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Research Article

Risk evaluation of above-knee amputation and mortality according to ABO blood groups in patients with diabetic foot

Diyabetik ayaklı hastalarda ABO kan gruplarına göre diz üstü amputasyon ve mortalite risk değerlendirmesi

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Abstract

Aim: This study aimed to assess the distribution of ABO blood groups in diabetic patients who underwent major joint amputation and to identify which blood group is related to the risk of above-knee amputation (AKA) and mortality.

Material and Methods: This retrospective study included 120 diabetic foot patients who underwent major lower-extremity amputation between January 2020 and January 2024. Demographic, clinical, and laboratory data were retrospectively collected from electronic patient records. Patients were stratified by ABO blood group, and the frequency of AKA and mortality rates were compared across groups.

Results: The mean age of patients were 66.5 ± 11.9 years and median disease duration was 17 years. The frequency of AKA was 46.3% in blood group A, 54.2% in blood group B, 50% in blood group AB, and 28.2% in blood group O. AKA and mortality rates were higher in patients with non-O blood groups than in those with blood group O (28.2% vs. 49.4%, p = 0.032 for AKA; 48.7% vs. 67.9%, p = 0.048 for mortality; respectively). Independent of other confounders, blood group O had a 3.12-fold (1/OR) lower risk of AKA (OR =0.32, p = 0.049) and a 2.17-fold (1/HR) lower risk of mortality (HR =0.46, p = 0.045) compared to non-O blood groups.

Conclusion: This study identifies ABO blood group as a potential factor influencing amputation severity and mortality in diabetic foot patients. Blood group O appears to confer a protective effect against AKA and mortality, whereas non-O groups, particularly B, show a tendency toward worse outcomes.

Keywords: ABO blood group, diabetic foot, above-knee amputation, survival

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Öz

Amaç: Bu çalışmada, majör eklem amputasyonu geçiren diyabetik hastalarda ABO kan gruplarının dağılımını değerlendirmek ve hangi kan grubunun diz üstü amputasyon (AKA) ve mortalite riskiyle ilişkili olduğunu belirlemek amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2020 ile Ocak 2024 arasında majör alt ekstremite amputasyonu geçiren 120 diyabetik ayak hastası dahil edilmiştir. Demografik, klinik ve laboratuvar verileri elektronik hasta kayıtlarından retrospektif olarak toplanmıştır. Hastalar ABO kan grubuna göre sınıflandırılmış ve AKA sıklığı ve mortalite oranları gruplar arasında karşılaştırılmıştır.

Bulgular: Hastaların ortalama yaşı 66,5 ± 11,9 yıl ve ortanca hastalık süresi 17 yıldı. AKA sıklığı A kan grubunda %46,3, B kan grubunda %54,2, AB kan grubunda %50 ve O kan grubunda %28,2 idi. AKA ve mortalite oranları O kan grubu olmayan hastalarda O kan grubu olanlara göre daha yüksekti (%28,2'ye karşı %49,4, p = 0,032 AKA için; %48,7'ye karşı %67,9, p = 0,048 mortalite için; sırasıyla). Diğer karıştırıcı faktörlerden bağımsız olarak, O kan grubunun AKA riski 3,12 kat (1/OR) daha düşüktü (OR =0,32, p = 0,049) ve mortalite riski 2,17 kat (1/HR) daha düşüktü (HR =0,46, p = 0,045).

Sonuç: Bu çalışma, diyabetik ayak hastalarında amputasyon şiddetini ve mortaliteyi etkileyen potansiyel bir faktör olarak ABO kan grubunu tanımlamaktadır. O kan grubu, AKA ve mortaliteye karşı koruyucu bir etki sağlıyor gibi görünmektedir, buna karşın O olmayan gruplar, özellikle B, daha kötü sonuçlara doğru bir eğilim göstermektedir.

Anahtar sözcükler: ABO kan grubu, diyabetik ayak, diz üstü amputasyon, sağkalım

Introduction

Diabetic foot ulceration (DFU) is a severe complication of diabetes mellitus, affecting approximately 15% of diabetic patients over their lifetime [1, 2]. DFU frequently lead to infection and progressive tissue necrosis, often necessitating lower-extremity amputation (LEA) to prevent life-threatening complications [3]. Among these, above-knee amputation (AKA) represents the most extensive and debilitating form of limb loss, associated with a significantly poor prognosis [4]. The five-year post-amputation survival rate for patients undergoing major diabetes-related amputations is estimated to be 40–79% [5, 6]. This high mortality rate underscores the critical need to identify risk factors that contribute to severe diabetic foot outcomes to improve early intervention strategies and patient management.

Emerging evidence suggests that inherited factors, such as ABO blood type, may influence the progression and severity of diabetes-related complications. Previous studies have demonstrated a relationship between ABO blood group and type 2 diabetes mellitus (T2DM) susceptibility, with individuals of blood type B exhibiting a higher predisposition to T2DM, while those with blood type O appear to have a lower risk [7]. Moreover, ABO blood type has been implicated in diabetes-associated vascular complications, particularly peripheral arterial disease (PAD), a key contributor to diabetic foot pathology [8, 9]. Notably, non-O blood groups have been associated with increased severity and complexity of PAD [10]. Furthermore, an analysis of amputation cases indicated a disproportionate representation of non-O blood types, particularly B positive group, among patients undergoing dysvascular amputations [11].

Despite these findings, data remain limited regarding how specific blood types might predispose patients to above-knee amputation and increased mortality in patients with diabetic foot. Based on the current evidence, we hypothesize that diabetic foot patients with non-O blood groups are more likely to undergo above-knee amputation and exhibit higher mortality rates compared to those with blood group O. Therefore, this study aimed to assess the distribution of ABO blood groups in diabetic patients who underwent major joint amputation and to identify which blood group is related to the risk of above-knee amputation and mortality.

Material and Methods

This retrospective study was carried out at the Başkent University Practice and Research Hospital Orthopedic Clinic between January 2020 and January 2024, adhering to the ethical principles outlined in the Declaration of Helsinki. Approval was obtained from the Başkent University Hospital Ethics Committee (Date: 21/05/2024, Project no: KA24/220). Given the retrospective nature of the study, the Local Ethics Committee waived the requirement for informed consent.

Study population

During the study period, 152 diabetic patients who underwent major joint amputation and were followed up in the Orthopedic Clinic were retrospectively assessed for study eligibility. Patients were included in the study if they had a confirmed diagnosis of diabetic foot ulceration that necessitated major amputation, which was defined as any amputation at or above the ankle level. Amputation decisions were made by a multidisciplinary diabetic foot committee, which included specialists in orthopedic surgery, vascular surgery, endocrinology, and infectious diseases. Patients who did not undergo major lower-extremity amputation, such as those with minor amputations limited to the toes or forefoot, were excluded. Additionally, individuals who had undergone knee disarticulation were not included. Patients who had been referred to another diabetes center and had incomplete follow-up data were also excluded. Furthermore, individuals with a history of malignancy, which could independently influence both survival and diabetes progression, were not included in the analysis. Lastly, patients with a prior history of lower-extremity surgery or those who had undergone revision surgery following an initial amputation were excluded to prevent confounding related to prior surgical interventions. After applying these exclusion criteria, a total of 120 patients met the inclusion criteria and were included in the final analysis.

Data collection

Demographic, clinical, and laboratory data were retrospectively collected from electronic patient records. The demographic variables included age, sex, body mass index (BMI), ABO blood group, and Rh factor status. Clinical characteristics such as diabetes duration, type of diabetes treatment (insulin therapy or combination therapy with oral antidiabetic drugs), and presence of comorbidities, including cardiovascular disease, endocrinological disorders, PAD, and hemodialysis dependence, were documented. Amputation-related variables, including the laterality of the procedure (right, left, or bilateral) and the level of amputation, were recorded, with a particular focus on distinguishing between below-knee amputation (BKA) and AKA.

To evaluate the infectious profile of the patients, microbiological culture results from wound specimens were examined, and patients were categorized as having either culture-positive or culture-negative infections. Laboratory parameters obtained prior to amputation included glycated hemoglobin (HbA1c), C-reactive protein (CRP), blood urea nitrogen (BUN), and serum creatinine levels. Postoperative outcomes were assessed by recording the incidence of AKA and mortality. Mortality data were retrieved from hospital records and, where necessary, verified through national death registries.

Statistical analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean ± standard deviation values, while non-normally distributed variables are given as median (25th-75th quartiles) values. ANOVA test (post-hoc: Bonferroni test) or Kruskall Wallis H test (post-hoc: Dunn's test) were used for comparisons between more than two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. The effect of ABO blood groups on AKA was analyzed using logistic regression, with findings presented as odds ratios (OR) and 95% confidence intervals (CI). Cox regression analysis was employed to evaluate mortality, with results reported as hazard ratios (HR) and 95% CI. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

This study involved 120 patients, with a mean age of 66.5 ± 11.9 years, the majority being male (57.5%). The median disease duration was 17 years. The ABO blood group distribution was 34.2% A, 20% B, 13.3% AB, and 32.5% O, with 7.5% of patients being Rh-negative. Bilateral diabetic foot was detected in 8.3% of cases. Hypertension was found in 70% of patients, cardiovascular disease in 25.8%, endocrine disorders in 55.0%, and PAD in 30%. Among the patients, 49.2% had positive culture results. The prevalence of AKA was 41.7%, and the mortality rate was 61.7%.

Demographic characteristics showed no significant differences among ABO blood groups (Table 1). Patients with O blood group had lower CRP levels than those with blood groups A, B, and AB. While this group had lower rates of AKA and mortality compared to blood groups A, B, and AB, the difference did not achieve statistical significance (Table 1).

Similarly, demographic characteristics did not differ between non-O and O blood groups. However, AKA and mortality rates were significantly higher in patients with non-O blood groups than in those with blood group O (28.2% vs. 49.4%, $p = 0.032$ for AKA, Figure 1; 48.7% vs. 67.9%, $p = 0.048$ for mortality; respectively) (Table 2). This association remained statistically significant even after adjusting for potential confounders (Table 3). Independent of other confounders, blood group O had a 3.12-fold (1/OR) lower risk of AKA (OR =0.32, $p = 0.049$) and a 2.17-fold (1/HR) lower risk of mortality (HR =0.46, $p = 0.045$) compared to non-O blood groups (Figure 1) (Table 3).

Table 1. Demographic and clinical characteristics of patients.

Variables	ABO blood group				P-value
	A n = 41	B n = 24	AB n = 16	O n = 39	
Age, years	64.5 ± 9.5	69.5 ± 14.1	62.6 ± 11.6	68.3 ± 12.6	0.155
Male gender, n (%)	25 (61.0)	15 (62.5)	8 (50.0)	21 (53.8)	0.813
BMI, kg/m2	30.7 ± 3.8	28.8 ± 2.3	30.2 ± 2.8	28.9 ± 6	0.660
Rh (+), n (%)	37 (90.2)	23 (95.8)	15 (93.8)	36 (92.3)	0.959
DM duration, years	15 (5-30)	21 (7-40)	18.5 (10-20)	17 (3.5-37)	0.506
Treatment, n (%)					
Insulin	13 (31.7)	5 (20.8)	6 (37.5)	9 (23.1)	0.557
OAD&Insulin	25 (61.0)	12 (50.0)	10 (62.5)	25 (64.1)	0.730
Comorbidity, n (%)					
Hypertension	30 (73.2)	19 (79.2)	12 (75.0)	24 (61.5)	0.496
CAD	17 (41.5)	10 (41.7)	7 (43.8)	11 (28.2)	0.531
Endocrine diseases	25 (61.0)	13 (54.2)	8 (50.0)	20 (51.3)	0.825
PAD	14 (34.1)	9 (37.5)	5 (31.3)	8 (20.5)	0.438
Hemodialysis, n (%)	11 (26.8)	6 (25.0)	6 (37.5)	11 (28.2)	0.849
Side, n (%)					
Right	22 (53.7)	15 (62.5)	7 (43.8)	15 (38.5)	0.532
Left	15 (36.6)	7 (29.2)	8 (50.0)	21 (53.8)	
Bilateral	4 (9.8)	2 (8.3)	1 (6.3)	3 (7.7)	
Culture findings, n (%)					
Negative	20 (48.8)	11 (45.8)	7 (43.8)	23 (59.0)	0.643
Positive	21 (51.2)	13 (54.2)	9 (56.3)	16 (41.0)	
Laboratory findings					
HBA1C	9.3 ± 1.9	9.3 ± 1.6	9.1 ± 2.5	9.2 ± 2.3	0.836
CRP	159.5 (87-203)	188 (97-206)	138 (81-186.5)	96 (45-103)	0.048*
BUN	32 (20-52)	30 (18.5-44)	35.5 (18.5-55.5)	35 (23-61)	0.668
Creatinine	1.3 (0.9-2.5)	1.5 (1.0-2.5)	1.4 (1.5-2.4)	1.4 (0.7-3.8)	0.582
Outcomes, n (%)					
Above knee amputation	19 (46.3)	13 (54.2)	8 (50.0)	11 (28.2)	0.180
Mortality	27 (65.9)	17 (70.8)	11 (68.8)	19 (48.7)	0.487

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery diseases; CRP, C-reactive protein; HbA1c, glycated hemoglobin.

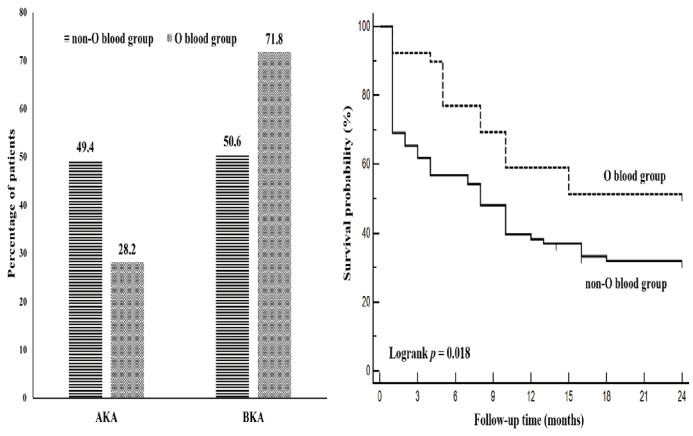

Figure 1. Above-knee amputation frequency (left) and mortality risk (right) according to ABO blood groups.

Discussion

To the best of our knowledge, this study is the first to highlight variations in AKA and mortality risk across ABO blood groups in patients undergoing major amputation for diabetic foot. The results indicate that blood group O is linked to a lower likelihood of AKA and mortality relative to other blood groups. These results suggest a potential role of ABO blood type in modulating diabetic foot outcomes, possibly through mechanisms related to coagulation, endothelial dysfunction, and inflammatory pathways.

Our findings indicate that non-O blood groups are linked to an increased risk of AKA and mortality in diabetic foot patients, whereas blood group O appears to have a protective effect

Table 2. Comparison of demographic and clinical characteristics of patients with non-O blood group and O blood group.

Variables	ABO blood group		P-value
	Non-O n = 81	O n = 39	
Age, years	65.6 ± 11.6	68.3 ± 12.6	0.203
Male gender, n (%)	48 (59.3)	21 (53.8)	0.694
BMI, kg/m2	30.2 ± 3.3	28.9 ± 6.0	0.613
Rh (+), n (%)	75 (92.6)	36 (92.3)	0.999
DM duration, years	17 (5-40)	17 (3.5-37)	
Treatment, n (%)			
Insulin	24 (29.6)	9 (23.1)	0.518
OAD&Insulin	47 (58.0)	25 (64.1)	0.557
Comorbidity, n (%)			
Hypertension	61 (75.3)	24 (61.5)	0.137
Cardiovascular disease	34 (42.0)	11 (28.2)	0.163
Endocrine diseases	46 (56.8)	20 (51.3)	0.696
PAD	28 (34.6)	8 (20.5)	0.139
Hemodialysis, n (%)	23 (28.4)	11 (28.2)	0.999
Side, n (%)			
Right	44 (54.3)	15 (38.5)	0.217
Left	30 (37.0)	21 (53.8)	
Bilateral	7 (8.6)	3 (7.7)	
Culture findings, n (%)			
Negative	38 (46.9)	23 (59.0)	0.246
Positive	43 (53.1)	16 (41.0)	
Laboratory findings			
HBA1C	9.1 ± 1.9	9.2 ± 2.3	0.984
CRP	130 (83-376)	96 (45-103)	0.035*
BUN	31.5 (9-144)	35 (23-61)	0.215
Creatinine	1.5 (0.3-90)	1.4 (0.7-3.8)	0.747
Outcomes, n (%)			
Above knee amputation	40 (49.4)	11 (28.2)	0.032*
Mortality	55 (67.9)	19 (48.7)	0.048*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery diseases; CRP, C-reactive protein; HbA1c, glycated hemoglobin.

Table 3. Effect of O blood group compared with non-O blood group on above-knee amputation and mortality based in crude and adjusted models.

Variables	Above-knee amputation			Mortality		
	OR	95% CI	P-value	HR	95% CI	P-value
Crude	0.43	0.18-0.92	0.030*	0.56	0.33-0.92	0.031*
Adjusted Model I	0.38	0.12-0.95	0.038*	0.55	0.28-0.95	0.038*
Adjusted Model II	0.32	0.10-0.98	0.049*	0.46	0.23-0.98	0.045*

Regression Model I adjusted for the effects of age, sex, BMI, diabetes duration, and diabetes treatments. Regression Model II for the effects of comorbid conditions, culture findings, and laboratory parameters in addition to the Model I. Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

against these outcomes. The increased risk of AKA in non-O blood groups is consistent with prior studies linking ABO blood type to vascular complications. Non-O blood group individuals frequently exhibit the rs505922 variant at the ABO locus (9q34), which has been linked to a higher risk of pancreatic cancer and other diabetes-related complications [12, 13]. Patients suffering from both diabetes and PAD are highly susceptible to severe complications, with amputation being one of the most critical risks [14]. Non-O blood groups have been associated with higher prevalence and severity of PAD [9]. In the Multi-Ethnic Study of Atherosclerosis, blood type A was associated with prevalent PAD and reduced ankle–brachial index (a measure of leg circulation) [14, 15]. This relationship may be driven by the pro-thrombotic profile of non-O blood groups, characterized by elevated levels of von Willebrand factor (vWF) and Factor VIII, which predispose individuals to arterial thrombosis and ischemia [16, 17]. In this study, ABO blood groups showed variations in PAD, which is a key factor influencing amputation risk. Non-O individuals had more PAD, suggesting that blood type 0 might be somewhat protective against limb ischemia. Better blood flow in blood type 0 could help limit the extent of tissue necrosis in the foot, possibly resulting in fewer major amputations. By contrast, A or B blood types, with higher PAD propensity, may present with more extensive arterial blockages requiring AKA when ulcers occur.

Another potential mechanism could be the higher predisposition of non-O blood groups to atherosclerosis and cardiovascular diseases [9]. The presence of A or B antigens may promote atherosclerosis through poorly understood mechanisms (possibly involving lipid profile or endothelial function). Epidemiological data show a modest but significant increase in coronary and cerebral arterial disease risk for non-O blood groups [18, 19]. Furthermore, a previous study identified non-O blood groups as independent predictors of both PAD and coronary artery disease [9]. While ABO effects are less pronounced in microvasculature than in large vessels, there is some evidence that ABO-related endothelial differences could impact microcirculation. The ABO gene significantly affects levels of soluble E-selectin, an adhesion molecule on endothelium involved in leukocyte trafficking. Individuals with blood group O (genotype OO) have markedly higher soluble E-selectin levels than those with A or AB alleles, indicating differences in endothelial activation [20]. Higher E-selectin might reflect an enhanced ability to recruit blood flow or immune cells to injured tissue. Conversely, lower E-selectin (in A or AB individuals) could mean attenuated inflammatory signaling in microvessels, potentially impairing wound healing or collateral circulation development [20, 21]. While direct links to diabetic microangiopathy are not fully proven, it's notable that ABO polymorphisms modulate endothelial function markers that are relevant to tissue perfusion and repair. On the other hand, diabetic wounds often have impaired healing due to microvascular thromboses. Non-O blood group, tends to have the highest vWF levels and has been observed to confer particularly high thrombosis risk in some studies [22, 23]. Such a thrombotic propensity could manifest as extensive microvascular clotting in an infected diabetic foot, leading to demarcation and tissue loss that extends further up the leg. Clinically, this could explain why patients with blood group AB have disproportionately high rates of AKA, as their circulatory compromise is worsened by microvascular clots. These results align with previous studies that have identified a strong correlation between dysvascular amputation and non-O blood groups, particularly blood group B [11].

Another possible mechanism could be the increased vulnerability of certain ABO blood groups to infections. A previous systematic review and meta-analysis reported that non-O blood group individuals are more prone to viral and non-viral infections than those with blood blood group O [24]. Our findings indicate that patients with blood group O showed a tendency toward a lower incidence of positive cultures than those with non-O blood groups. To our knowledge, no study has reported infection or mortalite rates based on ABO blood groups in diabetic foot patients. The collective impact of the aforementioned potential risk factors may play a role in the elevated mortality risk observed in non-O blood groups. However, the current study's findings are in agreement with reports from other diseases indicating that non-O blood group is associated with an increased mortality risk [25-28].

This study has some important limitations. The retrospective design may introduce selection bias, and causality cannot be firmly established. While the association between ABO blood group and amputation risk reached statistical significance, the sample size for each blood group, particularly AB, was relatively small, which may limit the generalizability of the findings. A larger, multi-center study is required to validate these results. Although potential biological explanations have been proposed, the study did not measure plasma vWF levels or endothelial function. Future research should incorporate biomarker analyses to directly assess the mechanistic role

of ABO blood type in diabetic foot complications. Finally, ABO blood group distribution varies across populations, and regional differences in diabetes prevalence, healthcare access, and surgical decision-making may influence amputation rates. Future studies should explore ABO blood group associations in diverse ethnic cohorts to ensure broader applicability.

Conclusion

Our study indicates that non-O blood groups are associated with an increased risk of AKA and mortality among diabetic patients undergoing major joint amputation. These findings suggest that ABO blood grouping could serve as a valuable marker in risk stratification and management of diabetic patients with foot complications. Further research is necessary to confirm these associations and to explore the potential benefits of incorporating blood group analysis into clinical practice for personalized patient care.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

This study was approved by Başkent University Institutional Review Board (Date: 21/05/2024, Project no: KA24/220).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

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