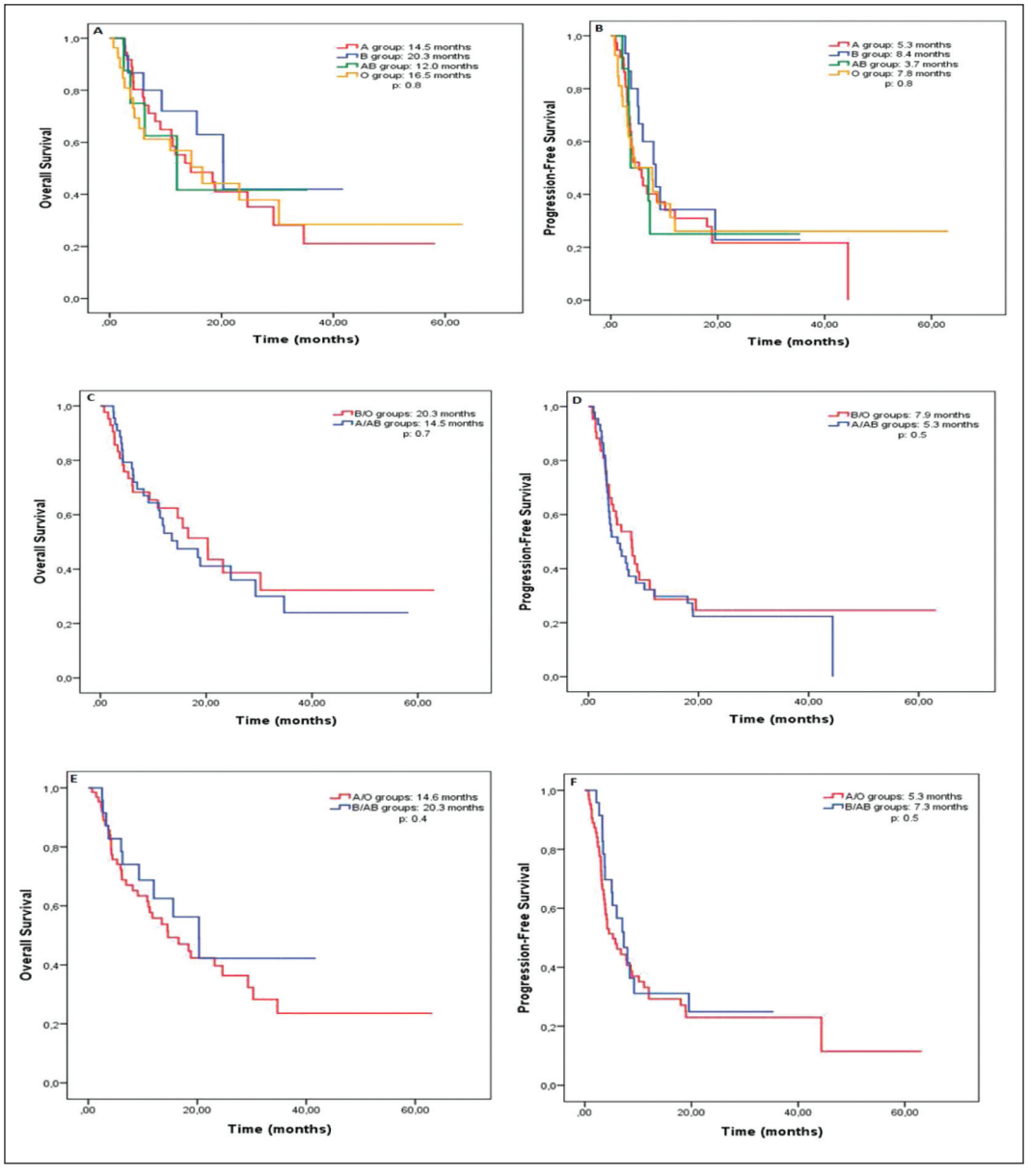

FIGURE 1: Kaplan-Meier curves for overall survival and progression-free survival. **A)** Overall survival of all patients. **B)** Progression-free survival of all patients. **C)** Overall survival based on the presence of the A antigen. **D)** Progression-free survival based on the presence of the A antigen. **E)** Overall survival according to the presence of the B antigen. **F)** Progression-free survival according to the presence of the B antigen.

TABLE 2: The efficacy of nivolumab.

	A group	B group	AB group	O group	p-value
PFS (median) (95 CI%)	5.3 (2.5-8.0)	8.4 (4.6-11.2)	3.7 (0.5-8.7)	7.8 (3.0-12.5)	0.8
OS (median) (95 CI%)	14.5 (3.5-25.5)	20.3 (13.6-27.0)	12.0 (1.0-23.1)	16.5 (6.7-26.7)	0.8
Partial response	33%	44%	25%	23%	0.3
Stable disease	33%	20%	30%	38%	0.6
Disease control rate	66%	64%	55%	61%	0.8
Progression	34%	36%	45%	39%	0.8

PFS: Progression-free survival; OS: Overall survival; CI: Confidence interval.

dian OS (median=38 months), which was followed by the OS of type O (27.6 months), type AB (21.7 months), and type A (15.8 months) patients, respectively. Similarly, in our study, though statistically not significant, the longest survival was observed in patients with the B blood group. Although the number of patients in that study was similar to that in our study, the agent used was different. Although it is incorrect to compare a vector vaccine with an ICI, both had roughly similar effects as immunostimulants. The last study on this subject was conducted by us in 2021. In that study, we investigated the predictive and prognostic effects of the ABO blood group in patients using nivolumab as a single agent in advanced melanoma.[8] In patients with melanoma, the longest PFS and the longest OS were observed in patients with blood group B (16.1 and 20.3 months for PFS and OS, respectively). However, a comparison of the 4 arms showed no significant difference. When the patients were divided into groups based on the presence of the B antigen (B/AB vs. A/O), the presence of the B antigen was found to be significantly associated with longer survival. The design of this study was similar to that of our study on melanoma, except for the diagnosis of cancer. In this study, subgroup analysis was performed according to the presence of antigen, but the difference was not statistically significant. When these studies are evaluated together, it suggests that B blood group may respond better to immunotherapy. However, due to the low number of patients in all three studies, a clear inference could not be made.

In recent years ICIs have shown promising results in cancer treatment. However, responses vary between patients. Predictive factors, such as PDL-1 level in lung cancer and MSI in colorectal cancer, are the most used predictive factors. However, these biomarkers cannot accurately predict the response in every patient. Regarding RCC, no biomarker can predict the ICI response. Using the ABO blood group system, which is an easily accessible and inexpensive test, we might be able to select patients who can respond to ICIs more efficiently. Therefore, validation of these results by performing studies with more patients is necessary for finding suitable biomarkers.

Our study had some limitations. The most important limitation was that this was a retrospective study conducted with data from very few patients. Due to the small sample size, the survival differences were not significant. Second, because we included patients who were administered nivolumab in the 2nd, 3rd, and 4th-line treatment, a heterogeneous patient population was formed that might have affected the oncologic outcomes. Third, we did not conduct an adverse event analysis. We hypothesized that blood type might be associated with adverse events; however, we could not perform the analysis due to missing data.

CONCLUSION

In this study, we examined the relationship between the ABO blood groups and the efficacy of ICIs in mRCC patients treated with nivolumab. Although the survival of the patients did not differ significantly among the groups, patients with the B blood group survived longer. Based on the results of this study and other studies, we conclude that the ABO blood group might predict the ICI response. Thus, this issue should be further investigated with more patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Yakup Ergün;* ***Design:*** *Yakup Ergün, Gökhan Uçar;* ***Control/Supervision:*** *Yakup Ergün, Selin Aktürk Esen;* ***Data Collection and/or Processing:*** *Murat Bardakçı, Ziya Kalkan, Zuhat Urakçı, Erdoğan Şeyran, Mutlu Doğan, Gökşen İnanç İmamoğlu, Ozan Yazıcı, Seda Kahraman, Yusuf Açıkgöz;* ***Analysis and/or Interpretation:*** *Yakup Ergün;* ***Literature Review:*** *Yakup Ergün, Selin Aktürk Esen;* ***Writing the Article:*** *Yakup Ergün;* ***Critical Review:*** *Mutlu Doğan, Doğan Uncu;* ***References and Fundings:*** *Yakup Ergün;* ***Materials:*** *Yakup Ergün, Gökhan Uçar.*

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. [Crossref] [PubMed]
2. Tran J, Ornstein MC. Clinical review on the management of metastatic renal cell carcinoma. JCO Oncol Pract. 2022;18(3):187-96. [Crossref] [PubMed]
3. Navani V, Heng DYC. Treatment selection in first-line metastatic renal cell carcinoma-the contemporary treatment paradigm in the age of combination therapy: a review. JAMA Oncol. 2022;8(2):292-9. [Crossref] [PubMed]
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Kidney Cancer. April 10, 2022. [Crossref]
5. Raimondi A, Sepe P, Zattarin E, et al. Predictive biomarkers of response to immunotherapy in metastatic renal cell cancer. Front Oncol. 2020;10:1644. [Crossref] [PubMed] [PMC]
6. Van Alsten SC, Aversa JG, Santo L, et al. Association between ABO and Duffy blood types and circulating chemokines and cytokines. Genes Immun. 2021;22(3):161-71. [PubMed] [PMC]
7. Franchini M, Liumbruno GM, Lippi G. The prognostic value of ABO blood group in cancer patients. Blood Transfus. 2016;14(5):434-40. [PubMed] [PMC]
8. Ergun Y, Esen SA, Bardakci M, Ucar G, Kalkan Z, Urakci Z, et al. Predictive and prognostic effect of ABO blood group on immune checkpoint inhibitors. Cancer Biomark. 2022;34(2):329-36. [Crossref] [PubMed]
9. Luiz C. de MattosHaroldo W. Moreira. Genetic of the ABO blood system and its link with the immune system. Rev. Bras. Hematol. Hemoter. 2004;26(1):60-3. [Crossref]
10. Barbalic M, Dupuis J, Dehghan A, et al. Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. Hum Mol Genet. 2010;19(9):1863-72. [PubMed] [PMC]
11. Becker J, Pavlakovic H, Ludewig F, et al. Neuroblastoma progression correlates with downregulation of the lymphangiogenesis inhibitor sVEGFR-2. Clin Cancer Res. 2010;16(5):1431-41. [Crossref] [PubMed] [PMC]
12. Shibata MA, Ambati J, Shibata E, et al. The endogenous soluble VEGF receptor-2 isoform suppresses lymph node metastasis in a mouse immunocompetent mammary cancer model. BMC Med. 2010;8:69. [Crossref] [PubMed] [PMC]
13. Anthony HM. Blood groups and the response to immunotherapy. Cancer Immunol Immunother. 1981;11:287-9. [Crossref]
14. Muthana SM, Gulley JL, Hodge JW, et al. ABO blood type correlates with survival on prostate cancer vaccine therapy. Oncotarget. 2015;6(31):32244-56. [Crossref] [PubMed] [PMC]