ORIGINAL RESEARCH

DOI: 10.37047/jos.2020-79248

Association Between Blood Type and Epidermal Growth Factor Receptor Mutation Positivity in Lung Adenocarcinoma Patients

Mustafa GÜRBÜZ[a], Erman AKKUŞ[b], Bilgin KARAALİOĞLU[a], Elif Gizem AKTAŞ[b], Elif Berna KÖKSOY[a], Hilal ÖZAKINCI[c], Serhat HAYME[d], Yüksel ÜRÜN[a], Serpil DİZBAY SAK[c], Ahmet DEMİRKAZIK[a], Güngör UTKAN[a]

[a]Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, TURKEY
[b]Ankara University Faculty of Medicine, Department of Internal Medicine, Ankara, TURKEY
[c]Ankara University Faculty of Medicine, Department of Pathology, Ankara, TURKEY
[d]Ankara University Faculty of Medicine, Department of Biostatistics, Ankara, TURKEY

ABSTRACT Objective: Specific ABO blood group and Rh antigens are found to be associated with several malignancies and lung cancer. However, the relationship between blood type and Epidermal Growth Factor Receptor (EGFR) mutation in lung cancer remains poorly investigated. **Material and Methods:** In this retrospective case-control study, 105 EGFR mutation-positive and 169 EGFR mutation-negative lung adenocarcinoma patients were included. Baseline characteristics of the patients were determined. Odds ratios were calculated for the relationship of EGFR mutation positivity according to the ABO and Rh blood type. Overall survival difference according to the blood types was analyzed in metastatic patients that were diagnosed in the EGFR-mutant group. **Results:** There was no statistically significant increase observed in the relationship of EGFR mutation positivity for any of ABO and Rh types (OR and p-value, respectively; A: 1.15-0.57, B: 0.68-0.28, AB: 1-0.98, O: 1.06-0.82, Rh: 1.04-0.91). There was no statistically significant overall survival difference between ABO types (16, 21.1, 18.9, 24.9 months for O, A, B, AB blood groups, respectively). **Conclusion:** No significant association between blood type and EGFR mutation positivity in lung adenocarcinoma could be established.

Keywords: Lung adenocarcinoma; EGFR; blood type; ABO-Rh

Lung cancer is the most common cancer worldwide in both females and males.[1] The non-small cell lung cancer (NSCLC) distribution among all lung cancer is approximately 85%, and adenocarcinoma is the most common histological subtype in both sexes, constituting almost half of all lung cancers.[2,3]

EGFR is an important therapeutic target in lung adenocarcinoma.[4] Oral tyrosine kinase inhibitors (TKIs) can be used in patients with driver mutations in EGFR.[5] EGFR mutations were observed in ~10-15% of NSCLC patients in Western populations and up to 50% in Asian populations.[6,7] In a previous study, the EGFR mutation rate in adenocarcinomas was 33.9% for women and 9.4% for men in 499 cases, and the overall mutation rate was 14%.[8] Also, EGFR mutations are more frequently detected in female patients and non-smokers.[9]

The blood group antigens are biochemical components of the red blood cell membrane.[10] Specific ABO blood group and Rh antigens are found to be associated with several malignancies.[11] Several studies have investigated the association of ABO-Rh blood type and prognostic and predictive role of other antigens with lung cancer risk.[12-20] However, to our knowledge, only two studies have investigated the relationship between blood type and EGFR mutation in lung cancer, and thus it remains poorly investigated.[21,22]

The study aims to evaluate the relationship between blood type and EGFR mutation positivity in lung adenocarcinoma patients.

Correspondence: Mustafa GÜRBÜZ
Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, TURKEY/TÜRKİYE
E-mail: mgurbuz@ankara.edu.tr

Peer review under responsibility of Journal of Oncological Sciences.

Received: 16 Nov 2020 ***Received in revised form:*** 27 Dec 2020 ***Accepted:*** 30 Dec 2020 ***Available online:*** 02 Feb 2021

MATERIAL AND METHODS

STUDY DESIGN

This is a retrospective, case-control study. Records of lung adenocarcinoma patients from 2014 through 2020 were screened via the hospital database. Before 2018, formalin-fixed paraffin-embedded (FFPE) tumor tissues of these patients were examined for EGFR mutations in exons 18, 19, 20, and 21 by PCR-based direct Sanger sequencing. The final nucleotide mutations detected by sequencing were compared with the NCBI database. Between 2018 and 2020, FFPE tumor tissues of studied cases were analyzed for all insertions/deletions, point mutations in hot spot regions of the EGFR gene by Qiagen GeneReader next-generation sequencing **(**NGS) System, using commercial DNA panel. Patients were divided into two groups, EGFR positive and EGFR negative, according to the EGFR mutation status.

Blood types as ABO and Rh were determined serologically. EGFR mutation-positive and negative lung adenocarcinoma patients were sub-grouped according to their blood types. In a group of patients that are EGFR mutation-positive and metastatic at the time of diagnosis, the overall survival (OS) difference between the different blood group types was analyzed. OS was defined as the duration between treatment initiation and death or last known follow-up. Gender, age, smoking history, The Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) status, primary tumor localization, metastasis at the time of diagnosis, metastatic sites, and mutation type in the EGFR-mutant group were recorded as baseline characteristics.

The local Ethics Committee at the Ankara University Faculty of Medicine approved this study in compliance with the Helsinki Declaration (Decision number: İ4-236-20).

STATISTICAL ANALYSES

Continuous variables were given as median (minimum (min)-maximum (max)). Categorical variables were represented as a percentage. Cross-tabs and chi-square tests were used to determine differences in proportions and to calculate the odds ratio. The survival analysis was evaluated by Kaplan-Meier methods with the log-rank test. All p-values were based on a 2-tailed test of significance (p=0.05). All the statistical analyses were conducted using software SPSS version 22 (SPSS Inc, USA).

RESULTS

CHARACTERISTICS

Overall, 105 EGFR mutation-positive and 169 EGFR mutation-negative patients were included. Table 1 shows the characteristics of the patients. The median age was 62 in both groups. There was a female dominancy in the EGFR-mutant group (53%) compared to the EGFR mutation-negative group (26%). The majority of the EGFR-mutant patients had never smoked, but most of the patients without EGFR mutation were ex-smokers. Primary tumor localization was mainly right-sided in both groups. Fifty-two percent of the patients in the EGFR- mutation-positive group and sixty-five percent of the patients in the EGFR mutation-negative group were metastatic at the time of diagnosis. The mutations of exon 19 and 21 were detected in 55% and 28% of the EGFR-mutant patients, respectively.

EGFR MUTATION-POSITIVE LUNG ADENOCARCINOMA ACCORDING TO THE BLOOD TYPE

The frequency of the blood types in EGFR mutation-positive and negative groups and odds ratios for the EGFR-mutant lung adenocarcinoma are shown in Table 2. There was no statistically significant increase noticed in the relationship between the ABO and Rh types and lung cancer incidence.

OS-BLOOD TYPE IN EGFR MUTATION-POSITIVE LUNG ADENOCARCINOMA

The patients, which were metastatic at the time of diagnosis in the EGFR-mutant group, were analyzed for OS (Table 3). All patients included in the survival analysis received an anti-EGFR-TKI as the first- or second-line therapy. Forty-five (82%) of 55 EGFR mutation-positive patients were treated with erlotinib and 10 (18%) patients with afatinib, respectively. There was no statistically significant survival difference observed between ABO types and between Rh-negative and positive patients (Figure 1, Figure 2).

TABLE 1: The demographic and clinicopathological features of the patients.

	EGFR mutation+ (n=105)	EGFR mutation- (n=169)
Age median (min-max)	62 (25-81)	62 (33-86)
Gender n (%)		
Male	49 (47)	125 (74)
Female	56 (53)	44 (26)
ECOG PS n (%)		
0	34 (32)	47 (28)
1	61 (58)	101 (60)
2	10 (10)	21 (12)
Smoking n (%)		
Never-smoker	58 (55)	32 (19)
Ex-smoker	38 (36)	106 (63)
Active smoker	9 (9)	31 (18)
Packet/year median (min-max)	30 (8-120)	40 (10-100)
Primary tumor localization n (%)		
Right	62 (59)	113 (67)
Left	43 (41)	56 (33)
Pleural effusion n (%)	18 (17)	19 (11)
De novo metastatic n (%)	55 (52)	110 (65)
Metastatic site number n (%)		
1	26 (25)	58 (34)
2	22 (21)	29 (17)
3	4 (4)	13 (8)
4	3 (3)	10 (6)
Metastatic site n (%)		
Contralateral lung	18 (17)	17 (10)
Brain	16 (15)	27 (16)
Liver	5 (5)	9 (5)
Bone	29 (28)	34 (20)
Pleura	18 (17)	19 (11)
Adrenal	5 (5)	25 (15)
Distant lymph node	7 (1)	17 (10)
Other	1 (1)	5 (3)
Mutation type n (%)		
Exon 19	58 (55)	-
Exon 21	29 (28)	
Other	18 (17)	

DISCUSSION

In this case-control study, no relationship between blood type and EGFR mutation positivity in lung adenocarcinoma could be found. A statistically insignificant OS difference between blood types in EGFR-mutant patients was observed. As expected, the female gender and non-smokers were dominant in the EGFR-mutant group.

Although blood type and lung cancer risk have already been studied previously, the findings were conflicting. One study found an association of non-O blood type and Rh negativity with lung cancer risk; another study highlighted the association of A and AB blood types with male sex, whereas two studies did not find any relationship.[12,13,15,20]

TABLE 2: Blood types and EGFR mutation positivity in lung adenocarcinoma.

	EGFR mutation+ n (%)	EGFR mutation- n (%)	OR (95% CI)	p
A	49 (47)	73 (43)	1.15 (0.70-1.87)	0.57
Non-A	56 (53)	96 (57)		
B	13 (12)	29 (17)	0.68 (0.33-1.38)	0.28
Non-B	92 (88)	140 (83)		
AB	10 (10)	16 (9)	1.00 (0.43-2.31)	0.98
Non-AB	95 (90)	153 (91)		
Non-O	33 (31)	51 (30)	1.06 (0.62-1.79)	0.82
	72 (69)	118 (70)		
Rh+	93 (89)	149 (88)	1.04 (0.48-2.22)	0.91
Rh-	12 (11)	20 (12)		

TABLE 3: OS according to the blood types in EGFR-mutant metastatic lung adenocarcinoma.

Blood type (n)	OS months (95% CI)	p
ABO		
O (21)	16 (1.0-30.9)	0.4
A (23)	21.1 (16.5-25.7)	
B (8)	18.9 (1.2-36.6)	
AB (3)	24.9 (1.8-47.9)	
Rh		
Positive (49)	21.1 (17.1-25.1)	0.1
Negative (6)	2.9 (0–12.2)	

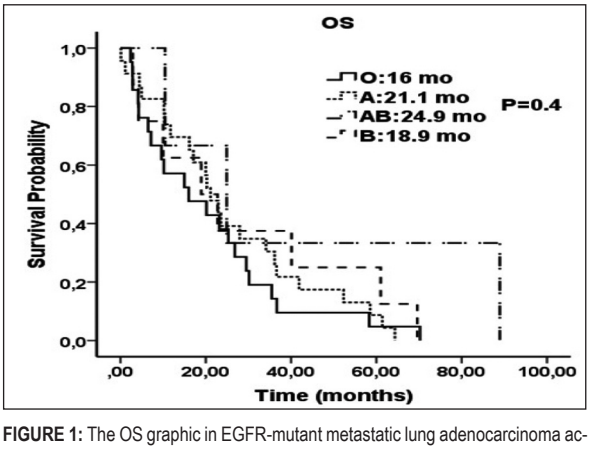

FIGURE 1: The OS graphic in EGFR-mutant metastatic lung adenocarcinoma according to ABO blood types.

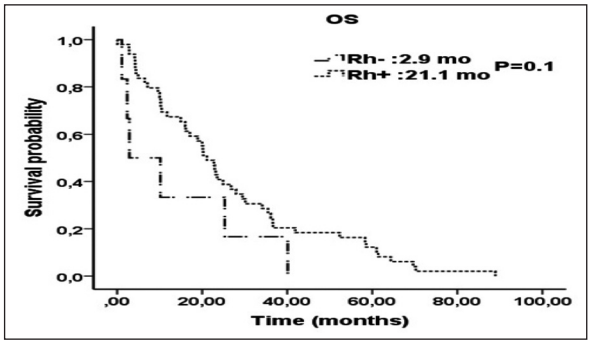

FIGURE 2: The OS graphic in EGFR-mutant metastatic lung adenocarcinoma according to Rh blood types.

The mutation rate of EGFR was lower in patients with AB blood type (25%) compared to those with other blood types (49.4%, 46%, and 50% in A, B, and O blood types, respectively, all $p<0.05$) in Chinese population.[21] However, in this study, 15.3% of the non-adenocarcinoma patients also had EGFR mutations. Another study revealed a significant relationship between blood type and EGFR mutation; however, the investigators did not mention the specific blood type, and analyses were secondary.[22] Also, EGFR mutation was not associated with smoking history in this study. The current case-control study included only lung adenocarcinoma patients with the main objective to evaluate blood type as a predictive factor for EGFR mutation status.

Several previous studies investigated the relationship between blood group and target alterations for other cancer types. In a study of 100 upper gastrointestinal cancer patients, any relationship could not be established between human epidermal growth factor receptor 2 (HER2)-positivity and blood type.[23-25] Any relationship between blood type and HER2 positivity could not be found in breast cancer in another study.[24] Another study with 426 breast cancer patients detected no relationship between blood type and HER2, estrogen, and progesterone receptor positivity.[25]

An earlier study revealed that curatively resected NSCLC patients with blood type B and O had significantly prolonged OS.[14] In another study, no treatment response and survival difference according to the blood type were detected in non-metastatic locally advanced 81 NSCLC patients.[19] Furthermore, Fukumoto *et al*. showed that the ABO blood group was an independent prognostic factor.[18]

In our study, OS analysis was performed only in metastatic and EGFR mutation-positive patients at the time of diagnosis. It was a statistically insignificant difference, but a numerical difference was observed, especially between Rh-positive and-negative patients. However, the number of patients in B, AB, blood groups, and Rh-negative groups was very low in this study. Moreover, the treatments and other prognostic factors of the groups were not evaluated in this study in order to define the primary relationship between blood type and EGFR mutation status.

CONCLUSION

To our knowledge, this is the first study in the literature to investigate the relationship between blood group type and OS in EGFR mutation-positive lung adenocarcinoma. The current study could not establish any relationship between blood type and EGFR mutation positivity in lung adenocarcinoma. There was not any OS difference in EGFR positive patients according to the blood type. Prospective cohort studies with a higher number of patients might be more informative to understand this relationship. Further studies, including clinical prognostic parameters and treatment modalities, are suggested for better prognosis and treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424. [Crossref] [PubMed]
2. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016. [Based on November 2018 SEER data submission, posted to the SEER web site, April 2019]. Bethesda, MD: National Cancer Institute 2019.
3. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6:244-285. [Crossref] [PubMed] [PMC]
4. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. Jama. 2014;311:1998-2006. [Crossref] [PubMed] [PMC]
5. Doval DC, Desai CJ, Sahoo TP. Molecularly targeted therapies in non-small cell lung cancer: The evolving role of tyrosine kinase inhibitors. Indian J Cancer. 2019;56:S23-s30. [Crossref] [PubMed]
6. Marchetti A, Martella C, Felicioni L, et al. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. J Clin Oncol. 2005;23:857-865. [Crossref] [PubMed]
7. Shi Y, Au JS-K, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). Journal of thoracic oncology. 2014;9:154-162. [Crossref] [PubMed] [PMC]
8. Musayeva M, Sak SD, Ozakinci H, Boyacıgil Ş, Coşkun Ö. Evaluation of epidermal growth factor receptor mutations and thyroid transcription factor-1 status in Turkish non-small cell lung carcinoma patients: A study of 600 cases from a single center. Turk Gogus Kalp Damar Cerrahisi Derg. 2020;28:143-150. [Crossref] [PubMed] [PMC]
9. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer research. 2004;64:8919-8923. [Crossref] [PubMed]
10. Hosoi E. Biological and clinical aspects of ABO blood group system. The journal of medical investigation. 2008;55:174-182. [Crossref] [PubMed]
11. Vasan SK, Hwang J, Rostgaard K, et al. ABO blood group and risk of cancer: A register-based cohort study of 1.6 million blood donors. Cancer epidemiology. 2016;44:40-43. [Crossref] [PubMed]
12. Chrysanthakopoulos N, Dareioti N. ABO blood group and the risk of lung cancer in Greek adults: a case-control study. Experimental oncology 2018. [Crossref]
13. Hsiao LT, Liu NJ, You SL, Hwang LC. ABO blood group and the risk of cancer among middle-aged people in T aiwan. Asia-Pacific Journal of Clinical Oncology. 2015;11:e31-e36. [Crossref] [PubMed]
14. Li N, Xu M, Li CF, et al. Prognostic role of the ABO blood types in Chinese patients with curatively resected non-small cell lung cancer: a retrospective analysis of 1601 cases at a single cancer center. Chin J Cancer. 2015;34:475-482. [Crossref] [PubMed] [PMC]
15. Urun Y, Utkan G, Cangir AK, et al. Association of ABO blood group and risk of lung cancer in a multicenter study in Turkey. Asian Pac J Cancer Prev. 2013;14:2801-2803. [Crossref] [PubMed]
16. Graziano SL, Tatum AH, Gonchoroff NJ, Newman NB, Kohman LJ. Blood group antigen A and flow cytometric analysis in resected early-stage non-small cell lung cancer. Clin Cancer Res. 1997;3:87-93.
17. Lee JS, Ro JY, Sahin AA, et al. Expression of blood-group antigen A--a favorable prognostic factor in non-small-cell lung cancer. N Engl J Med. 1991;324:1084-1090. [Crossref] [PubMed]
18. Fukumoto K, Taniguchi T, Usami N, et al. The ABO blood group is an independent prognostic factor in patients with resected non-small cell lung cancer. J Epidemiol. 2015;25:110-116. [Crossref] [PubMed] [PMC]
19. Unal D, Eroglu C, Kurtul N, Oguz A, Taşdemir A, Kaplan B. ABO blood groups are not associated with treatment response and prognosis in patients with local advanced non- small cell lung cancer. Asian Pac J Cancer Prev. 2013;14:3945-3948. [Crossref]
20. Oguz A, Unal D, Tasdemir A, et al. Lack of any association between blood groups and lung cancer, independent of histology. Asian Pac J Cancer Prev. 2013;14:453-456. [Crossref] [PubMed]
21. Zhou J, Mo W, Zhao J, Zheng J, Ding W, Zhou J. Clinicopathological features associated with EGFR gene mutation in non-small cell lung cancer patients. Zhonghua yi xue za zhi. 2014;94:2332-2336.
22. Wang CD, Wang XR, Wang CY, Tang YJ, Hao MW. Relevance of EGFR gene mutation with pathological features and prognosis in patients with non-small-cell lung carcinoma. Asian Pac J Trop Med. 2015;8:249-252. [Crossref]
23. Hejna M, Birner P, Preusser M, et al. Lack of correlation between blood group and HER-2 status in adenocarcinomas of the upper gastrointestinal tract. Mol Clin Oncol. 2013; 1:1079-1083. [Crossref] [PubMed] [PMC]
24. Urun Y, Utkan G, Altundag K, et al. ABO and Rh blood groups frequency in women with HER2 positive breast cancer. J buon. 2012; 17:457-460.
25. Klimant E, Glurich I, Mukesh B, Onitilo AA. Blood type, hormone receptor status, HER2/neu status, and survival in breast cancer: a retrospective study exploring relationships in a phenotypically well-defined cohort. Clin Med Res. 2011;9 :111-118. [Crossref] [PubMed] [PMC]