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Blood group B and decreased risk of coronary artery disease in hypertensive elderly.

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Keywords: ABO blood groups; cardiovascular disease; elderly; hypertensive; Gensini score.

Abstract. Although ABO blood groups have been associated with cardiovascular disease, little is known about whether ABO blood groups contribute to the risk of the presence and severity of coronary artery disease (CAD) in elderly individuals with hypertension. This study was aimed to explore this association. A total of 793 hypertensive patients aged ≥60 years out of 2095 patients who underwent primary coronary angiography were retrospectively included. They were divided into CAD and non-CAD groups. Demographic and clinical characteristics, ABO blood groups and other biochemical parameters were compared. Further evaluation was performed to determine the impact of ABO blood groups on CAD severity using the Gensini score and the number of significantly diseased vessels. A logistic regression model was constructed to identify the association of ABO blood groups with CAD. There was a substantial difference in the distribution of ABO blood groups in elderly and hypertensive adults with and without CAD (p=0.022). Hypertensive patients with CAD had a significantly lower proportion of the blood group B than those without CAD (p=0.008). Compared to those with non-Blood group B, hypertensive elderly with a blood group B tended to have significantly lower concentrations of TC, LDL-C and Apo B, and a lower number of significantly stenosed vessels. The blood group B was found to be an independent protective factor for CAD in elderly with hypertension. The blood group B is significantly associated with a decreased risk of CAD and is inversely correlated with the severity of coronary stenosis in the elderly with hypertension.

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Grupo sanguíneo B y disminución del riesgo de enfermedad arterial coronaria en ancianos hipertensos.

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Palabras clave: tipo de sangre ABO; enfermedades cardiovasculares; anciano; presión arterial alta; puntuación de Gensini.

Resumen. Aunque los tipos de sangre ABO están asociados con enfermedades cardiovasculares, se sabe poco sobre si los tipos de sangre ABO estás relacionados con la presencia y gravedad de la enfermedad arterial coronaria (CAD) en pacientes de edad avanzada con hipertensión. El objetivo de este estudio fue explorar esta relación. Se incluyeron retrospectivamente un total de 793 pacientes hipertensos de ≥60 años tomados de un grupo de 2095 pacientes sometidos a angiografía coronaria primaria. Se dividieron en el grupo de cardiopatía coronaria (CAD) y el grupo sin cardiopatía coronaria (no-CAD). Se compararon las características demográficas y clínicas, el grupo sanguíneo ABO y otros parámetros bioquímicos. El efecto del grupo sanguíneo ABO sobre la gravedad de la CAD se evaluó con la puntuación Gensini y el número de vasos sanguíneos patológicos significativos. Se construyó un modelo de regresión logística para determinar la relación entre el grupo sanguíneo ABO y la CAD. Hubo una diferencia significativa en la distribución de los grupos sanguíneos ABO entre los ancianos con y sin cardiopatía coronaria y los adultos con hipertensión (P=0,022). La proporción del grupo sanguíneo B en pacientes hipertensos con cardiopatía coronaria fue significativamente menor que en pacientes sin cardiopatía coronaria (P=0,008). En comparación con los grupos sanguíneos no B, las concentraciones de TC, LDL - C y Apolipoproteína B en los ancianos hipertensos del Grupo B fueron significativamente menores, y el número de estenosis vascular fue significativamente menor. El Grupo B es un factor protector independiente de la CAD en pacientes de edad avanzada con hipertensión. El Grupo B se correlacionó significativamente con la reducción del riesgo de cardiopatía coronaria y negativamente con la gravedad de la estenosis coronaria en pacientes de edad avanzada con hipertensión.

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INTRODUCTION

Coronary artery disease (CAD) is a well-documented major threat to human health worldwide and it accounts for approximately 17.8 million deaths annually. It is the leading cause of mortality and disability, and it is preventable [1-4]. There is robust evidence that environmental and genetic factors contribute to the risk of CAD [5-6]. Hypertension is a significant risk factor for CAD in most populations.

The ABO blood group, as a genetic risk factor, has been demonstrated to be related to cardiovascular disease and cardiac deaths in the overall population. Although the relationship is still controversial, multiple studies have reported that people with

blood Group A are more vulnerable to coronary stenosis than those with non-A blood groups. And individuals with blood Group O have been linked to a lower risk of CAD [7-8]. However, a study performed on Bangladeshi people revealed that the blood group O was associated with a substantially increased risk of CAD [9]. In addition, the blood group AB has been reported to play an important role in a decreased risk of CAD [10]. Thus, the association of ABO blood groups with the development of CAD is inconsistent in different races and populations.

On the other hand, a possible protective effect of the Blood group B against several diseases, including cardiovascular events, has been observed. In addition, it has been reported that patients with the blood group B are less likely to develop pancreatic neuroendocrine tumors and other pancreatic masses in the Chinese population [11]. Meanwhile, a nationwide cohort study suggested that blood group B conferred a lower risk of aortic aneurysms than the blood group O[12]. A meta-analysis including 241.868 Hepatitis B virus (HBV)-infected subjects and 6.487.481 uninfected subjects also found that blood group B was associated with a lower risk of HBV infection (RR=0.92, 95% CI 0.86 to 0.98) [13]. Thus, whether ABO blood groups are related to CAD and other diseases and which antigen is a protective or a risk factor remains controversial.

Individuals with blood group B account for approximately 25% of the Chinese population. It is necessary to pay more attention to the relationship between CAD and blood group B due to its large proportion of the community. To the best of our knowledge, whether blood group B contributes to CAD risk and the severity of CAD has not been definitely established.

Moreover, age itself is a well-established risk factor for the development of cardiovascular disease, and older adults are associated with increased CAD because of age-mediated damage [14]. Several conventional risk factors for incident CAD, including smoking, male sex, hyperlipidemia and a prior history of hypertension, are different between older and young patients [15-17]. A study conducted on Chinese Taiwanese young adults indicated that blood group A was an independent risk factor for CAD and myocardial infarction compared to non-A blood groups [18]. However, evidence is not fully available regarding the relationship between the distribution of ABO blood groups and CAD risk and severity as assessed by the Gensini score and the significantly diseased vessels in subjects aged 60 years or older, especially in those with hypertension. Hypertension is one of the most common chronic diseases in Chinese adults. A total of 23.2% of the adult population has hypertension.

Therefore, we performed this study to elucidate the relationship between ABO blood groups and CAD by retrospective analysis of the data from elderly adults with hypertension undergoing primary diagnostic coronary angiography (CAG) at our center.

PATIENTS AND METHODS

Study participants

A total of 793 elderly patients with hypertension (mean age of 69.13± 5.81 years, 62.6% were men) from among 2095 subjects hospitalized due to angina, coronary myocardial infarction or heart failure symptoms were consecutively included. All the study patients underwent primary CAG at the Department of Cardiology, Wujin Hospital, affiliated with the Jiangsu University, between 2014 and 2018.

Ineligible patients were excluded if they (1) had severe hepatic or renal dysfunction (n=2) or hyperthyroidism or hypothyroidism (n=29); (2) underwent lipid-lowering therapy during the three months prior to our study (n=136); (3) lacked information about their ABO blood groups or lipid profiles (n=381); (4) were younger than 60 years (n=480); or (5) did not have hypertension.

Two experienced cardiologists evaluated the CAG results. CAD was defined as

stenosis of 50% or more of the diameter of the major coronary vessels. Patients were divided into CAD and non-CAD groups based on the CAG results.

Written informed consent was not obtained from the included patients because the relevant data were retrospectively obtained from their electronic medical records. Nevertheless, our study complied with the Declaration of Helsinki (2013) and was approved by the Ethics Committee of Wujin Hospital, affiliated with Jiangsu University, Changzhou, China.

Baseline parameter analysis

The investigators collected baseline characteristics regarding sex, age, smoking, drinking, and diabetes mellitus (DM) from the electronic medical records. Venous blood samples were collected from study cases in a fasting state on the morning following the admission day. The ABO blood groups of all of the patients were determined. Plasma lipid levels, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-1 (ApoA-1) and apolipoprotein B (Apo B), were obtained using standard techniques. The atherogenic index of plasma (AIP) was calculated as Log (TG/HDL-C). The number of diseased coronary vessels with ≥ 50% stenosis was calculated for the patients according to the results of coronary angiography.

Gensini score assessment

The severity of coronary artery stenosis was also evaluated by the Gensini score (GS) based on the results of CAG for the included cases. Reductions in coronary lumen diameter of 25%, 50%, 75%, 90%, and 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 left circumflex artery (LCX), 1.5 for the mid-segment of the LAD, 1.0 for the distal segment of the LAD, mid-distal region of the LCX, the obtuse marginal artery, the right coronary artery and the posterolateral artery, and 0.5 for other segments. The final score was calculated by adding the scores of each segment[19].

Definitions

Hypertension was defined as systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg or the use of any antihypertensive drug. DM was defined as a fasting plasma glucose ≥ 7.0 mmol/L, a nonfasting plasma glucose ≥ 11.1 mmol/L, or the current use of antidiabetic medications, including insulin or oral hypoglycemic agents. Smoking was defined as cigarette intake (current or stopped < 1 year ago). Drinking was defined as current alcohol intake (once per month to ≤ 4 times per week [moderate], or daily/almost daily [high]).

Statistical analysis

Continuous data with a normal distribution are presented as the mean ± standard deviation (SD). The significance was evaluated by using Student's t-test or ANOVA. The remaining continuous data are represented as the median [quartile range (QR)] and compared using the Mann–Whitney *U* test among groups. Categorical data are reported as frequencies and percentages. The chi-square test was used to evaluate the significance. Multivariate logistic regression analysis was applied to detect the effect of the ABO blood group on CAD. The regression model was established using the forward Wald method. The inclusion level was set as 0.5, and the exclusion level was 0.1. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were computed. All statistical analyses were conducted using SPSS 25.0 statistics software. A P value of < 0.05 was considered to be statistically significant.

RESULTS

The baseline characteristics of the study participants

As shown in Table 1, the elderly and hypertensive patients were assigned to the CAD group (n=556, aged 69.67±5.89 years, 62.6% men) and non-CAD group (n=237, aged 67.88±5.42 years, 44.3% men). Male sex was more prevalent in the CAD group. There were more smokers in the CAD group than in the non-CAD group ($p < 0.001$). CAD patients were older, had a higher prevalence of DM, and had significantly higher LDL-C, Apo B and AIP values than non-CAD (all $p < 0.05$). Compared with the non-CAD group, the CAD group had significantly lower HDL-C and Apo A-1 (all $p < 0.01$). There were no differences in TC and TG levels between the two groups.

The overall distribution of ABO blood groups was different between those with and without CAD (A 36.0% vs. 29.5%, AB 12.1% vs. 8.0%, B 24.6% vs. 33.8%, O 27.3% vs. 28.7%, $p=0.022$). A statistically lower frequency of blood group B was observed in the CAD group than in the non-CAD group (33.8% vs. 24.6%, $p=0.008$).

Lipid profiles between blood group B and group non-B in elderly individuals with hypertension

Comparison of lipid profiles between blood group B and non-B groups are presented in Table 2. The data revealed that hypertensive elderly individuals in the blood group B had significantly lower TC, LDL-C, and Apo B concentrations than those in the non-blood group B (p= 0.008, 0.010 and 0.007, respectively). However, there were no

Table 1
Baseline characterstics of study participants with and without coronary artery disease.

Variables	Hypertensive elderly with CAD (n=556)	Hypertensive elderly without CAD (n=237)	P
Male, n (%)	348 (62.6)	105(44.3)	< 0.001
Smoking, n (%)	196 (35.3)	44(18.6)	< 0.001
Drinking, n (%)	67(12.1)	22(9.3)	0.258
Age, y	69.67±5.89	67.88±5.42	< 0.001
DM, n (%)	185 (33.3)	53(22.4)	0.002
TC, mmol/L	4.61±1.05	4.46±0.99	0.053
TG, mmol/L	1.49(1.08-2.04)	1.40(1.03-2.06)	0.280
HDL-C, mmol/L	1.10±0.26	1.17±0.31	0.001
LDL-C, mmol/L	2.91±0.90	2.61±0.78	< 0.001
Apo A-1, g/L	1.21±0.23	1.27±0.24	0.001
Apo B, g/L	0.95±0.26	0.89±0.24	0.005
AIP	0.15±0.28	0.11±0.29	0.047
ABO, n (%)			0.022
A	200 (36.0)	70 (29.5)	0.080
AB	67(12.1)	19(8.0)	0.094
B	137 (24.6)	80(33.8)	0.008
O	152 (27.3)	68 (28.7)	0.697

CAD: coronary artery disease; DM: diabetes mellitus; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo A-1: apolipoprotein A-1; Apo B: apolipoprotein B; AIP: atherogenic index of plasma.

Table 2
Lipid profiles between blood group B and group non-B.

Lipids	blood group B (n=217)	blood group non-B (n=576)	*P*
TC, mmol/L	4.41±0.97	4.63±1.06	0.008
TG, mmol/L	1.4(1.01-2.04)	1.49(1.09-2.07)	0.237
HDL-C, mmol/L	1.11±0.28	1.12±0.28	0.778
LDL-C, mmol/L	2.70±0.73	2.86±0.92	0.010
Apo A-1, g/L	1.21±0.25	1.24±0.23	0.123
Apo B, g/L	0.89±0.25	0.94±0.26	0.007
AIP	0.13±0.28	0.15±0.28	0.377

TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo A-1: apolipoprotein A-1; Apo B: apolipoprotein B; AIP: atherogenic index of plasma.

significant differences in the HDL-C, Apo A1 and AIP levels between the two groups (p = 0.778, 0.123 and 0.377, respectively).

Severity of coronary artery stenosis and blood group B in hypertensive elderly individuals

Table 3 shows that hypertensive elderly patients in the blood group B were likelier to have a significantly lower number of diseased coronary vessels than those in the non B -blood group (p=0.031). In addition, after the Gensini score was assigned to the 1st tertile (0-11.5), 2nd tertile (11.5-35.5) and 3rd tertile (>35.5), the data revealed that blood group B tended to be associated with a significantly lower Gensini score tertile than the non- Bs blood groups. However, there was not a significant difference (p= 0.215).

Logistic regression analysis of the blood group B and CAD in elderly individuals with hypertension

Binary multivariate logistic regression was conducted to establish whether the blood group B was an independent factor for CAD risk in the patients. According to the univariate regression results shown in Table 4, variables including age (OR 1.057, 95% CI 1.028-1.087), male sex (OR 2.103, 95% CI 1.545-2.863), smoking (OR 2.388, 95% CI 1.648-3.460), DM (OR 1.731, 95% CI 1.217-2.464), HDL-C (OR 0.375, 95% CI 0.219-0.642), LDL-C (OR 1.524, 95% CI 1.262-1.840), Apo A1 (OR 0.338, 95% CI 0.177-0.645), Apo B (OR 2.420, 95% CI 1.299-4.510) and blood group B (OR 0.642, 95% CI 0.461-0.894) were included in the model.

After adjustment for such cardiovascular risk factors, multiple logistic regression analysis indicated that the blood group B remained an independent protective factor for CAD (OR 0.642, 95% CI 0.450-0.916) in elderly patients. Moreover, age, male sex, smoking, DM, LDL-C and AIP were significantly related to an increased risk of CAD (OR= 1.068, 95% CI 1.037-1.100; OR= 1.972, 95% CI 1.329-2.928; OR= 1.966, 95% CI 1.244-3.108; OR= 2.085, 95% CI 1.420-3.060, OR= 1.706, 95% CI 1.388-12.096, and OR=1.737, CI 1.006~2.998, respectively). HDL-C was an independent protective factor for CAD (OR= 0.422, 95% CI 0.236-0.753), Table 5.

DISCUSSION

In this study, we explored the association of ABO blood groups with the incidence of CAD and CAD severity in elderly individuals with hypertension. We obtained two cru-

Table 3
Coronary stenosis severity between blood group B and blood group non-B.

Variable	blood group B (n=217)	blood group non-B (n=576)	*P*
Number of diseased vessels			0.031
0	80(36.9)	158(27.4)	
1	64(29.5)	184(31.9)	
≥2	73(33.6)	234(40.6)	
Gensini score			0.215
1st tertile (0-11.5), n (%)	82(37.8)	181(31.4)	
2ed tertile (11.5-35.5), n (%)	65(30.0)	199(34.5)	
3rd tertile (>35.5), n (%)	70(32.3)	196(34.0)	

Table 4
Univariate regression analysis for risk factors and coronary artery disease.

Variable	B	S.E	Wald	Sig.	Exp (B)	95% CI
Male	0.744	0.157	22.308	0.000	2.103	1.545~2.863
Age	0.055	0.014	15.413	0.000	1.057	1.028~1.087
Smoking	0.871	0.189	21.174	0.000	2.388	1.648~3.460
Drinking	0.292	0.259	1.271	0.260	1.339	0.806~2.225
DM	0.549	0.180	9.295	0.002	1.731	1.217~2.464
TC	0.147	0.076	3.726	0.054	1.159	0.998~1.346
TG	0.061	0.071	0.737	0.391	1.063	0.924~1.223
HDL-C	-0.981	0.275	12.734	0.000	0.375	0.219~0.642
LDL-C	0.421	0.096	19.108	0.000	1.524	1.262~1.840
Apo A1	-1.086	0.330	10.812	0.001	0.338	0.177~0.645
Apo B	0.884	0.318	7.750	0.005	2.420	1.299~4.510
AIP	0.552	0.279	3.927	0.048	1.737	1.006~2.998
Blood group B	-0.444	0.169	6.893	0.009	0.642	0.461~0.894

CAD: coronary artery disease; DM: diabetes mellitus; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo A-1: apolipoprotein A-1; Apo B: apolipoprotein B; AIP: atherogenic index of plasma.

cial results about the association between blood group B and newly angiography-diagnosed CAD in hypertensive elderly individuals. First, after adjusting for confounding factors, an association of blood group B with a decreased risk of CAD was observed in elderly individuals with hypertension. Second, a statistically lower number of significantly diseased coronary vessels was detected in hypertensive elderly individuals with blood group B than those without this group.

ABO blood group antigens are expressed not only on the surface of red blood cells but also on various human tissues, such as the epithelium, platelets, and vascular endothelium [20]. Thus, the ABO blood group is considered a risk factor for cardiovascular and thrombotic diseases [21-24]. It has been

Table 5
Multiple logistic regression analysis for risk factors for coronary artery disease.

Variable	B	S.E	Wald	Sig.	Exp (B)	95% CI
Age	0.065	0.015	18.893	0.000	1.068	1.037~1.100
Male	0.679	0.202	11.352	0.001	1.972	1.329~2.928
Smoking	0.676	0.234	8.379	0.004	1.966	1.244~3.108
DM	0.735	0.196	14.068	0.000	2.085	1.420~3.060
HDL-C	-.864	0.296	8.521	0.004	0.422	0.236~0.753
LDL-C	0.534	0.105	25.828	0.000	1.706	1.388~2.096
Blood group B	-.443	0.181	5.973	0.015	0.642	0.450~0.916

CAD: coronary artery disease; DM: diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

shown in previous studies that individuals with blood group A have a higher risk of CAD compared with non-A blood groups. Furthermore, a second CAG indicates that in-stent restenosis is significantly more prevalent in individuals with blood group A compared to other blood groups [25]. However, several studies revealed that ABO blood groups are not associated with CAD in the general population[26-27]. Whether blood group B is associated with CAD in the Chinese population remains controversial. Few reports have focused on the association of blood group B with CAD risk and severity, especially in elderly and hypertensive subjects who suffer from a cardiovascular disease burden.

In the present study, we investigated the association between ABO blood types and CAD defined by primary CAG in the Chinese elderly population with hypertension. Our results do not reveal a significantly higher frequency of blood group A in elderly and hypertensive patients with CAD than in the rest of the population. This finding is inconsistent with the results of a previous study, which found that blood group A is an independent risk factor for CAD and MI in a young Chinese population [18]. To our knowledge, the available evidence suggests that blood group O is related to a decreased risk of CAD in general subjects. Furthermore, research conducted in India showed that the blood group B reduced the risk of CAD due to an associated higher concentration of HDL-C in the general population [10]. However, our study did not observe these relationships among elderly adults.

Our data revealed that hypertensive elderly individuals with blood group B had a significantly lower risk of CAD than those with non-B blood groups. Further analysis suggested that blood group B was an independent protective factor against incident CAD. These results are inconsistent with observations of the blood group B as a predictor of CAD among general subjects [28]. The possible mechanism underlying these variations is the enrollment of patients from different races or populations. Furthermore, a recent study suggested that although there were no differences between blood group O or B compared with A or AB for serum inflammatory cytokines, patients with blood group O or B had a reduced disease severity and multiorgan dysfunction in COVID-19 [29]. Moreover, it has been reported that patients with blood group O have decreased levels of factor VII and von Willebrand factor, which may account for the underlying protective effect against cardiovascular disease [22,30]. Central to these findings, additional studies are required to define the biological mechanisms of our results, which have not been elucidated due to a lack of essential data.

It has long been recognized that TG and LDL-C are common risk factors, and HDL-C and Apo A1 are protective factors against cardiovascular disease and major adverse cardiac events after percutaneous coronary intervention [31-33]. AIP is strongly associated with atherogenesis of the coronary artery. In the present study, we similarly found that patients with CAD were more likely to have higher levels of LDL-C Apo B and AIP and lower concentrations of HDL-C and Apo A-1. Schmitz and Kaminski [34] found that the prototypic ATP binding cassette transporter ABCA2, which plays a pivotal role in transmembrane cholesterol export, and the ABO gene are both located on chromosome 9q34. Based on these findings, studies have been conducted to explore the potential relationship of ABO blood groups with lipid metabolism in the incidence and development of CAD. Higher plasma levels of TC and LDL-C are involved in the association between the ABO blood group and incident CAD. Approximately 10% of the effect of non-O type on CAD and myocardial infarction susceptibility was mediated by its influence on LDL-C levels [35-37]. Consistent with previous findings, our data revealed that hypertensive older individuals with blood group B had significantly lower LDL-C and Apo B concentrations than those with non-B blood groups. Likewise, the results of our study demonstrated that TC, LDL-C, and Apo B might play an essential mediating role in the effect of blood group B on the decreased risk of CAD. Consistent with previous studies, LDL-C was associated with an increased risk of CAD, and HDL-C was a protective factor against CAD.

As a risk factor for CAD, the A blood group has been shown to be positively associated with the severity of coronary atherosclerosis as assessed by the Gensini score [7]. Inconsistent with this study, a study conducted on young Chinese showed no consistent association of ABO blood groups with CAD severity estimated using significantly diseased vessels [18]. However, our work findings reflected that hypertensive elderly individuals with blood group B were more likely to have a significantly lower number of diseased vessels. In addition, although a significant difference was not observed, hypertensive older individuals with blood group B were prone to have low Gensini scores, which provided additional evidence for the association. These factors might lead to benefits for seniors with hypertension and blood group B. This may help identify high-risk elderly individuals early and reduce the risk of cardiovascular events.

There were several limitations in the present study. First, this study was retrospective, in which several risk factors, including BMI and uric acid, were not considered. Second, it was a single-center study conducted on a selected group of Chinese patients. The results might be biased due to its relatively small sample. Third, there is no known mechanism to explain the association of blood group B with CAD. Therefore, larger samples and multicenter and prospective studies are necessary to confirm our findings in elderly patients with hypertension.

The current study reveals that blood group B is associated with decreased CAD risk in Chinese hypertensive subjects aged 60 years or older. In the future, more research is needed to clarify the mechanism underlying the protective effect of blood group B against CAD in these individuals.

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Conflict of interest

The authors declare that they have no competing interests.

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Author Participation

- Conception or the design of the manuscript: YS.
- Analysis and interpretation of the data: YS.
- Draft and revise the manuscript: YS, WL.
- Read and approve the final version of the manuscript: YS, WL.

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