ASSOCIATION OF ABO AND Rh D BLOOD GROUPS WITH RHEUMATOID ARTHRITIS AMONGST THE ELDERLY IN PORT HARCOURT METROPOLIS

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ABSTRACT
Background: Rheumatoid arthritis which is an autoimmune disease is a health problem and it is strongly correlated or associated with modifiable risk factors such as presence or absence of blood group antigens amongst other factors.
Aim: This study aimed at determining the association of ABO and Rh D blood groups with rheumatoid arthritis amongst the elderly in Port Harcourt Metropolis.
Methodology: A total of one hundred (100) human subjects aged 45–90 years were recruited for the study. Blood samples were collected through venipuncture for the determination of ABO/Rh D blood groups and Rheumatoid factor. The study was carried out within the period of 13th August, 2023 to 27th September, 2023. ABO and Rh D blood grouping were determined manually with reagents manufactured by Atlas Medical, Cambridge. Rheumatoid arthritis (rheumatoid factor) was determined manually with latex reagents manufactured by Spectrum for Diagnostic Industries, Ismalia, Egypt. Results were statistically analyzed by calculation of percentages, odd ratios, relative risks and likelihood ratios using Graph-pad prism, version 8.
Results: The results revealed female subjects were 51%, while male subjects were 49%. The prevalence of Rh D positive was 95%, while Rh D negative was 5%. Blood group O has the highest frequency of (59) 59% followed by A with frequency of 33 (33%) then B 7 (7%) and AB 1 (1%). The odd ratio (OR) and likelihood ratio (LR) from the study revealed the following: blood group B (OR = 5.31, LR = 4.08); A (OR = 0.06, LR = 0.09); O (OR = 0.03, LR = 0.08); and AB (OR = 0.00, LR = 0.00). For Rh D blood groups: Rh D negative individuals recorded OR = 4.75, LR = 4.00; while Rh D positive individuals recorded OR = 0.002, LR = 0.06.
Conclusion: Distribution of ABO and Rh D blood groups amongst the studied subjects is in the order of O>A>B>AB and Rh D+ > Rh D–. Gender is not a risk factor for Rheumatoid Arthritis in the studied population. Based on the odd and likelihood ratio, the likelihood for rheumatoid arthritis to occur amongst the blood groups under study, is in the order of B>A>O>AB, and Rh D– > Rh D+, which is suggestive that Rh D+ individuals may be associated with less risk for rheumatoid arthritis, and blood group B individuals may be associated with high risk of developing rheumatoid arthritis.
Keywords: Rheumatoid Arthritis, ABO blood group, Rh Blood groups, Elderly.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is common and it is characterized by inflammation, painful and progressive joint destruction, leading to significant morbidity and impaired quality of life for affected individuals. Patients with RA are at a greater risk for serious infection, respiratory disease, osteoporosis, cardiovascular disease, cancer, and mortality (Sparks, 2019).

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With an estimated global prevalence of 0.5% to 1%, RA remains a major public health concern (Alamanos *et al.,* 2006). Despite extensive research, the exact etiology of RA remains elusive, and it is believed to arise from a complex interplay of genetic and environmental factors (Gabriel, 2001).

Among the various genetic factors that have been implicated in RA susceptibility, the association between blood groups and rheumatoid arthritis has garnered increasing attention in recent years. The ABO blood group system, discovered by Karl Landsteiner in the early 1900s, classifies individuals into four major blood types: A, B, AB, and O, based on the presence or absence of specific antigens on the surface of red blood cells (RBCs). Similarly, the Rh D blood group system determines the presence or absence of the Rh antigen on RBCs, resulting in individuals being classified as Rh D-positive or Rh D-negative (Megan, 2021).

The potential links between blood groups and RA are biologically plausible. Blood group antigens have been implicated in various immune processes, including the regulation of inflammatory responses and modulation of immune cell interactions. Specific blood group antigens have also been found to influence the expression and function of immune-related molecules, such as cytokines and cell adhesion molecules, which play crucial roles in RA pathogenesis (Xavier, 2008).

While RA can occur in individuals of any age, certain demographic groups are more susceptible to its effects, including those engaged in smoking cigarettes, hard labour and the elderly. Research has shown that individuals who engage in physically demanding occupations, such as construction workers, farmers, and assembly line operators, have a higher risk of developing rheumatoid arthritis. Repetitive joint stress and strain associated with heavy labour can trigger an inflammatory response, increasing the likelihood of RA development (England, 2022).

The risk of developing rheumatoid arthritis increases with age, with the elderly being particularly susceptible. A comprehensive study by Myasoedova, (2010) reported a significant rise in RA incidence among individuals aged 60 and above, highlighting the age-related vulnerability to this condition. For both hard laborers and the elderly, the consequences of rheumatoid arthritis can be debilitating. Joint pain and stiffness can interfere with work productivity for laborers and disrupt daily activities and independence for the elderly. A study published (Barton, 2010), emphasized the profound impact of RA on the quality of life in affected individuals.

Emerging evidence suggests that certain blood groups may confer an increased or decreased risk of developing RA. Several studies have explored the potential associations between ABO and Rh blood groups with RA susceptibility, severity, and clinical outcomes. For instance, a study by Salem *et al.,* (2021) found a higher prevalence of RA in individuals with blood group A and Rh-D positive status. In contrast, some other investigators have reported conflicting results, with no significant associations between blood groups and RA (Sari *et al.,* 2008).

Paucity of scientific research on association of ABO and Rh D blood groups with RA amongst those in Rivers especially within the Port Harcourt metropolis and its environs is rare. Understanding and linking the relationship between blood groups and RA could have important clinical implications. If a significant association is established, blood group status might serve as a valuable biomarker for RA risk assessment, enabling earlier diagnosis and personalized therapeutic approaches. Furthermore, such findings could provide novel insights into the underlying mechanisms of RA and contribute to the development of targeted therapies.

This research seeks to shed light on the potential role of blood groups as genetic risk factors associated with the occurrence of rheumatoid arthritis; based on this, the study aimed to determine the association of ABO and Rh D blood groups with rheumatoid arthritis amongst the elderly in Port Harcourt Metropolis.

MATERIALS AND METHODS
Study Area
The study was conducted in Port Harcourt Metropolis. Port Harcourt, the capital of Rivers State is located on latitude 4.75^ON and longitude 7.00^OE, it is a city which lies along the Bonny River and is located in the Niger Delta and covers an area of $369km^2$. Port Harcourt has an estimated population of 1,865,000 inhabitants, up from, 1,382,592 as of 2006 (McKenna, 2023). The analysis was also carried at the Haematology Laboratory, Department of Medical Laboratory Science, Rivers State University, Nkpolu-Oroworukwo, Port Harcourt, Rivers State.
Study Population
Based on convenient sampling, a total of one hundred (100) human subjects were recruited. The One hundred human subjects were within Port Harcourt Metropolis, ranging between the ages of 45 to 90 years.
Eligibility of Subjects and Informed Consent
Individuals below the age of 45 and also those not within Port Harcourt metropolis were excluded from the study, and only willing and apparently healthy subjects within Port Harcourt, aged 45 to 90 years were enrolled for the study. Informed consent was obtained from subjects prior to enrolment after letter of introduction by the Department of Medical Laboratory Science, Rivers State University.
Sample Collection and Processing
After pre-test counseling and explanation, venous blood sample was drawn from the antecubital fossa of the subject with the use of a sterile syringe as described by Cheesebrough, (2010). A total of five (5.0) mL of venous blood was collected; three (3.0) mL into a sample bottle that contains 0.5mL of 1.2 mg/mL of dipotassium

ethylene diamine tetra-acetic acid (EDTA), for serological determination of ABO and Rh D blood groups; and two (2.0) mL into a plain sample bottle for the determination of rheumatoid factor. Blood samples were analyzed within 24 hours of collection. Collected samples were all transported under cold chain (ice packs in air tight and sealed thermo-container at $2\text{-}8^O$C) from the site of collection to the laboratory where analysis was carried out.

Laboratory Analysis
Determination of ABO and Rh D Blood Group using Anti-A Monoclonal Reagent, Atlas Medical, Lot No: 23041702; Expiry Date: 2025/04/27, Anti-B Monoclonal Reagent, Atlas Medical GmbH, Lot No: 23021231; Expiry Date: 2024/12/03, Anti-D IgG/IgM Blend Reagent, Atlas Medical GmbH, Lot No: 23041705; Expiry Date 2025/04/25.

Principle: The presence or absence of the A, B, and D antigen on human red blood cells can be determined by testing the red blood cells with the respective antisera, specifically Anti-A, Anti-B, Anti-AB and Anti-D. The procedure is based on the principle of agglutination. Agglutination indicates the presence of an antigen-antibody reaction while lack of agglutination indicates the absence of an antigen-antibody reaction (Cheesbrough, 2010).

Procedure: For ABO blood group, a drop (1 ml) of anti-A, anti-B, and anti-AB (atlas medical), each was placed in a clean glass tube labeled A, B and AB. A drop (1 volume) of 3-5% red blood cell of subjects was added to the part labeled A, B and AB, the contents was mixed gently by tapping the base of the tubes. The tubes were left at a room temperature for 5 minutes and then centrifuged at 1500rpm for 1 minute, then the tubes were observed for agglutination. Presence of agglutination in tube with antiserum A indicates the blood group is A, presence of agglutination in tube with antiserum B indicates the blood group is B, presence of agglutination in tube with antiserum AB indicates the blood group is AB, no agglutination in all tubes indicates the blood group is O.

Same procedure was applied for Rh blood group, a drop of anti-D (atlas medical) was placed in a clean glass tube labeled D. A drop (1 volume) of subject's red cell was added to same tube, the content was mixed gently, left in a room temperature for 5 minutes and then centrifuged at 1500rpm for 1minute, observe for agglutination. Presence of agglutination indicated a positive result while absence of agglutination indicates a negative result (Cheesbrough, 2010).

Determination of Rheumatoid Factor (RF) using Latex reagent, Spectrum for Diagnostic Industries, Ismalia, Egypt. Lot No: SRFSR0206021-4; Expiry Date: 12/2023

Principle: Spectrum RF latex reagent is a suspension of polystyrene particles sensitized with human gamma globulin. When the latex reagent is mixed with a serum containing rheumatoid factor, visible agglutination occurs. The latex reagent has been produced so that agglutination will take place only when the level of RF is greater than 10 IU/mL (Spectrum, 2023).

Procedure: All reagents and specimen were brought to room temperature. One drop (50 ul) of the positive control and 50 ul of the patient serum was placed into separate circles on the glass slide. The RF latex reagent was shaken gently and one drop (45ul) was added on each circle next to the sample to be tested and control. A disposable stirrer was used to mix the mixture well and spread mixture over the whole test area, the slide was tilted gently, agitated for 2 minutes by hand and observed for the presence or absence of agglutination (Spectrum, 2023).

Interpretation of Results

Negative result: No agglutination of the latex particles suspension within two minutes.

Positive result: An agglutination of the latex particles suspension will occur within two minutes, indicating an RF level of more than 10 IU/mL.

Statistical Analysis

Data collected were statistically analyzed by simple percentage calculation. Odd Ratios, Relative Risk and Likelihood Ratio were analyzed using Graph-Pad Prism version 8. Data are presented in Tables.

RESULTS

Demographic Details of Study Participants

A total of 100 subjects participated in the study. Males were 49 while females were 51. Details are shown in Table 1.

Table 1: Demographic Details of Study Participants

Parameters	Number	Percentage (%)
Total number of subjects	100	100
Total number of males	49	49
Total number of females	51	51
Age Bracket	45-90	Years
Age Interval		
45-50	53	53
51-56	11	11
57-62	12	12
63-68	12	12
69-74	4	4
75-80	5	5
81-86	2	2
87-92	1	1

Frequency Occurrence and Percentage Distribution of ABO and Rh D Blood Groups

The frequency and percentage distribution of ABO blood groups were analyzed and recorded. For ABO blood group, the order of O>A>B>AB was observed. The frequency and percentage distribution of Rh D blood groups were analyzed and recorded also and the order of Rh D+ > Rh D- was observed. Details are shown in Table 2.

Table 2: Frequency Occurrence and Percentage Distribution of the Studied ABO Blood Group

Blood Group	Frequency	Percentage (%)
A	33	33%
B	7	7%
AB	1	1%
O	59	59%
RhD+	95	95%
RhD-	5	5%

Frequency and Percentage Distribution of ABO and Rh D Blood Groups based on Gender

The frequency and percentage distributions of ABO blood group system based on Gender were analyzed and recorded. Details are shown in Table 3.

Table 3: Frequency and Percentage Distribution of the Studied ABO Blood Group based on Gender

Blood Group	Total Population N(% distribution)	Frequency Occurrence	Percentage Distribution (%)
A	33 (33%)	M=17	M = 17%
		F=16	F = 16%
B	7(7%)	M=4	M = 4%
		F=3	F = 3%
AB	1(1%)	M=1	M = 1%
		F= 0	F = 0 %
O	59(59%)	M=27	M = 27%
		F=32	F = 32%
RhD+	95 (95%)	M=47	M=47%
		F=48	F=48%
RhD-	5 (5%)	M=2	M=2%
		F=3	F=3%

Frequency Occurrence and Percentage Distribution of Rheumatoid Arthritis Infection in the Studied Population

Out of 100 participants, 6% tested positive for Rheumatoid factor. Amongst those that tested positive, 4% were females while 2% were males. The infection ratio based on gender is 67:33 for females and males respectively. Details are shown in Table 4.

Table 4: Frequency Occurrence and Percentage Distribution of Rheumatoid Arthritis Infection in the Studied Population

Parameter	Frequency	Percentage (%)
Rheumatoid Arthritis in Total Population	6	6
Rheumatoid Arthritis in Females	4	4
Rheumatoid Arthritis in Males	2	2
Rheumatoid Arthritis Infection Ratio	Females 67%	Males 33%

Frequency Occurrence and Percentage Distribution of Rheumatoid Arthritis Based on Blood Group Differences

The frequency occurrence and percentage distributions of rheumatoid arthritis based on blood group differences were analyzed and recorded. Details are shown in Table 5.

Table 5: Frequency Occurrence and Percentage Distribution of Rheumatoid Arthritis Based on Blood Group Differences

Blood Group	Frequency of Blood Group Occurrence	% of Blood Group Occurrence	Frequency of Infection Occurrence	% of Infection Occurrence
A	33	33	1	17
B	7	7	3	33
AB	1	1	0	0
O	59	59	3	50
Rh D Positive	95	95	5	83
Rh D Negative	5	5	1	17

Odd Ratios, Relative Risks and Likelihood Ratios of Studied Parameters in Relation to Risk of Having Rheumatoid Arthritis Infection

The likelihood for blood group B subjects to be infected with Rheumatoid Arthritis is high comparable to blood group A, O and AB. For Rh D blood group, Rh D negative subjects are more likely to have Rheumatoid Arthritis than Rh D positive individuals. For gender, the likelihood for Male or Female subjects to be infected with Rheumatoid Arthritis is low based on values of odd ratios and likelihood ratios; this shows that Gender is not a risk factor for Rheumatoid Arthritis amongst the subjects. Details are shown in Table 6.

Table 6: Odd Ratios, Relative Risks and Likelihood Ratios of Studied Parameters in Relation to Risk of Having Rheumatoid Arthritis based on Blood Group and Gender Differences

Blood Group	Odd Ratio	Relative Risk	Attributable Risk	Likelihood Ratio	p-value
A	0.06 CI $^{0.006\ to\ 0.373}$	0.09 CI $^{0.015\ to\ 0.473}$	0.29 CI $^{0.187\ to\ 0.460}$	0.09	0.0004 [S]
B	5.31 CI $^{0.902\ to\ 27.30}$	4.35 CI $^{1.01\ to\ 15.82}$	0.17 CI $^{-0.024\ to\ 0.548}$	4.08	0.1062 [NS]
AB	0.00 CI $^{0.00\ to\ 900}$	0.00 CI $^{0.00\ to\ 214}$	0.01 CI $^{-0.109\ to\ 0.955}$	0.00	>0.9999 [NS]
O	0.03 CI $^{0.011\ to\ 0.121}$	0.08 CI $^{0.028\ to\ 0.233}$	0.53 CI $^{0.424\ to\ 0.670}$	0.08	<0.0001 [S]
Rh D Positive	0.002 CI $^{0.000\ to\ 0.011}$	0.05 CI $^{0.022\ to\ 0.118}$	0.89 CI $^{0.851\ to\ 0.996}$	0.06	<0.0001 [S]
Rh D Negative	4.75 CI $^{0.327\ to\ 44.1}$	4.13 CI $^{0.636\ to\ 20.9}$	0.12 CI $^{-0.045\ to\ 0.595}$	4.00	0.2593 [NS]
Females	0.08 CI $^{0.030\ to\ 0.231}$	0.15 CI $^{0.057\ to\ 0.362}$	0.42 CI $^{0.302\ to\ 0.568}$	0.15	<0.0001 [S]
Males	0.04 CI $^{0.010\ to\ 0.170}$	0.08 CI $^{0.022\ to\ 0.280}$	0.44 CI $^{0.332\ to\ 0.587}$	0.08	<0.0001 [S]

Key: CI = Confidence interval, S = Significant, NS = Non-significant

DISCUSSION

The prevalence of the ABO blood group in the present study was in the order of O>A>B>AB. This outcome is in agreement with reports from Anifowoshe and colleagues, in their study amongst the six geopolitical zones in Nigeria (Anifowoshe *et al.,* 2017); and that of Christian and colleagues, in their study amongst indigenes of Ogoni in Rivers State (Christian *et al.,* 2020). Also, in congruent with another study (Enosolease and Bazuaye, 2008) in Benin region of Niger Delta; and moreso, with a study reported by Garratty and colleagues on 3,086,215 individuals belonging to different race in USA (Garratty *et al.,* 2004). However, the results gotten from this study are slightly different from a study in Madagascar that reported the trend O>B>A>AB (Randriamanantany *et al.,* 2012); and another study in Turkey by Kayiran et al. (2012), who reported the trend as A>O>B>AB. Differences observed might be due to genetic and environmental factors. From the foregoing we can deduced that the result is congruent with other studies from other parts of Nigeria where O is the predominant blood group (O > A > B > AB) but slightly different from data from Madagascar (O > B > A > AB) and Turkey.

On Rh D blood group percentage distribution, in this study, the prevalence was in the order Rh D+ > Rh D-. This finding is similar and in agreement with study by Anifowoshe *et al.* (2017) were they reported the trend of Rh D+ > Rh D- among the six geopolitical zones.

The study finding is also similar to that of Enosolease and Bazuaye (2008) and that of Christian *et al.* (2020) where they also reported that Rh D positive antigen dominates among the Benin region and Ogoni ethnic group. However, the results from this study were not in agreement with findings from the study by Garratty *et al.* (2004) were it was observed and recorded that Rh phenotype D negative was higher among different race in United States.

For percentage distribution of rheumatoid arthritis infection, 6 % tested positive for rheumatoid factor. The infection ratio based on gender is 2:1 for females and males respectively. The percentage distribution in this study is low compared to those reported by other authors. A study by Christian *et al.* (2020), on assessment of some haemo-rheological parameters in decent of Rumuche, Emohua, Rivers State, Nigeria with rheumatoid arthritis disease recorded 45.3% (females: 31.4%; males: 13.9%). A study by Salem *et al.* (2021), recorded 61.8%; study by Çildağ *et al.* (2017), recorded 38.6% and lastly a study by Ohagwu *et al.* (2020), recorded 72.2% which are all higher when compared to the percentage gotten from this study. Differences might be due to different sample sizes, environmental factors, type of serological test kits used, and probably differences in genetic predisposition.

Based on the relationship of ABO and Rh D blood groups with rheumatoid arthritis, odd ratios find its usefulness in comparing the relative odds for the occurrence of the possible outcome of a disorder or disease (in this case, rheumatoid arthritis), taking into cognizance the presence of the blood group antigens. The odd ratio in this study determines the risk factor associated with the presence of the blood group antigens (ABO and Rh D) in relation to rheumatoid arthritis. An odd ratio of 1 (OR = 1): implies that the presence of that antigen will not affect the outcome, which is rheumatoid arthritis. An odd ratio that is greater than 1 (OR > 1): implies that the presence of such blood group antigen is associated with a higher risk of having rheumatoid arthritis. An odd ratio of less than 1 (OR < 1): implies that the presence of such blood group antigen is associated with a lower risk of having rheumatoid arthritis. The likelihood ratio gives the usefulness of the blood group outcomes in ascertaining which blood group is more prone to having rheumatoid arthritis. So, the combination of odd ratios and likelihood ratios will give a better picture of rheumatoid arthritis risk.

From this study, using the odd ratios for the blood groups under consideration in relation to associating them as a risk factor for rheumatoid arthritis, the likelihood occurrence of rheumatoid arthritis based on differences in blood groups, was in the order of (B) > (A) > (O) > (AB), for ABO blood group; and (Rh D–) > (Rh D+) for Rh D blood group.

Combining the likelihood ratio and odd ratio for ABO blood group system, this study has revealed that blood group B individuals may likely be at high risk compared to blood group A, O and AB individuals, in the order: (B>A>O>AB). The result recorded in this study is not in agreement with study the by Salem *et al.* (2021), where they reported that blood group A individuals were more infected with rheumatoid arthritis followed by B, O and AB blood group individuals, in the order of A>B>O>AB; even though, their study showed no significant difference in the distribution of ABO blood groups between patients with rheumatoid arthritis. Also, study by Nik *et al.* (2021), disagrees with the outcome of this study. Nik and colleagues recorded O>A>B>AB as likelihood order, with no statistically significant difference in the distribution of ABO blood groups between patients with rheumatoid arthritis.

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Finally, the results from this study were not in agreement with those observed by Çildağ *et al.* (2017), in which they reported the likelihood order to be A>O>B>AB. These differences or the higher incidence of rheumatoid arthritis in different blood types might be associated with different genetic predisposition and type of testing kits used.

For Rh D blood group, Rh D– (negative) subjects are more likely to have Rheumatoid Arthritis than Rh D+ (positive) individuals. These are based on their odd ratios and likelihood ratios. This study recorded (Rh D–) > (Rh D+) as it's order; this finding differs from the findings of Çildağ *et al.* (2017), which in their study observed a significant difference in the distribution of Rh factor in rheumatic diseases, giving the order of Rh D+ > Rh D–. Also, the finding of this study is not congruent with that of Salem *et al.* (2021), in which when rheumatoid arthritis was evaluated in terms of the distribution of the Rh D blood group, Rh D (+) was more prevalent in subjects with rheumatoid arthritis, although there was no significant difference between the groups of rheumatic diseases in terms of Rh D blood group distribution. In both studies from other authors, likelihood and odd ratio were not applied and considered in their statistical analysis, and differences may arise as a result of that, and also as a result of genetic predisposition.

Based on gender, the likelihood for male and female subjects to be infected with Rheumatoid Arthritis is statistically low from the values gotten from odd ratios. This shows that gender is not a risk factor for Rheumatoid Arthritis in the population studied.

CONCLUSION

The distribution of ABO blood group amongst the studied subjects is in the order of O>A>B>AB. Gender is not a risk factor for Rheumatoid Arthritis in the population studied. Based on odd ratios and likelihood ratios, the likelihood for rheumatoid arthritis to occur for ABO blood group is in the order of (B) > (A) > (O) > (AB); and for Rh blood group is (Rh D–) > (Rh D+). This implies that blood group B antigens may be associated as risk factor for rheumatoid arthritis, while Rh D+ antigens may be associated with less risk for rheumatoid arthritis.

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