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Research Article

# CAN ABO BLOOD TYPE DETERMINE SMALL CELL LUNG CANCER RISK?

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## ABSTRACT

**Aim:** Many cases of small cell lung cancer (SCLC) are diagnosed at an advanced stage, which remains the biggest barrier to improving survival. Identifying high-risk patients for early diagnosis and treatment is crucial. ABO blood groups and Rh factor may influence the risk of SCLC.

**Materials and Methods:** The medical records of 118 SCLC patients with confirmed ABO/Rh blood types were retrospectively reviewed. A control group was selected from healthy blood donors of the Turkish Red Crescent. The distribution of ABO/Rh blood groups between the patients and controls was compared.

**Results** The median age was 66 years (range: 39-87). A clear male predominance was observed (87.3% vs. 12.7%). Significant differences were found between patients and controls in terms of non-A vs. A (P=0.04391) and non-O vs. O (P=0.006289). Additionally, there was no significant difference between the patients and controls in the general distribution of ABO blood groups (P=0.1747). There were no statistically significant differences in terms of gender, age, or smoking status between the blood groups.

**Conclusion:** In the study population, ABO blood groups were associated with SCLC. Having blood group A was found to reduce the risk of SCLC, whereas having blood group O increased the risk. This study is the largest to compare ABO blood groups with SCLC patient data in the literature. However, further prospective studies are required to define how ABO blood groups may influence the risk of SCLC.

**Keywords:** ABO Blood-Group System; Small Cell Lung Cancer; Risk Factors; Cancer Epidemiology

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## INTRODUCTION

Lung cancer is the second most common cancer in both sexes and the leading cause of cancer-related deaths in developed countries. Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine subtype, marked by a rapid doubling time and the early onset of widespread metastases, resulting in a poor prognosis. Despite showing a high response rate to chemotherapy and radiotherapy at the start, most patients relapse within a few months to a year after initial treatment, often with significant resistance. The five-year survival rate varies between 1% and 13% (1,2). Risk factors for pulmonary malignancies include advanced age, male sex, smoking, radiation exposure, exposure to environmental and occupational carcinogens, enzyme polymorphisms, genetic predisposition and conditions leading to pulmonary fibrosis, tuberculosis and chronic pulmonary diseases such as chronic obstructive pulmonary disease (3). SCLC is almost exclusively observed in smokers (4). A case-control study reported that lung cancer accounts for only 2.9% of cases among women and is exceedingly rare in individuals who have never smoked (5).

Most SCLC cases are diagnosed at an advanced stage, making late-stage detection a major challenge in improving outcomes for this cancer. Early detection is therefore a vital prognostic factor. Since surgical resection is rarely performed on SCLC patients, fewer studies have been conducted on the genetic profiles of somatic mutations in primary SCLC tumors compared to other histological subtypes. Given that screening and early detection have proven to improve survival rates in various solid tumors, such as breast, colorectal, cervical, and lung cancers, it is crucial to identify high-risk individuals for screening. The National Lung Screening Trial showed that using low-dose computed tomography to screen high-risk individuals reduced lung cancer mortality by 20% compared to chest radiography. In this study, high-risk individuals were defined as those aged 55–74 years with a history of at least 30 pack-years of smoking (6).

Karl Landsteiner discovered the ABO blood group system in 1900 (7). Blood group antigens are chemical components found on the erythrocyte membrane; however, they are also present in various epithelial cells, including those lining the urothelium, gastrointestinal tract, lung mucosa, as well as in saliva and body fluids (8). The antigenic structure of ABO blood groups is formed by the addition of carbohydrates to the H antigen, which is regulated by the 'ABO' gene (9). Research on the correlation between ABO blood groups and diseases, particularly cancer, has been ongoing for decades. The first such association was reported by Aird et al. in 1953, when they observed a significant link between gastric cancer and blood group A.

They found that blood group A was more prevalent among gastric cancer patients compared to the general population, whereas blood group O was underrepresented (10). More recently, studies have explored the relationship between blood group type and survival outcomes in various malignancies, including colorectal cancer, nasopharyngeal carcinoma, esophageal cancer, breast cancer, and renal cell carcinoma (11–15).
When reviewing the literature, studies examining ABO/Rh blood groups in lung cancer patients are relatively common. However, there is a lack of studies specifically comparing SCLC with a control group as a distinct histopathological subtype. The aim of this study is to investigate the potential association between ABO/Rh blood groups and the clinicopathological characteristics of SCLC.

## MATERIALS AND METHODS

The medical records of 197 patients with histopathologically confirmed SCLC at Adnan Menderes University Training and Research Hospital between 2015 and 2021 were retrospectively reviewed. Only cases with serologically confirmed blood group and Rh factor were included in the study. Patients with a history of another primary malignancy or those diagnosed with limited-stage disease were excluded. A total of 118 patient records met the inclusion criteria. As the control group, voluntary healthy blood donors (aged 18–65 years) with a similar ethnic background, who donated blood to the **Turkish Red Crescent** between 2004 and 2011, were selected. The relationship between histopathological features and demographic characteristics such as gender, smoking status, and age at diagnosis was analyzed based on ABO/Rh blood groups. ABO/Rh distributions were compared between 118 SCLC patients and 3,022,883 controls. Additionally, variations in clinical characteristics were examined among the ABO/Rh subgroups within the patient cohort.

This study was approved by the Institutional Ethics Review Board of Aydın Adnan Menderes University and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Statistical analyses were performed using IBM SPSS version 22 (SPSS Inc., Chicago, Illinois). Continuous variables were expressed as median (minimum [min] – maximum [max]), while categorical variables were presented as frequencies and

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corresponding percentages. The chi-square test was used to assess differences in proportions. Comparisons between two independent groups for metric variables were conducted using the Mann-Whitney U test. Considering the imbalance in group sizes, these tests were chosen, as both tests are relatively robust against differences in sample size, thereby providing accurate and reliable results. A p-value of <0.05 was considered statistically significant.

## RESULTS

The median age of the patients included in the study was 66 years (range: 39–87). Among the patients, 87.3% were male. In the control group, 93% (2,818,330) were male, while 7% (204,553) were female. Patients received a pathological diagnosis an average of 5.8 days (range: 1–25) after tissue biopsy. The median Ki-67 proliferation index in the analyzed tissue samples was 60%. Additionally, 81.4% of the patients were smokers (Table 1).

**Table 1.** Demographic and clinicopathological features of the patients

| | | Number (n) | % Value |
|---|---|---|---|
| **Age, median (min-max) (year)** | 66 (39-87) | | |
| **Gender (male/female)** | Male | 103 | (87.3%) |
| | Female | 15 | (12.7%) |
| **Smoking Status** | Smoker | 96 | (81.4%) |
| | Never smoked | 22 | (18.6%) |
| **ECOG performance status score** | 0 | 55 | (46.61%) |
| | 1 | 63 | (53.39%) |
| **Histopathology** | CD 56+ | 107 | (90.7%) |
| | CD 56- | 11 | (9.3%) |
| | Ki-67 index (median) | %60 (30-99) | |

ECOG-PS: Eastern Cooperative Oncology Group Performance Score

There was no significant difference in blood group distribution based on age and sex within the control group. Table 2 presents the comparison of ABO blood groups and Rh factors between the control group and patients with SCLC. The overall distribution of ABO blood groups and Rh factors did not show a statistically significant difference between the control and SCLC groups (P = 0.1747). The distribution of blood groups among SCLC patients was as follows: A (33.1%), B (16.9%), AB (4.2%), and O (45.8%), whereas in the control group, the corresponding proportions were A (42.2%), B (16.3%), AB (7.6%), and O (33.9%). However, significant differences were observed between non-A vs. A (P = 0.04391) and O vs. non-O (P = 0.006289) groups. In contrast, the distribution of B vs. non-B, AB vs. non-AB, and Rh+ vs. Rh- did not differ significantly (Table 3). Similarly, no statistically significant associations were found between blood groups and sex, age, or smoking status among SCLC patients.

**Table 2.** ABO Blood Group and Rh Factor by Patient with Small Cell Lung Cancer and Controls

| ABO/Rh Blood Group | Number of Patients (%) | Control Group (%) |
|---|---|---|
| **A Rh +** | 36 (30.5) | 1,121,702 (37.1) |
| **A Rh -** | 3 (2.5) | 154,330 (5.1) |
| **B Rh +** | 18 (15.3) | 434,143 (14.4) |
| **B Rh -** | 2(1.7) | 59,626 (2.0) |
| **AB Rh +** | 5 (4.2) | 200,972 (6.60) |
| **AB Rh -** | 0 (0.0) | 28,582 (0.9) |
| **O Rh +** | 48 (40.7) | 894,210 (29.60) |
| **O Rh -** | 6 (5.1) | 129,318 (4.30) |
| **Total** | 118 (100) | 3,022,883 (100) |

P:0.1747

**Table 3.** ABO/Rh Blood Group Distribution

| Blood Group | SCLC Group n (%) | Control Group n (%) | p | Odds Ratio |
|---|---|---|---|---|
| **A** | 39 (33.1) | 1,276,032 (42.2) | 0.04391 | 0.6758 (95%CI. 0.4605-0.9918) |
| **Non-A** | 79 (66.9) | 1,746,851 (57.8 | | |
| **B** | 20 (16.9) | 493,769 (16.3) | 0.8566 | 1.045 (95%CI. 0.6463-1.691) |
| **Non-B** | 98 (83.1) | 2,529,114 (83.7) | | |
| **AB** | 5 (4.2) | 229,554 (7.6) | 0.1689 | 0.5384 (95%CI. 0.2199-1.319) |
| **Non-AB** | 113 (95.8) | 2,793,329 (92.4) | | |
| **0** | 54 (45.8) | 1,023,528 (33.9) | 0.006289 | 1.648 (95%CI. 1.147-2.367) |
| **Non-0** | 64 (54.2) | 1,999,355 (66.1) | | |
| **Rh +** | 107 (90.7) | 2,651,027 (87.7) | 0.3245 | 1.364 (95%CI. 0.7336-2.538) |
| **Rh -** | 11 (9.3) | 371,856 (12.3) | | |

## DISCUSSION

In the present study, we demonstrated an association between ABO blood group and SCLC. We found that the prevalence of blood group O was significantly higher among cancer patients compared to the normal population

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(45.8% vs. 33.9%, respectively), whereas blood group A was significantly lower (33.1% vs. 42.2%, respectively). Additionally, our findings suggest that having blood group A or a non-O blood group was associated with a 32.5% and 35.2% reduction in SCLC risk, respectively.
Although multiple studies have explored the relationship between lung cancer, blood groups, and the Rh D antigen, the results have been inconsistent. A study analyzing 81 lung cancer patients reported no significant effect of ABO blood group on prognosis (16). Similarly, a study performed by Chrysanthakopoulos et al. yielded comparable results (17). In contrast, an investigation involving approximately 2,000 lung cancer patients identified an association between Rh D-negative and O-negative blood groups and an increased risk of lung cancer; however, this study did not differentiate between histological subtypes (18). A case-control study conducted among the Jordanian population suggested that Rh positivity increased the risk of lung cancer compared to Rh negativity (19). Conversely, another study reported that Rh-negative individuals were more frequently observed in the SCLC group, although this study only compared patients within different lung cancer subtypes and did not include a control group (20).

Although there are many studies in the literature examining the relationship In the middle of lung cancer and blood groups, no study has directly compared SCLC and ABO/Rh blood groups with such a large sample size. In a study by Oguz et al., which analyzed 221 lung cancer patients, only 38 patients with SCLC were compared to a control group, and no significant differences were found (21).

Graziano et al. evaluated A antigen loss on the cell surface and performed flow cytometric analysis in 260 operable NSCLC patients, reporting that those with A antigen-negative primary tumors had a significantly shorter median survival compared to other groups ($p < 0.01$). The absence of antigen A has been identified as one of the prognostic factors for survival in operated NSCLC patients. (8). Similarly, another study reported that having blood group A antigen is a positive prognostic factor (22) In another survival analysis, no association was found between Rh blood group and overall survival in 89 SCLC patients. However, the same study indicated that distant recurrence was more frequent in Rh-positive patients compared to Rh-negative patients (20).

The biological mechanisms underlying the association between ABO blood groups and cancer development have become increasingly elucidated in recent years (23). The glycosyltransferase enzymes encoded by the ABO gene determine the presence of A and B antigens on the cell surface, which play crucial roles in cell–cell adhesion, membrane signal transduction, and immune recognition (24,25). Loss of A/B antigens may contribute to a more invasive and metastatic phenotype in tumor cells (24). Moreover, ABO polymorphisms can influence inflammatory markers (such as TNF-$\alpha$, ICAM-1, and E-selectin) and coagulation factors (particularly von Willebrand factor, vWF), thereby fostering a pro-inflammatory or pro-thrombotic tumor microenvironment (25,26). In individuals with blood group O, lower vWF levels may facilitate angiogenesis and early tumor growth, while in blood group A, elevated vWF levels may suppress metastasis yet increase thrombotic risk (26). Additionally, ABO antigens are implicated in modulating immune responses; the presence or absence of anti-A and anti-B antibodies may affect immune recognition of tumor cells. In group A individuals, retention of A antigen by tumor cells may be associated with a more differentiated and less invasive phenotype, whereas in group O, the lack of such antigenic shielding could predispose to a more aggressive tumor behavior (27). Epigenetic modifications of the ABO gene and interactions with adjacent genes (e.g., ADAMTS13) further complicate this biological interplay (24). Collectively, these mechanisms suggest that ABO blood groups may play a role in the development of SCLC, although establishing a causal relationship will require further molecular and prospective investigations.

Our findings indicate the potential role of ABO blood group distribution in SCLC risk. The observation that A blood group may have a protective effect and O blood group may have an increasing effect may be helpful in risk stratification and screening strategies. In clinical practice, these findings may contribute to the creation of a risk profile that will take into account ABO blood group in addition to existing risk factors such as smoking history and age. However, these findings cannot be used as a diagnostic or screening tool alone; they need to be confirmed by prospective studies and the biological mechanisms should be elucidated. Nevertheless, they may be helpful in the development of personalized screening programs in the future.

Our study includes the largest series of SCLC patients reported in the literature; however, it has several limitations. Due to its retrospective design, it carries a risk of selection bias, and potential confounding factors (e.g., smoking history) could not be fully controlled. Moreover, only ABO/Rh blood groups were evaluated, while molecular and genetic markers were excluded. The study

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population's restriction to a specific geographic and ethnic group may also limit the generalizability of the findings. Although the large control group increased the statistical power and allowed the detection of even small differences as significant, the relatively small patient group may limit the generalizability of the results. Therefore, the findings should be interpreted with caution, and prospective studies with larger and more diverse samples are needed to validate these results.

## CONCLUSION

In this study, ABO/Rh blood groups were associated with an increased risk of SCLC. Specifically, having blood group A (compared to B, AB, and O) was found to be protective against SCLC, whereas blood group O (compared to A, B, and AB) was associated with an increased risk of developing the disease. Further large-scale prospective cohort studies are warranted to determine whether blood groups could serve as a useful marker for identifying individuals at higher risk of developing lung cancer.

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### Authorship contributions
All authors have made substantial contributions to conception, design, acquisition of data; or analysis and interpretation of data; or have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave the final approval of the version to be published.

### Data availibity statement
The data sets and data analyzed in the study are available from the corresponding author on reasonable request.

### Declaration of competing interest
The authors have no conflicts of interest to declare.

### Ethics
Ethics committee approval was obtained from the Clinical Research Ethics Committee of Aydın Adnan Menderes University (E-53043469-050.04.04-2100005339, Decision No:16- 2020/214).

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