

Effect of ABO Blood Group on Survival of Resected Lung Cancer Patients: A Retrospective Study

Abstract

Introduction: A positive correlation between ABO blood group and survival has been suggested in several malignancies. The aim of this study is evaluate the effect of ABO blood group on survival of surgically resected lung cancer patients.

Materials and methods: A total of 139 patients with lung cancer who underwent curative surgery from January 2009 to November 2010 were enrolled in this retrospective study. Besides clinicopathological prognostic factors, we evaluated the prognostic value of ABO blood type on survival. Univariate analysis was performed by Kaplan-Meier survival analysis and multivariate analysis by Cox Regression Hazard model to measure 5-year Overall survival (OS), Progression free survival (PFS), Distant metastasis free survival (DMFS), Relapse free survival(RFS).

Results: The median follow-up period of 139 lung cancer patients was 37 months. The distribution of ABO blood type were 16 AB blood type patients (11.5%), 34 A blood group (24.5%), 42 blood group B (30.2%) and 47 blood group O (33.8%) respectively. Pearson Chi square test showed that ABO blood group was significantly associated with age ($P=0.015$), T stage ($P=0.047$) and histological grades ($P=0.001$), whereas there was no significant association ($P>0.05$) between ABO blood group and gender, smoking, alcohol, lymphnode status, tumor differentiation, tumor size and pathological type. In the Kaplan-Meier analysis ABO blood type was associated with OS, PFS, DMFS and RFS. The mean survival months were 67.9, 52.2, 54.2, 47.3 for blood type AB, A, B and O patients respectively($P=0.024$).The mean survival months were 63.3, 51.3, 47.2, 42.2 for blood type AB, A, B and O patients respectively(0.025).The mean survival months of distant metastasis free survival were 62.5, 59.6, 53.1, 43.6 months for AB, A, B and O blood type patients respectively ($P=0.029$).The mean survival months of relapse free survival were 62.4, 50.6, 60.9, 47.4 months for AB, A, B and O blood type patients respectively ($P=0.034$).Multivariate analysis also revealed that ABO blood type was significantly associated with OS (HR=0.159 with 95%CI=0.046-0.543, $P=0.003$), PFS(HR=0.313 with 95%CI=0.122, $P=0.015$), DMFS (HR=0.301 with 95%CI=0.160-0.568, $P<0.001$) and RFS (HR=0.483 with 95%CI=0.274-0.852, $P=0.012$)

Conclusion: Blood type AB is a favorable prognostic factor for patients with lung cancer than non-AB blood type (blood type A, B or O).

Keywords: Lung cancer; ABO blood group; Prognosis; Survival

Research Article

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Introduction

Lung cancer is the most deadly type of cancer that represents a major public health problem and it still remains the leading cause of cancer related death worldwide [1]. Despite diverse treatment methods including chemotherapy, surgery, radiotherapy and targeted therapies are used, the outcome of all type of lung cancers are disappointing, with 5-year overall survival rates estimating to 17.1% for non-small cell lung cancer(NSCLC) and 6.1% for small cell lung cancer [2]. Clinically it proves that lung cancer can metastasize to specific target organs, such as brain, liver, adrenal glands and bone. Recent findings have revealed that the prognosis of lung cancer patients is not only determined by the characteristics of tumors, but also the patients related factors. Identification of biomarkers that are readily available, inexpensive and reproducible could improve the prognosis of patients and

help physicians in providing individualized therapies.

The chromosome 9q34 consists of the ABO gene which encodes glycosyl Transferase that catalyse the transfer of nucleotide donor carbohydrates to the H antigen and forms the ABO blood group system [3]. ABO blood type antigens are expressed on the surface of red blood cells and other tissue types including cells from the gastrointestinal tract. The correlation between ABO blood group system and cancer has been a subject of interest since the mid 1900s. Laboratory investigations have provided several plausible mechanisms to explain the observed association between ABO blood group system and cancer. These proposed mechanisms involve inflammation, immune surveillance for malignant cells, intercellular adhesion and membrane signaling [4-6].

Recently, the positive association between ABO blood type and survival has been evaluated in several malignancies,

including colon cancer, pancreatic cancer, nasopharyngeal carcinoma, esophageal cancer, breast cancer, skin cancer, renal cell carcinoma and gastric cancer [7-14]. Although the study by Lee et al. established the survival of NSCLC patients who received curative surgery within the context of ABO blood group, the aim of their study was to investigate the prognostic role of expression of blood group antigen A in tumor cells [15]. However, to date, the controversy still remains over the clinical value of ABO blood group to predict the prognosis of NSCLC [16]. Therefore, the aim of this retrospective study was to clarify the correlation between ABO blood group system and survival analysis among all type of lung cancer patients who underwent curative surgery as their primary treatment.

Materials and Methods

Patients selection and data collection

This retrospective clinical study included 440 consecutive all type of lung cancer patients who underwent curative surgery (lobectomy, pneumonectomy) at Qilu Hospital of Shandong University from January 2009 to November 2010. Patients were eligible for the study if they met the following criteria: (1) Resected lung cancer with lobectomy or pneumonectomy and lymphnode dissection, (2) negative surgical margin (R0) and (3) No preoperative radiotherapy or chemotherapy. The main exclusion criteria were perioperative death and previous malignancies. The patients criteria which was not favorable with inclusion criteria that excluded from study group. Furthermore, patients without available data, death date and follow up were excluded. Hence after the rigorous exclusion process, a total of 139 patients were enrolled in our study. The protocol of the study was approved by the Institutional Ethics Committee of the Qilu Hospital of Shandong University. The extent of the disease was determined by TNM staging according to the new IASLC staging system [17]. Informed consent was obtained from all individual participants in the study. Data were collected from medical records in hospital database. Clinicopathological factors were used to assess the risk of death. Factors examined included age, gender, smoking habit, alcohol intake, tumor size, pT stage, lymphnode status, tumor differentiation, pathological type and ABO blood group.

Treatment and follow up

All patients underwent curative surgery, Lobectomy or pneumonectomy was performed according to the location or size of the lung neoplasm. Patients who had undergone exploratory thoracotomy without resection were excluded from our study. Systematic mediastinum lymph node dissection was performed in all patients. All patients received standardized follow-up at a 3-month interval for the first 2 years after operation, a 6-month interval in the third year and yearly thereafter. Evaluation comprised a physical examination, complete blood count, chest computed tomography, brain magnetic resonance imaging and abdominal ultrasound.

The following endpoints were estimated: Relapse-free survival (RFS), was defined as the duration from the date of surgery to the date when any relapse was diagnosed. Distant metastasis-free survival (DMFS) covered the date of definitive surgery to the confirmation date of diagnosis of distant metastasis. Relapse-

free survival (RFS) was defined as the time from surgery to any recurrence. Overall survival (OS) was calculated as the time from the date of surgery to death or date of last follow up.

Statistical analysis

The chi-square test was performed to evaluate the association between the clinicopathological variables and ABO blood group. All endpoints were estimated by the Kaplan-Meier survival analysis and compared by using Log-rank test. Multivariate analyses were carried out by using Cox Proportional Hazards model to identify important prognostic factors for OS, PFS, DMFS, RFS). P-values were two sided and statistical significance was accepted for P-values of <0.05. All statistical analyses were carried out using SPSS for Windows, Version 22 (SPSS Inc., Chicago, IL, United States).

Results

Patient characteristics

A total of 139 lung cancer patients were enrolled in our study. The baseline characteristics of the study population are listed in Table 1. The median age of the 139 patients enrolled into the study was 60 years (age range: 36-85 years). The distribution of ABO blood type was 16 AB blood type patients (11.5%), 34 A blood group (24.5%), 42 blood group B (30.2%), 47 blood group O (33.8%) respectively. According to the IASLC classification criteria for lung tumors, 52 (37.4%) of the tumors were squamous cell carcinoma, 56 (40.3%) adenocarcinoma, 9 (6.5%) small cell carcinoma, 9 (6.5%) bronchoalveolar carcinoma and 13 (9.4%) consisted of other types. There were 17 (12.2%) well differentiated, 73 (52.5%) moderately differentiated and 47 (33.8%) poorly differentiated. A total of 67 patients (48.2%) had experience of smoking and 51 (36.7%) of ingesting alcohol. According to the new IASLC staging system, 43 of the cases (30.9%) were stage T1, 51 (36.7%) stage T2, 42 (30.2%) stage T3, 3 (2.2%) stage T4. Pearson Chi square test showed that ABO blood group was significantly associated with age ($P=0.015$), T stage ($P=0.047$) and histological grade ($P=0.001$), whereas there was no significant association ($P>0.05$) between ABO blood group and gender, smoking, alcohol, lymphnode status, tumor differentiation, tumor size and pathological type.

Effect of ABO blood group on survival

The median follow-up period of 139 lung cancer patients was 37 months with consequently 43 patients being alive and 96 succumbing to cancer related death until the last follow-up. In the Kaplan-Meier analysis ABO blood type were associated with OS, PFS, DMFS, RFS (table 2). The 5-year overall survival rate were 81.3%, 32.4%, 23.8%, 19.1% and mean survival months were 67.9, 52.2, 54.2, 47.3 for blood type AB, A, B and O patients respectively ($P=0.024$, figure 1A). The 5-year progression free survival rate were 62.5%, 52.9%, 38.1%, 19.1% and mean survival months were 63.3, 51.3, 47.2, 42.2 for blood type AB, A, B, O patients respectively ($P=0.025$, figure 1B). The mean survival months of distant metastasis free survival were 62.5, 59.6, 53.1, 43.6 months for AB, A, B, O blood type patients respectively ($P=0.029$, figure 1C). The mean survival months of relapse free survival were 62.4, 50.6, 60.9, 47.4 months for AB, A, B, O blood type patients respectively ($P=0.034$, figure 1D).

Lymphnode status was also significantly associated with OS, PFS, DMFS and RFS and P value was <0.001 in all kind of survival analysis (figure 2). But tumor size was only significantly associated with OS (P=0.031). To determine whether ABO blood type could serve as an independent prognostic parameter, we examined OS, PFS, DMFS, RFS using the Cox proportional hazards model (table 3). All the parameters found to be significant in the univariate analysis were further analysed by multivariate analysis and the results revealed that ABO blood type was significantly associated with OS (HR=0.159 with 95%CI=0.046-0.543, P=0.003), PFS (HR=0.313 with 95%CI=0.122, P=0.015), DMFS (HR=0.301 with 95%CI=0.160-0.568, P<0.001) and RFS (HR=0.483 with 95%CI=0.274-0.852, P=0.012). We also observed that tumor size was only significantly associated with OS (HR=0.626 with 95%CI=0.404-0.970, P=0.036) whereas the lymphnode status was also significantly associated with OS (HR=0.395 with 95%CI=0.252-0.617, P<0.001), PFS (HR=0.388 with 95%CI=0.244-0.617, P<0.001), DMFS (HR=0.464 with 95%CI=0.303-0.711, P<0.001) and RFS (HR=0.377 with 95%CI=0.242-0.586, P<0.001).

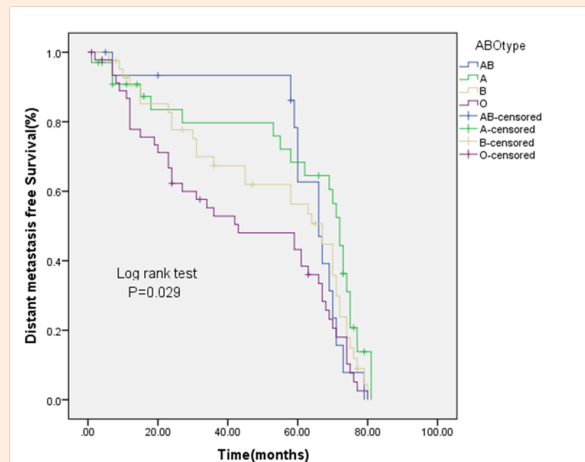


Figure 1C: Distant metastasis free survival of lung cancer patients according to ABO blood type.

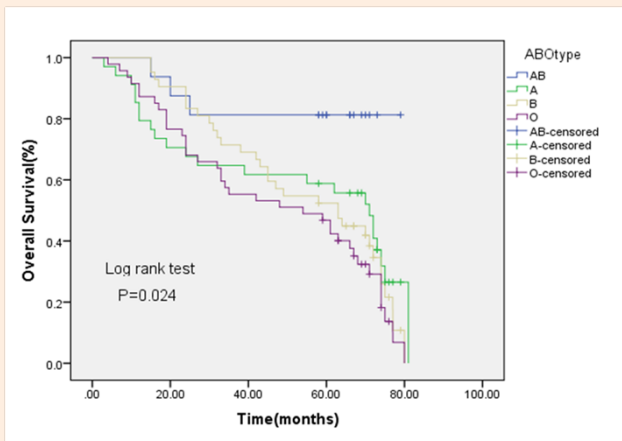


Figure 1A: Overall survival of lung cancer patients according to ABO blood type.

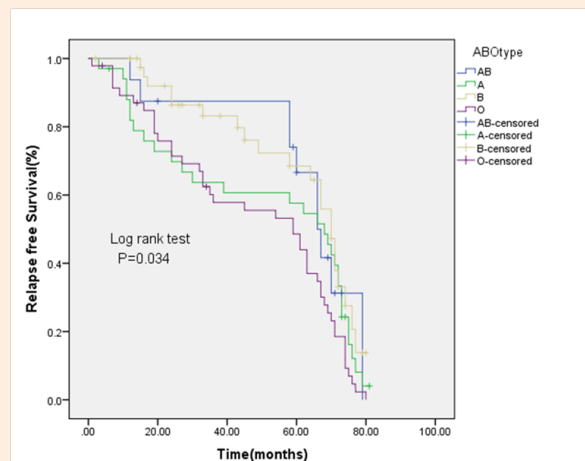


Figure 1D: Relapse free survival of lung cancer patients according to ABO blood type.

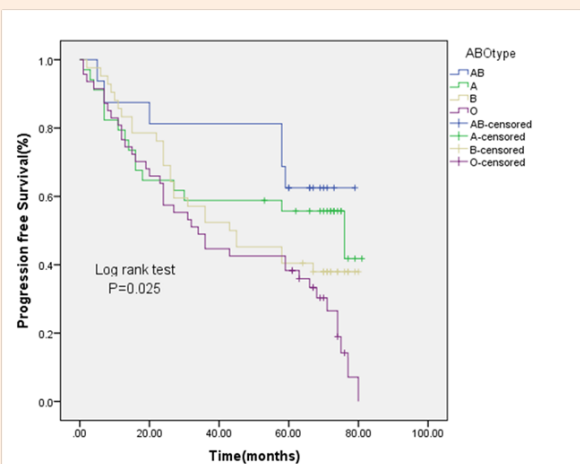


Figure 1B: Progression free survival of lung cancer patients according to ABO blood type.

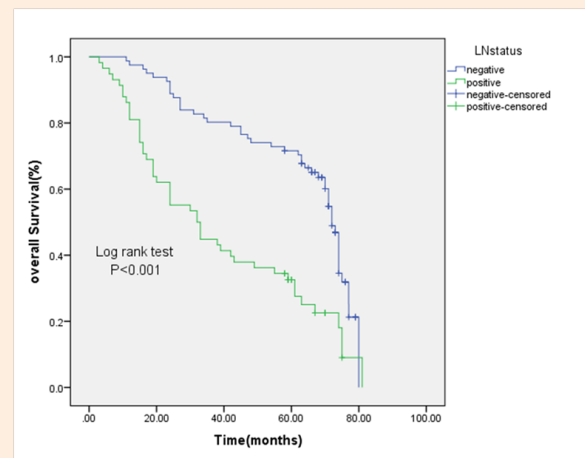


Figure 2A: Overall survival of lung cancer patients with lymph nodes status.

Table 1: Baseline characteristics of 139 lung cancer patients according to ABO blood type.

Characteristics	All patients	Patients ABO blood type				P
		AB (%)	A (%)	B (%)	O (%)	
	n=139	n=16(11.5%)	n=34(24.5%)	n=42(30.2%)	n=47(33.8%)	
Age						
≤60 Years	69	8(11.6%)	9(13.0%)	26(37.7%)	26(37.7%)	0.015*
>60 Years	70	8(11.4%)	25(35.7%)	16(22.9%)	21(30.0%)	
Gender						
Male	95	13(13.7%)	25(26.3%)	27(28.4%)	30(31.6%)	0.491
Female	44	3(6.8%)	9(20.5%)	15(34.1%)	17(38.6%)	
Smoking						
No	72	8(11.1%)	15(20.8%)	22(30.6%)	27(37.7%)	0.698
Yes	67	8(11.9%)	19(28.4%)	20(29.9%)	20(29.9%)	
Alcohol						
No	88	9(10.2%)	23(26.1%)	27(30.7%)	29(33.0%)	0.876
Yes	51	7(13.7%)	11(21.6%)	15(29.4%)	18(35.3%)	
Tumor Size						
≤3cm	50	8(16.0%)	11(22.0%)	16(32.0%)	15(30.0%)	0.577
>3cm	89	8(9.0%)	23(25.8%)	26(29.2%)	32(30.0%)	
pT stage						
T1	43	8(18.6%)	11(25.6%)	15(34.9%)	9(20.9%)	0.047*
T2	51	7(13.7%)	9(17.6%)	17(33.3%)	18(35.3%)	
T3	42	1(2.4%)	14(33.3%)	10(23.8%)	17(40.5%)	
T4	3	0(0.0%)	0(0.0%)	0(0.0%)	3(100%)	
Lymphnode Status						
Negative	81	10(12.3%)	22(27.2%)	25(30.9%)	24(29.6%)	0.631
Positive	58	6(10.3%)	12(20.7%)	17(29.3%)	23(39.7%)	
Histological Grade						
Grade 1	63	5(7.9%)	17(27.0%)	9(14.3%)	32(50.8%)	0.001*
Grade 2	54	8(14.8%)	8(14.8%)	25(46.3%)	13(24.1%)	
Grade 3	18	3(16.7%)	7(38.9%)	6(33.3%)	2(11.1%)	
Grade 4	4	0(0.0%)	2(50.0%)	2(50.0%)	0(0.0%)	
Differentiation						
Poorly	49	7(14.3%)	15(30.6%)	14(28.6%)	13(26.5%)	0.673
Moderately	73	7(9.6%)	16(21.9%)	24(32.9%)	26(35.6%)	
Well	17	2(11.8%)	3(17.6%)	4(23.5%)	8(47.1%)	
Pathological Type						
Squamous Cell ca	52	8(15.4%)	13(25.0%)	13(25.0%)	18(34.6%)	0.128
Adenocarcinoma	56	6(10.7%)	11(19.6%)	18(32.1%)	21(37.5%)	
Small Cell Carcinoma	9	2(22.2%)	2(22.2%)	5(55.6%)	0(0.0%)	
Bronchoalveolar Ca	9	0(0.0%)	1(11.1%)	3(33.3%)	5(55.6%)	
Other	13	0(0.0%)	7(53.8%)	3(23.1%)	3(23.1%)	

T: tumor

Table 2: Univariate analysis of association between prognosis and ABO blood type and other clinicopathological factors in patients with lung cancer.

Variables	Overall Survival(OS)			Progression Free Survival			Distant Metastasis Free Survival(DMFS)			Relapse Free Survival(RFS)		
	5-Year	Mean Survival	P	5 - Year PFS	Mean Survival	P	5-Year DMFS	Mean Survival	P	5-year RFS	Mean Survival	P
	(OS)(%)	(months)		(%)	(months)		(%)	(months)		(%)	(months)	
Age(Years)												
≤60	31.9	54.9	0.578	42	48.7	0.479	11.6	51.3	0.555	30.4	57.6	0.142
>60	30.00%	50.5		34.3	47		27.1	53.3		18.6	50.2	
Gender												
Male	31.6	51	0.591	35.8	45.4	0.205	18.9	49.6	0.303	27.4	52.3	0.743
Female	29.5	56.3		43.2	53.5		20.5	57.9		18.2	57	
Smoking												
No	26.4	50.2	0.116	36.1	45	0.295	25	52.1	0.767	23.6	49.9	0.13
Yes	35.8	55.2		40.3	50.9		13.4	52.4		25.4	58	
Alcohol												
No	29.5	50.2	0.371	38.6	46.2	0.646	25	51.3	0.658	27.3	51.8	0.589
Yes	33.3	56.9		37.3	51		9.8	54		19.6	57.1	
Tumor Size												
≤3cm	40	59.6	0.031*	40	51.8	0.403	12	54.6	0.493	24	58.6	0.079
>3cm	25.8	48.7		37.1	45.9		23.6	50.9		24.7	51	
pT stage												
T1	30.2	51.4	0.366	30.2	44	0.11	25.6	53.9	0.613	32.6	51.7	0.664
T2	33.3	57.9		47.1	56.2		13.7	57		21.6	58.8	
T3	26.2	46.7		33.3	40.2		19	44.3		21.4	49.6	
T4	66.7	57		66.7	54.7		33.3	54.7		0	52.6	
Lymphnode Status												
Negative	39.5	62.2	<0.001*	51.9	58	<0.001*	17.3	59.2	<0.001*	27.2	62.7	<0.001*
Positive	19	39.2		19	33.7		22.4	41.1		20.7	40.7	
Histological Grade												
Grade1	30.2	50.2	0.946	31.7	44.1	0.417	22.2	50.3	0.946	19	50.6	0.827
Grade2	29.6	54.9		40.7	51.4		16.7	54.2		29.6	56.3	
Grade3	33.3	52.1		44.4	46.2		22.2	51.2		33.3	55.7	
Grade4	50	60.8		75	61.5		0	60.2		0	60.2	
Differentiation												
Poorly	28.6	46.9	0.385	38.8	43.1	0.737	30.6	50.1	0.981	20.4	48.4	0.323
Moderately	30.1	54.7		37	48.7		15.1	52.7		28.8	56.2	
Well	41.2	60.2		41.2	56.2		5.9	55.4		17.6	59.3	
Pathological Type												
Squamous Cell Ca	28.8	53	0.982	42.3	49.5	0.781	21.2	54.5	0.738	26.9	54.9	0.417
Adenocarcinoma	32.1	52.2		32.1	45.4		16.1	49.2		25	53.2	
Small Cell Carcinoma	44.4	53.3		55.6	50.3		33.3	62.6		33.3	54.2	
Bronchoalveolar Ca	11.1	61.8		33.3	54.3		11.1	58.6		22.2	62.4	

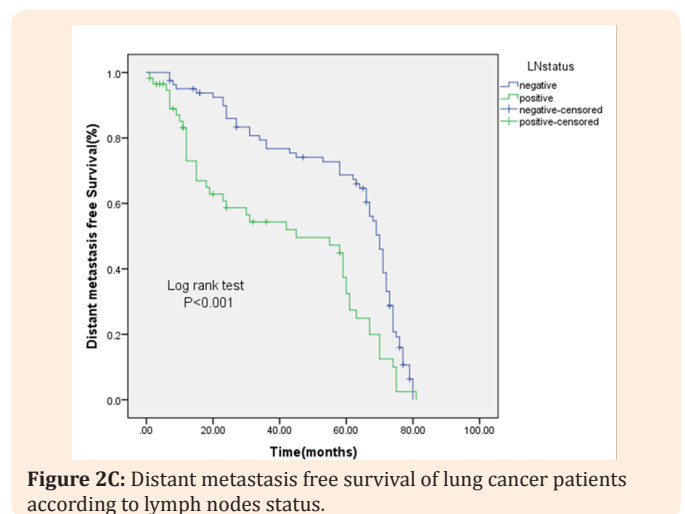
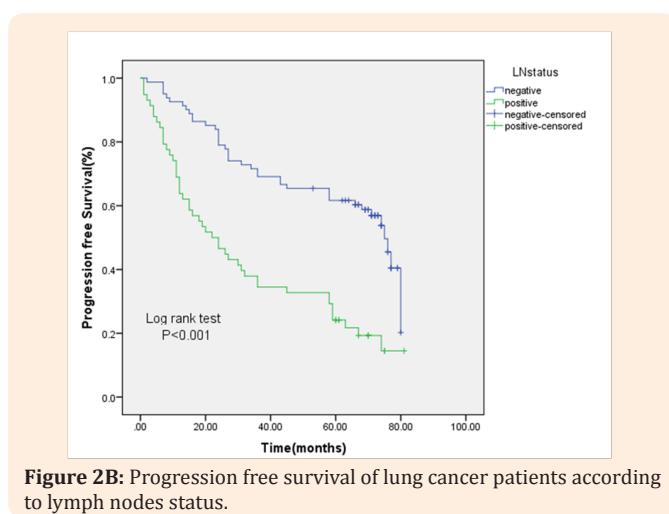
Other	38.5	46		38.5	43.1		23.1	45.1		7.7	45.1	
ABO Blood Type												
AB	81.3	67.9	0.024*	62.5	62.3	0.025*	18.8	62.5	0.029*	37.5	62.4	0.034*
A	32.4	52.2		52.9	51.3		35.3	59.6		11.8	50.6	
B	23.8	54.2		38.1	47.2		16.7	53.1		50	60.9	
O	19.1	47.3		19.1	41.2		10.6	43.6		6.4	47.4	

*And bold numbers are statistically significant
T: Tumor; Ca: Carcinoma

Table 3: Multivariate analysis for OS, PFS, DMFS, RFS of lung cancer patients.

Variables	Overall Survival(OS)			Progression Free Survival(PFS)			Distant Metastasis Free Survival(DMFS)			Relapse Free Survival(RFS)		
	HR	95%CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Tumor Size (≤3cm Vs >3cm)	0.626	0.404-0.970	0.036*	0.828	0.530-1.294	0.408	0.878	0.598-1.290	0.507	0.71	0.475-1.056	0.09
Histological Grade Grade1 and 2 Vs Grade 3 and 4	1.477	0.323-6.752	0.615	2.819	0.358-22.175	0.325	0.748	0.242-2.312	0.614	1.13	0.356-3.579	0.836
Differentiation Poorly Vs Well and Moderately	1.886	0.772-4.603	0.164	1.92	0.790-4.668	0.15	1.224	0.548-2.736	0.623	1.14	0.601-2.969	0.477
pT stage T1T2 Vs T3T4	3.358	0.431-26.138	0.247	4.408	0.563-34.519	0.158	2.086	0.456-9.536	0.343	1.53	0.412-1.663	0.526
Lymphnode status Negative Vs positive	0.395	0.252-0.617	<0.001*	0.388	0.244-0.617	<0.001*	0.464	0.303-0.711	<0.001*	0.38	0.242-0.586	<0.001*
ABO blood type	0.159	0.046-0.543	0.003*	0.313	0.122-0.801	0.015*	0.301	0.160-0.568	<0.001*	0.48	0.274-0.852	0.012*

*and bold numbers means statistically significant
HR: Hazard Ratio; CI: Confidence Interval; T: Tumor



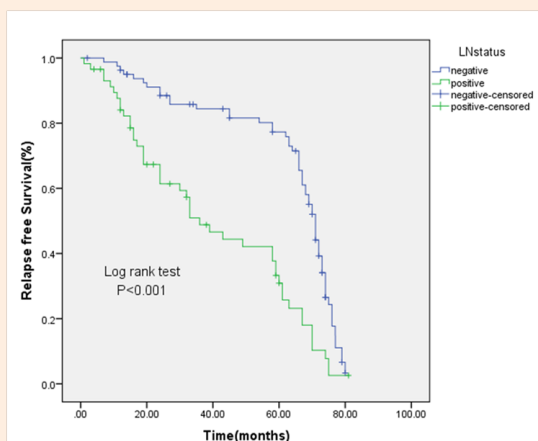


Figure 2D: Relapse free survival of lung cancer patients according to lymph nodes status.

Discussion

In recent years, several studies have suggested that importance of ABO blood group system in the development of hemostasis and neoplastic disease, because of ABO antigens are highly expressed on the surface of a variety of human cells and tissues [18]. However, to date, association between ABO blood type and lung cancer survival have not been well developed. Based on its unique aetiology, patients characteristics, ABO blood typing and long follow-up time, the current study is first to evaluate the effect of survival of ABO blood type among patients with resected lung cancer. Among the 139 lung cancer cases examined in this retrospective study from Qilu hospital of Shandong university, we observed significantly better survival for participants with blood group AB than non-AB blood group patients (blood groups A, B and O). The worst survival was observed for participants with blood type O and intermediate survival was observed for those with blood types A and B using multivariate analysis, significant associations with lung cancer survival were found for tumor size, positive regional lymphnodes and ABO blood group.

Although some earlier studies have reported associations between malignancies and ABO blood group system, the results have been inconsistent. Constantini et al. & Holdsworth et al. [19,20] have reported poor survival among breast cancer participants with blood type AB or B or any non-O blood type. In contrast, Gates et al. [21] indicated that ABO blood group was not associated with survival of breast cancer patients [21]. According to Nozoe et al. [22], a growing body of plausible mechanisms, including inflammation, immune-surveillance for malignant cells, intracellular adhesion and membrane signalling have been proposed to explain the relationships between ABO blood group and tumor metastasis and prognosis [22].

The ABO blood type is defined by the carbohydrate moieties displayed on the surface of red blood cells and attached to membrane proteins and lipids. Three variant alleles (A, B and O) of a single gene on chromosomes 9q34, the ABO gene determine a person's blood type by encoding three glycosyl transferases with different substrate specificities. Apart from their expression on the surface of red blood cells, the ABO blood antigens are highly expressed on the surface of many epithelial

cells, including gastrointestinal, bronchopulmonary, urogenital and skin cells [23,24]. Alterations of ABO antigen expression on the surface of cancerous cells, compared with normal epithelium, has been demonstrated for a variety of tumor types [23,25]. Glycosyltransferase specificity has broad implications, beyond explaining ABO blood type. Glycoconjugates are important mediators of intercellular adhesion and membrane signalling, two processes that are integral to malignant progression and spread of cancers [23]. These surface molecules are also recognized by host immune response and may have a role in facilitating immune-surveillance for malignant cells [26].

Alteration of host inflammatory state due to ABO blood group antigens may provide a further mechanism to explain the association between ABO blood group system and lung cancer progression. In recent decades, several studies have demonstrated a link between chronic inflammation and malignant initiation. A study has revealed that an inflammatory cytokine known to modulate cell apoptosis and inhibit tumourigenesis which has two single-nucleotide polymorphisms at the ABO locus was associated with serum levels of tumor necrosis factor-alpha [27,28]. Pare et al. [29,30] established that there is a statistically significant relationship between single-nucleotide polymorphisms at the ABO locus and plasma levels of intercellular adhesion molecule 1, a molecule which has classically been associated with functioning inflammatory response [29,30]. Barbalic et al. & Qi et al. [31,32] have studied this finding for other serum markers of inflammation, such as E-selectin and P-selectin [31,32]. These results reveals the possibility that chronic inflammation is significantly linked with tumor initiation and metastasis and also suggest an additional potential mechanism by which ABO blood group may influence lung cancer patients survival.

This retrospective study has several limitations that should be noted. Firstly, our study population was limited, secondly it was an open-level study and East Asians constitute most of our study population, which somewhat limits the generalizability of our results. Accordingly, the results of further investigations including more diverse populations from other institutes are needed to confirm our findings. Future well designed studies that include diverse ethnic populations are warranted to further analyze the prognostic role of ABO blood group system in Lung cancer patients. Additionally, other potential clinicopathological factors should be considered.

Conclusion

Our results suggested that the ABO blood types were significantly associated with lung cancer patients survival. In contrast to patients of AB blood type with non-AB (blood type A, B, O), patients with blood type AB were more likely to have a better OS, PFS, DMFS and RFS. The impact of ABO blood type on malignant potential and prognosis in patients with lung cancer remains an interesting area of research, which warrants additional investigations.

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