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RESEARCH ARTICLE

The Role of ABO Blood Group Phenotype in Cardiovascular Disease Risk

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Abstract

Background: International studies disagree on which ABO blood group carries the highest cardiovascular risk: the largest prospective cohort evidence (Nurses' Health Study/Health Professionals Follow-up Study, USA) has implicated group AB, a large meta-analysis has implicated group A, and case–control studies from Turkey, Switzerland, Pakistan, and India have implicated group B. No study conducted in Syria has previously examined the joint distribution of ABO and Rhesus (Rh) phenotypes in relation to cardiac disease. This study aimed to determine whether ABO blood group and Rh factor are independently associated with cardiac disease in a Syrian population.

Methods: We conducted a case–control study of 2,239 participants (1,005 cardiac cases; 1,234 controls without known cardiac disease) recruited from hospitals and clinics across multiple governorates of Syria, with data collected between 2015 and 2026. ABO/Rh phenotype and demographic characteristics were recorded retrospectively for both groups. Associations were tested using chi-square tests, independent-samples t-tests, and multivariable logistic regression adjusted for age and sex, with blood group O and phenotype O+ as reference categories.

Results: Blood group A was most prevalent (43.23%), followed by O (33.68%), B (15.19%), and AB (7.91%); 85.98% of participants were Rh-positive. On adjusted analysis, blood group B was independently associated with case status relative to O (adjusted odds ratio [aOR] 2.50, $p<0.001$), as was Rh-positivity (aOR 1.63, $p=0.002$). When ABO and Rh were analysed jointly, the association was concentrated in the B+ phenotype (aOR 2.61, 95% CI 1.85–3.69, $p<0.001$), while B− carriers showed no excess risk (aOR 1.16, $p=0.614$). The O− phenotype was independently associated with reduced odds (aOR 0.52, 95% CI 0.33–0.83, $p=0.007$). Blood group AB showed no significant association at either the group level or within either Rh stratum. Age and male sex remained the strongest independent demographic correlates of case status (both $p<0.001$).

Conclusions: In this Syrian case–control sample, blood group B and Rh-positivity — and specifically their combination (B+) — were independently associated with cardiac disease, while O− was independently associated with reduced odds and AB showed no association. This B-predominant pattern aligns with regional case–control evidence implicating group B but differs from the largest Western prospective cohort data implicating group AB and from a large meta-

analysis implicating group A, supporting population-specific heterogeneity in ABO-related cardiovascular risk rather than a single universal pattern.

Trial registration: Not applicable.

Keywords: ABO blood group; Rhesus factor; cardiovascular disease; case–control study; Syria; risk factors

Background

Cardiovascular disease (CVD) remains the leading cause of death globally and constitutes a growing health burden in the Middle East and North Africa (MENA) region. Global Burden of Disease (GBD) data indicate that the Syrian Arab Republic has one of the highest age-standardized incidence rates of CVD in the region [1,2].

The ABO blood group system and the Rhesus (Rh) factor have attracted increasing scientific interest as potential independent, non-modifiable risk markers for cardiac disease. Findings across the literature have, however, been notably inconsistent as to which specific blood group carries the highest relative risk. The largest prospective cohort analysis to date — pooling the Nurses' Health Study (NHS, 62,073 women) and the Health Professionals Follow-up Study (HPFS, 27,428 men) — followed participants for more than two decades and reported that, relative to blood group O, adjusted hazard ratios for incident coronary heart disease rose progressively across non-O groups: 1.06 for group A, 1.15 for group B, and 1.23 for group AB, which carried the single highest point estimate of any group [3]. A separate meta-analysis pooling 17 studies (225,810 participants) has instead implicated group A as carrying the highest pooled risk [4], while case–control studies from Turkey, Switzerland, Pakistan, and India have variously implicated group B [8,9,10,17], and a large Chinese cohort found no significant difference among non-O subgroups [15]. This heterogeneity has often been attributed to the well-established association between non-O status and higher circulating levels of von Willebrand factor and factor VIII, whose relative contribution across specific ABO subgroups may plausibly vary by population [11,13].

This Western cohort-derived pattern has not been consistently replicated in case–control studies from other populations. Reports from Turkey, Pakistan, and Switzerland have instead identified blood group B — rather than AB — as carrying the strongest association with myocardial infarction and coronary artery disease [8,9,10], raising the possibility that the identity of the highest-risk ABO group is population-specific rather than universal. ABO and Rh phenotype frequencies themselves vary substantially across populations and ethnic groups, and regional studies from Syria, Turkey, Iraqi Kurdistan, Lebanon, and Gulf countries have documented this variability [3,4,5,6,7,12], underscoring the importance of population-specific characterization for understanding cardiovascular risk within a given population.

Despite this body of evidence, no adequately powered case–control study has, to our knowledge, examined the joint distribution of ABO and Rh phenotypes and their association with cardiac disease in a Syrian population, nor tested for a possible interaction between the two systems rather than treating them as independent risk factors. This study aimed to address that gap and to establish a baseline of Syrian-specific evidence, drawing on a relatively large sample (n=2,239) of participants recruited from multiple governorates across the country, to guide and encourage future follow-up research on this topic in the region.

Methods

Study design and setting

This was a case–control study conducted at a network of private and public hospitals and medical clinics across multiple governorates of Syria; participants were recruited from diverse geographic regions of the country rather than a single centre, in order to improve the representativeness of the sample. Data were extracted from patient records and structured interviews over the period between 2015 and 2026. The study was conducted in accordance with the Declaration of Helsinki. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for case–control studies [18]. To the best of our knowledge, this is the first study conducted in Syria to examine this specific research question.

Participants

Cases (n=1,005) were individuals with a pre-existing, physician-confirmed diagnosis of cardiac disease, identified through hospital and clinic records. Controls (n=1,234) were individuals with no known cardiac disease, drawn from both inpatient/outpatient and community settings. Both groups were recruited from multiple, geographically distinct governorates across Syria rather than a single locality. Exposure status (ABO/Rh phenotype) was ascertained retrospectively for both groups after case/control status had already been determined. Inclusion criteria were availability of blood group data; exclusion criteria were incomplete data or a history of recent blood transfusion.

Variables and data sources

A structured questionnaire captured age, sex, cardiac disease status (yes/no), ABO blood group (A, B, AB, O), and Rh factor (positive/negative). ABO/Rh phenotype was ascertained from medical records.

Statistical analysis

Descriptive statistics (frequencies, percentages, means, standard deviations, medians) characterized the sample. Between-group comparisons used the chi-square test of independence for categorical variables and the independent-samples t-test for continuous variables (age). Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) with 95% confidence intervals for the independent association between ABO/Rh phenotype and case status, adjusting for age (standardized) and sex; blood group O and the O+ phenotype served as reference categories. Model fit was assessed using McFadden's pseudo-R^2. Statistical significance was set at two-sided $p<0.05$. Analyses were performed in Python (version 3.11), using the pandas (version 2.2) and NumPy (version 1.26) libraries for data management, SciPy (version 1.13) for chi-square and t-tests, and statsmodels (version 0.14) for multivariable logistic regression modelling. Statistical code was implemented with the assistance of an AI-based tool under the direct supervision and verification of the authors, who reviewed all analytic steps and take full responsibility for the accuracy of the reported results and confirm this use of an AI tool is documented here in accordance with journal policy.

Results

Sample characteristics

A total of 2,239 participants were analysed: 1,005 cases (44.9%) and 1,234 controls (55.1%). Mean age was 44.8 ± 16.9 years (median 47; interquartile range 30–58; range 1–98 years). Males comprised 59.4% (n=1,329) of the sample. Table 1 summarizes the demographic characteristics of the sample.

Table 1. Demographic characteristics of the study sample (N = 2,239)

Characteristic	Value
Sample size (n)	2,239
Mean age ± SD	44.8 ± 16.9 years
Median age (IQR)	47 (30–58) years

Characteristic	Value
Age range	1–98 years
Male sex	1,329 (59.4%)
Female sex	910 (40.6%)
Cases (cardiac disease)	1,005 (44.9%)
Controls (no cardiac disease)	1,234 (55.1%)
Blood group A / B / AB / O	43.23% / 15.19% / 7.91% / 33.68%
Rh-positive / Rh-negative	85.98% / 14.02%

ABO and Rh phenotype distribution

Blood group A was the most common phenotype (43.23%), followed by O (33.68%), B (15.19%), and AB (7.91%); this A > O > B > AB pattern matched previously reported distributions from Syria [3]. Rh-positivity was observed in 85.98% of participants. The combined ABO×Rh phenotype distribution showed A+ as most frequent (39.30%) and AB− as rarest (1.12%) (Fig. 1).

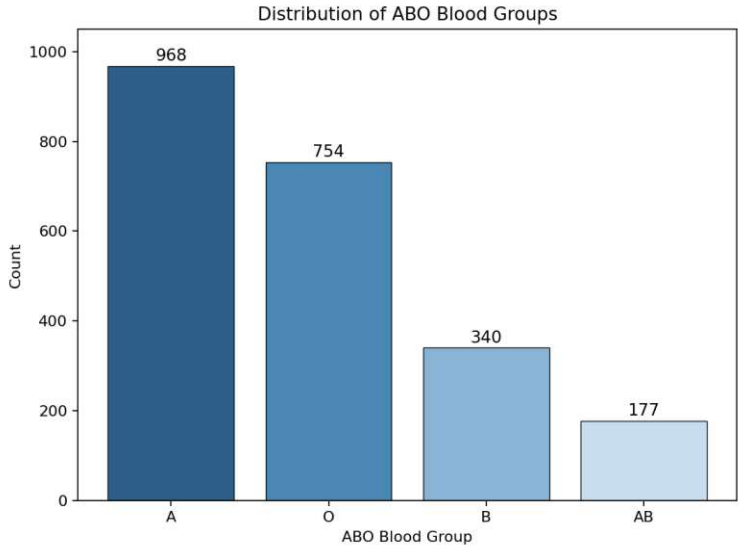


Fig. 1 Distribution of ABO blood groups in the overall study sample (N = 2,239)

Bivariate associations with cardiac disease

Cases were substantially older than controls (53.3 ± 14.0 vs. 37.8 ± 15.8 years; $t=24.53$, $p<0.001$). The proportion of cases within each blood group varied significantly ($\chi^2=34.29$, $df=3$, $p<0.001$), ranging from 40.2% (group O) to 58.8% (group B). Male sex was strongly associated with case status (55.2% of males vs. 29.9% of females were cases; $\chi^2=139.36$, $df=1$, $p<0.001$). Rh-positivity was also associated with a higher within-group case proportion (46.4% vs. 35.4% for Rh-negative; $\chi^2=13.42$, $df=1$, $p<0.001$). Analysis of the eight combined ABO×Rh phenotypes showed the largest

spread: B+ carried the highest within-phenotype case proportion (62.5%) and O− the lowest (27.8%) — a difference of approximately 35 percentage points (χ^2=53.26, df=7, p<0.001).

Multivariable logistic regression

After adjustment for age and sex, blood group B remained independently associated with case status relative to group O (aOR 2.50; p<0.001), while groups A and AB showed no significant difference from O (aOR 1.14, p=0.265; and aOR 1.01, p=0.963, respectively). Rh-positivity was independently associated with case status (aOR 1.63; p=0.002). Age (standardized) and male sex were the strongest independent demographic correlates (aOR 2.56 and 1.76, respectively; both p<0.001). Model pseudo-R^2 (McFadden) was 0.23.

Table 2 presents the adjusted logistic regression results for the combined ABO×Rh phenotype (reference: O+), which was the primary analysis of interest given the bivariate findings above.

Table 2. Multivariable logistic regression of combined ABO×Rh phenotype and cardiac disease, adjusted for age and sex (reference category: O+)

Phenotype (ref: O+)	Adjusted OR	95% CI	p-value
A+	1.11	0.87–1.41	0.404
A−	1.04	0.61–1.75	0.892
B+	2.61	1.85–3.69	<0.001
B−	1.16	0.65–2.06	0.614
AB+	0.96	0.64–1.46	0.866
AB−	0.77	0.27–2.18	0.624
O−	0.52	0.33–0.83	0.007

Notably, the B+ phenotype was the only non-reference category with a fully significant excess odds ratio after adjustment, whereas B− (same ABO group, Rh-negative) showed no elevated risk (aOR 1.16, p=0.614). The AB group — combining both the AB+ and AB− subgroups — showed no significant excess risk at either the group level (aOR 1.01, overall) or within either Rh stratum (AB+: aOR 0.96, p=0.866; AB−: aOR 0.77, p=0.624). Conversely, O− was independently associated with reduced odds of cardiac disease (aOR 0.52, p=0.007), while O+ itself (reference) showed no such signal. This asymmetry — risk concentrated in B+ and a significant protective signal isolated to O− — is consistent with a possible interaction between the B antigen and Rh-positivity, rather than two independent, additive main effects of ABO and Rh.

Menopausal status: an internal validity check

As an internal validity check, we compared ABO blood group distribution between pre- and post-menopausal women in the sample. Distribution did not differ significantly between the two groups (χ^2=2.08, df=3, p=0.555), a result that is theoretically expected, since blood group is a fixed hereditary trait determined at birth and is not biologically linked to physiological aging or menopausal status. This null finding thus serves as a sanity check confirming that the pre- and post-menopausal subgroups were statistically comparable in genetic background, supporting the validity of subsequent stratified analyses. Furthermore, the association between ABO blood group and cardiac disease status was not statistically significant within either subgroup when analysed separately (pre-menopausal: χ^2=2.46, p=0.483; post-menopausal: χ^2=3.81, p=0.283), a pattern consistent with reduced statistical power within each smaller subgroup rather than evidence against the overall association observed in the full sample.

Discussion

In this case–control study of 2,239 Syrian participants, blood group B and Rh-positivity — and specifically their combination in the B+ phenotype — were independently associated with cardiac disease after adjustment for age and sex, while the O− phenotype was independently associated with reduced odds. Age and male sex remained the dominant demographic correlates of case status, consistent with well-established cardiovascular epidemiology.

Comparison with international evidence on the highest-risk ABO group

A striking feature of the global literature on ABO blood group and cardiac disease is the lack of consensus, across populations, as to which specific non-O group carries the highest relative risk. Table 3 summarizes the identity of the highest-risk ABO group reported across a purposive sample of large or frequently cited studies from different countries, alongside the present findings.

Table 3. Reported highest-risk ABO group across selected international studies of ABO blood group and coronary/cardiac disease

Study / population	Design	Highest-risk group (vs. O)
Present study (Syria, n=2,239)	Case–control	B (B+ phenotype specifically)
He et al., NHS/HPFS (USA, n=89,550) [3]	Prospective cohort	AB (graded A<B<AB)
Sari et al. (Turkey) [8]	Case–control	B

Study / population	Design	Highest-risk group (vs. O)
Nydegger et al. (Switzerland) [9]	Case–control	B (histo-blood group B allele)
Sheikh et al. (Pakistan) [10]	Case–control	B
Amirzadegan et al. (Iran) [14]	Cross-sectional	A+ (men); AB+ (women)
Fuwai Hospital Han cohort (China, n=3,823) [15]	Prospective cohort	Non-O overall; no significant A/B/AB difference
Cross-sectional study (China) [16]	Cross-sectional	A
Chakrabarti et al. (Bengali, India) [17]	Case–control	B
Chen & Yang meta-analysis (17 studies, n=225,810) [4]	Meta-analysis	A (pooled estimate)

As Table 3 illustrates, our finding that group B — and specifically its Rh-positive (B+) combination — carries the strongest association with cardiac disease (aOR 2.50 overall; aOR 2.61 for B+) converges with case–control evidence from Turkey, Switzerland, Pakistan, and an Indian Bengali sample, all of which have similarly implicated group B as the highest-risk group [8,9,10,17]. It stands in contrast, however, to the largest prospective cohort evidence available, the pooled NHS/HPFS analysis (n=89,550), which reported a graded increase in risk from A through B to AB, with AB carrying the single highest hazard ratio (1.23 vs. O) [3]; a pooled meta-analysis of 17 studies has instead implicated group A as carrying the highest pooled risk [4]; and a large Chinese angiography cohort found no significant difference among non-O subgroups [15]. In our sample, group AB showed no significant association with cardiac disease at either the group level (aOR 1.01) or within either Rh stratum (AB+: aOR 0.96; AB−: aOR 0.77).

This pattern of partial agreement and partial divergence across studies is best explained by considering three axes along which these studies differ. The first is study design: prospective cohort studies such as the NHS/HPFS analysis and the Fuwai Hospital cohort measure incident disease accrued over years of follow-up in an initially disease-free population, whereas case–control studies such as ours, the Turkish, Swiss, Pakistani, and Indian studies, measure prevalent disease at a single time point; these designs can, in principle, weight different aspects of the disease process and carry different susceptibility to bias, which may partly explain why case–control studies cluster more consistently around group B while the largest cohort evidence points to AB. The second axis is population genetic background: ABO allele frequencies (including A1/A2 subtype ratios) and their downstream haemostatic correlates, particularly circulating von Willebrand factor and factor VIII, vary substantially across ethnic groups, and both are plausible biological mediators of any ABO–cardiovascular association [11,13]. The third axis is the local

prevalence and interaction of other cardiometabolic and environmental exposures, which can modify the apparent strength of an ABO association even if the underlying biological effect of each antigen is similar across populations. Taken together, these considerations suggest that the identity of the 'highest-risk' ABO group is unlikely to be a fixed, universal biological constant, and is instead better understood as a population- and design-dependent empirical pattern. Our data extend this literature by suggesting that Syrian, and possibly wider Middle Eastern and South Asian, populations may follow a B-predominant rather than an AB- or A-predominant pattern of ABO-related cardiovascular risk, a hypothesis that direct, harmonized cross-population comparisons would be needed to confirm.

The B+ phenotype and a possible ABO–Rh interaction

A further contribution of this study is the joint analysis of ABO and Rh as a combined phenotype rather than as separate factors. The concentration of risk in B+ (aOR 2.61) with near-null risk in B− (aOR 1.16), together with a statistically significant protective signal isolated to O− (aOR 0.52, p=0.007) rather than the O group broadly, raises the hypothesis of a biological interaction between the B and Rh-D antigens — for example, at the level of endothelial or platelet surface glycosylation — rather than simple additive effects. To our knowledge, no established molecular mechanism for such an ABO–Rh interaction has been described in the literature, and none of the international studies discussed above examined ABO and Rh jointly. This finding should therefore be regarded as exploratory and hypothesis-generating, warranting confirmation in larger, prospective, multi-centre cohorts before firm biological inference.

Regional context

The overall ABO distribution in our sample (A > O > B > AB) closely mirrors previously reported distributions from Syria, and is broadly consistent with a recent Syrian–Turkish comparative study of 77,588 Syrian blood donors, which found both group O and group B significantly more prevalent among Syrians than among neighbouring Turkish populations [12]. This external concordance across independent Syrian samples strengthens confidence that the relatively high prevalence of group B observed here reflects a genuine population characteristic rather than a sampling artifact, and underscores the potential population-level relevance of the B-associated cardiac risk identified in this study.

Strengths and limitations

- Retrospective case–control design without prior matching of cases and controls on age or sex, necessitating statistical adjustment rather than design-based control of confounding.
- The ABO×Rh interaction, while consistent across several analytic approaches, remains exploratory and requires replication in adequately powered, prospective, multi-centre studies with a defined biological mechanism.
- Single-country, hospital/clinic-based recruitment may limit generalizability beyond the Syrian population.
- Direct comparison with international cohort and case–control data is limited by differences in study design.

Conclusions

In this large Syrian case–control study — to the best of our knowledge the first study conducted in Syria to examine the association between ABO/Rh phenotype and cardiac disease — blood group B and Rh-positivity, concentrated specifically in the B+ combined phenotype, were independently associated with cardiac disease after adjustment for age and sex (aOR 2.61, $p<0.001$), while B− carriers showed no comparable excess risk and the O− phenotype was independently associated with reduced odds (aOR 0.52, $p=0.007$). This B-predominant pattern converges with case–control evidence from Turkey, Switzerland, Pakistan, and India, but contrasts with the largest available prospective cohort evidence from the USA, which identified group AB as carrying the highest relative risk, and with a large Chinese cohort and a multi-study meta-analysis that have instead implicated group A or found no significant non-O subgroup difference. These findings support population-specific heterogeneity in ABO-related cardiovascular risk rather than a single universal risk pattern, and suggest a previously undescribed ABO–Rh interaction meriting dedicated investigation. Prospective, harmonized, multi-population studies are needed to confirm whether the identity of the highest-risk ABO group genuinely differs across populations and to clarify the biological basis of any such difference.

List of abbreviations

CVD: cardiovascular disease; MENA: Middle East and North Africa; GBD: Global Burden of Disease; Rh: Rhesus; aOR: adjusted odds ratio; CI: confidence interval; NHS: Nurses' Health Study; HPFS: Health Professionals Follow-up Study; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

This study has been reviewed and approved by the Faculty Research Committee, Faculty of Pharmacy, Yarmouk Private University, Syria. The study was conducted in accordance with the Declaration of Helsinki and adhered to core ethical principles throughout: informed consent was obtained from all participants before they disclosed their data, and the confidentiality and privacy of patient information were strictly maintained at every stage of data collection and analysis.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wafaa Alyounes (WA): conceptualisation, methodology, formal analysis, supervision, writing – original draft, writing – review and editing; guarantor. Fatema Abdul Ghani (FAG): data curation. Sedra Mohammad (SM): data curation. Maria Alissa (MA): data curation. All authors, including Wafaa Alyounes, Fatema Abdul Ghani, Sedra Mohammad, and Maria Alissa, read and approved the final manuscript.

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