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# The Study of Some Possible Risk Factors for Arterial Thrombosis in the Example of Georgian Patients

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## Abstract

Cardiovascular diseases (CVD) are the most common cause of death worldwide. As arterial as venous thrombosis are major cause's morbidity and mortality. There is an exponential increase in the risk of arterial and venous thrombotic events with age, gender, smoking habits, diet type etc. The association of arterial and venous thrombosis and ABO histo-blood group is well established. Our research aim was to find a possible relationship between age, gender, smoking habit, ABO, Rh, Kell, MN blood group and arterial thrombosis in the example of the Georgian population. The study material comprised the blood samples of 100 patients with arterial thrombosis. Also, control (donor) groups were studied. The Control group included individuals without cardiovascular disease during the 2019–2020 periods. They were asymptomatic, healthy persons. The immunoserological express method with universal monoclonal antibodies were used. 77% of the studied patients were males. The majority of patients were over the 60 years old. 35% of our studied patients are non-smoker, 39% are ex-smoker, and 26% are active smokers. A similar distribution has the ABO and Rh phenotypes in patients and donors. M+ N+ (MN) the phenotype is relatively high in the patient group to comparing to donors. Kell antigen prevalence was relatively high in studied patients. Our study has shown maleness as a higher risk factor for arterial thrombosis. The smokers have a more predicted chance for arterial thrombosis. K+ phenotype and M+ N+ characteristics are a high prevalence in patients. There is no correlation between ABO and Rh blood groups with arterial thrombosis.

**Keywords:** risk factor, arterial thrombosis, red blood cells, ABO group, Rh group

## 1. Introduction

Cardiovascular diseases (CVD) are the most common causes of death worldwide. As already well known, the CVD has several risk factors such as blood pressure, glucose, lipids, blood pressure, glucose, lipids, blood pressure glucose, lipids etc. As arterial as venous thrombosis are major cause's morbidity and mortality.

There is an exponential increase in the risk of arterial and venous thrombotic events with age, gender, smoking habits, diet type, etc. [1].

The reason of arterial thrombosis (AT) is rupture of atherosclerotic plaque and formation of platelet-mediated thrombi, which can cause ischemic injuries. The clinical manifestations of atherothrombosis in most cases are cardiac ischemia and stroke. After the acute Myocardial Infarction (MI) and stroke, venous thrombosis (VT) is most common vascular disease. Venous thrombi are produced by fibrin and red blood cells. VT and AT are associated with variety of causes. For example, VT is associated with hypercoagulatin or reduced blood flow, while AT has been linked to atherosclerosis [1].

The thrombocyte activation, which is triggered by major endothelial injury, creates main background for thrombus formation in the heart and arterial circulation. However, the high rate of blood flow prevents thrombus and clot formation. Activation and adherence of platelets are major predisposing circumstance for thrombus formation beneath the high shear stress in arteries [2]. Arterial thrombi (defined as “white”) have been traditionally proposed to be composed mainly of fibrin and platelet aggregates. The Venous thrombi (defined as “red”) have been proposed as mostly being enriched in fibrin and erythrocytes [3].

The significant determinant for AT is the complex interaction of lipids, inflammation and immune system, which is less, but, important for venous thrombosis as well [1]. The major mechanisms triggers intravascular thrombosis, lies at cellular and molecular levels, is known as “Virchow’s triad” and includes endothelial injury, stasis or turbulent blood flow and blood hypercoagulability. Endothelial injury leading to platelet activation almost inevitably underlies thrombus formation in the heart and the arterial circulation, where the high rates of blood flow impede clot formation. Platelet adherence and activation is a necessary prerequisite for thrombus formation under high shear stress, such as exists in arteries [4].

Abnormal blood flow contributes to AT by causing endothelial injury or dysfunction. Furthermore, chaotic blood flow forms countercurrents and local pockets of stasis. Stasis is major factor in the development of venous thrombi. Under conditions of normal laminar blood flow all blood cells are found mainly in the center of the vessel lumen, separated from the endothelium by a slower moving layer of plasma, but static blood flow contributes to thrombosis. Hypercoagulability is high tendency of the blood to clot. It is an important risk factor for venous thrombosis [5].

Some peripheral blood biomarkers are useful preventive markers for arterial and venous thrombosis. The association of venous thrombosis and the ABO histo-blood group is well established. Numerous studies have demonstrated the association between the ABO blood system and venous thrombosis. It has already been frequently revealed in various populations that venous thrombosis is less frequent in the O group than in individuals with other ABO blood groups. Individuals including A, B and AB (non-O) blood group have increased of venous thrombotic disease incidence compared to the O blood group individuals.

The non-OO blood group carriers are at more significant, two-fold risk of thrombosis rather than the individuals falling into the OO blood group carriers. Accordingly, the significant serious risk of thrombosis was higher in B alleles’ carriers than in those carrying A alleles [6]. Many scientific data showed the blood group’s possible protective effect with venous thrombosis [7].

Under an increased risk of venous thrombosis discussed, the ABO blood group influences plasma levels of the coagulation glycoprotein named von Willebrand factor (vWF). The vWF levels are 25% lower in the O group individuals compared to other blood groups. The mechanism of how the ABO group determines plasma vWF levels has not been clearly determined. It is already known that ABO (H)

carbohydrate antigenic determinants are expressed on the N-linked glycan chains of circulating plasma vWF [8].

As it already mentioned vWF is a risk factor as AT as VT. It is the molecular player in pathogenesis of thrombosis. The high level of vWF is correlated with arterial thrombosis, and especially morphological changes of vWF is a risk factor of cardiovascular disease, through promoting the platelet binding to damaged endothelium and platelet aggregation [9]. In the case of venous thrombosis, vWF is essential for flow reduction-induced thrombus formation in deep veins (Deep vein thrombosis (DVT)). The vWF-mediated platelet recruitment in DVT in the setting of blood flow disturbance plays an important pathogenic role. The gene mutations and polymorphisms, aging, hormone status, ABO blood groups, and systemic inflammation, have been involved in the modulation of both VTE predisposition and plasma levels of vWF [10].

Aging and ABO blood type influence in the bidirectional and combined way on vWF and FVIII levels. There are many studies shown that vWF significantly elevated in centenarians and type non-O individuals achieved much earlier in life the high vWF levels [11–13].

It has been investigated that the rate of venous thromboembolism is higher in black rather than white populations. Also, the non-O blood types have been associated with a notably high risk of venous thromboembolism. Since the majority of black population has an O blood and B blood type, thus may expect low cases of this disease. But it is paradoxical to find that VT prevalence has been observed to be higher in blacks than whites [14]. Due to the study to reveal suppose association between ABO and VT in blacks separately was, find out that the rate of VT was quite higher in non-O blood type individuals comparing to those with O blood groups, which also previously fixed in whites. Obtained data suggests that non-O blood type may consider as protective factor against VT in blacks too. The VT rate was higher in both, black and white non-O blood group individuals and was higher in males comparing to females and increasing with age. Further studies also confirmed above mentioned association with O group, that it may be a protective factor against VT, regardless of age and gender.

Various studies have also been reported similar to AT [15], while in different studies, this similarity was not found [6]. The study done in Switzerland reported that 2.5 times higher prevalence of B allele among MI patients than controls [16]. Underlined mechanism where may B allele is involved in pathogenesis of MI is still uncertain, since the role of ABH antigen is still unclear. In this regards various possibilities can be discussed.

The association between ABO histo-blood group, factor VIII and vWF have currently been revealed by O'Donnell and Laffan et al., [17] where BB homozygous had significantly high levels of vWF. The mechanism how B blood type affects vWF plasma levels is uncertain, but it is already defined that epitopes of N-linked oligosaccharide on the serum proteins modulate their half-lives. Hence it may be suggested that the ABH epitopes affect vWF plasma levels which cause elevation of vWF plasma levels, which is highly associated with increased risk of MI.

There are two major pathophysiological explanations tell that B antigen determines an aggregation of platelets, which may be a precursor of MI. The first mechanism is that removal of B antigen from multimeric glycoprotein by  $\alpha$ -galactosidase decreases ristocetin cofactor activity [18] and the second is the fact which is claiming that increased platelet adhesiveness is shown in non O group individuals.

A study confirms the link between some vascular disorders and the non-O blood groups. The study has shown that there was a similar effect of ABO(H) on the level of vWF, but further research is required for obtaining more details on O(H) antigen expression levels in thrombosis. However, as A1A, A1B and BB composed of the



meaningful proportion of the population attributable fraction of VT, there may be a role for more widespread adoption of ABO(H) typing in testing strategies [19]. The study of the Iranian population has not shown a significant association between ABO blood groups and coronary artery diseases. Similar results have been shown in the cases of different blood groups as well [20]. Similar results were revealed according to the study of the cardiovascular risk factors and MI in the Turkish cohort. The study showed no difference according to the cardiovascular risk factors and different blood groups within patients with MI and healthy population [21]. No association of the blood group B with MI in the sample population in Malaysia has been revealed [22].

Our research aimed to find a possible relationship between the blood groups, such as ABO, Rh, Kell, MN and AT, based on the cases of the Georgian population. The cardiovascular system diseases are also topical for Georgia, which is proved by “The European Heart Network” (EHN) (based in Brussels, EHN is an alliance of different countries together with non-governmental organizations and “Heart Foundations”). According to the research conducted by the alliance, in 2015, 29.007 deaths were reported in men and 33.509 in women ([European Cardiovascular Disease Statistics 2017 (<http://www.ehnheart.org/cvd-statistics.html>)).

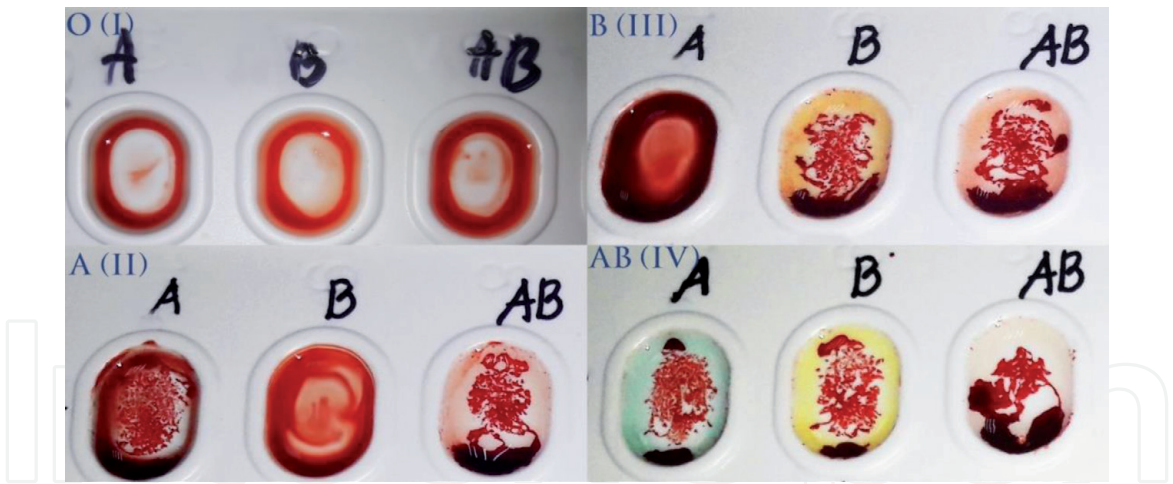
## **2. Research materials and methods**

In our study, we aimed to determine blood group antigens in patients with AT. The study material consisted of blood samples of 100 patients with AT which were further processed according to the appropriate methodology.

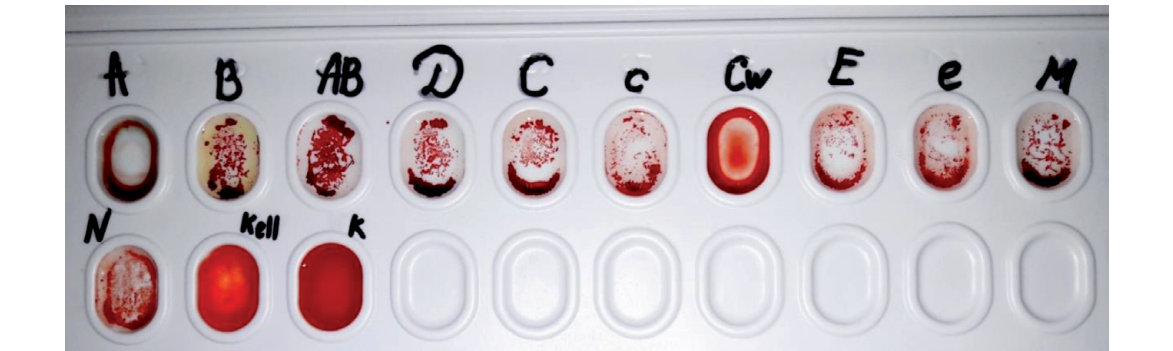
The research materials were collected at the Heart Disease Department of Batumi Referral Hospital (Republic of Georgia). The research was implemented of the two years of 2019–2020. This work received financial support from the Batumi Shota Rustaveli State University (Grant project №02–12/57. 15.02.2019). Also, the control group was studied. The Control group included individuals without cardiovascular disease during the period from 2019 to 2020. They were asymptomatic, healthy persons. All participants in the control group were from the Adjara Region (Republic of Georgia). The age range of male and female individuals in both groups (patients and controls) was 40–93. All donors and patients gave their written informed consent for participation in this study, which has been duly approved by the Ethics Committee from the “UnimedAdjara” Ltd. (Adjara, Georgia). (Ethic approval number is BAH-15-1026-4/1 26.10.2015).

The express forward and reversed method with universal monoclonal antibodies was applied in order to type blood groups and reveal the blood group system antigens. Anti-A, anti-B, anti-AB monoclonal antibodies were used for ABO blood group typing (**Figure 1**). Five monoclonal antibodies, anti-D; anti-C; anti-c; anti-E and anti-e were used to identify Rh system antigens. MN blood group phenotypes have been typed by two anti-M and anti-N antibodies and Kell system antigens were determined by anti-Kell and anti-k antibodies (Bio-Rad, cypress diagnostics) (**Figure 2**). Also, for research purposes, standard O(I), (II), (III) group erythrocytes and standard O(I), A(II), B(III), AB(IV) serums were used. For identifying erythrocyte blood group antigens ID cards such as ABO/D + Reverse Grouping (Bio-Rad) (**Figure 3**) were used. The Obtained material has been studied and processed statistically.

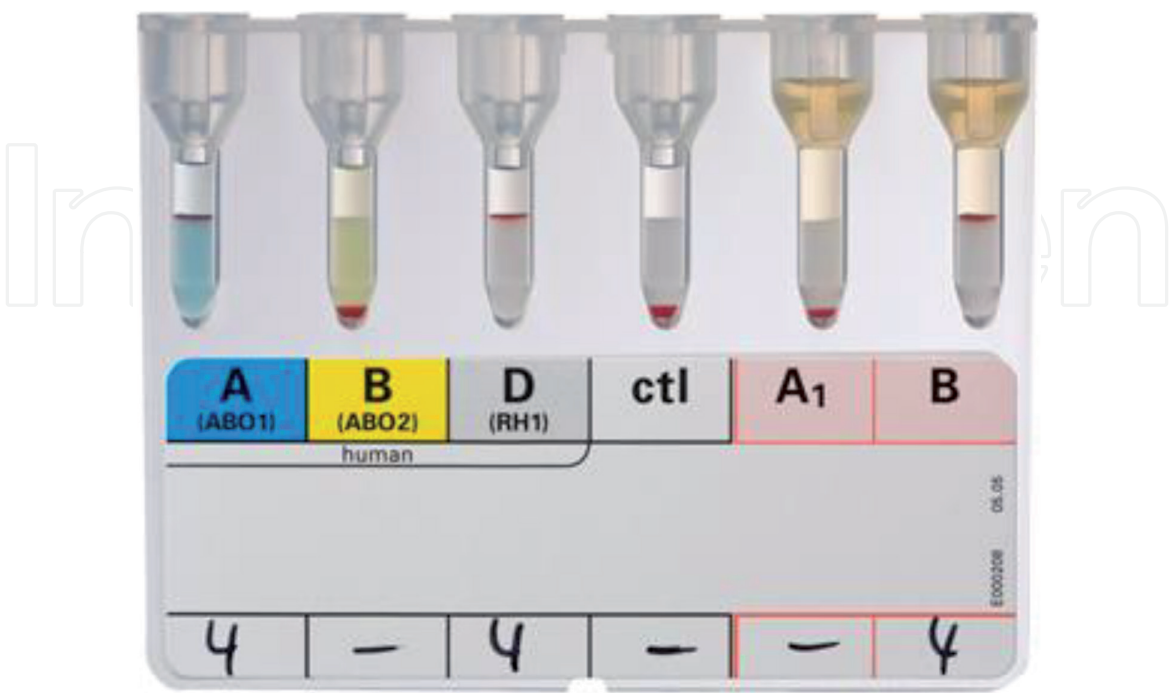
The results were processed with the bio statistical methods. The rates between donors and patients groups were compared by Chi-square analysis of proportions.



**Figure 1.**  
*ABO blood group typing by monoclonal antibodies.*



**Figure 2.**  
*ABO, Rh, MN, Kell blood group typing.*



**Figure 3.**  
*ABO/D + Reverse Grouping ID card.*

The level of statistical significance was set at 0.05 in all analyses. The donors and patient cohort are the same profile. All participants have the same nationality. They are Georgians and age intervals are the same for both cohort.

We used the general formula for calculating chi-square ( $\chi^2$ ).

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

This test allows assessing the difference between observed (O) and expected (E) values. We used as on-variable chi-square as in some case two-variable chi-square criterion.

Gene distribution frequency of the ABO system in the studied cohorts was also analyzed. Their frequency was calculated using the formula used in the study of the three-allelic genetic system. Where O, A and B are the ration of people carrying O (I), A (II) and B(III) groups to the total number of research objects.

$$r = \sqrt{O}; p = 1 - \sqrt{A + O}; q = 1 - \sqrt{B + O}$$

Alleles of the Kell and Rh system were also analyzed in the studied cohorts. Different frequencies of p(K), p(D) and q (k), q (d) were found in the target groups.

$$q = \sqrt{\frac{n_{aa}}{N}} \quad p = 1 - q$$

Where  $n_{aa}$  is a recessive homozygote according above mentioned locus (kk,dd), N is the total number of examined individuals.

The frequency of MN blood group alleles are calculated by bellow mentioned formula:

$$q = \frac{n_A + \frac{1}{2}n_{AB}}{N} \quad p = \frac{n_B + \frac{1}{2}n_{AB}}{N}$$

where  $n_A$  means the number of carriers of the phenotype M,  $n_{AB}$  indicates MN phenotypes,  $n_B$  means the number of carriers of the phenotype N.

### 3. Age, gender, smoking and arterial thrombosis

#### 3.1 Age, gender and arterial thrombosis

As already well known, aging is considered a physiological process with the gradually ongoing accumulation of numerous structural alterations in cells, tissues, and organs. Accordingly, most alterations are associated with functional changes and have significantly increased susceptibility toward some diseases. There is an exponential increase in the risk of both arterial and venous thrombotic events with aging. This fact has been proven by several studies that revealed the increased



plasma concentration of V, VII, VIII, IX factors, fibrinogen as well as vWF levels which is increasing progressively along the age [12, 23]. In addition, it has revealed that high plasma levels of fibrinogen supposedly cause the high incidence of cardiovascular events in age [24].

The activity of proteolytic enzymes (PEs) in the blood serum changes with age [25]. Physiological aging also correlates with increased plasma levels of numerous blood coagulation proteins and fibrinolysis impairment. The studies confirm that there is an association between vascular and thromboembolic diseases and aging. Thus, the state of hypercoagulability tends to increase the risk for the development of thrombosis. Accordingly, hypercoagulability considers a significant marker associated with impairment in advanced age [26]. The blood coagulation capacity increases according to age in healthy individuals because of increases in the most procoagulant factors [27]. The blood coagulation potential a gradual increase during young adulthood and an almost 2-times elevated in old age [28]. The study confirmed that aged 53–64 years is associated with significantly higher fibrinogen levels than younger aged 20 [29]. The plasma concentration of several clotting factors increase with progressing age in healthy [30]. It suggests that thrombotic diseases are found more frequently in subjects with higher plasma levels of factor VII [26].

In the human body PEs have a significant role. PEs is responsible for numerous processes in health and disease. Moreover, PEs is considered a significant factor in several physiological processes, including morphogenesis, cell differentiation, etc. [31]. According to the physiological coagulation mechanism, the calcium and platelet together contain a PEs like the trypsin, which transforms prothrombin to thrombin [32]. Paczek et al. aimed to investigate the associations between the aging process and PEs activity (including trypsin, elastase, plasmin, and active MMP-9). As they found, the active MMP-9 concentration and trypsin activity decreased according to age. Notably  $\alpha$  1-antitrypsin concentration and plasmin activity are elevated. This study suggests that individual PEs activity in the serum changes with age [33].

We have studied 100 patients with AT. The materials have been taken randomly. The 77% of patients were males and the rest of 23% were females. 100 volunteers were used as the controls group in the study. All volunteers were healthy. Age interval was the same for donor cohort as well. The gender ratio was not equal in patients and donors. 51% males and 49% females were studied in our controls group (**Table 1**).

As our research has shown, the gender ratios between patients and controls are different. In this case, we used a two-variable chi-square criterion. Statistically revealed a high number of chi-square criteria for both variations. This data indicates the relationships between qualitative variables. In this particular case, the value  $\chi^2$  effectively rejects the null hypothesis ( $E = 0$ ). The value of  $\chi^2$  in the case of males is 64.32, and in the case of females equals to 39.94. These numbers are much higher than the critical value (CV) of the criterion of the degree of freedom (d.f. = 1), which is equal to 3,841. The P-Value is  $< .00001$ . The result is significant at  $p < .05$  (**Table 1**).

Gender	Patients	Control	$\chi^2$ , (d.f.) = 1	
Male	77 $\pm$ 4,2	51 $\pm$ 4,99	64,32	CV = 3,841
Female	23 $\pm$ 4,2	49 $\pm$ 4,99	39,94	

**Table 1.**  
*Gender ratio in donors and in the control group.*



№	Age category	Patients		Control	
		Male	Female	Male	Female
1	40-49	11	0	6	3
2	50-59	10	3	6	7
3	60-69	25	4	16	20
4	70-79	23	11	17	11
5	80-89	7	4	6	6
6	90-99	1	1	0	2
n		77	23	51	49

**Table 2.**  
*Age category and gender in donors and control group.*

In our study we have been allocated six age categories (**Table 2**) as well in patients as in control cohort. As it has presented on the table in young categories, age range between 40–49, there are not female patients, however from the alternative gender, 11 patients belongs to current age group. The majority of patients (56 males and 20 females) are over the 60 years old.

As our data shows, AT is much more common in males than in females. Men have a higher risk of first and recurrent venous thrombosis than women. The pathophysiology of this phenomenon is yet unknown [34]. In the United States, cardiovascular diseases are the leading cause of death; for example, in 2013 death in both sexes were equal. However, several cardiovascular diseases occur early in age-onset within men than women, like MI and coronary heart disease (CHD), where women’s prevalence is ~10-year delay in onset [35–37].

**3.2 Smoking and arterial thrombosis**

The harmful habits such as smoking, alcohol, drugs have a negative impact on human health. In particular, they have some implications to provoke diseases of the cardiovascular system. The cigarette smoke exposure (CSE) is known to increase the risk of AT. The almost 40% of smoking-related deaths are associated with cardiovascular disease. Both active and passive CSE predispose to cardiovascular events.

It is known that cigarette smoking increases inflammation, thrombosis, and oxidation of low-density lipoproteins (LDL). Several clinical and experimental data support that cigarette smoke increases the cell’s oxidative stress that can promote cardiovascular dysfunction [38]. In some studies are reported that acute CSE leads to functional changes in both fibrinogen and platelets, affecting clot dynamics, which were correlated with an alteration in fibrin structure [39].

We have analyzed the possible association between cigarette smoking and AT. Accordingly, three target groups were allocated: active smokers, non-smokers, and ex-smokers. 35% of patients were non-smokers, 39% were ex-smokers and 26% were active smokers (**Table 3**).

As it is shown from the table (**Table 3**), 35% of patients with arterial thrombosis had no exposure to tobacco use, while in the controls group nonsmoker are 1.7 times more (60%). Statistically revealed a high number of chi-square criteria, which indicates the relationships between qualitative variables. In this particular case, the value  $\chi^2$  is quite effective for rejecting the null hypothesis ( $E = 0$ ). The value of  $\chi^2$  in the case is 55, 05. These numbers are much higher than the critical value (CV) of

Category	Smokers	Non-smoking	Ex-smokers	$\chi^2$ (d.f. = 2)	CV
Patients	26 ± 4,38	35 ± 4,76	39 ± 4,85	55,05	5,991
Control	26 ± 4,38	60 ± 4,89	14 ± 3,46		

**Table 3.**  
*Smokers, non-smokers and ex-smoker among patients with arterial thrombosis and control.*

Age	Smokers (26)		Non-smokers (35)		Ex-smokers (39)	
	Male	Female	Male	Female	Male	Female
40-49	8	0	0	0	3	0
50-59	2	0	3	2	4	1
60-69	12	0	2	4	11	0
70-79	3	0	6	10	15	1
80-89	1	0	3	4	3	0
90-99	0	0	0	1	1	0

**Table 4.**  
*Smokers, non-smokers and ex-smokers among patients with arterial thrombosis (by age and sex).*

the criterion of the degree of freedom (d.f. = 2), which is equal to 5,991. The result is significant at  $p < .05$ .

We have also been analyzed the age and gender groups of smokers, non-smokers and ex-smokers among patients with AT (**Table 4**). As it is shown on the table there are not female patients in the smokers' (n = 26) category. All 26 active smoker patients are males. As we can see, the highest rates of AT is revealed in the category of smokers, in which only men between 60–69 years of age were observed, (12 individuals in total) and further more in the category of ex-smokers males dominates as well with the age of 70–79 (15 males and 1 female). Among whole research group 39% of patients were ex-smokers.

It is a wonder why the number of ex-smokers exceeds to the active smokers in our research? We do not have sufficient information when and with what a reason ex-smoker patient group gave up smoking. The high prevalence of ex-smokers in patients may be due to the fact that they had to quit smoking due to deterioration their health condition. On the other side the ex-smokers have a greater experience of smoking (at least 10 years), they have accumulated more toxic substances in the body, atherosclerotic plaques, have abnormal fibrin structure and etc., which may also be one of the considerable reasons for high incidence [40, 41].

#### 4. Blood groups and arterial thrombosis

##### 4.1 ABO blood group and arterial thrombosis

Many studies have found that blood group phenotypes play as an important genetic risk factor in many diseases. For example, in hemostasis, the ABO blood group has a great influence since it is a crucial determinant of the vWF and therefore, to coagulation factor VIII (FVIII). Besides, an individual with O blood group has around 25% lower vWF and FVIII circulating levels comparing to other blood group individuals. Some experimental studies show that several inflammatory

Category	O (I)	A (II)	B (III)	AB (IV)	ABO system Genes frequency			$\chi^2$ (d.f. = 3)	CV
					r	p	q		
Patients	47 ± 4,99	38 ± 4,83	13 ± 3,36	2 ± 1,4	0,69	0,08	0,23	0,09	7,815
Control	48 ± 4,99	38 ± 4,83	12 ± 3,24	2 ± 1,4					

**Table 5.**  
*ABO blood group phenotypes distribution among patients with AT and control.*

cytokines and cholesterol levels may be the most likely mechanisms to explain an association between ABO blood group and cardiovascular diseases [42–45].

Numerous studies have established an association between venous thrombosis and the non-O group. The mechanism of an association with the ABO blood group and cardiovascular disease has not been fully explored. However, there is a hypothesis that ABO glycosyltransferases modify glycoproteins and glycolipids on platelets’ surface effects on the platelet function. The antigens of the ABO system are not presented only on the erythrocyte surface; There are also founded on the cells of epithelium platelet and vascular endothelium, as well [46]. Thus, they are extending potential pathophysiology into other areas of cardiovascular disease and postoperative outcomes.

According to the authors, it is suggested that venous and arterial thrombotic disorders have different pathophysiological backgrounds; for example, arterial thrombosis has extended by platelet activation, while venous thrombosis is based on the clotting system activation [3].

Our study aimed to find an association between blood groups and arterial thrombosis. 100 patients with arterial thrombosis and the same number (100) healthy control group’s were investigated. In the control group, the distribution of ABO blood group phenotypes was as follows: group O – 48%; group A – 38%; group B –12%; and group AB – 2%. A similar distribution was revealed in the patients as well (**Table 5**). As the obtained data confirms, the correlation was not found between the ABO blood group and AT. The prevalence of ABO blood group phenotypes (O, A, B, AB) is the same in the patients and the controls. ABO system gene frequency is the same both cohort. The r allele frequency is 0,68, p – 0,08 and q – 0,23.

In this case, we have a Null hypothesis ( $E = 0$ ). This means that there is no association between the two variables. The value of  $\chi^2$  criteria is equal to 0,09, which is much less than the critical (CV) value of the degree of freedom (d.f. = 3), equal to 7,815. The P-Value is.029291. The result is significant at  $p < .05$ . Our result is the same as the study, including Iranian patients with coronary artery disease. The association with particular ABO blood groups was not found based on the comparison analysis between coronary artery disease general population [20]. The same data is in the study of risk factors and myocardial infarction (MI) in a Turkish cohort. The Turkish population study shows that ABO blood group antigens’ frequency was the same in the patients and the control group [21]. There is no association of blood group B with MI in the sample population in Malaysia [22].

4.2 Rh factor and arterial thrombosis

Our aim was also to find a possible correlation between Rh blood group antigens and AT. Next to the ABO system, the Rh blood group system is the second significant human blood group system [47], which comprises 49 blood group antigens, among them the five D, C, c, E, and e antigens are the clinically most important

Category	Rh <sup>+</sup>	Rh <sup>-</sup>	Rh system gene frequency		$\chi^2$ (d.f. = 1)	CV
			q	p		
Patients	78	22	0,46	0,54	0,05	3,841
Control	79	21				

**Table 6.**  
*Distribution of Rh positive and Rh-negative blood group in patients and control.*

antigens. Rh blood group is associated with the hemolytic disease of the newborn. The hemolytic condition occurs when there is an incompatibility between the mother and the fetus's Rh blood types.

The majority of the available studies involved ABO blood group and risk of cardiovascular diseases, while there is a lack of data on the Rh factor's effect on MI's risk and prognosis. Serum cholesterol varied significantly in the Rh system, but not in the ABO system [48].

The Rh family proteins include none erythroid Rh homologs found on the epithelial tissues of different organs, such as kidney, liver, brain, and skin [49]. Some data points to the coincidence of certain cardiovascular risk factors with the Rh blood group [50]. It has been described that positive Rh is an independent risk factor for low levels of high-density lipoprotein (HDL) cholesterol, which is a well-known risk factor for cardiovascular disorders. Except for that, several clinical studies reported that the Rh genotype is correlated with systolic blood pressure [51].

Rh factor was studied in both patients and control cohort. 78 studied patients were Rh-positive and the remaining 22 were Rh-negative. The prevalence of the Rh phenotypes was similar in the control group (79 – Rh-positive and 21 - Rh-negative) (**Table 6**). Rh system gene frequency is the same for both cohorts. The frequency of q allele is 0,46, p allele – 0,54.

In our study, the prevalence of the Rh blood group phenotypes (Rh-negative and Rh-positive) is the same in the patients and the controls. Based on our study, we could not found any correlation between arterial thrombosis and Rh blood group because the Rh phenotypes in the controls and patients groups are equally distributed. We are not able to reject the Null hypothesis ( $E = 0$ ). There is no reliable difference between the two categories. The value of  $\chi^2$  criteria, in this case, is equal to 0.05, which is much less than the Critical Value (CV) of the degree of freedom (d.f. = 1), which is equal to 3,841. The P-Value is.025347. The result is significant at  $p < .05$  (**Table 6**).

### 4.3 MN blood group and arterial thrombosis

The MNS antigen system is a human blood group system based upon two genes (glycophorin A and glycophorin B) on the 4th chromosome 4q28.2-q13.1. There are currently 46 antigens in the system [52], but the five most important are called M, N, S, s, and U. We have studied 2 antigens from this system. Based on this, we have allocated 3 phenotypes (M group, N group, and MN group) in the control cohort and the patients. There is little information about MN blood group correlation with some kind of infectious disease [53, 54].

No information could have been obtained through the scientific literature about the correlation between MN blood groups and AT. But there are some information about association of MN blood group and hypertension. Males with the MN phenotype had significantly higher unadjusted systolic and diastolic blood pressures than those who were homozygous MM or NN [55]. The increased of



Category	M+N+	M+N-	M-N+	MN allele frequency		$\chi^2$ , (d.f. = 2)	CV
				q	P		
Patients	43	48	9	0,695	0,305	8,95	5,991
Control	30	55	15	0,7	0,3		

**Table 7.**  
*MN group system phenotype frequency in patients and control group.*

erythrocyte sodium-lithium counter-transport activity associated with hypertension. Erythrocyte sodium-lithium counter-transport genetically is heritable, but it is not monogenic inheritance [56]. It is complex genetically characteristics. Some authors studied the association of blood pressure, sodium-lithium counter-transport and two genetic markers – MN Blood group system and haptoglobin in Michigan population example. They find genetic linkage between the MN locus and red blood cell sodium-lithium counter-transport activity. The authors suggested that the relation between MN phenotype and systolic blood pressure is different in men and women. The men with the MN phenotype and having high systolic blood pressure had significantly elevated red blood cell sodium-lithium counter-transport activity [57].

Delanghe et al., study suggested that detection age of hypertension was lower for patients with MN phenotype. The increasing age of detection the distribution of MN phenotype gradually decreases. The hypertensive with MM blood group had a lower prevalence of cerebrovascular accidents [58].

Sobha R. et al., found that the distribution of MN blood groups differs significantly in asthma patients and controls (chi-square - 15.1160, d.f. 2, Pp > .2) suggesting that blood group MM is resistant to asthma. The comparison of NN blood type reveals non-significant differences between asthma patients and controls [59].

In our studies the prevalence of MN blood group phenotypes was not equal in controls and patients groups (**Table 7**). The frequency of M+ N+ (MN) phenotype was relatively high in the patient groups compared to the controls. 43/100 patients and 30/100 donors carry the M+ N+ (MN) phenotype. In contrast, the major part of the control group (n = 55) had M+ N- (MM) phenotype, which is 1,14 times higher than in the patients' group (n = 48). The study also has revealed the differences according to the prevalence of the M-N+ (NN) phenotype control and patients' groups. The nine patients had the M-N+ phenotype characteristics, which is 1,8 times less than in the donors (n = 15). The study of MN system alleles frequency do not show any significant differences between to cohorts (**Table 7**).

The  $\chi^2$  criteria is 8,95, which is only 3 units higher then CV (d.f. = 3). In this case, the chi-square criterion indicates the existence of relationship between the two qualitative variables and the rejection of the null hypothesis (E = 0). The P-Value is < .00001. The result is significant at p < .05 (**Table 7**).

**4.4 Kell blood group system and arterial thrombosis**

The Kell blood group system is a complex and contains many highly immunogenic antigens. The locus of Kell blood group system is highly polymorphic and gives rise to many Kell antigens in human being. The Kell system gene locus is found on chromosome 7, at 7q33 and contains 19 exons. This locus encoding the 25 antigens and majority of Kell blood group system antigens are glycoproteins. Some of them are highly immunogenic. The Kell antigen is expresses only by erythroid progenitor cells and mature erythroid cells. There are two codominant allelic genes that produce two main antigens: Kell (K) and Cellano (k). These antigens differ to

Category	k	Kell	Kell system alleles frequency		$\chi^2$ , (d.f. = 1)	CV
			q	p		
Patients	79	21	0,88	0,12	51,73	3,841
Control	87	13	0.93	0,07		

**Table 8.**  
*Kell and k phenotype frequency in patients and control group.*

each other by a single amino acid. The prevalence of these antigens is not same. The k antigen is more common in most world population. K–K+ phenotype is found in 98% of Blacks and 91% of Caucasians. These antigens are the third most potent antigens after ABO and Rh blood groups, triggering an immune reaction [60].

Kell blood group system is important not only transfusion but also clinically is associated with the Hemolytic Disease of the Newborn (HDN). HDN caused by anti-Kell1 antibody is the second most common after Rh disease. Anti-Kell is becoming relatively more important as the prevention of Rh disease is also becoming more effective.

Unlikely to Rhesus and ABO immunosensibilization, HDN attributable to Kell sensitization is caused by anti-K antibody suppressing the fetal red blood cell (RBCs) production. The main reason of this is well known. The Kell antigens generally expressed on the surface of RBCs precursors, and anti-K antibodies initiated immune destruction of K positive erythroid precursor cells by macrophages in the fetal liver. The RBCs progenitor cells do not contain hemoglobin. There is releasing less amount of bilirubin and newborn very rarely presents a jaundice phenotype of anemia [61].

We could not have obtained any information about the correlation between the Kell blood group antigens and cardiovascular disease. The study according to the Kell system 2 phenotypical groups (K+ and K- phenotypes), showed that the frequency of K+ phenotype (KK or Kk) is high in the patients compared to the controls. 87 of the studied control have the K-negative (kk) phenotype, and as for the patients with arterial thrombosis, the prevalence of the above-mentioned phenotype is 79. The Kell antigen prevalence was relatively high in the studied patients (n = 21) and 13 healthy control were carriers of Kell antigen. K+ phenotype characteristics are highly prevalent in patients than in donors. Kell system alleles frequency are not same between to cohort (**Table 8**). In this case, quite a high number of  $\chi^2$  criteria was observed, which indicates the relationship between qualitative variables.  $\chi^2$  value is equal to 51,73. Which is much more than CV (3,841) of df (d.f. = 1). The P-Value is < .00001. The result is significant at < .05 (**Table 8**).

### 5. Conclusion

Thus, our study has shown maleness as a higher risk factor for AT. The study also revealed that smokers have a more predicted chance for AT compared to non-smokers. K+ phenotype and M+ N+ characteristics are of the high prevalence in the patients than in the donors. The correlations of the Kell and MN blood groups with AT have practical significance. There is no correlation between the ABO and Rh blood groups with AT based on our research; however, we think that finding the possible association needs to be identified with multicenter, prospective, and large-scale studies. Based on our research, it is possible to single out high-risk groups of disease and implement preventive arrangements on the individuals of these groups.

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## Conflict of interest

The authors declare no conflict of interest.

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