

ABO Blood Group and the Risk and Prognosis of Lymphoma

Ling Qin¹, Dongli Gao¹, Qian Wang¹, Xuwei Zheng², Jingjing Wang², Xingang Chen², Dongliao Fu², Haodi Ma², Junjia Tan³, Qinan Yin² 

¹The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, People's Republic of China; ²Laboratory for Precision Medicine, School of Medical Technology and Engineering, Henan University of Science and Technology, Luoyang, People's Republic of China; ³Section for Statistical Analysis and Data Collection, Luoyang Branch, Bank of China, Luoyang, People's Republic of China

Correspondence: Qinan Yin, School of Medical Technology and Engineering, Henan University of Science and Technology, No. 263 Kaiyuan Avenue, Luoyang, 471000, People's Republic of China, Tel +86-13939928711, Email qinanyin@haust.edu.cn

Abstract: ABO blood group antigens exhibit alternative phenotypes and genetically derived structures that are located on the red cell surface. The role of ABO blood group in cancer biology has been intensely reported by several studies, and it is now widely recognized that ABO antigens are associated with the risk and prognosis of several types of tumors, namely gastric cancer and pancreatic cancer. However, there have been contentious limited issues with the association between the ABO blood group and lymphoma. In this narrative review, based on literature data, we discuss the role of ABO blood group in the risk and prognosis of lymphoma and summarize the current knowledge of the underlying pathogenic mechanisms of the association. The possible association of ABO blood group with racial disparities and pathological classification in lymphoma patients is also discussed.

Keywords: ABO blood group, lymphoma, survival, disease susceptibility, race

Introduction

The ABO blood group is one of the most important human blood group systems. The *ABO* gene is located on chromosome 9q34 and encodes two alleles (i.e., A and B) for specific glycosyltransferases which catalyze the covalent linkage of N-acetyl-D-galactose or D-galactose to a common precursor side chain (i.e., the H antigen), eventually forming A and B antigens respectively.^{1,2} Unlike A and B alleles, the O variant encodes a non-functional glycosyltransferase, so H antigen is unmodified.³ The ABO blood group antigens are defined by carbohydrate moieties on the extracellular surface of red blood cell membranes. ABO blood group is classified into type A, type B, type AB and type O based on the antigens expressed on erythrocytes. People with blood type A have antigen A on their erythrocytes, and those with blood type B have antigen B.⁴ Individuals with blood type AB have both antigens A and B in the surface of erythrocytes, while those with blood type O lack either antigen.⁵ Studies have shown that these antigens are also highly expressed on the surface of a large number of human cells and tissues, including endothelial, neurons, platelets, and body fluids.⁶⁻⁸

The association between ABO blood groups and tumors has been reported in the early stage.⁹ There is also growing evidence from recent literatures of a critical involvement of the ABO blood group in the development of various types of cancers. Relevant studies demonstrated that blood group A significantly increases the risk of gastric and pancreatic cancer.¹⁰⁻¹² The reason may be that tumor cells expressing “A-like antigen” in individuals with blood type A are not easy to be recognized by the body for immune rejection.¹³⁻¹⁶ A study in Shanghai also showed that blood group AB is associated with significantly increased risk of liver cancer.¹⁷ Study has noted a direct link of single nucleotide polymorphisms at the ABO locus to serum levels of tumor necrosis factor-alpha, an inflammatory cytokine that regulates liver cancer risk.^{18,19} But the mechanism by which blood type AB is associated with an increased risk of liver cancer is not very clear. In addition, patients with blood type O have a poor prognosis for multiple myeloma (MM).²⁰ This may be due to serum levels of lactic dehydrogenase (LDH) is higher in MM patients with blood type O than other blood types.²⁰

High serum LDH levels may be associated with an extramedullary lesion in MM patients.²¹ So far there is limited understanding of ABO blood group in the risk and prognosis of lymphoma. Moreover, the potential mechanisms underlying remain largely unknown. The association between ABO blood groups and lymphoma is addressed in this concise review through analyzing the published literature and pathogenic mechanisms.

Methods

We systematically reviewed the scientific literature published so far on the relationship between ABO blood group and lymphoma. The PUBMED[®] electronic database was searched without time limit under English language restrictions. The following medical subject headings and keywords were used: “ABO blood group”, “lymphoma”, “disease susceptibility”, “distribution”, “survival”, “prognosis”, and “non-Hodgkin’s lymphoma” (HL). Furthermore, we also manually searched the reference lists for relevant items.

The relationships between ABO blood type and clinical variables were assessed using Chi-square test. A two-tailed $P < 0.05$ was considered statistically significant. The statistical software package SPSS 26.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations.

Pathogenic Effects of ABO Blood Group on Lymphoma

The underlying mechanisms that the ABO blood group may interact with the development and progression of cancers including lymphoma are still poorly understood. Several plausible potential pathogenic ways encompass: 1) Deletion of ABO blood group antigens caused by multiple regulators enhances the motility and migration of tumor cells, resulting in poor prognosis;^{15,22–27} 2) Tumor markers that are ABO blood group antigens can evade the immune surveillance of host and allow tumors to grow;^{13–16} 3) Dysregulation of ABO glycosyltransferases, which are mainly involved in altering the modulator of angiogenesis during the tumorigenesis, is related to tumor;^{28–31} and 4) The influence of ABO blood group antigens on tumor growth, invasion and migration is mainly related to the ABO gene locus involved in regulating the mediators of inflammation and immune responses (Figure 1).^{18,32–36}

The decrease or absence of ABO blood group antigen expression seems to play a role in the progression of tumors. There are several factors for the decrease or absence of ABO blood group. First, the deletion of ABO allele or hypermethylation of the ABO promoter region causes relative down-regulation of the glycosyltransferase necessary for blood group antigen synthesis.^{22,37–40} Second, some microRNAs (miRNAs) affect the expression of blood group antigens by regulating the activity of glycosyltransferase, such as miR-331-3p and miR-1980-5-p.²⁷ Third, mutations in the ABO gene. For example, the mutation of the GATA motif in intron 1 of the ABO gene could reduce the expression of the B antigen, and mutation of RUNX1 causes the loss of A antigen.^{25,26} Loss of blood group antigen expression may lead to increased cell motility and migration, which enhances malignancy of tumors and is associated with poor prognosis.^{15,23,24} So how does the deletion of blood group antigens enhance malignancy of tumors? It may be ascribable to the glycosylation of ABO blood group antigens on the regulation of integrin receptors activity.⁴¹ Integrin is an important component of cell adhesion molecules. In addition, the glycosylation of ABO blood group antigens can lead to conformational changes in proteins that not only affects intercellular signaling, cell adhesion, and immune surveillance, but also stimulates tumor growth and metastasis.^{42–47} The absence of ABO blood antigen is observed in hematological malignancies, including HL.^{48,49} We hypothesize that some of these factors may cause decreased expression of ABO blood group antigens on the surface of red blood cells in patients with lymphoma, leading to disease progression.

Some tumor antigens, which are the known product of certain blood type precursors/antigens, escape from immune surveillance and cause adverse prognosis. Many of those tumor antigens are similar to the A antigen, which are known as “A-like antigens.” “A-like antigens” was once considered to be an Across-reacting antigen (e.g., Forssman antigen, or Tn antigen), but it was later found to be the real A antigen.^{14–16} The discovery of the A antigen in non-A cancers indicates that ABO antigens can act as cancer risk factors.^{50,51} It is reported that under the immune surveillance theory, tumor cells expressing “A-like antigen” in individuals with blood type O can be detected by host immune surveillance at an early stage and are more likely to suffer immunologic rejection.¹⁵ However, it is difficult for type A persons to recognize tumor cells expressing “A-like antigen” as foreign cells as type O persons do.¹³ This may explain the increase in type A patients compared to type O patients in many malignancies. It is also found that the efficacy of immune checkpoint inhibitors

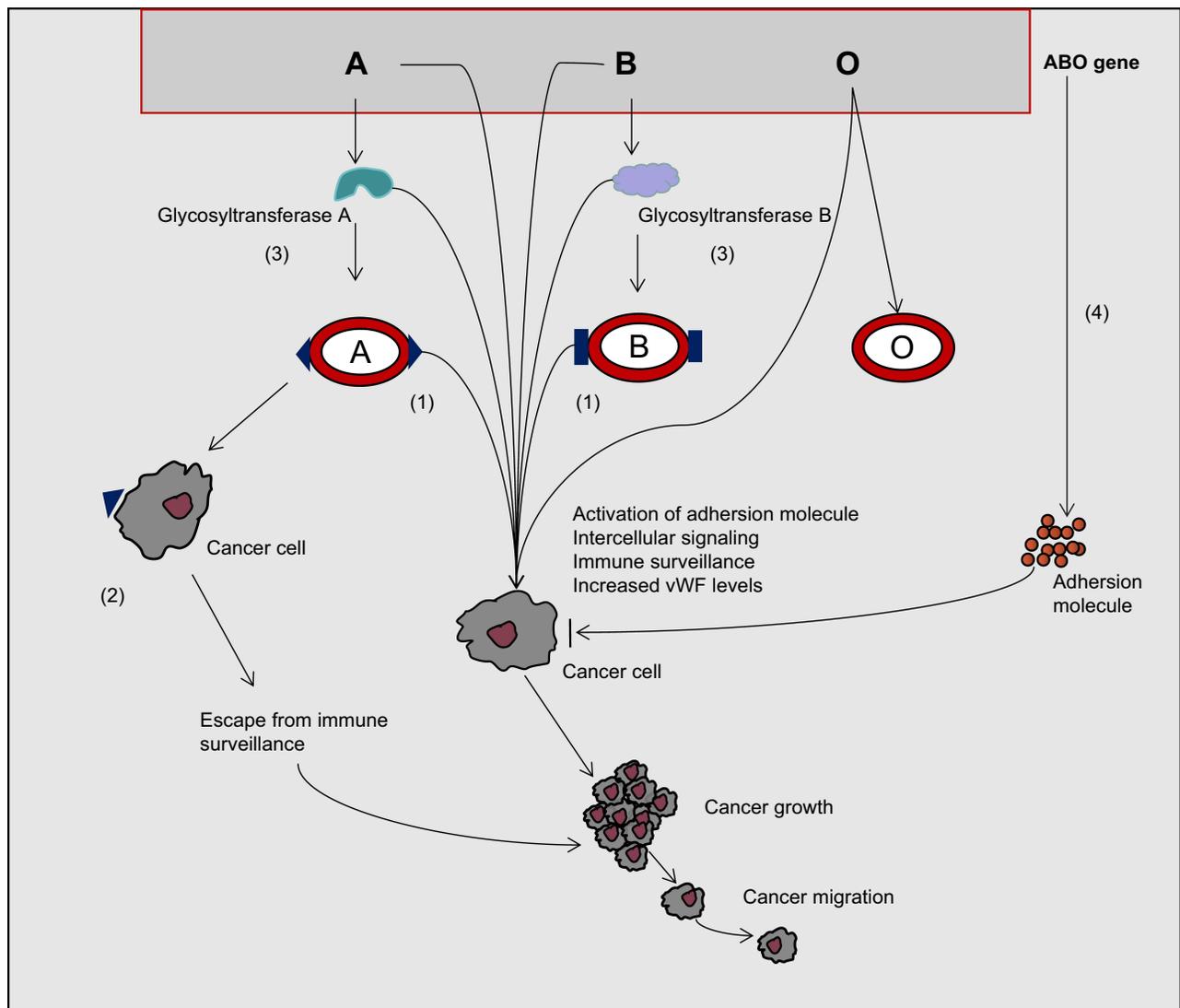


Figure 1 Pathogenic mechanism of ABO blood group on lymphoma. Potential mechanisms by which ABO blood groups may interact with the development and progression of cancers, including lymphoma: 1) Multiple regulators lead to the deletion of ABO blood group antigens, especially the A and B antigens, which enhances the motility and migration of tumor cells, resulting in poor prognosis; 2) Tumor markers that are ABO blood group antigens can evade the immune surveillance of host and allow tumors to grow; 3) Dysregulation of ABO glycosyltransferases, which are mainly involved in altering the modulator of angiogenesis during the tumorigenesis, is related to tumor; and 4) The influence of ABO blood group antigens on tumor growth, invasion and migration is mainly related to the ABO gene locus involved in regulating the mediators of inflammation and immune responses.

(ICIs) could be influenced by the ABO blood group, and advanced malignant melanoma patients with type B or AB had significantly longer overall survival (OS) than other blood types after using ICIs.⁵² Similar findings have been found in other blood group systems. For example, CD44, which is identical to the blood group antigen In b, is associated with lymphocyte (T cell) activation, hematopoietic development, and metastasis of malignant lymphoma.^{53–56} Thus, we hypothesize that there are tumor markers that are essentially ABO blood group antigens in lymphoma that contribute to disease progression.

Dysregulation of ABO glycosyltransferases, which are mainly involved in altering the modulator of angiogenesis during the tumorigenesis, is related to tumor. The mechanism is similar to how ABO glycosyltransferase regulates plasma von Willebrand factor (vWF) levels to affect the risk of venous thromboembolism (VTE).^{29,31,57} VWF plays an important role in inhibiting angiogenesis, promoting wound healing, and promoting tumor cell apoptosis; particularly, angiogenesis and apoptosis are also involved in tumorigenesis.^{28,30,58,59} ABO glycosyltransferase may promote the development of lymphoma by regulating plasma vWF levels.

It is possible that ABO blood group antigens influence tumor progression and metastasis by changing the inflammatory state of the host. The researchers found that the ABO gene locus is associated with circulating levels of tumor necrosis factor- α , soluble intercellular adhesion molecule (ICAM)-1, E-selectin, and P-selectin.^{18,32,33} All of these adhesion molecules are important mediators of chronic inflammation and immune cell recruitment. The correlation between ABO blood group and the occurrence and prognosis of chronic inflammatory diseases, such as inflammatory bowel disease and autoimmune diseases have been reported.^{60–72} Chronic inflammation is related to tumor growth, invasion, and migration.^{34–36} Therefore, we speculate that these inflammatory mediators directly correlate ABO blood groups with tumor development and spread. Chronic inflammation is also associated with lymphatic malignancies.⁷³ For example, Epstein–Barr virus is connected with large B cell lymphoma in immunocompromised patients and in patients with Burkitt's lymphoma or HL.⁷⁴ Another example is the lymphomas that appear in GM-CSF- and IFN γ -deficient mice, which are caused by infections and subside after antibiotic treatment.⁷⁵ Thus, ABO blood group may be associated with lymphoma initiation and spread by changing the inflammatory state of the host.

Epidemiological and Clinical Data

Several epidemiological studies have assessed the impact of ABO blood group antigens on the risk (Table 1) and prognosis of lymphoma (Table 2). ABO blood group is found to be associated with the susceptibility of lymphoma and could be worked as an independent predictor of prognosis in lymphoma patients.^{76,77} It was observed that individuals with blood type A have a lower risk of lymphoma than those with other blood types.⁷⁶ Besides, lymphoma patients with blood type B have a poorer prognosis, while patients with blood type O have a better prognosis.^{77,78} Currently, racial disparities in incidence and survival exist for patients with lymphoma.^{79,80} Racial differences in ABO blood groups also

Table 1 Studies of the Association Between ABO Blood Group and the Risk Factors of Developing Lymphoma

First Author, Year ^{Ref}	Study Design	Subjects	Main Findings
Levitani, 1959 ⁸³	Retrospective	500 patients with Hodgkin's lymphoma	The incidence of blood group B is higher in HL patients than in controls
Williams, 1966 ⁸⁶	Retrospective	100 patients with Burkitt's lymphoma	No significant association between Burkitt's lymphoma and ABO blood groups
Saichua, 1978 ⁸⁷	Retrospective	80 patients with leukemia and 34 patients with lymphoma	No significant association between ABO blood group and lymphoma ($P > 0.05$)
Janardhana, 1991 ⁸⁸	Retrospective	558 Caucasian patients of European descent with leukemia or lymphoma	No significant association between ABO blood group and lymphoma ($P > 0.05$)
Vadivelu, 2004 ⁷⁶	Retrospective	63 patients with HL, 78 patients with non-Hodgkin's lymphoma, 116 patients with acute myeloid leukemia, 522 patients with acute lymphoblastic leukemia	Blood group B (45.6%) was significantly associated with an increased risk for HL (95% CI: 6.8–84.5), blood group A (56.5%; 52.9%) was significantly associated with a decreased risk for HL and NHL (95% CI: 19.9–85.4; 95% CI: 18.1–82.6)
Gharouni, 2008 ⁸⁴	Retrospective	36 patients with primary central nervous system lymphoma	The percentage of patients with blood group A was lower in the PCNSL group ($n = 3$, 8.3%) than in the control group ($n = 371$, 37.1%)
Abouzari, 2012 ⁸⁵	Retrospective	202 patients with secondary central nervous system lymphoma	The percentage of patients with blood group A was lower in the SCNSL group ($n = 10$, 5%) than in the control group ($n = 371$, 37.1%)
Petrosyan, 2022 ⁸²	Retrospective	798 patients with hematological malignancies including 577 patients with acute lymphoblastic leukemia, 84 patients with acute myeloid leukemia (AML), 81 patients with HL, 40 patients with NHL, and 16 patients with chronic myeloid leukemia	Patients with blood group A were more likely to develop hematological malignancies in comparison with the other blood groups

Table 2 Studies of the Association Between ABO Blood Group and Survival in Patients with Lymphoma

First Author, Year ^{Ref}	Study Design	Subjects	Main Findings
Oberhuber, 1997 ⁹⁰	Retrospective	89 patients with gastric mucosa-associated lymphoid tissue lymphoma and 95 patients with upper gastrointestinal complaints including 5 patients with mucosa-associated lymphoid tissue lymphoma	No significant difference in survival was observed among patients with different ABO blood types ($P = 0.18$)
Li, 2017 ⁷⁷	Retrospective	697 patients with extranodal natural killer (NK)/T-cell lymphoma	The 5-year overall survival rate in patients with blood type O was significantly higher than that in patients with non-O blood type (62% vs. 48.9%, $P = 0.001$)
Osada, 2020 ⁷⁸	Retrospective	523 patients with malignant lymphoma	Blood group B was associated with a lower 5-year overall survival rate compared with non-B blood groups (40.9% vs. 57.3%, $P < 0.01$)
Tizro, 2020 ⁸⁹	Retrospective	37 patients with diffuse large B-cell lymphoma	The average number of days of survival was lower in patients with 3 group B patients compared to 5 non-B group patients (254 days vs. 537 days, $P = 0.03$)
Ulu, 2022 ⁹¹	Retrospective	206 patients with diffuse large B-cell lymphoma	Cox regression analysis revealed no significant association of ABO blood groups with prognosis

exist and are well characterized.⁸¹ An awareness could be raised in the effects of racial differences in ABO blood group on clinical variables seen in lymphoma.

ABO Blood Groups and the Risk of Lymphoma

ABO blood groups have been reported to be associated with the occurrence of lymphoma.^{82,83} An increasing proportion of B blood group and a decreasing proportion of A blood group were observed in HL.^{76,83} Furthermore, studies on central nervous system lymphoma showed a significantly lower risk of both primary central nervous system lymphoma (PCNSL) and secondary CNS lymphoma (SCNSL) in blood group A individuals.^{84,85} However, a number of studies indicated that ABO blood group was not associated with lymphoma susceptibility in both children and adult patients (Table 1).^{86–88}

ABO Blood Groups and the Prognosis of Lymphoma

The prognostic value of ABO blood group in lymphoma were evaluated in a number of studies. A study of 697 patients with extranodal natural killer (NK)/T-cell lymphoma (ENKTL) revealed that ABO blood group was an independent predictor of clinical outcome for patients with ENKTL.⁷⁷ Studies in patients with diffuse large B-cell lymphoma (DLBCL) confirmed the association of ABO blood group with OS in lymphoma patients.^{78,89} Blood group B was also identified as an independent predictor of shorter OS in male DLBCL patients.⁷⁸ However, other studies indicated that ABO blood group was not significantly associated with the prognosis of patients with lymphoma (Table 2).^{90,91}

Association of ABO Blood Group with Racial Disparities and Pathological Classification in Lymphoma Patients

We summarized and analyzed the clinical characteristics among a total of 3118 lymphoma patients reported in 13 studies, of which the vast majority were performed in Caucasians and a few in Asians and Africans (Table 3). Among a total of 1623 Caucasian lymphoma patients, the greatest frequency of A, B, AB and O blood group was reported in Turkey (45.2%), Iran (56.7%), America (6.7%) and Australia (49.9%) respectively (Table 3). The Asian lymphoma patients had the greater reported frequency of both B (27.3%) and AB (8.8%) blood group as compared to Caucasian and African (Table 4). A greatest frequency of O blood group (53%) was observed in African patients and that of A blood group (33.3%) in Caucasian (Table 4). There are significant differences in the distribution of ABO blood groups in lymphoma patients of different races ($P < 0.001$, Table 4).

Table 3 Summary of the Characteristics of Lymphoma Patients in Reported Studies

First Author, Year	Region	Race	Lymphoma Classification	Gender		Age Range (Years)	Cases with Different ABO Blood Types (%)				Total
				Males	Females		O	A	B	AB	
Levitan, 1959 ⁸³	America	Caucasian	HL	ND	ND	ND	224 (44.8)	174 (34.8)	73 (14.6)	29 (5.8)	500
Oberhuber, 1997 ⁹⁰	Austria	Caucasian	Gastric MALT lymphoma ^a	44	50	NA	36 (38.3)	39 (41.5)	13 (13.8)	6 (6.4)	94
Janardhana, 1991 ⁸⁸	Australia	Caucasian	N/A	ND	ND	ND	213 (49.9)	158 (37.0)	40 (9.4)	16 (3.7)	427
Gharouni, 2008 ⁸⁴	Iran	Caucasian	PCNSL ^a	24	12	18~73	20 (55.6)	3 (8.3)	10 (27.8)	3 (8.3)	36
Abouzari, 2012 ⁸⁵	Iran	Caucasian	SCNSL ^a	113	89	16~80	60 (29.7)	10 (5.0)	125 (61.9)	7 (3.5)	202
Tizro, 2020 ⁸⁹	America	Caucasian	DLBCL ^a	37	0	37~93	19 (51.4)	11 (29.7)	6 (16.2)	1 (2.7)	37
Ulu, 2022 ⁹¹	Turkey	Caucasian	DLBCL ^a	105	101	24~93	80 (38.8)	93 (45.2)	20 (9.7)	13 (6.3)	206
Petrosyan, 2022 ⁸²	Armenia	Caucasian	HL and NHL	N/A	N/A	0~18	38 (31.4)	52 (43.0)	17 (14.0)	14 (11.6)	121
Saichua, 1978 ⁸⁷	Thailand	Asian	N/A	15	19	15~80	11 (32.4)	7 (20.6)	11 (32.4)	5 (14.7)	34
Vadivelu, 2004 ⁷⁶	Indian	Asian*	HL and NHL	ND	ND	0~12	62 (44.0)	14 (9.9)	59 (41.8)	6 (4.3)	141
Li, 2017 ⁷⁷	China	Asian	ENKTL ^a	492	205	10~82	255 (36.6)	195 (28.0)	188 (27.0)	59 (8.5)	697
Osada, 2020 ⁷⁸	Japan	Asian	N/A	293	230	18~99	164 (31.4)	183 (35.0)	123 (23.5)	53 (10.1)	523
Williams, 1966 ⁸⁶	Nigerians	African	Burkitt's lymphoma ^a	60	40	5~15	53 (53.0)	23 (23.0)	21 (21.0)	3 (3.0)	100

Notes: ^aThe pathological type of these lymphomas is classified as non-Hodgkin lymphoma. ⁹²The study was carried out in Tamil Nadu, a state in southern India where the majority of the population was Asian.

Abbreviations: ND, not done; N/A, not applicable; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; PCNSL, primary central nervous system lymphoma; SCNSL, secondary primary central nervous system lymphoma; Gastric MALT lymphoma, gastric mucosa-associated lymphoid tissue lymphomas; ENKTL, extranodal natural killer (NK)/T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma.

Table 4 ABO Blood Group Distribution of Lymphoma Patients by Race

Race	Total	Cases with Different ABO Blood Types (%)				P value*	Reports
		O	A	B	AB		
Asian	1395	492 (35.3)	399 (28.6)	381 (27.3)	123 (8.8)	0.000	4 studies ^{76-78,87}
Caucasian	1623	690 (42.5)	540 (33.3)	304 (18.7)	89 (5.5)		8 studies ^{82-85,88-91}
African	100	53 (53.0)	23 (23.0)	21 (21.0)	3 (3.0)		1 study ⁸⁶

Notes: *P value was derived from a comparative analysis of ABO blood group distribution of lymphoma patients in Asian, Caucasian and African.

Previous studies in Asians have demonstrated no significant association between ABO blood group and the incidence of lymphoma.^{77,87} Only one study conducted in Tamils in Indian demonstrated the significant decrease of A blood group in HL and non-HL (Table 3).⁷⁶

A total of 3118 lymphoma patients were studied its association with ABO blood groups. Among them, non-HL accounted for 47.8%, followed by HL (20.7%) and the remaining 31.6% was not reported its classification (Table 3). The non-Hodgkin lymphoma patients had the greater reported frequency of B blood group (28.1%) as compared to Hodgkin lymphoma (17.5%), while the greatest frequency of A (33.7%), AB (6.8%) and O (41.9%) blood groups were observed in Hodgkin lymphoma patients (Table 5). There are significant differences in ABO blood group distribution among

Table 5 ABO Blood Group Distribution of Patients by Different Categories of Lymphoma

Lymphoma Classification	Total	Cases with Different ABO Blood Types (%)				P value*	Reports
		O	A	B	AB		
NHL	1490	577 (38.7)	397 (26.6)	419 (28.1)	97 (6.5)	0.000	8 studies ^{76,77, 84–86,89–91}
HL	644	270 (41.9)	217 (33.7)	113 (17.5)	44 (6.8)		
Classification unreported	984	388 (39.4)	348 (35.4)	174 (17.7)	74 (7.5)		

Notes: *P value was derived from a comparative analysis of ABO blood group distribution in NHL, HL and classification unreported.

Abbreviations: HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma.

patients with different classification of lymphoma ($P < 0.001$, Table 5). Whereas these differences may be difficult to explain currently, we could not eliminate a hypothesis that the ABO blood group could be associated with racial disparity and pathological classification in lymphoma patients.

Conclusions

A number of literatures report an association between ABO blood group and lymphoma risk and prognosis. Several plausible mechanisms have been proposed to support this association, including cell motility, inflammation, immune surveillance, and glycosyltransferase activity. However, the molecular mechanisms underlying these association remain poorly understood. The results evaluating the risk and prognostic value of ABO blood groups in lymphoma varied significantly among studies due to unstageable patients, unidentical treatment and unstandardized study design. Besides, an association of ABO blood group with racial disparities and pathological classification in lymphoma patients may exist, yet little is known about the basis for the differences. To be better understand the role of ABO blood groups in lymphoma and the mechanism of their association, future experimental studies are recommended in larger number of lymphoma patients as well as at molecular level of ABO blood groups. Public health endeavors should focus on refining the clinical data of lymphoma patients on race and ethnicity.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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