ORIGINAL ARTICLE

Association of ABO blood group with incidence and outcome of acute pulmonary embolism

ABO kan grubunun akut akciğer embolisinin insidans ve sonlanımıyla ilişkisi

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ABSTRACT

Objective: Association of ABO blood type with occurrence of pulmonary embolism (PE) has been demonstrated, and association of blood type with disease mortality and morbidity has recently been reported. Presently described was a retrospective study of mortality and morbidity according to blood group.

Methods: Blood type and medical data of 230 patients with confirmed PE was abstracted from medical records. Two control groups were used for data analysis; the 1st included blood donors (Control 1), the 2nd included hospital staff born in the same region (Control 2).

Results: In PE patients, blood group A was the most common phenotype (46.1%), followed by blood groups O (25.2%), B (20.4%), and AB (8.2%). Among the control groups, no significant difference was found in distribution of A vs non-A (36.4% vs 36.6%, respectively) or O vs non-O (66.6% vs 66.4%, respectively) blood groups. Blood group A was significantly more prevalent than non-A in patients with PE, compared to both control groups (p=0.002 and 0.03, respectively), and blood group O was significantly less prevalent than non-O in patients with PE, compared with both control groups (p=0.009 and 0.04, respectively). No significant difference was found in PE patients regarding in-hospital and midterm (6–36 months follow-up) mortality (p=0.36 and 0.15, respectively) based on blood groups.

Conclusion: Blood group A was significantly more common, and blood group 0 significantly less common, in patients with PE. No association was found regarding blood type and in-hospital outcome or midterm mortality.

ÖZET

Amaç: Daha önceleri ABO kan grubuyla akciğer embolisinin (AE) ilişkisi gösterilmiştir. Son zamanlarda bazı makalelerde kan tipiyle hastalığın mortalite ve morbiditesi arasındaki ilişki rapor edilmiştir. Kan gruplarına göre hastaların mortalite ve morbiditesini araştıran geriye dönük bir çalışma yürüttük.

Yöntemler: Akciğer embolisi olduğu doğrulanmış 230 hastanın tıbbi kayıtlarından tıbbi verileri elde edildi. Veri analizi için iki kontrol grubu kullanıldı. Birinci grup kan bağışı yapanlar (kontrol 1) ve ikinci grup (kontrol 2) aynı bölgede doğmuş hastanemiz personelini içermekteydi.

Bulgular: Akciğer embolisi hastalarında A grubu kan en sık bulunan fenotip (%41.6) olup ardından O (%25.2), B (%20.4) ve AB (%8.2) grubu gelmekteydi. A grubu olan ve olmayanlar (%36.4 ve %36.6) veya O grubu olan ve olmayanlarla (%66.6 ve %66.4) kontrol grupları arasında fenotiplerin dağılımı açısından önemli bir farklılık yoktu. Her iki kontrol grubuyla karşılaştırıldığında AE'si olan hastalarda A kan grubu, diğer kan gruplarına göre anlamlı derecede daha yaygındı (sırasıyla, p=0.002 ve 0.03). O kan grubu ise diğer kan gruplarına göre daha az görüldü (sırasıyla, p=0.009 ve 0.04). Kan gruplarına dayanarak hastanede yatan ve izlemin 6–36. aylarında bulunan AE hastaları arasında mortalite açısından herhangi bir önemli farklılık yoktu (sırasıyla, p=0.36 ve 0.15).

Sonuç: Akciğer embolisi hastalarında A grubu kanın görülme sıklığı anlamlı derecede yüksek iken O kan grubu anlamlı derecede daha düşük sıklıktaydı. Kan tipiyle hastanedeki sonlanım veya orta vadede mortalite arasında herhangi bir ilişki yoktu.

Among cardiovascular diseases, pulmonary embolism (PE) is a leading cause of mortality and morbidity, affecting people of all ages.[1,2] Risk factors have been a subject of interest, as prevention is the most effective means of decreasing mortality.[3,4]

Correlation of blood type and increased risk of certain diseases has been suggested. For example, associations have been demonstrated between ABO phenotypes and cardiovascular, gastrointestinal, and infectious diseases,[5] as well as malignancies includ-

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ing cancers of the stomach,[6] pancreas,[7,8] ovary, salivary gland,[9] and skin,[10] as well as stent restenosis.[11] The role of non-O blood groups in increased incidence of PE has been suggested.[7,12] Moreover, cardiovascular complications can be attributed to levels of 2 proteins involved in blood clotting– the von Willebrand factor (vWF) and factor VIII– which are influenced by blood type.[13]

Strong association has been demonstrated between non-O blood groups and risk of cardiovascular complications such as myocardial infarction and ischemic stroke.[14] The first description of the association between ABO blood group and thromboembolic complication was reported in 1969, and a lower susceptibility of blood group O to thromboembolic events was reported.[15]

Influence of blood type on short- and long-term mortality in cases of PE requires further investigation. Bakker et al. investigated risk of short- and long-term cardiovascular mortality in vascular surgery patients,[16] and found no association.

The aim of the present retrospective study was to investigate association of ABO blood group with incidence and outcome of PE.

METHODS

The present retrospective, single-center study included a population of 230 patients admitted with a first episode of PE between January 2012 and July 2014 at the Shahid Madani hospital. The study was approved by the Cardiovascular Research Center of the Tabriz University of Medical Science. Data collection included review of medical records and hospital discharge summaries. Informed consent was not required, due to descriptive and retrospective study design, though patient privacy was maintained throughout the process. Diagnosis of PE was based on clinical symptoms and confirmed by computed tomography (CT) angiography.

Obtained were recorded medical histories that included congestive heart failure (clinical signs according to the New York Heart Association, previous hospitalization for decompensated heart failure), recent cancer, and chronic obstructive pulmonary disease. Further information was gathered regarding age, sex, hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg in non-diabetics, systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg in diabetics, or use of antihypertensive medication), and lipid profile including high-density lipoprotein, total cholesterol, and triglyceride. Clinical outcome measures including administered medication (particularly fibrinolytic drugs), need for mechanical ventilation or inotropic agents, surgical embolectomy, and possible death were recorded. End points were incidence of PE and short- and midterm outcome among patients with O or non-O, and A or non-A blood types.

Abbreviations:

CT	*Computed tomography*
DVT	*Deep vein thrombosis*
FVIII	*Clotting factor VIII*
PE	*Pulmonary embolism*
TR	*Tricuspid regurgitation*
VTE	*Venous thromboembolism*
vWF	*von Willebrand factor*

Two control groups were included. The first comprised 81,970 asymptomatic and healthy volunteers without history of thrombosis or vascular disease who attended Tabriz blood donation centers during the study period. The second control group comprised 265 sex-matched healthy members of hospital staff, selected due to recent reports suggesting that blood donors may not be suitable candidates for control groups in case-control studies.[17] Thus, study design was amended to include 2 control groups: healthy blood donors (Control Group 1) and hospital staff (Control Group 2).

Continuous variables were expressed as mean±SD, frequency, and percentage. Kolmogorov-Smirnov test was performed to determine normalcy of data distribution. Independent sample t-test, chi-square test, and Fisher's exact test were used to evaluate differences between the 2 groups, and p values of less than 0.05 were considered significant. SPSS software (v. 17.0; SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

A total of 230 patients diagnosed with PE between January 2012 and July 2014 were enrolled. PE confirmation was based on clinical scenario and results of CT angiography, in which 64-slice Siemens multidetector CT scanner (Siemens Healthcare, Inc., Erlangen, Germany) was used. Women comprised 48.3% (111) of patients, and mean age of study population was 61.24±1.8 years. Median follow-up time was 21 months (follow-up period was 6–36 months). According to echocardiography findings, 143 patients (64.7%) had right ventricular enlargement, 87 patients

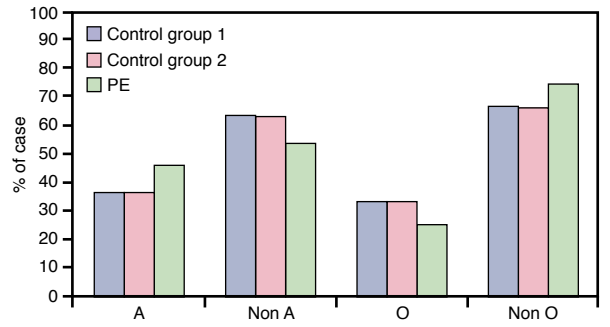

Figure 1. Prevalence of pulmonary embolism according to blood group, compared with controls.

(42.9%) had tricuspid regurgitation (TR) gradient less than 30 mmHg, 98 patients (48.3%) had TR gradient of 30–60 mmHg, and 18 patients (8.9%) had TR gradient of more than 60 mmHg. Fifty-five patients (32.4%) had O_2 saturation of less than 90%, and only 27 patients (20.8%) had $PaCO_2$ of less than 35 mmHg.

Table 1. Distribution of blood types between two control groups

Blood type	Control 1		Control 2		*p*
	n	%	n	%	
A	29868	36.4	97	36.6	0.956
non-A	52102	63.6	168	63.4	
O	27365	33.4	89	33.6	0.954
non-O	54605	66.6	176	66.4	
A	29868	36.4	97	36.6	0.518
B	17277	21.1	49	18.5	
AB	7460	9.1	30	11.3	
O	27365	33.4	89	33.6	

Control Group 1 included volunteer blood donors; Control Group 2 included hospital staff.

Patients were divided into O or non-O and A or non-A blood groups. Among PE patients, blood group A was the most common phenotype, in 106 patients (46.1%), followed by group O in 58 (25.2%), group B in 47 (20.4%), and AB in 19 (8.2%) patients. Among the control groups, blood group A was also the most common phenotype, presenting in 36.4% of patients in Control Group 1 and 36.6% of patients in Control Group 2 (Figure 1).

No significant difference in distribution of blood groups was found between the 2 control groups (Table 1). Incidence of A vs non-A, and O vs non-O blood groups in PE patients, compared with the control groups, was also evaluated. Blood group A was significantly more prevalent than non-A in patients with PE, compared with the control groups (p=0.002 and 0.03, respectively), and blood group O was significantly less prevalent than non-O in patients with PE, compared to the control groups (p=0.009 and 0.04, respectively) (Table 2). Baseline demographic, clinical, and cardiac biomarker characteristics in O and non-O patients are shown in Table 3.

No significant differences regarding age, sex, and medical history were found between O and non-O groups. In the PE group, lactate dehydrogenase was significantly lower in patients with blood group A (p=0.02), and white blood cell count was higher in those with group O (p=0.01). Adverse events were defined as presence of saddle emboli, need for mechanical ventilation, embolectomy, and fibrinolytic administration. No difference was found between O and non-O, and A and non-A blood groups, according to adverse events and mortality.

Also evaluated were short-term (in-hospital) death, midterm (home) mortality, and number of hospitalization days among O and non-O blood groups. No sig-

Table 2. Frequency of A vs non-A, and O vs non-O blood groups in patients with PE, compared with Control Groups 1 and 2

Blood type	Control 1		PE		*p*	Control 2		PE		*p*
	n	%	n	%		n	%	n	%	
A	29868	36.4	106	46.1	0.002	97	36.6	106	46.1	0.032
non A	52102	63.6	124	53.9		168	63.4	124	53.9	
non O	54605	66.6	172	74.8	0.009	176	66.4	172	74.8	0.042
O	27365	33.4	58	25.2		89	33.6	58	25.2	

PE: Pulmonary embolism.

Table 3. Clinical and cardiac biomarker characteristics in non-O and O blood groups

Characteristic of patient	All patients			Non-O blood type (n=172)			O blood type (n=58)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Male gender	113	48.9		80	46.5		33	56.9		0.171
Age, years			62.17±1.12			61.20±1.34			65.03±1.99	0.138
Heart rate			98.78±1.43			97.50±1.62			102.35±2.96	0.135
Systolic blood pressure			118.78±1.40			119.31±1.50			117.26±3.28	0.519
Diastolic blood pressure			73.41±0.89			73.39±1.02			73.47±1.78	0.971
Congestive heart failure	18	7.8		15	8.7		3	5.2		0.573
Hypertension	74	32.6		53	30.8		21	36.2		0.447
COPD	24	10.4		21	12.2		3	5.2		0.130
Cancer	12	5.2		5	2.9		7	12.1		0.013
Immobility	37	16.1		26	15.1		11	19.0		0.490
Surgery	36	15.7		25	14.5		11	19.0		0.422
OCP using	6	2.6		5	2.9		1	1.7		0.527
Blood sugar			136.42±62.72			135.88±63.68			137.93±60.66	0.851
Total cholesterol			169.27±42.24			170.45±42.93			165.74±40.28	0.464
Triglycerides			137.08±59.88			137.87±55.49			134.72±71.84	0.730
Creatinine			1.19±0.72			1.16±0.74			1.26±0.63	0.400
Hemoglobin			12.73±2.32			12.76±2.34			12.67±2.68	0.782

COPD: Chronic obstructive pulmonary disease; OCP: Oral contraceptive pill.

nificant difference was found regarding rates of early or midterm mortality and number of hospitalization days. In other words, non-O blood type was not associated with in-hospital or increased mortality at 21±3 months (Table 4). Subgroup analysis for total death based on gender difference was performed, and it was determined that male patients with O blood type had significantly higher rates of total mortality (p=0.01) (Table 5).

DISCUSSION

There are 4 common types of blood in the ABO blood group system, depending on antigens on the red cell

Table 4. Adverse events and death according to O and non-O blood types

Outcomes	Total		Non-O blood type (n=172)		O blood type (n=58)		*p*	OR*	95% CI
	n	%	n	%	n	%			
Adverse events** and early death	85	36.9	66	38.4	19	32.8	0.444	0.782	0.417–1.467
Presence of saddle emboli	39	16.9	27	15.7	12	20.7	0.381	1.401	0.657–2.985
Use of fibrinolytic	58	25.2	48	27.9	10	17.2	0.106	0.538	0.252–1.149
Mechanical ventilation	8	3.5	5	2.9	3	5.2	0.419	1.822	0.422–7.872
Total death	59	25.6	39	22.7	20	34.5	0.075	1.795	0.938–3.433
Late death (home mortality)	31	13.5	20	11.6	11	19.0	0.157	1.779	0.795–3.979
Early death (hospital mortality)	28	12.1	19	11.0	9	15.5	0.368	1.479	0.628–3.481

*OR: Odds ratio. **Adverse events: Sum of need for Mechanical ventilation, embolectomy or fibrinolytic administration.

Table 5. Association of gender and total mortality according to blood group

Gender	Blood type	Total death				*p*
		No		Yes		
		n	%	n	%	
Male	Non-O	69	86.3	11	13.8	0.017
	O	22	66.7	11	33.3	
Female	Non-O	64	69.6	28	30.4	0.596
	O	16	64.0	9	36.0	

membranes. These antigens are mainly found on the surface of erythrocytes, but can also be found on other cells, particularly on the endodermal epithelial cells (e.g., oral, gastrointestinal, bronchopulmonary, and urogenital cells), as well as on several types of parenchymal cells, including kidney parenchymal cells.[9,18] This explains the role of ABO blood type in tissue transplantation. Use of blood antigens as receptors or ligands for certain immunologic molecules and microbes has been confirmed.[19] In addition to the importance of blood groups in transfusion medicine, blood groups have been shown to play a significant role in bleeding, clotting, and increasing risk of thromboembolic events.[14,19]

The ABO blood group was the first antigen system identified, in 1901. The ABO gene is located on chromosome 9 and the 3-allele theory of Mendel and Bernstein explains its inheritance.[20] New predictive genetic factors such as ABO blood groups, fibrinogen gene haplotypes, factor V, factor VIII, and factor XIII Val34Leu polymorphisms were identified by Bezemer and Rosendaal as possible variants for coagulation impairment. Blood group O exhibits bleeding propensity and blood group A shows a tendency to thromboembolic events due to higher circulating level of clotting factor VIII (FVIII) and vWF.[21]

Expression of ABO antigens on plasma proteins such as vWF, FVIII, and α2-macroglobulin is clear.[22] The efficiency of proteolysis of vWF by ADAMTS13 is influenced by the attachment of ABO blood antigens through N-linked oligosaccharides to this factor. Therefore, presence of these antigens decreases vWF clearance. This mechanism has yielded a primary theory, which can explain the increased circulating vWF level in the non-O group, relative to that in the O group.[23] The effect of ABO blood group on vWF synthesis and secretion within the endothelial cells has been explained in alternate theories.[24] Plasma level of factor VIII is also higher in non-O patients, due to the high level of its carrier, vWF. It has been estimated that vWF level is 25% lower in patients with O blood group than in those with non-O blood group.[24]

Higher vWF level in non-O blood groups has been noted in several studies as a predictive factor for increased risk of future thrombotic events, including coronary heart disease events, myocardial infarction, ischemic stroke, peripheral arterial disease, and venous thromboembolism (VTE).[14,24] VTE and subsequent PE are recognized as life-threatening events with serious outcomes. The present results demonstrated that PE occurred more frequently in patients with non-O blood type, particularly type A; patients with O blood type had decreased risk of developing PE.

Golding et al. showed that a suitable control group for non-genetic studies of diseases could not be composed of blood donors, who may be significantly different from the general population in certain aspects. It is presently suggested that a control group comprising large numbers of blood donors may aid in achieving acceptable results, but that more precise results require a group that more accurately represents the general population.[17]

Jukic et al. found that non-O blood type was associated with thrombosis, in a study that included 154 thrombosis patients. The strongest association was observed in patients with AB blood type. However, the strongest association in the present study was found in patients with type A blood.[25] In 2 large cohort investigations, 77025 women and 30105 men were included. During follow-up, it was found that PE occurred in 499 participants. Non-O blood type, particularly in smokers, was found to have a strong

association with PE.[7] Larsen et al. conducted a case-control study in which 71729 pregnant women were included, 129 of whom developed VTE. Blood groups A and AB were associated with increased risk of deep vein thrombosis (DVT) and PE during pregnancy and puerperium.[12]

In spite of the association of non-O blood type with increased risk of thromboembolic diseases, Bakker et al. reported no increase in risk of short- or long-term cardiovascular mortality in vascular surgery patients with non-O blood type.[16] After 21±3 months of follow-up, similar results in patients with PE were presently demonstrated. Hence, although there has been a trend in associating high total mortality rate with type O blood (p=0.07), and in spite of decreased risk of thromboembolism, patients with non-O blood had rates of in-hospital and midterm mortality statistically similar to patients with type O blood.

In subgroup analysis, men with type O blood had higher total mortality than men with non-O blood. Contrary to the present results, it has been suggested in recent articles that patients with non-O blood had increased rate of cardiovascular mortality.[26] However, it has also been suggested that separate analysis per disease is necessary. van Langevelde et al. showed that DVT and PE risk factors were not the same, suggesting that they instead be considered separate aspects of the venous thrombus spectrum. Presence of pneumonia and chronic obstructive pulmonary disease increased risk of PE, but had little or no effect on DVT in their study.[27] Factor V Leiden mutation increases risk of DVT more than PE (factor V Leiden paradox).[28] Although increased tendency for blood clotting in those with non-O blood increases susceptibility for VTE, this phenomenon may ultimately be beneficial for survival, granting protection against bleeding.[29] Thus, while patients with type O blood have lower susceptibility for PE due to lower levels of FVIII and vWF, intensive long-term anticoagulant therapy may increase bleeding tendency and death, particularly in males. Higher recurrence of thromboembolism in non-O[30] and increased bleeding in O blood types can explain the almost equal rates of mortality of these patients. Further studies can assist in evaluating this theory. Currently, association between ABO blood type and cause-specific or total disease mortality has been investigated in few studies.

In a population with resected colon cancer, Cao et al. showed that patients with AB blood type had better survival than those with non-AB types.[31] Suadicani et al. followed 3346 male participants aged 53–74 years for 16 years, and 170 (5.1%) participants died from lung cancer. By referencing those with blood type B/AB, the lung cancer mortality hazard ratio for blood type O was found to be 2.05 (1.18–3.55).[32] Complications have been considered in several studies. Dentali et al. conducted a retrospective study of 268 patients with confirmed proximal DVT, with or without PE. Increased risk of residual vein obstruction was found in patients with non-O blood after 6 months of standard anticoagulant therapy.[33]

To the best of our knowledge, the present study was the first to evaluate the effect of gender on total mortality of PE patients according to blood group. The Shahid Madani hospital is a main cardiovascular referral center that accepts patients with massive PE from nearby general hospitals. In the present study, 25% of patients included received fibrinolytic therapy, and 37% developed adverse events and death during hospitalization.

Conclusion

Frequency of blood group A was significantly higher, and blood group O significantly lower, in patients with PE. In spite of increased total midterm mortality in men with O blood type, no association was found between blood type and in-hospital outcome or midterm mortality.

Conflict-of-interest issues regarding the authorship or article: None declared

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Keywords: ABO blood group; blood donor; mortality; pulmonary embolism.

Anahtar sözcükler: ABO kan grupları; kan bağışçısı; mortalite; pulmoner emboli.