

Research Paper

Prognostic Impact of ABO Blood Group on the Survival in Patients with Ovarian Cancer

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Abstract

Purpose: The impact of ABO blood group on the survival of patients with ovarian cancer remains uncertain. The aim of this study was to evaluate the prognostic value of the ABO blood group in ovarian cancer patients.

Methods: 256 ovarian cancer patients who received a cytoreductive surgery were retrospectively reviewed. The prognostic impact of the ABO blood group with respect to overall survival (OS) was analyzed.

Results: The median follow-up time was 57 months and the 5-year OS was 70.1%. The 5-year OS were 55.0%, 83.3%, 82.5%, and 70.0% in patients with A, B, AB, and O blood type, respectively ($p = 0.003$). Patients with blood type A had a poorer 5-year OS than patients with blood type non-A (55.0% vs. 75.0%, $p = 0.001$), especially in patients with age > 50 years (40.0% vs. 62.5%, $p = 0.004$). Univariate Cox analyses showed that blood type A was significantly associated with OS than those with non-A types (hazard ratio (HR) 2.210, 95% confidence interval (CI) 1.373-3.557, $p = 0.001$). Blood type A remained an independent prognostic factor for OS than those with non-A blood types in multivariate analyses (HR 2.235, 95% CI 1.360-3.674, $p = 0.002$).

Conclusion: ABO blood group is associated with survival in patients with ovarian cancer, patients with blood type A had a significantly worse OS than patients with non-A blood types, especially in patients with age > 50 years.

Key words: Ovarian cancer, ABO blood group, prognosis, cytoreductive surgery, overall survival

Introduction

Ovarian cancer is a highly fatal gynecologic cancer and the fifth leading cause of cancer mortality in women, with 14,030 deaths occurring in the United States per year (1). In China, ovarian cancer is the tenth cancer incidence rate of 7.95 per 100,000 women during 2009 (2). Most cases of ovarian cancer are di-

agnosed at an advanced stage and quickly progress, resulting in a poor outcome.

At present, prognostic factors for ovarian cancer reflect the intrinsic biology of a tumor (e.g. histological subtype, grade of differentiation), cancer stage, residual disease and the performance status (3-5).

Although prognostic factors for ovarian cancer have conducted intensive studies, including in the field of molecular biology, but for the prognosis of ovarian cancer can be different despite similar stages and grades. A better understanding of an ideal biomarker with readily available, inexpensive and reproducible of ovarian cancer could improve the prognosis of patients and provide therapies that are more appropriate.

Recently, the associations between ABO blood group and survival have been evaluated in several malignancy, including pancreatic cancer (6), esophageal squamous cell carcinoma (7), colon cancer (8), nasopharyngeal carcinoma (9), and breast cancer (10). Previous studies suggested that blood type A was associated with an increased risk of ovarian cancer (11,12), while another study presence of the B antigen was positively associated with ovarian cancer incidence (13). However, to date, studies of the impact of ABO blood group on the survival of patients with ovarian cancer remained uncertain. Therefore, the aim of the retrospective analysis was to analyze the relationship between ABO blood type and the survival of patients with ovarian cancer underwent cytoreductive surgery as their primary treatment in Chinese population.

Materials and methods

Patients

Two hundred fifty-six patients with primary ovarian cancer who underwent cytoreductive surgery at the Sun Yat-Sen University Cancer Center between December 2004 and March 2012 were retrospectively analyzed. Cytoreductive surgery was considered to have achieved optimal debulking when the residual disease was < 1 cm. Patients with synchronous or metachronous tumors, borderline tumors and advanced stage (stage IV) ovarian cancer were excluded. Other patients with missing data were also excluded. Patients who with indications for chemotherapy did not complete at least four cycles of chemotherapy were excluded. Patients were considered eligible only when the following data were available. The study was approved by the ethics committee of Sun Yat-Sen University Cancer Center. All patients provided written consent for storage of their information in the hospital database, and for the research use of the information.

Clinicopathological factors

Clinicopathological factors were used to assess the risk of death. Factors examined included age, histological type, histological type grade, lymph node status, FIGO stage, CA125 at diagnosis, and ABO blood group.

Follow-up and survival endpoints

Follow up was performed every 3-6 months. The follow-up visits consisted of a physical examination and laboratory studies at least every 6 months or when clinically indicated. The endpoint of the study was overall survival (OS). OS was calculated as the period from the date of diagnosis to the date of death from any cause or the date of last follow-up.

Statistical analysis

The χ^2 and Fisher's exact tests were used to analyze the differences between qualitative data. Calculation of survival rates were plotted by the Kaplan-Meier method, and compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed. Multivariable analyses were performed for factors which were significantly associated with OS in univariate analyses. All data were analyzed the SPSS statistical software package, version 16.0 (IBM Corporation, Armonk, NY, USA). A value of p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 256 eligible patients with ovarian cancer were identified at our institution during the study period from December 2004 to March 2012. The median age of the patients was 50 years (range, 19-76 years). The distribution of the ABO blood type was 60 blood type A patients (23.4%), 52 blood type B patients (20.3%), 120 blood type O patients (46.9%), and 24 blood type AB patients (9.4%). Table 1 summarizes the characteristics of the study population. χ^2 test showed that ABO blood type positively correlated with age ($p < 0.001$) and CA-125 at diagnosis ($p = 0.046$).

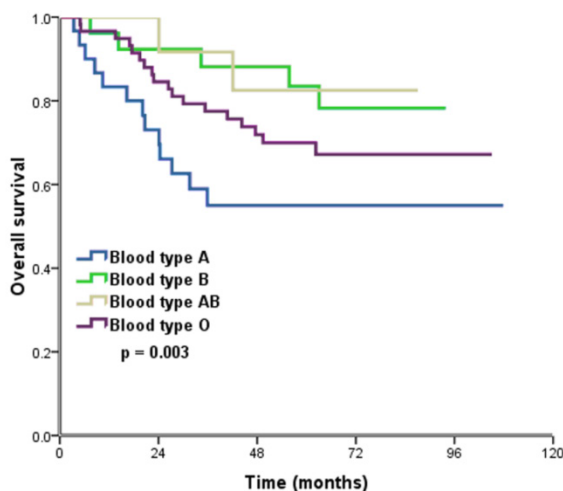
Effect of ABO blood group on survival

The median follow-up time was 57 months (range, 8.2-107.9 months) at the last clinical follow-up. A total of 76 patients died, 73 of whom died of ovarian cancer-related diseases, 3 died of other diseases. The 5-year OS for all patients was 70.1%. In the Kaplan-Meier analysis, ABO blood type was associated with OS, the 5-year OS were 55.0%, 83.3%, 82.5%, and 70.0% in patients with A, B, AB, and O blood type, respectively ($p = 0.003$) (Figure 1). Furthermore, we compared the prognostic impact of the ABO groups with type A and non-A types, patients with non-A types had a better 5-year OS than patients with blood type A (75.0% vs. 55.0%, $p = 0.001$) (Figure 2).

We examined the prognostic effect of the ABO blood type according to different age group and dif-

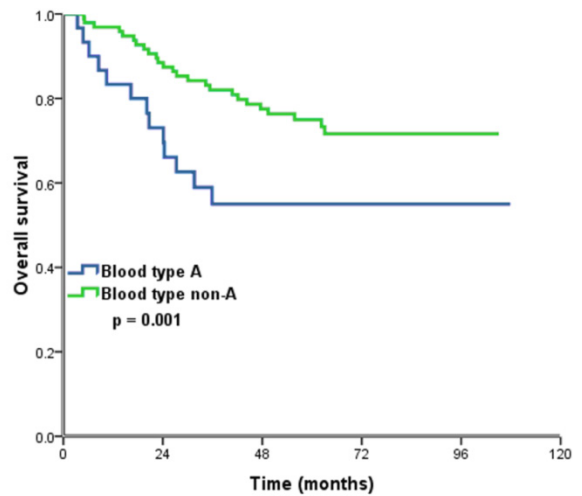
ferent FIGO stage. Significant differences in 5-year OS between the type A and non-A types ovarian cancers were observed in patients with age > 50 years (40.0% vs. 62.5%, $p = 0.004$) (Figure 3A). However, for age ≤ 50 years patients, ABO groups showed no association with OS ($p = 0.611$) (Figure 3B). In patients with FIGO stage II, type A tumors had worse OS than those with non-A types (5-year OS 37.5% vs. 87.3%, $p < 0.001$) (Figure 4B), but there was no significant difference from the OS of FIGO stage I ($p = 0.118$) (Figure 4A) and III ($p = 0.537$) (Figure 4C) according to different blood group.

To determine whether ABO blood type could serve as an independent prognostic factor, we examined OS using the Cox proportional hazards model. Compared with patients with blood type A, the hazard ratios (HR) for OS in univariate analysis among patients with blood type B, AB, and O were 0.318 (95% confidence interval [CI] 1.153-0.662, $p = 0.002$), 0.280 (95% CI 0.098-0.802, $p = 0.018$), and 0.555 (95% CI 0.335-0.920, $p = 0.220$), respectively. However, no significant differences in OS were observed for patients with blood type O or AB in univariate analysis when compared with patients with blood type B. We next examined the effect of ABO blood group in terms of type A and non-A types. Blood type A was significantly associated with OS than those with non-A types (HR 2.210, 95%CI 1.373-3.557, $p = 0.001$) in univariate analysis. In addition, the higher risks of death for patients with type A vs. non-A types remained significant in multivariate analyses (HR 2.235, 95% CI 1.360-3.674, $p = 0.002$). Other significant prognostic factors included age, histological grade, and FIGO stage.



Number at risk					
	0	24	48	72	96
Type A	60	42	22	8	4
Type B	52	46	42	18	
Type AB	24	24	18	4	
Type O	120	98	76	16	6

Figure 1. Overall survival for patients with ovarian cancer according to different ABO blood types.



Number at risk					
	0	24	48	72	96
Type A	60	42	22	8	4
Type non-A	196	168	136	38	6

Figure 2. Overall survival for patients with ovarian cancer with blood type A and non-A blood types.

Table 1. Correlation between ABO blood group and clinicopathological characteristics

Characteristic	A (n = 60)	B (n = 52)	O (n = 120)	AB (n = 24)	p-value
Age (y)					
≤ 50	18	30	68	18	< 0.001
> 50	42	22	52	6	
Histology					
Serous	52	42	98	16	0.210
Non-serous	8	10	22	8	
Grading					
Well	8	10	8	2	0.160
Moderate	34	22	58	12	
High	18	20	54	10	
Lymph node stats					
Negative	44	30	78	20	0.101
Positive	16	22	42	4	
FIGO stage					
I	18	18	36	10	0.385
II	16	16	26	8	
III	26	18	58	6	
CA-125 at diagnosis (U/ml)					
≤100	24	16	34	4	0.046
>100-300	12	6	20	4	
>300-600	2	8	16	8	
> 600	22	22	50	8	

Table 2. Univariate and multivariate Cox regression analyses in patients with ovarian cancer

Characteristic	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (y)						
≤50	1			1		
> 50	3.228	1.964-5.303	< 0.001	3.047	1.831-5.069	< 0.001
Histology						
Serous	1			1		
Non-serous	0.201	0.073-0.550	0.002	0.470	0.155-1.425	0.182
Grading						
Well	1			1		
Moderate	3.667	0.873-15.395	0.076	3.199	0.754-13.578	0.115
High	7.637	1.854-31.468	0.005	6.971	1.670-29.108	0.008
Lymph node stats						
Negative	1			1		
Positive	2.758	1.755-4.333	< 0.001	1.504	0.853-2.651	0.158
FIGO stage						
I	1			1		
II	2.210	1.003-4.871	0.049	3.625	1.625-8.087	0.002
III	4.627	2.343-9.138	< 0.001	4.255	2.145-8.440	< 0.001
CA-125 at diagnosis (U/ml)						
≤100	1			1		
>100-300	2.097	1.068-4.116	0.031	2.020	0.554-2.073	0.064
>300-600	0.492	0.166-1.455	0.200	0.567	1.244-3.785	0.342
> 600	1.666	0.950-2.920	0.075	1.072	1.831-5.068	0.836
Blood type						
Non-A	1			1		
A	2.210	1.373-3.557	0.001	2.235	1.360-3.674	0.002

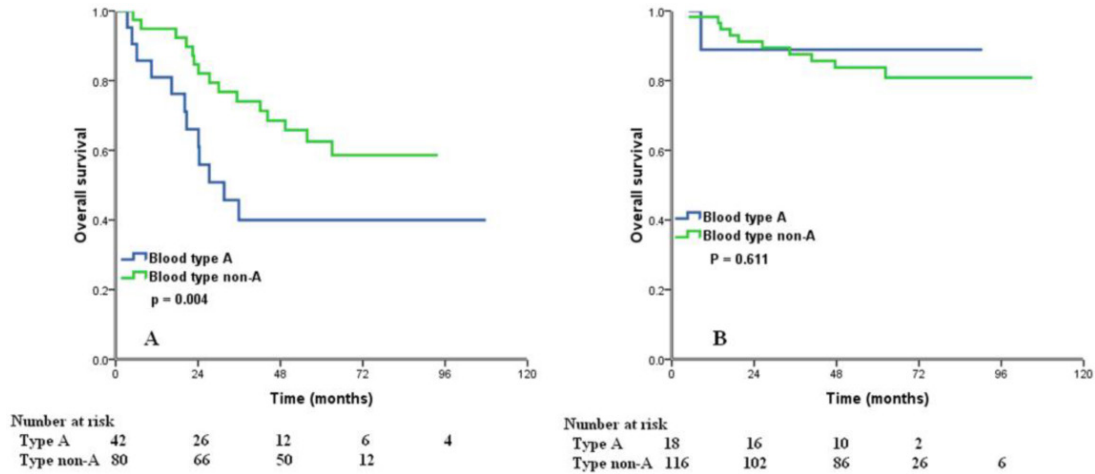


Figure 3. Overall survival for patients with ovarian cancer with blood type A and non-A blood types in patients with age > 50 years (A) and age ≤ 50 years (B).

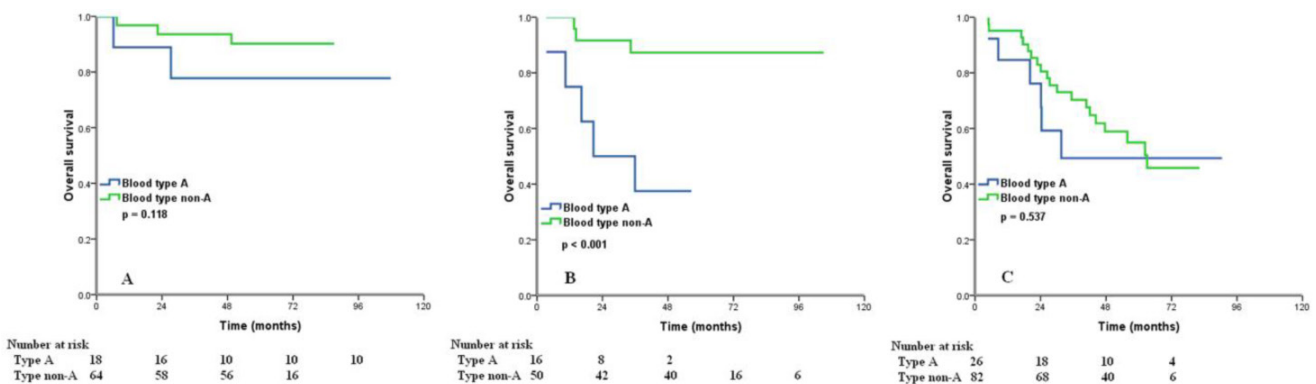


Figure 4. Overall survival for patients with ovarian cancer with blood type A and non-A blood types in patients with FIGO stage I (A), II (B), and III (C).

Discussion

The present study assessed the cytoreductive surgery results from Chinese patients with ovarian cancer to determine the prognostic value of different ABO blood group. Our results showed that patients with A blood group predicted a poorer OS than that patients with non-A blood group.

The role of inherited blood group antigens in cancer risk and progression has been intensely studied across many different types of solid organ and hematologic malignancies (13-16). At present, the impacts of ABO blood group on the survival of patients with ovarian cancer are limited. To the best of our knowledge, only one investigation is available that has reviewed the relationship between the ABO blood group and prognosis in ovarian cancer patients. In 92 patients with ovarian cancer, blood type A was found to be occur more frequently than in those with the other blood types and patients with blood group A was associated with a poor prognosis (17). 256 patients enrolled in the present study, and the proportions of blood types A, B, O, and AB were approximately similar to those of the cases in the Nurses' Health Study with the proportions were 31.2%, 17.5%, 41.0%, and 10.3%, respectively (13). And our study further clarified the prognostic value of ABO blood groups in ovarian cancer with patient survival in Chinese population.

Recently studies have demonstrated that the risk for ovarian cancer of being significantly higher in patients with blood group A (11,12). Owing to these data, we hypothesized that the predisposing environmental and genetic background associated with blood group A might develop ovarian cancer to a poorer prognosis. Our findings are quite similar to previous studies in nasopharyngeal carcinoma (9) and breast cancer (18), while the other studies showed that non-AB blood types in colon cancer (8), O blood type in bladder cancer (19) and esophageal squamous cell carcinoma (20) were poor prognostic factors. Conversely, studies indicated that ABO blood group was not associated with survival of triple negative breast cancer (21), gastric adenocarcinoma (22), and renal cell carcinoma (23). Proposed reasons for these conflicting results include heterogeneity of study populations, differences in ABO distribution or other demographics, and limited study sizes.

It is remained uncertain why ABO blood groups affect the survival of patients with ovarian cancer. However, growing studies discussed the possible mechanisms of the ABO blood groups affect the survival. The associations between the ABO blood group and tumor prognosis including inflammation, immunosurveillance for cancer cells, intracellular adhe-

sion, and membrane signaling have been proposed (24). It was also found that ABO blood group antigen expression on cancer cells was modified by hypermethylation of ABO gene promoter (25), which might be related with the tumor invasion and metastasis. Previous studies showed that the number of methylated gene promoters increased with age (26,27), which may partly explain the reason for patients with age > 50 years had worse OS in this study.

The ABO gene is located on chromosome 9q34 encodes glycosyltransferases, which is frequently lost in ovarian cancer (28). The gene encodes for glycosyltransferases, which catalyze the step-by-step transfer of nucleotide donor sugars to the H antigen to form the A and B antigen (29). Aberrant glycosylation represents a hall mark of cancer development and progression (30). Thus, we hypothesize that patients with blood type A have impacted tumor cell invasion and immune responses of ovarian cancer cells and more susceptible to disease failure. Further studies of the impact of blood type on tumor behavior or response to therapy would be important to elucidate the potential impact of blood type on tumor biology and might help guide individualized therapy for ovarian cancer.

There are some limitations of the current study. This study was a retrospective study performed in a single center with a relatively small number of patients enrolled, thus the findings may not be applicable to the general population, and We could not have a definite conclusion about the ABO blood group and survival of different FIGO stage ovarian cancer. Further studies are required to evaluate the correlation between ABO blood group and survival of different FIGO stage ovarian cancer. In addition, the patients enrolled in the present study was underwent cytoreductive surgery which achieved optimal debulking when the residual disease was < 1 cm. Therefore, the metastatic cases with FIGO stage IV were excluded and not discussed in this study.

Conclusion

In conclusion, the results of the present study show that ABO blood group is a prognostic factor for survival in ovarian cancer patients after cytoreductive surgery. Patients with blood type A had a significantly worse OS than those with non-A types, especially in patients with age > 50 years. However, our result should be verified by further studies, and the related mechanism should be studied to elucidate the association between the ABO blood group and tumor genetic or biological differences.

Abbreviations

FIGO, The International Federation of Gynecology and Obstetrics

cology and Obstetrics; OS, overall survival; HR, hazard ratios; CI, confidence interval.

Acknowledgments

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Conflict of interest

The authors declare that there are no conflicts of interest.

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