


CLINICAL ARTICLE

Correlation between an ABO Blood Group and Primary Femoral Head Necrosis: A Case–Control Study

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Objective: To investigate the relationship between primary femoral head necrosis (ONFH) and an ABO blood group.

Methods: This study was a retrospective case–control trial. An analysis of the clinical data of an ABO blood group with 516 patients (case group) with ONFH and 489 limb-fracture patients (control group) without previous hip pain was obtained from the Second Hospital of Shanxi Medical University from November 2015 to November 2018. The clinical data included gender, age, height, weight, a history of smoking, alcohol abuse, prior medical history, hormone use, and ABO blood type. A logistic regression model was used for univariate and multivariate analysis.

Results: From November 2015 to November 2018, there were 267 males and 249 females in the 516 cases of ONFH in the case group. The control group included 289 males and 200 females. In terms of age, the average age of the case group was significantly lower than that of the control group. In terms of body mass index (BMI), the BMI of the case group was significantly higher than that of the control group ($P < 0.05$). From the previous medical history of patients in the two groups (coronary heart disease, hypertension, cerebrovascular disease, diabetes, and peripheral vascular disease), there was no significant difference between the two groups from a statistical perspective ($P < 0.05$). However, according to the risk factors of ONFH (smoking, alcohol abuse, hyperlipidemia, and hormone-use history), there were significant differences between the case group and the control group. There was no statistical difference in the quantitative distribution ratio of the four blood types – A, B, O, and AB – between the case group and the control group. The outcomes of logistic multiple regression analysis presented that there was no significant correlation between the occurrence of ONFH and blood type A, B, AB, and O ($P > 0.05$). However, there are significant differences in the disease progression between the different blood types. There was a significant difference in the progression of disease between type A and type O. Among them, patients with ONFH and type A blood had the fastest progression with an average of 2.318 years, and the slowest progression was found in type O blood with an average of 5.15 years.

Conclusions: The ABO blood group has no correlation with the occurrence of ONFH, but the ABO blood type is closely related to the disease progression of ONFH.

Key words: ABO blood-group system; Blood group antigens; Disease progression; Primary femoral head necrosis; Thrombosis

Introduction

Several previous studies have shown that blood group antigens are closely related to infectious diseases, vascular diseases, autoimmune diseases, malignant tumors, and

other diseases^{1,2}. In 1962, Bronte-Stewart *et al.* first investigated the potential relationship between ABO blood types and blood clots. Their results showed that ischemic heart disease occurred more frequently in patients with type A and

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type B blood and the occurrence of type O blood was lower than in controls³. Carpeggiani *et al.* further showed that patients with type A and type B blood were more prone to myocardial infarction. Further analysis revealed that non-type O blood was a strong predictor of cardiogenic death in patients younger than 65 years of age, especially in women⁴. In 1963, Dick *et al.* additionally studied the relationship between blood types and venous thromboembolic diseases and found that non-type O people were more prone to venous thromboembolic diseases⁵. Spiezia retrospectively studied 712 Italian patients with deep venous thrombosis and 712 controls and found that the risk of renal venous thrombosis in blood group non-O was 2.2 times higher than that of the O type blood group⁶. These studies, therefore, show that people with different ABO blood types have a different propensity for thrombosis.

Primary femoral head necrosis (ONFH) is an ischemic disease caused mainly by insufficient blood supply to the femoral head. However, many causes result in insufficient blood supply to the femoral head, such as the degeneration and necrosis of cartilage tissue, collapse of the articular surface, structural changes of the femoral head, joint dysfunction, and so on. A further study of ONFH revealed that the main reason for poor blood supply to the femoral head is that the blood of the femoral head is in a state of high coagulation and prone to thrombosis⁷. Therefore, thrombosis plays a very important role in the development and progression of primary femoral head necrosis.

The pathogenesis of ONFH is relatively complex, which is caused by multiple factors such as blood circulation disorder in the bones and apoptosis of the bone cells⁸. The main causes of ONFH include hormones, alcohol, smoking, etc⁹. In China, some scholars have conducted statistical analysis on the coagulation indexes of patients with avascular femoral head necrosis and have found that osteonecrosis is closely related to intravascular coagulation and thrombosis¹⁰. The pathophysiological features of ONFH are vascular metabolism disorder in the femoral head and increased blood viscosity, leading to thrombosis. In addition, the accumulation of a large number of hyperplasia fat cells causes the swelling and rupture of capillary endothelial cells, activates the prothrombin activator, starts the coagulation system, and triggers intravascular coagulation and thrombosis¹¹. This further results in increased blood viscosity, synergism with hyperlipidemia, triggering intravascular coagulation, and ultimately leads to ONFH¹².

Whether the mechanism of blood group involved in thrombosis is associated with primary ischemic ONFH has not been studied. We designed a retrospective case-control study to investigate whether ABO blood types are associated with the development of ONFH and disease progression. Therefore, this paper aims to study whether the ABO blood group correlates with the occurrence of ONFH and the progress of the disease. This study aims to further demonstrate that the mechanism of the ABO blood group's correlation

with thrombosis plays an important role in the occurrence and development of the ONFH disease.

Materials and Methods

Subjects

This study was a retrospective case-control trial. Seven hundred and fifty-five cases of femoral head necrosis in III period or IV period were diagnosed in The Second Hospital of Shanxi Medical University from November 2015 to November 2018, in which 564 cases were primary femoral head necrosis and 191 cases were secondary necrosis of the femoral head. Among the patients with ONFH, there were two patients with a loss of height and weight information, 23 patients with a loss of smoking history and drinking information, 18 patients with a loss of previous medical history, and five patients with a loss of hormone-use history. Finally, 516 patients met the inclusion criteria and were selected as the case group. Additionally, 489 patients with extremities fractures but without hip pain before injury or femoral head lesions confirmed by an X-ray examination in our orthopaedics hospital were set as the control group. This study was approved by the ethics committee of the Second Hospital of Shanxi Medical University.

Inclusion and Exclusion Criteria

Inclusion criteria: (i) participants diagnosed with femoral head necrosis in III period or IV period¹³; (ii) patients who had detected ABO blood; (iii) patients aged 18–70 years; and (iv) all patients were generally engaged in moderate work.

Exclusion criteria: (i) patients that had a diagnosis combined with severe osteoporosis; (ii) patients with diseases of the immune system; and (iii) patients with severe infection, severe liver and kidney dysfunction, coagulation dysfunction, malignant tumors, etc.

Data Collection

The clinical data of the subjects were observed and recorded, including age, height, weight, smoking history, alcohol abuse history, previous history of hypertension, history of diabetes, hyperlipidemia, history of coronary heart disease, history of cerebrovascular disease, history of peripheral blood vessels, history of hormone use, and ABO blood group detection.

Collection Criteria for ONFH

The collection criteria for ONFH included the patients' medical history, clinical symptoms, and physical signs, combined with the gold standard MRI for diagnosis of ONFH¹⁴: T1WI: low band signal, T2WI: double line sign, and T2WI lipostatic: high signal band around necrotic foci; T2WI lipostatic: bone marrow of the femur head and neck except the lesion area edema and low band signal on T1WI.

Related Variable Collection Criteria

(i) Hypertension was defined as systolic blood pressure higher than 140 mm Hg or diastolic blood pressure higher

than 90 mm Hg (1 mm Hg = 0.133 kPa, measured at least 3 times); (ii) dyslipidemia was defined as total cholesterol (TC) > 5.2 mmol/L, or triglyceride (TG) > 1.7 mmol/L; (iii) diabetes was defined as diabetes symptoms + fasting blood glucose \geq 7.0 mmol/L or random blood glucose \geq 11.1 mmol/L, and 2 h blood glucose \geq 11.1 mmol/L in the oral glucose tolerance test (OGTY) (at least two times); (iv) the patients that were defined as smokers were those who smoked at least 100 cigarettes (five packs) in their entire life¹⁵; and (v) binge drinking was defined as heavy drinking with a daily alcohol intake of 80 grams and more for over 5 years, ethanol content (g) = alcohol consumption (mL) \times ethanol concentration (%) \times 0.8¹⁶.

Outcome Measures

The clinical data included gender, age, height, weight, a history of smoking, alcohol abuse, prior medical history, hormone use, ABO blood type, etc.

ABO Blood Type

The ABO blood group system was a blood type system based on the presence or absence of specific antigens on the surface of red blood cells. In this study, before measuring ABO blood type, we collected the blood from the case and control groups and put it into a 3 mL vacuum tube containing potassium EDTA2 as an anticoagulant. Then, the blood samples were centrifuged at 34,000 r/min for 5 min. The ABO blood group test was performed manually by microcolumn gel detection. Antigens of the ABO/Rh system (microtubes A/B/D/C/E/Ctl) were determined as the following: (i) preparing a 5% red blood cell suspension in DG Gel Sol (50 μ L of red blood cell sediment or concentrate in 1 mL of DG Gel Sol); (ii) adding 10 μ L of 5% red blood cell suspension into each of the microtubes indicated; (iii) the determination of the reverse ABO group (microtubes N). Then, the vials of A₁/B reagent red blood cells were homogenized. Fifty μ L of A₁ reagent red blood cells into microtube N_{/A1} and 50 μ L of B reagent red blood cells were dispensed into microtube N_{/B}. Finally, 50 μ L of serum or plasma was added and centrifuged for DG Gel cards.

Body Mass Index (BMI)

Body mass index (BMI) is one of the most important international measures of obesity and health. The specific method of measurement is as follows: body mass index (BMI) = weight (kg)/ height (m)²(kg/m²).

Statistical Methods

All data were analyzed using SPSS version 22.0 software (IBM, Chicago, USA). Continuous variables were expressed as mean \pm SD. Discontinuous variables were expressed as a percentage (%). For the multiple comparisons, each value was compared by a one-way ANOVA following a Dunnett test when each datum conformed to a normal distribution, while the non-normally distributed continuous data were compared using non-parametric tests. The counting data

were tested by a chi-square test. The correlation analysis of ONFH and ABO blood group was performed by univariate and multivariate logistic regression analysis and the correlation factors of age, gender, body mass index, hyperlipidemia, hormone-use history, smoking history, and alcohol-abuse history was adjusted. An ANOVA was used for the progression differences among the blood groups and a further Bonferroni multiplicity correction was performed. $P < 0.05$ was considered statistically significant.

Results

General Information of the ABO Blood Group and ONFH

In our study, there were 267 males and 249 females in the 516 cases of ONFH in the case group. The control group included 289 males and 200 females. In terms of age, the average age of the case group was 56.8 ± 12.0 years, the average age of the control group was 65.1 ± 20.3 years old. The age of the patients in the case group was significantly lower than that of the control group. In terms of body mass index (BMI), the BMI of the case group was 24.3 ± 3.8 kg/m², the BMI of the control group was 23.7 ± 4.1 kg/m², the BMI of the case group was significantly higher than that of the control group ($P < 0.05$). From the previous medical history of patients in the two groups (coronary heart disease, hypertension, cerebrovascular disease, diabetes, and peripheral vascular disease), there was no significant difference between the two groups from a statistical perspective ($P < 0.05$). However, according to the risk factors of ONFH (smoking, alcohol abuse, hyperlipidemia, and hormone-use history), there were significant differences between the case group and the control group (Table 1).

Distribution of the ABO Blood Group in ONFH

In the case group, there were 110 (21.3%) cases of A blood, 187 (36.2%) cases of B blood, 44 (8.5%) cases of AB blood, and 175 (33.9%) cases of O blood. In the control group, there were 97 (19.8%) cases of A blood, 164 (33.5%) cases of B blood, 55 (11.2%) cases of AB blood, and 1173 (35.4%) cases of O blood. There was no statistical difference in the quantitative distribution ratio of the four blood types A, B, O, and AB between the case group and the control group. When comparing group A with non-group A, there was no statistically significant difference between the two groups. Using the same method, the differences between group B and non-group B, group O and non-group O, and group AB and non-group AB was not statistically significant ($P > 0.05$) (Table 1).

The results in Table 2 show that age, gender, BMI, smoking, alcohol abuse, hyperlipidemia, and hormone-use history were correlated with ONFH by univariate logistic regression analysis ($P < 0.05$).

Additionally, the relationship between blood type and the ONFH disease was analyzed by logistic multiple regression analysis. In 1–5 models, four basic blood types, A, B, O,

TABLE 1 Baseline data for ONFH and control group

Index	Case group (n = 516)	Control group (n = 489)	χ^2 /t value	P value
Age ($\bar{x} \pm s$, years)	56.8 \pm 12.0	65.1 \pm 20.3	7.815	<0.001***
Male	267 (51.7%)	289 (59.1%)	5.497	0.019*
Body mass index ($\bar{x} \pm s$, kg/m ²)	24.3 \pm 3.8	23.7 \pm 4.1	-2.267	0.002**
Smoking	145 (29.7%)	110 (21.3%)	9.211	0.002**
Alcohol abuse	57 (11.0%)	27 (5.5%)	10.006	0.892
Hypertension	114 (22.1%)	102 (20.9%)	0.227	0.634
Diabetes	39 (7.6%)	45 (9.2%)	0.886	0.346
Peripheral blood vessels	5 (1.0%)	2 (0.4%)	1.138	0.286
Cerebrovascular disease	24 (4.7%)	25 (5.1%)	0.115	0.734
Coronary heart disease (CHD)	24 (4.7%)	14 (2.9%)	2.207	0.137
Hyperlipidemia	236 (45.7%)	15 (3.1%)	243.951	<0.001***
History of hormone use	137 (26.6%)	2 (0.4%)	143.962	<0.001***
ABO blood group				
A	110 (21.3%)	97 (19.8%)		
B	187 (36.2%)	164 (33.5%)		
AB	44 (8.5%)	55 (11.2%)		
O	175 (33.9%)	173 (35.4%)		
Non-A	406 (78.7%)	392 (80.2%)	0.337	0.562
Non-B	329 (63.8%)	325 (66.5%)	0.807	0.369
Non-AB	472 (91.5%)	434 (88.8%)	2.092	0.148
Non-O	341 (66.1%)	316 (64.6%)	0.238	0.626

Note: * $P \leq 0.05$, ** $P \leq 0.005$, *** ≤ 0.001 .

and AB, as well as A and non-A, B and non-B, AB and non-AB, O and non-O were classified respectively. Risk factors such as age, sex, body mass index, smoking history, alcohol-abuse history, hormone-use history, and hyperlipidemia were adjusted in the analysis of the five models. The results showed that there was no significant correlation between the

occurrence of ONFH and blood type A, B, AB, and O ($P > 0.05$) (Table 3 and Fig. 1).

Disease Progression among the ABO Blood Types

The re4 show that there are significant differences in the disease progression between the different blood types. As a result of the further Bonferroni multiplicity correction, we found that there was a significant difference in the progression of disease between type A and type O. Among them, patients with ONFH and type A blood had the fastest

TABLE 2 Single factor regression analysis of ABO blood group and ONFH

Index	Univariate regression analysis OR (95% CI)	P value
Age	0.970 (0.963-0.978)	<0.001***
Male	0.742 (0.578-0.952)	0.019*
Body mass index	1.044 (1.005-1.083)	0.025*
Smoking	0.643 (0.483-0.856)	0.002**
Alcohol abuse	2.125 (1.320-3.420)	0.002**
Hypertension	1.076 (0.796-1.454)	0.634
Diabetes	0.807 (0.515-1.262)	0.347
Peripheral blood vessels	2.383 (0.460-12.338)	0.301
Cerebrovascular disease	0.905 (0.510-1.608)	0.734
Coronary heart disease (CHD)	1.655 (0.846-3.238)	0.141
Hyperlipidemia	26.634 (15.484-45.814)	<0.001***
History of hormone use	88.020 (21.653-357.804)	<0.001***
A	1.095 (0.806-1.487)	0.562
B	1.126 (0.869-1.460)	0.369
AB	0.736 (0.485-1.117)	0.149
O	0.937 (0.723-1.216)	0.626

Note: * $P \leq 0.05$, ** $P \leq 0.005$, *** ≤ 0.001 .

TABLE 3 Multivariate logistic regression analysis of ABO blood group and risk of ONFH

Model	OR (95% CI)	P value
Model 1		
O	1.000	
A	1.226 (0.705-2.133)	0.470
B	1.087 (0.680-1.736)	0.728
AB	1.045 (0.535-2.042)	0.897
Model 2		
A	1.000	
Non-A	0.840 (0.513-1.376)	0.488
Model 3		
B	1.000	
Non-B	0.984 (0.652-1.484)	0.938
Model 4		
AB	1.000	
Non-AB	1.030 (0.554-1.914)	0.925
Model 5		
O	1.000	
Non-O	1.120 (0.745-1.685)	0.585

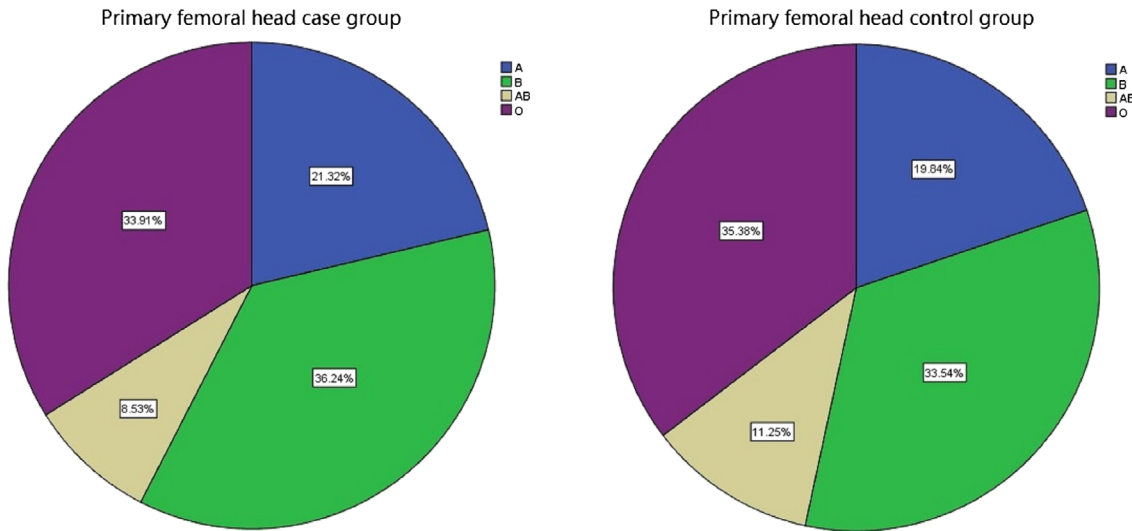


Fig. 1 There was no significant correlation between the occurrence of ONFH and blood type A, B, AB and O.

progression, with an average of 2.318 years and the slowest progression was found in type O blood with 5.15 years (Table 4 and Fig. 2).

Discussion

The outcomes of this study presented that there was no significant difference in the ABO blood group distribution between the case group and the control group. This result indicates that there is no correlation between the occurrence of ONFH and the ABO blood type. However, after the analysis of variance (ANOVA), there were significant differences in the disease progression of ONFH in patients with different blood groups.

Distribution of the ABO Blood Group in ONFH

This paper aims to study whether the ABO blood group is correlated with the occurrence of ONFH and the progress of the disease. This study aims to further demonstrate that the mechanism of the ABO blood group’s correlation with thrombosis plays an important role in the occurrence and development of the ONFH disease. In our single-factor and multi-factor regression analysis, the ABO blood group was

not correlated with the occurrence of ONFH, consistent with previous studies by Rios *et al.*¹⁷. However, this result is inconsistent with the studies of Bronte-Stewart *et al.*³ and Carpeggiani *et al.*⁴. There are several reasons to consider when two distinct outcomes occur. Firstly, the design method and sample size of each experimental study directly affect the experimental results. Some hypotheses, for example, that blood group A and blood group B is associated with the progression of a thromboembolic event, are generated from the sub-analyses of small cohorts and should be confirmed with larger datasets. Secondly, since the study

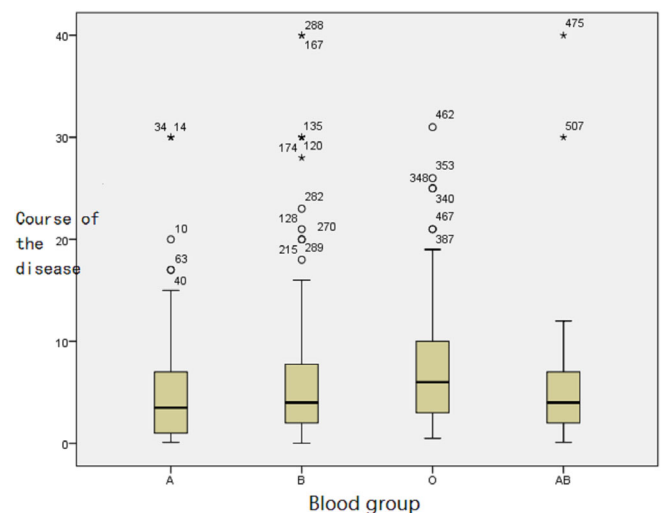


Fig. 2 There was a significant difference in the progression of disease between type A and type O. Among them, patients with ONFH of type A blood had the fastest progression, with an average of 2.318 years, and the slowest progression of type O was 5.15 years.

TABLE 4 Variance analysis of ABO blood group and disease progression			
Blood type	The mean	F value	P value
A	5.10	3.424	0.017*
B	6.01		
O	7.42		
AB	5.78		

Note: *P ≤ 0.05, **P ≤ 0.005, *** ≤ 0.001.

population and inclusion criteria differ considerably, all the cases should be in the III period and IV period and there were no early cases or outpatient cases.

Pathogenesis of ONFH

The pathogenesis of ONFH is relatively complex, which is caused by multiple factors such as blood circulation disorder in the bones and apoptosis of the bone cells⁸. This study retrospectively analyzed the relationship between the ABO blood group and ONFH. After a series of analyses, our results showed that smoking, alcohol abuse, and hormone use were independent risk factors for ONFH.

Relationship between the ABO Blood Group and ONFH

Preston and Barr first proposed the relationship between the ABO blood type and hemostasis in February 1964. There are increasing analyses of whether ABO blood types are correlated with thrombosis. At present, the mechanism of blood type and thrombosis is not clear. High levels of von Willebrand factor (vWF) are a risk factor for thrombus formation and progression. In 1971, it was first identified that the decrease of vWF could cause the occurrence of hemorrhagic diseases and, with the continuous studies on vWF, it was shown that the increase of vWF could promote the formation of thrombosis¹⁸. vWF is synthesized by vascular endothelial cells and marrow megakaryocytes, which can connect collagen and platelets, initiate the coagulation process, and play a bridging role in thrombus¹⁹. Jukic *et al.* found that people with non-O blood types are more likely to develop blood clots (*OR* 2.08, *CI* 1.32–3.27)²⁰. Wiggins *et al.* found that blood type A and B were significantly correlated with MI, VTE, myocardial infarction, and ischemic stroke²¹. Interestingly, we found that ONFH was closely related to gender, age, body mass index, and hyperlipidemia. During our regression analysis, we also found that the ABO blood group was not correlated with the distribution of ONFH, suggesting that the mechanism of the ABO blood group involved in thrombosis was not involved in ONFH thrombosis.

However, we found that the ABO blood group is closely related to the progression of the ONFH disease through our ANOVA analysis. The reasons are as follows: a recent study found that rs8176704 in the ABO gene sequence is associated with c-reactive protein (CRP), interleukin-6 (IL-6), and tumor

necrosis factor (TNF)²². These inflammatory cytokines play a role in promoting the development of ONFH and the progression of the disease. It can be inferred that inflammatory cytokines related to the ABO blood group also play a role in the progression of the ONFH. In addition, our results also showed that hyperlipidemia is a risk factor for ONFH. Li, from the FuWai hospital in China, conducted a study on the ABO blood group and plasma lipids. The results showed that the level of blood lipids in patients in the non-O blood group was higher than that in patients in the O blood group. Furthermore, the level of blood lipids was positively correlated with the development of lipid-related diseases²³. This may be related to the differences in blood lipid levels between the different blood types. Finally, the mechanism of blood types affecting blood lipid levels may also play a role in accelerating the progression of ONFH.

Limitations

Firstly, this trial was only a retrospective trial, not a randomized controlled trial. Secondly, this study was only a single-center trial and the sample size was limited. Thirdly, the specific mechanism of blood types affecting blood lipid levels remains unknown and needs further research. Fourthly, there was not enough data about the subgroup analysis in this recent study. Another subgroup analysis according to the clinical follow-up, clinical improvement, implants evaluation or functional evaluation is still necessary and valuable in the future. Fifthly, there was not enough data about the subgroup analysis of the relationship between ABO blood type and the classification of femoral head ARCO classification which should be researched further in the future.

Conclusion

In conclusion, this study shows that the ABO blood group is not related to the occurrence of ONFH but is closely related to the development of ONFH. These findings need to be externally validated in larger prospective studies.

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