Blood group B can be a predictor of the EGFR mutations in patients with lung adenocarcinoma

Pham Van Luan[1]*, Nguyen Minh Hai[1], Vu Xuan Nghia[1] and Nguyen Dinh Tung[2]

[1]108 Military Central Hospital, [2]College of Health Sciences, VinUniversity

Summary

Background: The relationship between ABO blood and EGFR mutations in lung adenocarcinoma is still unclear. The purpose of this study was to evaluate the association between ABO blood and EGFR mutations percentage in patients with lung adenocarcinoma. *Subject and method:* A cross-sectional descriptive study, 276 lung adenocarcinoma patients were tested for EGFR mutations and ABO blood from January 2020 to April 2023. The relationship between the ratio of EGFR mutations with ABO blood and clinical, paraclinical characteristics was analyzed univariate and multivariate. *Result:* Median age of patients was 64 years old, male/female ratio was 3.5/1 and 73.6% of patients had a history of smoking. The percentage of EGFR mutations was 34.8%. Blood group O accounted for the highest percentage with 50%, followed by group B with 25% and group A 21%, only 4% of patients with group AB. Univariate analysis showed that the rate of EGFR mutations in patients with group B was 23.2%, lower than the rate of EGFR mutations in patients with non-B group, the difference was statistically significant with p=0.02. There was no association between groups O, A and AB with the ratio of EGFR mutations (p>0.05). Female and smoking history were also two factors associated with the ratio of EGFR mutations in univariate analysis. However, multivariate analysis showed that only female and non-B blood were the two independent factors associated with the EGFR mutations with OR = 3.4, p=0.037 and OR = 2.07, p=0.03, respectively. *Conclusion:* Blood group B can be a prognostic factor for the EGFR mutations in patients with lung adenocarcinoma. Further studies need to be conducted to further elucidate the prognostic role of ABO blood in lung cancer patients.

Keywords: ABO blood, EGFR mutations, lung adenocarcinoma.

I. Background

The ABO blood group system was first described by Landsteiner K. in 1901 based on the expression of two antigens A and/or B on the surface of red blood cells. Because expression of these antigens is predominant, patients may therefore have group A, group B, or group AB expression patterns. Lack of expression of these two antigens results in the O phenotype[1]. While many studies have shown an association between ABO blood and the risk of developing cancers such as blood group A, which increases the risk of stomach cancer reported since 1953[2], or pancreatic cancer related to ABO blood reported in 2009[3]. The relationship between ABO blood group and the risk of lung cancer was not conclusive. Ashley DJ et al studied 1257 lung cancer patients treated in Wales, the results showed no association between ABO blood and lung cancer[4]. Another recent study by Urun Y et al in Türkiye showed that non-O blood group increased the risk of developing lung cancer[5]. However, another independent study also in Turkey did not find a relationship between ABO blood in patients with non-small cell lung cancer and small cell lung cancer[6].

***Received**: 11 November 2023, **Accepted**: 25 December 2023*

***Corresponding author**: drluan108@gmail.com - 108 Military Central Hospital*

In patients with lung cancer, adenocarcinoma is the most common histopathologic type with an incidence of approximately 40% of patients. This histopathological type usually has a gene mutation called EGFR (Epidermal Growth Factor Receptor)[7]. EGFR was first discovered by Carpenter G et al in 1978, that was a 170kDa transmembrane protein, consisting of 486 amino acids, that has the ability to tyrosine kinase activates the intracellular signaling pathway in lung epithelial cells[8, 9]. Studies showed that EGFR mutations have a higher rate than patients of Asian origin, patients with adenocarcinoma, women, and patients without a history of smoking, in which, Vietnam was a country with the highest rate of EGFR mutations at 64.2%[10, 11]. However, a question arises as to whether there was a relationship between EGFR mutations and the ABO blood that has received little attention. Although the study of Gürbüz M et al in 2021 in Turkey did not find an association between ABO blood and EGFR mutations in patients with lung adenocarcinoma[12], but subsequent studies to clarify this relationship was necessary. Because there are differences between geographical regions in the rate of EGFR mutations as well as differences in the rate of ABO blood groups that may affect the research results. Therefore, the objective of this study was to evaluate the association between EGFR mutations and ABO blood in patients with lung adenocarcinoma.

II. SUBJECT AND METHOD

2.1. Subject

Patients with lung adenocarcinoma were tested for the EGFR mutations, ABO and Rh blood treated at the Department of Respiratory Medicine - 108 Military Central Hospital from January 2020 to April 2023.

2.2. Method

This was a cross-sectional study. The sample size of the study was calculated using the formula:

$$n = \frac{Z^2_{1-\alpha/2}\, p\,(1-p)}{d^2}$$

In which, "n" was the minimum sample size. $Z_{1-\alpha/2}$ was the value from the normal distribution, calculated based on the level of statistical significance ($Z_{1-\alpha/2}$ = 1.96 with statistical significance level of 0.05). "p" was the estimated percentage of EGFR mutations in lung adenocarcinoma patients, according to study by Shigematsu H et al, it was 40%[13]. "d" was acceptable absolute error level, take 5%.

According to the formula, the minimum sample size required for this study was 181 patients, in this study, we have received 276 patients to participate.

Protocol: Patients were examined by clinical examination, laboratory tests, lung tumor biopsy or pleural effusion. Types of specimens used for pathological diagnosis were bronchial biopsies, postoperative tumors, and pleural fluid cell block. Lung adenocarcinoma specimens were tested for EGFR mutations and patients were performed ABO and Rh blood groups. The relationship between EGFR mutations and ABO blood and some clinical and paraclinical characteristics were analyzed and evaluated.

EGFR mutations testing by realtime PCR assay with AmoyDx EGFR 29 mutations detection kid at Department of Molecular Biology - 108 Military Central Hospital. ABO and Rh blood testing were performed by both serology and erythrocyte samples running on an automatic machine using a matrix card at the Department of Blood transfusion - 108 Military Central Hospital.

Data processing: The data was processed according to statistical algorithms using SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA). The relationship between EGFR mutations and ABO blood and clinical, paraclinical characteristics were analyzed univariate by chi square test. Factors with a statistically significant association with EGFR mutations were included in multivariate analysis by regression. The difference was statistically significant when $p<0.05$.

III. RESULT

276 patients participated in the study with the median age was 64 ± 10.66 years old, the highest was 98 years old, the lowest was 31 years old, the

majority of patients were 60 years old or older, accounting for 72.8%. The male/female ratio was about 3.5/1. Most of the patients had a history of smoking at 73.6%. There were 34.8% patients carrying EGFR mutations. Bone metastases accounted for the highest rate of 40.9%, followed by pleural metastases 30.1% and brain metastases 26.4%. Liver and adrenals metastases were 10.1% and 7.2%, respectively. The results were shown in Table 1.

Table 1. Characteristics of patients

Characteristics		Number	Percentage (%)
Age	median	64 ± 10.66 (31-98)	
	≥ 60	201	72.8
	< 60	75	27.2
Gender	Male	214	77.5
	Female	62	22.5
Smoking history	Yes	203	73.6
	No	73	22.6
EGFR mutations	Positive	96	34.8
	Negative	180	65.2
Location of metastasis	Brain	73	26.4
	Bone	113	40.9
	Liver	28	10.1
	Adrenals	20	7.2
	Pleural	83	30.1

Blood group O accounted for the highest percentage with 50%, followed by patients with blood group B 25%. There were 21% of patients with blood group A and only 4% of patients with blood group AB. 100% of patients have Rh blood positive (Figure 1).

The rate of EGFR mutations in female (58.1%) was higher than male (28%) ($p<0.05$), according to the smoking history: EGFR mutationts in the non-smokers at 52.1% were higher than in the smokers (28.6%) ($p<0.05$). Patients with pleural metastasis with 43.3% had a higher rate of EGFR mutations than patients without pleural metastasis (31.3%), $p=0.049$. There was no association between EGFR mutations and metastatic sites of bone, brain, liver, adrenal glands (Table 2).

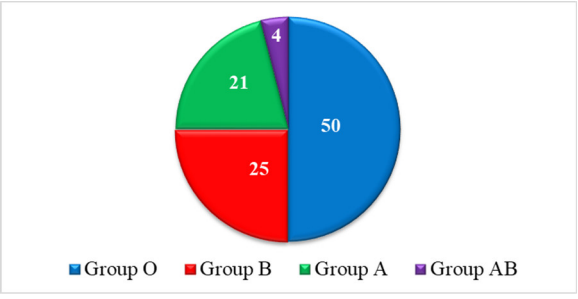

Figure 1. Ratio of blood groups ABO (n = 276)

Table 2. Rate of EGFR mutations according to some clinical and paraclinical characteristics

Characteristics		EGFR positive		EGFR negative		p
		n	%	n	%	
Gender	Male	60	28	154	72	0.000
	Female	36	58.1	26	41.9	
Smoking history	Yes	58	28.6	145	71.4	0.000
	No	38	52.1	35	47.9	
Bone metastasis	Yes	44	38.9	69	61.1	0.23
	No	52	31.9	111	68.1	
Brain metastasis	Yes	28	38.4	45	61.6	0.45
	No	68	33.5	135	66.5	
Liver metastasis	Yes	10	35.7	18	64.3	0.9
	No	86	34.7	162	65.3	
Adrenals metastasis	Yes	6	30	14	70	0.64
	No	90	35.2	166	64.8	
Pleural metastasis	Yes	36	43.4	47	56.6	0.049
	No	60	31.3	133	68.9	

The percentage of EGFR mutations in patients with blood B were 23.2% lower than that of non-B blood type (38.6%), the difference was statistically significant with p=0.02. There was no relationship between the rate of EGFR mutations and blood groups O, A and AB. The results were demonstrated in Table 3.

Table 3. Relationship between ABO blood and EGFR mutations

ABO blood	EGFR positive		EGFR negative		p
	n	%	n	%	
Blood O	53	38.4	85	61.6	0.206
Non-O blood	43	31.2	95	68.8	
Blood B	16	23.2	53	76.8	0.02
Non-B blood	80	38.6	127	61.4	
Blood A	23	39.7	35	60.3	0.38
Non-A blood	73	33.5	145	66.5	
Blood AB	4	36.4	7	63.6	0.9
Non-AB blood	93	34.7	173	65.3	

Multivariate analysis showed there was a relationship between gender and B blood with the ratio of EGFR mutations. Specifically, female patients had a 3.4 times higher rate of EGFR mutations than male patients, p=0.037. Patients with non-B blood group had a percentage of EGFR mutations 2.07 times that of patients with B blood, p=0.03. No association between smoking history and pleural metastasis with EGFR mutations were found in multivariate analysis (Table 4).

Table 4. Multivariate analysis of the association between EGFR mutations with gender, smoking history, B blood and pleural metastasis

Characteristics		OR	CI 95%	p
Gender	Female	3.4	1.07 - 10.5	0.037
	Male			
Smoking history	Yes	0.97	0.32 - 2.89	0.96
	No			
Blood group	Non-B blood	2.07	1.08 - 3.95	0.03
	B blood			
Pleural metastasis	Yes	0.72	0.4 - 1.27	0.26
	No			

IV. DISCUSSION

In the world as well as in Vietnam, lung cancer is usually middle-aged or older people, men and related to a history of smoking[5, 11, 12]. This was also the trend observed in our study. Regarding EGFR mutations, current studies showed that this mutation was more common in Asian patients than in patients in Europe or America. Results from 2 meta-analyses on the ratio of EGFR mutations in NSCLC patients demonstrated that the rate of EGFR mutations in Asians was 38.4%-49.1%, higher than in Europeans at 14.1% and 12.8%, respectively, in patients with the Americas, this percentage was 24.4%[10, 13]. In which, patients with adenocarcinoma have a rate of EGFR mutations of 38%[10]. In this study, we recorded that EGFR mutations appeared in 96 patients, accounting for 34.8%. This result was equivalent to the study of Dang Huynh Anh Thu et al., in patients with adenocarcinoma, the ratio of EGFR mutation was 35.7%[15], but it was lower than the results of some other studies such as the PIONEER study[11]. This can be explained because in this study we have up to 77.5% of patients were male and 73.6% of patients have a smoking history. We also analyzed the relationship between the percentage of EGFR mutations with gender characteristics, smoking history, and found that the ratio of EGFR mutations was higher in women than in men and in non-smokers than with smokers, the difference was statistically significant with p=0.000. Although, in our study, the proportion of patients who were male and have a smoking history was more than 70%, however, our results also share the trend with current studies on EGFR mutations[11, 15]. Evaluating the relationship between EGFR mutations and the rate of distant metastatic sites including bone, brain, liver, adrenal and pleural metastases, we found a relationship between pleural metastasis with EGFR mutations, particularly, pleural metastases patients have higher rates of EGFR mutations than patients without pleural metastases with p=0.049. In research by Kuijpers C.C.H.J. et al., the authors also found that, in patients with EGFR mutations positive, the percentage of pleural metastasis was 37.5% higher than that in the group without EGFR mutations, accounting for only 24.1%[16].

Regarding the ratio of blood groups in the ABO system, data in Vietnam recorded that blood group O accounted for the highest rate with 42%, followed by group B 30%, group A ranked third with 22% and low group was AB blood accounts for only 5%. This proportion was similar to Thailand and Chinese in Guangzhou, however, in some other Asian countries such as Japan and Korea, the percentage of blood A accounts for the highest[17]. In this study, we had 50% of patients with group O and this rate was 2 times higher than patients with group B. Patients with group A and AB accounted for a lower proportion, 21% and 4%, respectively. When evaluating the relationship between blood types O, B, A and AB

with the ratio of EGFR mutations, we found that, while there was no association between this mutation and blood O, A and AB, then blood B has a statistically significant lower rate of EGFR mutations than non-B blood patients with p=0.02. Multivariate analyzing, the results showed that, along with gender, blood B was a prognostic factor for the ratio of EGFR mutations, particularly, patients without blood B have a higher rate of EGFR mutation was 2.07 times higher than patients with blood B with p = 0.03. Up to now, among the literature, only the study of Gürbüz M et al (2021) in Turkey has evaluated the association between ABO blood group and EGFR mutations in patients with lung adenocarcinoma. However, in this study, the authors did not find any association occurring[12]. This difference can be explained because Turkey was a country in the European region with a percentage of EGFR mutation about 15% lower than the rate of this mutation in Vietnam. Besides, in Türkiye, the proportion of blood group A was highest, followed by blood groups O, B and AB. This rate was different from the ratio of ABO blood in Vietnam. Therefore, this was a new point in our study, which can be a premise for further studies to clarify this relationship.

V. CONCLUSION

Through the study of 276 lung adenocarcinoma patients tested for EGFR mutations and ABO blood, we found that blood B can be a prognostic factor for the EGFR mutations. Further studies need to be conducted to further clarify the prognostic role of ABO blood in patients with lung cancer and EGFR mutations.

Declarations

Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Consent for publication: Not applicable.

Acknowledgements: Not applicable.

Declaration of Conflicting interests: The authors declare that there is no conflict of interest.

Funding: The authors received no specific funding for this study.

Authors' contributions:

PVL, MD, PhD, Department of Respiratory Medicine, 108 Military Central Hospital, Vietnam: formal analysis, principal investigation, methodology, resources, writing original draft, review, editing and corresponding.

NMH, MD, PhD, Head of Department of Respiratory Medicine, 108 Military Central Hospital, Vietnam: Investigation, Methodology, resources, review, and editing.

VXN, MD, PhD, Associate Professor, Vice Head of Department of Blood transfusion, 108 Military Central Hospital, Vietnam: Investigation, Methodology, and resources.

NDT, MD, resident doctor in the College of health sciences, VinUniversity, Vietnam: Investigation, resources, software.

All authors have read and approved the manuscript.

REFERENCES

1. Landsteiner K (1901) *Zur Kenntniss der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe.* Zentralbl. Bakteriol 27: 357-366.
2. Aird I, Bentall HH, Roberts JA (1953) *A relationship between cancer of stomach and the ABO blood groups.* Br. Med. J 1(4814): 799-801.
3. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ et al (2009) *Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer*. Nat. Genet 41(9): 986-990.
4. Ashley DJ (1969) *Blood groups and lung cancer*. J. Med. Genet 6(2): 183-186.
5. Urun Y, Utkan G, Cangir AK et al (2013) *Association of ABO blood group and risk of lung cancer in a multicenter study in Turkey*. Asian Pac. J. Cancer Prev 14(5): 2801-2803.
6. Oguz A, Unal D, Tasdemir A et al (2013) *Lack of any association between blood groups and lung cancer,*

independent of histology. Asian Pac. J. Cancer Prev 14(1): 453-456.

7. Zappa C, Mousa SA (2016) *Non-small cell lung cancer: current treatment and future advances*. Transl Lung Cancer Res 5(3): 288-300.
8. Carpenter GM, King LJr, Cohen S (1978) *Epidermal growth factor stimulates phosphorylation in membrane preparations in vitro.* Nature 276: 409- 410.
9. Siegelin MD and Borczuk AC (2014) *Epidermal growth factor receptor mutations in lung adenocarcinoma.* Laboratory invertigation 94: 129-137.
10. Zhang YL, Yuan JQ, Wang KF et al (2016) *The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis*. Oncotarrget 7(48): 78985-78993.
11. Shi Y, Au JSK, Thongprasert S et al (2014) 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 9(2): 154-162.
12. Gürbüz M, Akkuş E, Karaalioğlu B et al (2021) *Association between blood type and epidermal growth factor receptor mutation positivity in lung adenocarcinoma patients*. J Oncol Sci 7(1): 20-24.
13. Shigematsu H, Lin L, Takahashi T et al (2005) *Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers*. Journal of the National Cancer Institute 97(5): 339-346.
14. Melosky B, Kambartel K, Häntsche M et al (2022) *Worldwide prevalence of epidermal growth factor receptor mutations in non*-small *cell lung cancer: A meta-analysis*. Molecular Diagnosis & Therapy 26: 7-18.
15. Dang ATH, Tran VU, Tran TT et al (2020) *Actionable Mutation Profiles of non-small cell Lung cancer patients from Vietnamese population.* Scientific RepoRtS 10: 2707.
16. Kuijpers CCHJ, Hendriks LEL, Derks JL et al (2018) *Association of molecular status and metastatic organs at diagnosis in patients with stage IV non-Squamous non-small cell lung cncer*. Lung cancer 121: 76-81.
17. Racial and ethnic distribution of ABO blood types. Bloodbook.com. Archived from the original on 4 March 2010. Retrieved 1 August 2010.