ABO Blood Type Has No Impact on Survival in Patients with Endometrial Carcinoma – A cohort study of 1074 patients

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Abstract

Background: Endometrial carcinoma is one of the three major malignant tumors in gynecology. ABO blood type is associated with the prognosis of a variety of malignancies. This study assessed the relationship between ABO blood type and prognosis of endometrial carcinoma.

Methods: We retrospectively analyzed the relationship between ABO blood type and endometrial carcinoma prognosis in patients with primary endometrial carcinoma who underwent surgery from Shengjing Hospital affiliated to China Medical University from January 2012 to February 2017. Univariate analysis, multivariate analysis, and stratified analysis were performed.

Results: In the multivariate analysis, 2009 FIGO stage (HR=2.806, 95% CI=1.289, 6.109), Pathological tissue type (HR=0.199, 95% CI=0.079, 0.503) was an independent and important risk factor for OS. We divided the ABO blood type into A and non-A groups, B and non-B groups, O and non-O groups, AB and non-AB groups, and failed to measure the significant results of OS. After we excluded 9 patients who had recurrence, metastasis, or death within 1 year of enrollment, the OS-significant results were similar to those described above.

Conclusions: Our study suggest that there is no association between ABO blood type and EC prognosis, and additional cohort studies are needed for validation.

1. Introduction

Endometrial carcinoma (EC) is one of the three major malignant tumors in gynecology. In the United States, there are 61,880 new cases each year, second only to breast cancer, lung and bronchial cancer, and colorectal cancer. There are 12,160 deaths, second only to lung and bronchial cancer, breast cancer, colorectal cancer, pancreatic cancer and Ovarian cancer, ranked sixth. [1] The most important risk factors in EC are obesity, persistent endogenous or exogenous hyperestrogen (polycystic ovary, tamoxifen treatment, anovulation and nulliparity), hypertension and diabetes. Moreover, women with Lynch syndrome (LS or hereditary non-colon cancer) have a significantly increased risk of developing EC. Most patients with EC have a good prognosis, but have a survival rate of less than 50% for patients with high-risk early stage disease or advanced diagnosis. [2]

The ABO blood group system is the first blood type system discovered and determined by Landsteiner in 1900. A blood type system classified according to the presence or absence of specific antigens (aggregates) A and B on the surface of red blood cells. According to the distribution of agglutinogens A and B, blood is divided into four types: A, B, AB, and O. Studies have shown that the risk of diffuse gastric cancer in patients with type A blood is increased by 20% compared with people with type O blood, [3] people with type A blood have an increased risk of breast cancer. [4,5] In addition, studies have shown that patients with type B or AB blood have lower survival rates and increased risk of recurrence after breast cancer. [6] Chang et al. showed that type A blood is associated with a higher incidence and metastatic rate of malignant melanoma of the skin, [7] blood type B It also significantly reduced the risk of stomach cancer and bladder cancer, while blood type AB significantly increased the risk of liver cancer. [8] Moreover, studies have shown that ABO blood type has no effect on the survival of patients with epithelial ovarian cancer. [9]

Previous studies have shown that regardless of menopausal status, body mass index, oral contraceptive use or family cancer history, blood group A is positively associated with EC risk in Chinese women [10] . To investigate the relationship between ABO blood group and prognosis of EC, we conducted a retrospective study at Shengjing Hospital of China Medical University.

2. Material And Methods

2.1 Study population

Approved by the Institutional Review Committee (Ethical No.2017PS292K) of the Shengjing Hospital affiliated to China Medical University, we conducted a retrospective study of EC patients from January 2012 to February 2017 at Shengjing Hospital of China Medical University. Includes patients who have been diagnosed with primary EC and undergo surgery. The patient exclusion criteria were as follows: 1. Patients with other tumors at the same time; 2. Patients undergoing treatment for recurrent disease; 3. Patients receiving chemotherapy or radiotherapy at Shengjing Hospital after surgery in other hospitals; 4. Patients under 15 years of age 5. Patients with incomplete data for variables or covariates analyzed in this study.

2.2 Data collection

According to the electronic medical records of the electronic information system of Shengjing Hospital affiliated to China Medical University, we collected the following demographic and clinical variables: age of diagnosis, menopause, birth history, degree of tumor differentiation, 2009 FIGO stage, Depth of infiltration(layer), lymphatic vessel interstitial infiltration, Lymph node metastasis, pathological tissue types, etc. At the same time, the blood type of the patient before the operation was obtained through the Shengjing Hospital inspection system. All data were collected by experienced gynaecologists and pathologists. Tumor staging was calculated according to the 2009 International Obstetrics and Gynecology Alliance (FIGO) staging standard. The degree of differentiation of tumors is divided into high differentiation, high-medium differentiation, medium differentiation, medium-low differentiation, and low differentiation. The depth of infiltration(layer) is divided into mucosal layers, less than 1/2, greater than or equal to 1/2. According to the pathological tissue type, it is divided into adenocarcinoma and non-adenocarcinoma

2.3 Follow-up and outcome

After surgery, all enrolled patients were followed up by telephone for follow-up. The primary endpoint was overall survival (OS), which was defined as the date from completion of the procedure to the patient's death for any reason, or the date of the last follow-up of the surviving patient (2018.7), the cause of death was from telephone follow-up and proof of death.

2.4 Statistical analysis

The Chi-square test was used to compare continuous and categorical variables in different blood types, respectively. Age at diagnosis is summarized as means±SD. Follow-up time is summarized as the median of the inter-quartile range (IQR). The categorical variables are expressed as numbers and percentages. The Cox proportional hazard model was used to estimate risk ratios (HRs) and 95% confidence intervals (CIs). We use the likelihood ratio test to assess the proportional hazard assumption. The ABO blood type is divided into four groups: A, B, O, and AB. In addition, we conducted the following four subgroups, group A and non-group A, group B and non-group B, group O and non-group O, group AB and non-group AB.

At the same time, we performed Multivariable adjusted analyses, including the following potential confounders: age at diagnosis, menopause, birth history, degree of tumor differentiation, FIGO stage, Depth of infiltration(layer), lymphatic vessel infiltration, Lymph node metastasis, pathological tissue type. In addition, we conducted a subgroup analysis of stratification of potential confounding factors by appeal. A likelihood ratio test was performed to check whether the association between ABO blood group and OS was modified by the following pre-specified potential effect modifiers: menopause, birth history, degree of tumor differentiation, FIGO stage, Depth of infiltration(layer), lymphatic vessels Interstitial infiltration, Lymph node metastasis, pathological tissue type. We further excluded by sensitivity analysis: patients with recurrence, metastasis, or patients who died within 1 year of study enrollment. P value <0.05 was considered statistically significant. All analyses were performed using the IBM SPSS Statistics 24 software.

3. Results

3.1 Patient characteristics

As shown in Figure 1, information of variables and covariates were incomplete after the exclusion, a total of 1074 patients were included in the study. Among them, 17 patients had recurrence, 30 patients had metastasis, and 40 patients died. The demographic and clinical characteristics of patients with EC according to ABO blood type are shown in Table 1. The median age of blood type A, B, O, AB was 56.14 (±8.38), 56.19 (±9.00), 56.02 (±8.92), 55.54 (±9.11). Blood type A, B, O and AB accounted for 28.6%, 34.0%, 26.7% and 10.7%, respectively. There were no significant differences in ABO blood type in terms of demographics and clinical characteristics.

Table 1
Selected demographic and clinical characteristics of Endometrial carcinoma patients according to ABO blood type

Variables	ABO blood type				P value
	O	A	B	AB	
Total case	287	307	365	115	
Age at diagnosis(years)	56.02±8.92	56.14±8.38	56.19±9.00	55.54±9.11	0.917
Follow-up time(years)	3.66(2.29~4.59)	3.94(2.58~4.98)	3.89(2.50~5.04)	3.53(2.52~4.84)	0.057
Vital status(%)	287	307	365	115	0.656
Alive	273(95.1)	296□96.4□	354(97.0)	111(96.5)	
Died	14(4.9)	11□3.6□	11(3.0)	4(3.5)	
Recurrence status					0.120
Yes	8	6	2	1	
No	279	301	363	114	
Metastasis					0.230
Yes	11	10	5	4	
No	276	297	360	111	
Menopause					0.672
Yes	95	216	241	37	
No	192	91	124	78	
Birth history					0.787
Yes	270	289	347	107	
No	17	20	18	8	
Degree of tumor differentiation					0.717
High differentiation	132	136	156	51	
High-medium differentiation	44	45	46	14	
Medium differentiation	65	75	89	33	
Medium-low differentiation	21	28	32	5	
Low differentiation	25	23	42	12	
2009 FIGO stage					0.477
Stage I	235	253	286	90	
Stage II, III, IV	52	54	79	25	
Depth of infiltration(layer)					0.703
Mucosal layer	54	60	61	25	
□1/2	171	168	216	61	
≥1/2	62	79	88	29	
Lymphatic vessels Interstitial infiltration					0.625
Yes	263	285	330	103	
No	24	22	35	12	
Lymph node metastasis					0.587
Yes	266	288	334	104	
No	21	19	31	11	
Pathological tissue type					0.390
Adenocarcinoma	6	9	15	2	
Non-adenocarcinoma	281	298	350	113	

3.2 Multivariate analyses of the demographic and clinical characteristics

Table 2 summarizes the adjusted OS-related patient characteristics. In the multivariate analysis, 2009 FIGO stage (HR=2.806, 95% CI=1.289, 6.109), Pathological tissue type (HR=0.199, 95% CI=0.079, 0.503) was an independent and important risk factor for poor OS. Age, Menopause, birth history, Degree of tumor differentiation, Depth of infiltration (layer), Lymphatic vessels Interstitial infiltration, Lymph node metastasis is not significantly associated with OS.

Table 2
Selected demographic and clinical characteristics according to overall survival among endometrial carcinoma patients

Variables	OS		P value
	No./Events	HR (95%CI)†	
Age at diagnosis(years)			
≤55	468/11	Reference	
55	606/29	1.671(0.739 3.775)	0.217
Menopause			
No	347/7	Reference	
Yes	727/33	1.256 0.482,3.275	0.641
Birth history			
No	63/1	Reference	
Yes	1011/39	2.103(0.280,15.782)	0.470
Degree of tumor differentiation			0.737
High differentiation	475/9	Reference	
High-medium differentiation	149/5	1.252(0.414,3.788)	0.691
Medium differentiation	262/12	1.499(0.616,3.653)	0.372
Medium-low differentiation	86/7	1.881(0.648,5.454)	0.245
Low differentiation	102/7	1.923(0.665,5.562)	0.228
2009 FIGO stage			
Stage I	864/21	Reference	
Stage II, III, IV	210/19	2.806(1.289,6.109)	0.009
Depth of infiltration(layer) (%)			0.120
Mucosal layer	200/3	Reference	
1/2	616/19	2.184(0.632,7.550)	0.217
≥1/2	258/18	3.571(0.983.12.979)	0.053
Lymphatic vessels Interstitial infiltration			
No	981/32	Reference	
Yes	93/8	0.251(0.033,1.895)	0.180
Lymph node metastasis			
No	992/31	Reference	
Yes	82/9	3.057(0.406,23.021)	0.278
Pathological tissue type			
No	32/7	Reference	
Yes	1042/33	0.199(0.079,0.503)	0.001

3.3 Association of ABO blood type and survival of EC patients

Multivariate analysis in table 3 suggested that Pathological tissue type was an independent risk factor for OS (HR=0.206, 95% CI=0.080, 0.533), but no other variables including ABO blood group were significantly associated. We grouped ABO blood type into blood type A and blood type non-A, blood type B and blood type non-B, blood type O and blood type non-O, blood type AB and blood type non-AB. And we failed to measure the significant results of OS. (Table 4-5).

At the same time, we excluded the 9 patients who had recurrence, metastasis or death within 1 year, and the OS significant results were similar to the above results.

Table 3
Prognostic factors for overall survival by multivariate analysis.

Variables	OS		P value
	HR	95%CI	
Menopause			
No	Reference	-	
Yes	1.630	0.696,3.819	0.260
Birth history			
No	Reference	-	
Yes	2.061	0.275,15.446	0.482
Degree of tumor differentiation			0.746
High differentiation	Reference	-	
High-medium differentiation	1.261	0.416,3.821	0.682
Medium differentiation	1.517	0.624,3.689	0.358
Medium-low differentiation	1.963	0.676,5.702	0.215
Low differentiation	1.816	0.622,5.299	0.275
2009 FIGO stage			
Stage I	Reference	-	
Stage II, III, IV	2.519	1.144,5.548	0.022
Depth of infiltration(layer) (%)			0.099
Mucosal layer	Reference	-	
1/2	2.014	0.588,6.897	0.265
≥1/2	3.618	0.992,13.199	0.051
Lymphatic vessels Interstitial infiltration			
No	Reference	-	
Yes	0.321	0.044,2.335	0.261
Lymph node metastasis			
No	Reference	-	
Yes	2.517	0.348,18.185	0.360
Pathological tissue type			
No	Reference	-	
Yes	0.206	0.080,0.533	0.001
ABO blood type			0.567
Type A	Reference	-	
Type B	0.687	0.220,2.147	0.519
Type O	0.638	0.282,1.446	0.278
Type AB	0.582	0.259,1.305	0.189

Table 4

Hazard ratio (95% CI) for overall survival among endometrial carcinoma patients according to A and non-A blood type, B and non-B blood typ

Variables	Overall survival		P value	Overall survival		P value	Overall survival	
	Blood type A	Blood type non-A		Blood type B	Blood type non-B		Blood type O	Bl no
	HR(95%CI)	HR(95%CI)		HR(95%CI)	HR(95%CI)		HR(95%CI)	HI
All patients								
Menopause			0.252			0.931		
No	1.969(0.440,8.800)	Reference		0.683(0.132,3.523)	Reference		0.471(0.057,3.919)	Re
Yes	0.734(0.331,1.628)	Reference		0.746(0.347,1.605)	Reference		1.920(0.955,3.861)	Re
Birth history			0.968			0.972		
No	198.074(0.000,3.345E+10)	Reference		0.030(0.000,3035495.32)	Reference		0.030(0.000,3035495.32)	Re
Yes	0.836(0.407,1.716)	Reference		0.733(0.365,1.472)	Reference		1.629(0.847,3.134)	Re
Degree of tumor differentiation			0.573			0.986		
High differentiation	0.660(0.137,3.180)	Reference		0.567(0.118,2.729)	Reference		2.284(0.613,8.514)	Re
High-medium differentiation	3.341(0.558,20.010)	Reference		0.536(0.060,4.794)	Reference		0.628(0.070,5.619)	Re
Medium differentiation	0.542(0.119,2.474)	Reference		0.894(0.269,2.972)	Reference		1.542(0.464,5.122)	Re
Medium-low differentiation	0.904(0.175,4.681)	Reference		0.696(0.134,3.623)	Reference		2.093(0.447,9.804)	Re
Low differentiation	1.199(0.230,6.233)	Reference		0.548(0.106,2.833)	Reference		1.343(0.259,6.972)	Re
2009 FIGO stage			0.454			0.265		
Stage I	1.188(0.480,2.944)	Reference		0.448(0.151,1.333)	Reference		1.419(0.572,3.519)	Re
Stage II, III, IV	0.725(0.241,2.186)	Reference		1.003(0.395,2.547)	Reference		1.858(0.731,4.719)	Re
Depth of infiltration(layer) (%)			0.685			0.933		
Mucosal layer	1.129(0.102,12.451)	Reference		1.120(0.102,12.352)	Reference		1.386(0.126,15.286)	Re
1/2	1.171(0.445,3.083)	Reference		0.670(0.241,1.861)	Reference		1.972(0.793,4.904)	Re
≥1/2	0.633(0.208,1.922)	Reference		0.682(0.243,1.918)	Reference		1.346(0.479,3.779)	Re
Lymphatic vessels Interstitial infiltration			0.366			0.181		
No	1.080(0.511,2.280)	Reference		0.540(0.233,1.248)	Reference		1.496(0.721,3.103)	Re
Yes	0.424(0.052,3.447)	Reference		1.629(0.407,6.514)	Reference		1.892(0.452,7.925)	Re
Lymph node metastasis			0.278			0.306		
No	1.134(0.534,2.408)	Reference		0.562(0.242,1.305)	Reference		1.352(0.636,2.871)	Re
Yes	0.363(0.045,2.903)	Reference		1.264(0.339,4.709)	Reference		2.828(0.757,10.569)	Re
Pathological tissue type			0.935			0.654		
No	0.873(0.169,4.506)	Reference		0.523(0.101,2.696)	Reference		3.514(0.785,15.724)	Re
Yes	0.901(0.419,1.939)	Reference		0.716(0.333,1.540)	Reference		1.439(0.698,2.969)	Re

Table 5

Hazard ratio (95% CI) for overall survival among endometrial carcinoma patients according to A and non-A blood type, B and non-B blood type, O and no

Variables	Overall survival		P value	Overall survival		P value	Overall survival	
	Blood type A	Blood type non-A		Blood type B	Blood type non-B		Blood type O	B n
	HR(95%CI)	HR(95%CI)		HR(95%CI)	HR(95%CI)		HR(95%CI)	H
All patients								
Menopause			0.130			0.651		
No	3.834(0.641,22.953)	Reference		0.418(0.047,3.738)	Reference		0.727(0.081,6.513)	R
Yes	0.839(0.353,1.997)	Reference		0.731(0.307,1.739)	Reference		1.584(0.706,3.555)	R
Birth history			0.957			0.974		
No	198.074(0.000,3.345E+10)	Reference		0.030(0.000,3035495.32)	Reference		0.030(0.000,3035495.32)	R
Yes	1.028(0.471,2.245)	Reference		0.673(0.300,1.513)	Reference		1.479(0.692,3.160)	R
Degree of tumor differentiation			0.802			0.982		
High differentiation	0.763(0.154,3.784)	Reference		0.659(0.133,3.265)	Reference		1.733(0.414,7.257)	R
High-medium differentiation	2.206(0.310,15.675)	Reference		0.706(0.073,6.795)	Reference		0.848(0.088,8.156)	R
Medium differentiation	0.542(0.119,2.474)	Reference		0.894(0.269,2.972)	Reference		1.542(0.464,5.122)	R
Medium-low differentiation	1.574(0.261,9.495)	Reference		0.439(0.048,3.983)	Reference		1.742(0.268,11.313)	R
Low differentiation	239.745(0.000,267471512)	Reference		0.018(0.000,1837.883)	Reference		0.035(0.000,130692.197)	R
2009 FIGO stage			0.278			0.294		
Stage I	1.658(0.631,4.357)	Reference		0.403(0.116,1.403)	Reference		1.198(0.422,3.405)	R
Stage II, III, IV	0.727(0.203,2.606)	Reference		0.966(0.324,2.884)	Reference		1.797(0.602,5.362)	R
Depth of infiltration(layer) (%)			0.946			0.772		
Mucosal layer	1.129(0.102,12.451)	Reference		1.120(0.102,12.352)	Reference		1.386(0.126,15.286)	R
1/2	1.253(0.428,3.668)	Reference		0.470(0.133,1.667)	Reference		2.399(0.870,6.617)	R
≥1/2	0.979(0.302,3.181)	Reference		0.767(0.236,2.498)	Reference		0.658(0.146,2.973)	R
Lymphatic vessels Interstitial infiltration			0.584			0.106		
No	1.250(0.557,2.805)	Reference		0.456(0.172,1.211)	Reference		1.527(0.681,3.427)	R
Yes	0.711(0.079,6.364)	Reference		2.435(0.407,14.577)	Reference		0.820(0.092,7.336)	R
Lymph node metastasis			0.410			0.213		
No	1.332(0.589,3.014)	Reference		0.479(0.180,1.277)	Reference		1.348(0.582,3.125)	R
Yes	0.548(0.064,4.696)	Reference		1.559(0.315,7.728)	Reference		1.918(0.351,10.497)	R
Pathological tissue type			0.935			0.335		
No	1.064(0.195,5.816)	Reference		0.268(0.031,2.292)	Reference		4.750(0.957,23.574)	R
Yes	1.118(0.482,2.592)	Reference		0.735(0.307,1.760)	Reference		1.140(0.476,2.730)	R

4. Discussion

The ABO blood type is the most important blood type system in the human blood group system. The ABO gene is located on chromosome 9q34 and encodes two alleles of specific glycosyltransferases, namely A and B. [11] The blood group antigen is a secondary gene product, and the primary gene product is a various glycosyltransferase that binds a sugar molecule to an oligosaccharide chain. [12]

The ABO gene consists of 7 exons of more than 20KB of genomic DNA, and two key single base substitutions in the final coding exon result in amino acid substitutions, which result in a donor between A-transferase and B-transferase. The difference in nucleotide sugar substrate specificity. [13] The blood group O does not have the glycosyltransferase encoded by the A and B genes, and expresses a fucosylated variant (Ley) of the precursor structure. [14] Studies have shown that ABO blood group plays an important role in affecting circulating sP-selectin and sICAM-1 levels, which may be related to glycosylation of P-selectin/ICAM-1 from cell membrane detachment interaction. [15]

At present, multiple studies have shown that ABO blood group is associated with tumor prognosis. Cao et al [16] showed that Blood type AB is a favourable prognostic factor for patients with colon cancer. Studies by DONATAS STAKIŠAITIS have shown that type B blood is associated with prostate cancer and bladder cancer risk and can be assessed as a determinant of negative longevity.[17] A study by Ting Jin et al [18] showed that the OS of patients with blood group O was significantly shorter than that of other ABO patients. In addition, prospective studies have shown that type B and type AB blood are associated with a significant reduction in the risk of gastrointestinal and colorectal cancer, respectively, and type B blood reduces the risk of stomach cancer and bladder cancer, and type AB blood increases liver cancer. The risk, but not related to the risk of sarcoma, lymphoma, leukemia or other cell types of cancer. [8] A retrospective study by Li et al showed that there is an association between the ABO blood types and the survival of Chinese patients with resected NSCLC. And the overall survival, patients-free survival and locoregional relapse-free survival were significantly prolonged in patients with a blood group of O or B compared with patients with blood group A or AB.[19]

There are currently few studies on ABO blood type and EC. A retrospective cohort study of 203 patients with type I EC found that patients with type A blood had a lower risk of developing G3 tumors than patients with non-type A blood. [20] Type A blood is associated with a high risk of EC[21], whereas conversely, A case-control study of 440 patients with EC showed that the ABO blood group was not associated with the risk of EC. [22] Based on this, we have 1074 patients from Shengjing Hospital affiliated to China Medical University from January 2012 to February 2017. A retrospective study was conducted and a large number of subgroup analyses were performed. Multivariate analysis showed that histological type was an independent and important risk factor for OS, while other factors were not significantly associated with OS. At the same time, we divided the ABO blood type into A group and non-A group, B group and non-B group, O group and non-O group, AB group and non-AB group respectively for stratified analysis, no significant interaction, further we Sensitivity analysis was performed on patients who had relapsed, metastasized, and died within 1 year of enrollment. OS outcomes were similar. For our study, the sample size was larger compared to previous studies related to ABO blood group and EC. Moreover, our sample information comes from Shengjing Hospital affiliated to China Medical University, and its electronic medical record system is perfect, thereby minimizing the likelihood of recall bias. On the other hand, our study had a short follow-up period (median follow-up period was year), and the number of missing dependent variables and covariates was 1032. However, we found no difference between the patients included and excluded.

5. Conclusion

In summary, our data suggest that there is no association between ABO blood type and EC prognosis, and additional cohort studies are needed to validate.

6. Abbreviations

EC: endometrial cancer

FIGO: International Federation of Gynecology and Obstetrics

OS: overall survival

IQR: inter-quartile range

HR: Hazard Ratio

NSCLC: non-small cell lung cancer

Declarations

7. Ethics approval and consent to participate

Our study is approved by the Institutional Review Committee of the Ethics Committee of Shengjing Hospital of China Medical University (No.2017PS292K), and it conforms to the provisions of the Declaration of Helsinki.

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9. Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

10. Conflict of interest

The authors declare no conflict of interest.

11. Acknowledgements

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Figures

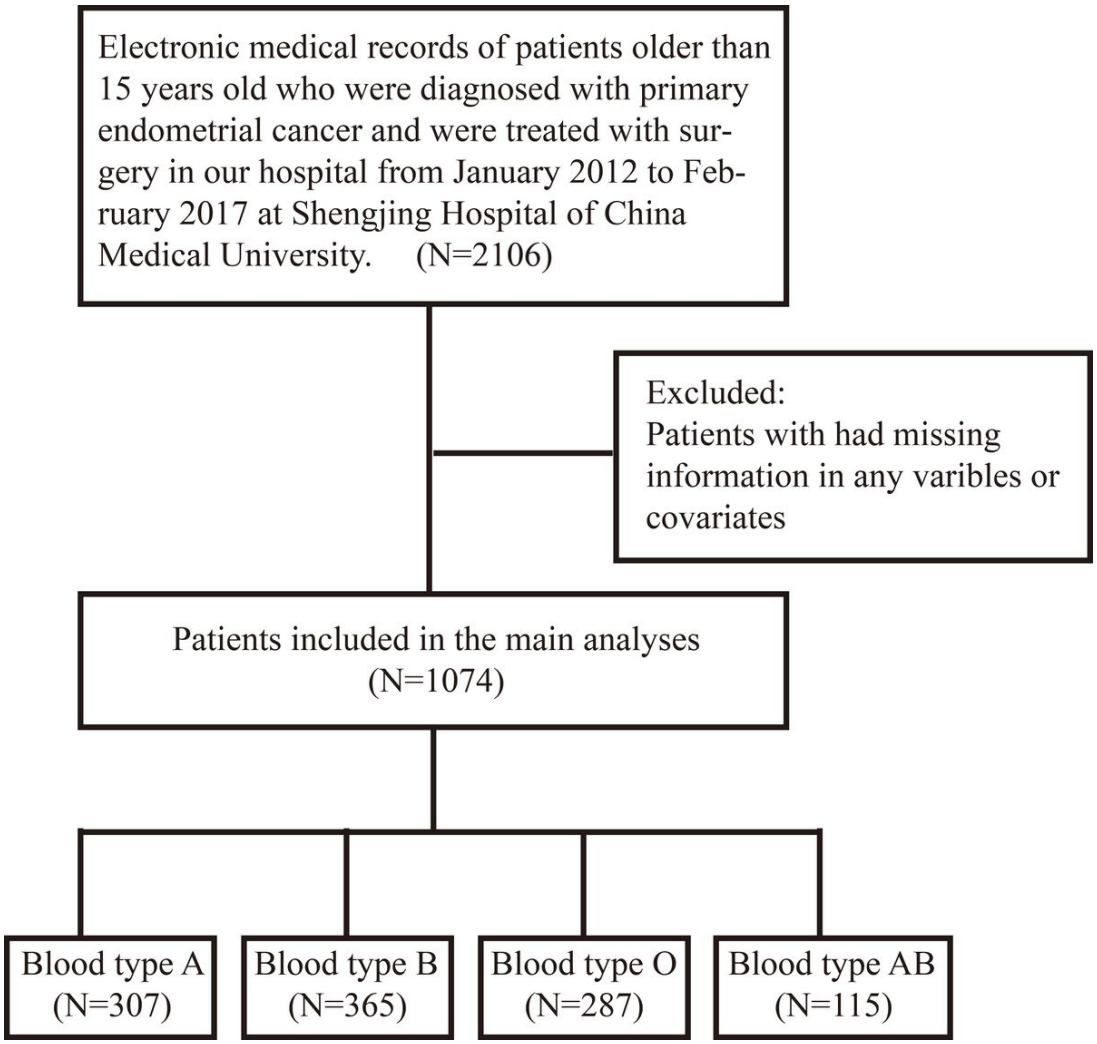

Figure 1

Flow diagram of the study population