Journal of Geriatric Cardiology (2019) 16: 701−705

Research Article · Open Access ·

Association of ABO blood groups with the severity of coronary artery disease: a cross-sectional study

Xu-Lin HONG, Ya LI, Guo-Sheng FU, Heng WU, Yao WANG, Chun-Xia GU, Wen-Bin ZHANG[#]

Department of Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

Abstract

Objective To investigate whether ABO blood groups is associated with the severity of coronary artery disease (CAD). **Methods** Between January 2015 and December 2017, 1425 first diagnosed CAD patients confirmed by selective coronary angiography were recruited into this cross-sectional study, and their baseline characteristics, ABO blood groups, Gensini score were collected. Multiple linear regression analysis was performed to test the association between the severity of CAD and ABO blood groups. **Results** The Gensini score was significantly higher in the blood group A than in the non-A groups (41.2 ± 32 *vs.* 38 ± 27; $P = 0.026$). After adjusting for age, male, smoking, family history of CAD, hypertension, diabetes mellitus and hypercholesterolemia, multivariate linear regression indicated that blood group A was associated with the severity of CAD (β = 3.298, 95% CI: 0.91–6.505, $P = 0.044$). In diabetes group, A blood type was also associated with increased Gensini score ($P = 0.02$) after adjusting for age, male, family history of CAD, hypercholesterolemia, smoking and hypertension. **Conclusion** In this cross-sectional study, the data indicated that blood group A was an independent risk factor of severity of CAD in Chinese population and Chinese patients with type 2 diabetes.

J Geriatr Cardiol 2019; 16: 701−705. doi:10.11909/j.issn.1671-5411.2019.09.005

Keywords: ABO blood groups; Coronary artery disease; Cross-sectional study

1 Introduction

The research on coronary artery disease (CAD) and ABO blood groups has a long history indicating that non-O blood groups have a higher risk of ischemic heart disease.[1,2] Furthermore, the Framingham Heart study and others suggested A blood groups have increased risk of CAD and myocardial infarction (MI).[3–6] Other investigators reported that groups B or AB have higher incidence of CAD.[7,8] However, some studies showed the opposite results and even identified no association between blood type and CAD.[9,10]

Diabetes mellitus is believed to be a risk equivalent of coronary artery disease, and type 2 diabetes patients often have multiple cardiac risk factors.[11] However, whether A blood groups is an independent risk factor of the severity of CAD in diabetes is unknown.

The mechanisms to explain the relationship between ABO blood type and CAD remains ambiguous. The following biologic mechanisms have been proposed. ABO blood groups are genetically transmitted, and the ABO locus was discovered to be associated with CAD related inflammatory makers.[12] Additionally, the ATP-binding cassette2 (ABCA2) gene, which plays a role in cholesterol homeostasis, is reported to be located at the same locus of ABO.[13,14] Interestingly, non-O groups were found to have higher cholesterol absorption rate, which was positively correlated with cardiovascular risk.[14] Plasma levels of von Willebrand factor (VWF) and coagulation factor VIII, which are positively associated with thrombosis, is indicated to be affected by ABO antigen.[15] VWF plasma levels are approximately 25% higher in non-O groups, compared with group O.[15–17] ABO(H) carbohydrate antigenic determinants expressing on VWF is the molecular basis of the connection between ABO blood group and VWF levels.[16,18]

To sum up, the association between ABO groups, especially the blood group A and the severity of CAD remains controversial and was also rarely evaluated in Chinese population. We conducted this cross-sectional study to evaluate the association between ABO blood groups and the severity of CAD in angiographic CAD patients.

2 Methods

2.1 Study design and population

Our cross-sectional study complied with the Declaration

[#]**Correspondence to:** Wen-Bin ZHANG, Department of Cardiology, Sir Run Run Shaw Hospital, Zhejiang 310016, China.
E-mail: 3313011@zju. edu.cn
Received: July 3, 2019 **Revised:** August 26, 2019
Accepted: September 16, 2019 **Published online:** September 28, 2019

of Helsinki and was approved by the hospital ethics review board (Sir run run shaw hospital, Zhejiang, China). From January 2015 to December 2017, a total of 2102 consecutive CAD patients confirmed by selective coronary angiography were evaluated. Patients with acute myocardial infarction, a history of percutaneous intervention (PCI) or coronary artery bypass surgery (CABG), active cardiopulmonary diseases, hematologic disorders, severe liver and/or renal insufficiency, thyroid dysfunction, significant infectious disease, and malignant disease were excluded. Finally, 1425 first diagnosed CAD patients were enrolled.

The baseline characteristics, including demographic, hematologic, imaging data were collected from all patients during hospitalization. The left ventricular ejection fraction (EF) was evaluated by echocardiograph. Hypertension was defined as repeated blood pressure measurements over 140/90 mmHg or currently taking antihypertensive drugs. Diabetes mellitus was defined as: (1) self-reported history of diabetes mellitus (DM) and/or (2) under current treatment of insulin or oral hypoglycemic medicine and/or (3) repeated fasting plasma glucose (FPG) ≥ 7.0 mmol/L and/or (4) glycated hemoglobin A1c (HbA1c) ≥ 6.5%. Hypercholesterolemia was defined as total cholesterol (TC) ≥ 200 mg/dL (5.2 mmol/L) or low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL (3.4 mmol/L). Smoking was defined as ever-smoked 100 cigarettes or currently smoking. Body mass index (BMI) was calculated by body weight (kg)/the square of his/her height (m^2).

2.2 Severity of coronary atherosclerosis

CAD was defined as > 50% stenosis in at least one major coronary branch and the severity of CAD was evaluated by Gensini score (GS) system. Reduction in coronary lumen diameter of 25%, 50%, 75%, 90%, 99%, and complete occlusion were counted as 1, 2, 4, 8, 16, and 32, respectively. A multiplier was then assigned to each main vascular segment based on the functional significance: 5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending (LAD) coronary artery, 2.5 for the proximal segment of the circumflex artery, 1.5 for the mid-segment of the LAD, 1.0 for the distal segment of the LAD, mid-distal region of the circumflex artery, the obtuse marginal artery, the right coronary artery and the posterolateral artery, 0.5 for other segments. The final score was calculated by adding the scores of each segment.

2.3 Statistical analysis

SPSS V.24.0 was used for all analyses. Continuous data was presented as mean ± SD or median (inter-quartile range) as appropriate. Data would be compared by the Student's *t*-test when normally distributed, otherwise, by the Wilcoxon rank-sum test. Categorical data was presented as number and percentage (%) and compared by chi-square test. The multivariable linear regression analysis was performed to test the association between the severity of CAD and the following variables: age, male, smoking, family history of CAD, hypertension, diabetes mellitus and hypercholesterolemia. A value of $P < 0.05$ was considered statistically significant.

3 Results

3.1 Patient characteristics

The baseline characteristics of the enrolled subjects were summarized in Table 1 according to blood type. In brief, A

Table 1. Baseline clinical characteristics by blood type.

Variables	A group (n = 436)	Non-A group (n = 989)	P value
Patients characteristics			
Gensini score	41.2 ± 32	38 ± 27	0.026
Age, yrs	65 ± 10	64 ± 10	0.888
Male	323 (73.7%)	689 (70.6%)	0.227
BMI, kg/m^2	24.6 ± 3.24	24.47 ± 3.29	0.515
Hypertension	304 (69.7%)	654 (66.1%)	0.198
Hypercholesterolemia	108 (24.7%)	235 (23.8%)	0.737
DM	114 (26.0%)	229 (23.2%)	0.254
Smoking	121 (27.6%)	268 (27.1%)	0.847
Family history of CAD	42 (9.6%)	84 (8.5%)	0.544
EF	65.5% ± 9.9%	65.9% ± 9.2%	0.440
Baseline SBP, mmHg	134 ± 19	133 ± 20	0.320
Baseline DBP, mmHg	75 ± 12	74 ± 12	0.026
Laboratory test			
Glucose, mmol/L	6.45 ± 2.64	6.42 ± 2.63	0.843
WBC, 109/L	6.58 ± 1.85	6.6 ± 2.03	0.838
hs-CRP	1.8 (0.9–4.4)	1.6 (0.6–3.9)	0.266
eGFR	85.16 ± 18.07	83.78 ± 18.33	0.191
Uric Acid, mmol/L	372.80 ± 95.70	363.75 ± 93.97	0.099
D-dimer, mg/dL	0.37 (0.25–0.56)	0.36 (0.23–0.54)	0.686
Fibrinogen, mg/dL	3.55 ± 0.91	3.49 ± 0.91	0.384
NT-ProBNP	98.0 (38.8–350.5)	102.0 (39.0–295.5)	0.438
PLT, 10^9/L	178.18 ± 55.15	183.22 ± 59.5	0.132
Lipid profile			
Triglyceride	1.40 (1.02–1.92)	1.42 (1.03–2.02)	0.971
TC	4.32 ± 1.24	4.34 ± 1.25	0.805
LDL-C	2.34 ± 0.92	2.33 ± 0.91	0.970
HDL-C	1.03 ± 0.29	1.03 ± 0.28	0.949
VLDL-C	0.67 (0.43–1.01)	0.69 (0.46–1.01)	0.349

BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low density lipoprotein; PLT: platelet; SBP: systolic blood pressure; TC: total cholesterol; VLDL-C: very low density lipoprotein; WBC: white blood cell.

blood groups (n = 436) had higher Gensini socre compared with the non-A groups (n = 989) ($P < 0.05$). There were no significant differences of other variables between the two groups ($P > 0.05$, respectively).

3.2 Association between GS and ABO blood groups

To evaluate the role of A blood groups in the presence and severity of CAD, Univariate and multivariate linear regression analysis were performed in our study. In univariate linear regression analysis, A blood type, age, male, DM were associated with increased Gensini score ($P < 0.05$, respectively, Table 2). After adjusting for DM, age, male, family history of CAD, A blood type (β = 3.214, 95% CI: 0.016–6.411, P = 0.049, model 4, Table 3) was significantly associated with the Gensini score. The final multiple linear regression model (adjusted for DM, age, male, family history of CAD, hypercholesterolemia, smoking, hypertension) also indicated a positive correlation between A blood type and Gensini score (P = 0.044, Table 3). In diabetes group, A blood type was also associated with increased Gensini score (P = 0.02, Table 4 & 5) after adjusting for age, male, family history of CAD, hypercholesterolemia, smoking, hypertension.

4 Discussion

Our data indicated that there was an association between A and non-A blood group with the severity of coronary atherosclerosis assessed by Gensini system. Blood A group was an independent risk factor of the severity of coronary lesion after adjusting for other cardiovascular risk factors. Moreover, analysis of diabetes patients showed that blood group A also had increased Gensini score than the non-A group. In this cross-sectional study, besides the similar exclusion criteria documented in previous studies, acute myocardial infarction patients were also excluded, since these patients may have various pathogenesis,[19] and difficult to evaluate the severity of coronary lesion using Gensini score.

Multiple factors, including hypertension, dyslipidemia, inactivity, abdominal obesity, smoking, age, gender and family history, are associated with an increased risk for coronary artery disease.[11,20] Efforts have been made applying data from Framingham and other studies to build prediction models that identify individuals at high risk of cardiovascular events.[21,22] Nevertheless, there remains a need to improve the ability to identify. Other risk factors are being researched. The association between ABO groups and CAD has been studied for a long time. In the last few decades, many reports showed a higher proportion of CAD

Table 2. Univariate linear regression analysis for Gensini score.

Variable	β (95%CI)	*P* values
A	3.673 (0.431 to 6.916)	0.026
Age	0.224 (0.078 to 0.371)	0.003
Male	4.024 (0.71 to 7.338)	0.017
smoking	–0.21 (–3.575 to 3.154)	0.903
Hypertension	3.113 (–0.078 to 6.304)	0.056
Hypercholesterolemia	–0.468 (–3.974 to 3.038)	0.793
DM	8.97 (5.494 to 12.445)	< 0.001
Family history of CAD	4.579 (-0.696 to 9.855)	0.089

CAD: coronary artery disease; DM: diabetes mellitus.

Table 3. Multivariate linear regression analysis for Gensini score.

Variable	β (95% CI)	*P* values
Unadjusted	3.673 (0.431 to 6.916)	0.026
Model 1	3.419 (0.202 to 6.636)	0.037
Model 2	3.439 (0.23 to 6.647)	0.036
Model 3	3.3 (0.097 to 6.503)	0.043
Model 4	3.214 (0.016 to 6.411)	0.049
Model 5	3.298 (0.91 to 6.505)	0.044

Model 1: adjusted for DM; Model 2: adjusted for DM, age; Model 3: adjusted for DM, age, male; Model 4: adjusted for DM, age, male, family history of CAD; Model 5: adjusted for DM, age, male, family history of CAD, hypercholesterolemia, smoking, hypertension. CAD: coronary artery disease; DM: diabetes mellitus.

Table 4. Univariate linear regression analysis for Gensini score in non-DM and DM patients.

Variable	Non-DM group		DM group	
	β (95%CI)	*P* values	B (95% CI)	*P* values
A	0.031 (–1.702 to 5.480)	0.302	0.126 (1.386 to 15.307)	0.019
Age	0.098 (0.095 to 0.430)	0.002	0.125 (0.042 to 0.758)	0.029
Male	0.096 (1.877 to 9.814)	0.004	0.034 (–5.415 to 10.262)	0.543
Smoking	–0.019 (–5.138 to 2.794)	0.562	0.041 (–5.229 to 11.221)	0.474
Hypertension	0.062 (0.109 to 7.022	0.043	–0.141 (–18.794 to 2.407)	0.011
Hypercholesterolemia	0.052 (–0.543 to 7.159)	0.092	–0.081 (–14.498 to 1.970)	0.135
Family history of CAD	0.070 (0.949 to 12.276)	0.022	0.089 (–2.070 to 25.825)	0.095

CAD: coronary artery disease; DM: diabetes mellitus.

Table 5. Multivariate linear regression analysis for Gensini score in non-DM and DM patients.

Variable	β (95%CI)	*P* values
Non-DM group	1.89 (–1.7 to 5.48)	0.30
DM group	8.35 (1.39 to 15.31)	0.02

Adjusted for age, male, family history of CAD, hypercholesterolemia, smoking, and hypertension. CAD: coronary artery disease; DM: diabetes mellitus.

patients with blood groups A, B or AB as compared with control groups.[23–25] The Framingham Heart Study also reported a higher incidence of non-fatal CAD in group A as compared to group O among men.[26] Medalie, *et al.* [27] conducted a 5-year prospective investigation which enrolled 10000 Israeli male government employees 40 years of age and over (including different races) and founded that blood group A1, B tended to have higher incidence rate of myocardial infarction and angina pectoris. Several meta- analyses were done due to heterogeneous results in different studies.[9,10] Interestingly, all of them demonstrated that non-O blood group appears to be an independent risk factor for CAD and MI.[28–30] Previous studies were mainly concerned about the blood group non-O and O, ignoring the blood group A and other blood types. Additionally, in those studies, association of ABO blood group with MI was often focused on. As a matter of fact, the type A blood group with severity of CAD remain unclear and controversial.[2–4,6,7,10] Moreover, date on ABO blood groups with coronary artery disease in Chinese population is much rarer. For diabetes, despite they are logical candidates for screening CAD, recent CAD screening studies in type 2 diabetes were unable to link the number of risk factors to inducible ischemia on perfusion imaging.[31] Thus, our study provided new evidence that blood group A may be an independent risk factor of severity of CAD in Chinese population and patients with type 2 diabetes. Our results are partially accordant with documented original observations and meta-analysis.[4,32] We expect that, in the near future, the ABO blood group analysis could be enrolled in the diagnostic workup of every CAD patient (especially type 2 DM patient) and improve our early recognition of the severe CAD and guide our therapeutic strategies for the secondary prevention of the disease.

Severe coronary atherosclerosis usually leads to poor cardiovascular outcome, such as MI, ischemic cardiomyopathy and sudden cardiac death. The Gensini score system is a relatively easy and useful way to quantify the severity of CAD.[33] Thus, the combination of cardiovascular disease risk factors with the score system could provide the best predictive information for cardiovascular prognosis. Unfortunately, the underlying mechanism of the relationship between blood group A and CAD could not been illuminated in our study despite the various hypothesis existed.

Aside from the intrinsic limitations of an observational study, other potential limitations in our study should be noted. Firstly, the result was based on Chinese population, therefore, it should not be extended to other ethnic groups. Moreover, the clinical outcomes of patients were unavailable since our data were obtained from the hospital database.

In conclusion, our date demonstrated that A blood groups might play a potential role in the severity of coronary atherosclerosis in Chinese population and patients with type 2 diabetes. Blood group A was an independent risk factor of the severity of CAD. A prospective, multicenter cohort study is needed to validate our findings.

Acknowledgments

This work is supported by grants from Clinical Vascular Grant in Chinese Physicians—VG. The funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no ethical conflicts to disclose and no conflicts of interest to declare.

References

1 Erikssen J, Thaulow E, Stormorken H, *et al*. ABO blood groups and coronary heart disease (CHD). A study in subjects with severe and latent CHD. *Thromb Haemost* 1980, 43: 137–140.
2 Carpeggiani C, Coceani M, Landi P, *et al*. ABO blood group alleles: A risk factor for coronary artery disease. An angiographic study. *Atherosclerosis* 2010; 211: 461–466.
3 Garrison RJ, Havlik RJ, Harris RB, *et al*. ABO blood group and cardiovacular disease: the Framingham study. *Atherosclerosis* 1976; 25: 311–318.
4 Whincup PH, Cook DG, Phillips AN, Shaper AG. ABO blood group and ischaemic heart disease in British men. *BMJ* 1990; 300: 1679–1682.
5 Rosenberg L, Miller DR, Kaufman DW, *et al*. Myocardial infarction in women under 50 years of age. *JAMA* 1983; 250: 2801–2806.
6 Lee HF, Lin YC, Lin CP, *et al*. Association of blood group A with coronary artery disease in young adults in Taiwan. *Intern Med* 2012; 51:1815–1820.
7 Nydegger UE, Wuillemin WA, Julmy F, *et al*. Association of ABO histo-blood group B allele with myocardial infarction. *Eur J Immunogenet* 2003; 30: 201–206.
8 Meade TW, Cooper JA, Stirling Y, *et al*. Factor VIII, ABO blood group and the incidence of ischaemic heart disease. *Br J Haematol* 1994; 88: 601–607.

9 Karabuva S, Carevic V, Radic M, Fabijanic D. The association of ABO blood groups with extent of coronary atherosclerosis in Croatian patients suffering from chronic coronary artery disease. *Biochemia Medica* 2013; 23: 351–359.

10 Biancari F, Satta J, Pokela R, Juvonen T. ABO blood group distribution and severity of coronary artery disease among patients undergoing coronary artery bypass surgery in Northern Finland. *Thromb Res* 2002; 108: 195–196.

11 Mortality after 16 years for participants randomized to the Multiple Risk Factor Intervention Trial. *Circulation* 1996; 94: 946–951.

12 Qi L, Cornelis MC, Kraft P, *et al*. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. *Hum Mol Genet* 2010; 19: 1856–1862.

13 Consortium CAD, Deloukas P, Kanoni S, *et al*. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet* 2013; 45: 25–33.

14 Silbernagel G, Chapman MJ, Genser B, *et al*. High Intestinal Cholesterol Absorption Is Associated With Cardiovascular Disease and Risk Alleles in ABCG8 and ABO Evidence From the LURIC and YFS Cohorts and From a Meta-Analysis. *J Am Coll Cardiol* 2013; 62: 291–299.

15 Jenkins PV, O'Donnell JS. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? *Transfusion* 2006; 46: 1836–1844.

16 Franchini M, Mannucci PM. ABO blood group and thrombotic vascular disease. *Thromb Haemostasis* 2014; 112: 1103–1109.

17 Gill JC, Endres-Brooks J, Bauer PJ, *et al*. The effect of ABO blood group on the diagnosis of von Willebrand disease. *Blood* 1987; 69: 1691–1695.

18 Matsui T, Titani K, Mizuochi T. Structures of the asparagine-linked oligosaccharide chains of human von Willebrand factor. Occurrence of blood group A, B, and H(O) structures. *J Biol Chem* 1992; 267: 8723–8731.

19 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018; 72: 2231–2264.

20 Drozda J Jr., Messer JV, Spertus J, *et al*. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart Association task force on performance measures and the american medical association-physician consortium for performance improvement. *Circulation* 2011; 124: 248–270.

21 Guzder RN, Gatling W, Mullee MA, *et al*. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. *Diabet Med* 2005; 22: 554–562.

22 Mount Hood 4 Modeling G. Computer modeling of diabetes and its complications: a report on the fourth mount hood challenge meeting. *Diabetes Care* 2007; 30: 1638–1646.

23 Allan TM, Dawson AA. ABO blood groups and ischaemic heart disease in men. *Br Heart J* 1968; 30: 377–382.

24 Bronte-Stewart B, Botha MC, Krut LH. ABO blood groups in relation to ischaemic heart disease. *Br Med J* 1962; 1: 1646–1650.

25 Nefzger MD, Hrubec Z. Venous thromboembolism and blood-group. *Lancet* 1969; 1: 887.

26 Havlik RJ, Feinleib M, Garrison RJ, Kannel WB. Blood-groups and coronary heart-disease. *Lancet* 1969; 2: 269–270.

27 Medalie JH, Levene C, Papier C, *et al*. Blood groups, myocardial infarction and angina pectoris among 10,000 adult males. *N Engl J Med* 1971; 285: 1348–1353.

28 Dentali F, Sironi AP, Ageno W, *et al*. ABO blood group and vascular disease: an update. *Semin Thromb Hemost* 2014; 40: 49–59.

29 Wu O, Bayoumi N, Vickers MA, Clark P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. *J Thromb Haemost* 2008; 6: 62–69.

30 Takagi H, Umemoto T. Meta-analysis of non-O blood group as an independent risk factor for coronary artery disease. *Am J Cardiol* 2015; 116: 699–704.

31 Wackers FJ, Young LH, Inzucchi SE, *et al*. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004; 27: 1954–1961.

32 Chen Z, Yang SH, Xu H, Li JJ. ABO blood group system and the coronary artery disease: an updated systematic review and meta-analysis. *Sci Rep* 2016; 6: 23250.

33 Sinning C, Lillpopp L, Appelbaum S, *et al*. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. *Clin Res Cardiol* 2013; 102: 495–503.