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Plasma von Willebrand Factor Antigen Levels and Its Relation with ABO Blood Group, Age and Sex

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Abstract

Background: The ABO blood antigens may influence the levels of vWF: Ag and put individuals at risk of coagulopathies. This study assessed the plasma vWF: Ag and its relation with ABO blood antigens among healthy adults in northern Ghana. *Methods*: This cross-sectional study recruited 84 blood donors, aged 18–50 years, at Tamale Teaching Hospital. Blood groups were determined using the standard tube method, and a complete blood count was measured with an automated haematology analyzer. Sandwich ELISA was used to assess plasma vWF: Ag levels. The data obtained were analyzed using SPSS version 22. *Results*: The frequencies of O, A, B, and AB blood groups were 34 (40.5%), 25 (29.8%), 20 (23.8%), and 5 (6.0%), respectively. vWF: Ag levels were higher among the non-O than group O individuals ($p = 0.008$). Plasma vWF: Ag levels were lower in group O compared to AB ($p = 0.015$) and A ($p = 0.013$) individuals. Males had higher vWF: Ag levels than females ($p = 0.002$). A moderately positive correlation was observed between age and vWF levels ($r = 0.497$, $p<0.001$). Blood group O participants had lower absolute neutrophil counts ($p = 0.039$), but higher RDW-SD ($p = 0.045$). *Conclusion*: The predominant blood group was O, followed by other groups in the order: O>A>B>AB. Plasma vWF: Ag levels were higher in non-group O compared with group O individuals. Males had higher vWF: Ag levels, and a positive correlation between age and vWF: Ag was observed. Again, blood group O participants had lower neutrophil counts, but higher RDW-SD. The relationship between ABO blood phenotypes and plasma vWF: Ag should be considered in clinical practice. The establishment of separate reference intervals of vWF: Ag for the various phenotypes of ABO is recommended. Also, the study recommends further multicenter studies to assess the link between ABO phenotypes and all the endothelial cell parameters.

Keywords: Blood Cell Indices; Blood Group; ELISA; vWF; Ag.

1. Introduction

The ABO blood group antigens are the most studied and genetically polymorphic blood group system among the over 300 different blood group antigens identified on the membranes of red blood cells (RBCs) [1]. Although the A, B,

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and H determinants, which make up the ABO blood group system, are typically thought to be found on red blood cells, they may also be expressed on a range of different cell types, including platelets, von Willebrand factor (vWF), and endothelial cells [2]. The ABO blood group phenotype is regarded as one important determinant of the wide variation of plasma vWF antigen (vWF: Ag) levels in normal individuals, even though other contributing factors such as age, stress, medications, and hormones have been identified [3, 4].

Earlier studies identified the quantitative influence of ABO blood antigens on vWF, and reported that the antigens may alter the rate of vWF synthesis or secretion within endothelial cells [5, 6]. Hernaningsih [7] and Leebeek & Eikenboom [8] studies showed the high risk of non-group O individuals for developing a venous thromboembolic illness, ischemic heart disease, and peripheral vascular disorders, probably due to the high levels of vWF in such individuals.

vWF is a large adhesive glycoprotein synthesized by endothelial cells and megakaryocytes, and circulates in the plasma as a series of heterogeneous multimers [9]. vWF has two major functions in haemostasis. Firstly, vWF is necessary for platelet sub-endothelium adhesion, platelet-to-platelet contacts, as well as platelet aggregation. Secondly, vWF is the specific carrier molecule for factor VIII (FVIII) in plasma and protects it from proteolytic degradation, prolonging its half-life in circulation, and efficiently localizing it at the site of vascular injury [10]. A previous study suggested that increased vWF levels are a significant thrombotic risk factor, despite the fact that a vWF deficit causes the haemorrhagic diathesis (von Willebrand disease) [11]. It has been reported that other gene loci may have significant quantitative influence on vWF plasma levels in addition to the vWF gene (12p12), and the most important of these loci is the ABO blood group locus situated on chromosome 9 (9q34) [12]. The wide range of plasma vWF in the healthy population (normal range, ~50-200 IU/dL) may be influenced by external contributors, including the ABO antigens, and this variation has a significant clinical effect on the individual [13, 14].

ABO blood antigens contribute to about 30% of the variances in plasma levels of vWF, with genetic differences responding for approximately 60% of those changes [13]. Previous studies have observed lower levels of vWF among group O individuals compared to non–group O members in a normal population, suggesting the higher risk of non-group O persons to thrombotic events [5, 15, 16]. Again, James and colleagues recently recommended that blood antigen-specific reference intervals for plasma vWF levels be considered during the diagnosis of von Willebrand disease (vWD) [17].

Despite the reported effects of ABO blood antigens on plasma vWF levels, there is a paucity of data in this regard in Ghana. Therefore, this study determined the plasma levels of vWF and its relation with the ABO blood antigens, age, and sex among apparently healthy adults in Tamale, Ghana.

2. Materials and Methods

2.1. Study Design/Study Site

This hospital-based cross-sectional study was conducted from June 2022 to October 2022 at the Tamale Teaching Hospital (TTH) in the Northern Region of Ghana. TTH is a tertiary-level referral facility located in Tamale, the capital of the Northern Region. The 484-bed capacity hospital serves inhabitants of the five Northern Regions: Savannah, Northern, North-East, Upper West, and Upper East. Tamale has a population of approximately 371,351 with the majority being farmers, and is located at a longitude of 0.8235°W and latitude of 9.3930°N. The digital address of the hospital is NT-0101-5777.

2.2. Study Population and Sample Size

The study recruited 84 blood donors attending the Blood Bank Unit of TTH. Apparently healthy, consenting adults between the ages of 18 and 49 years were included in the study. Children, the aged and individuals on medications such as anticoagulants, contraceptives, and anti-platelet drugs, including aspirin and herbal remedies, were excluded from the study.

2.3. Sample Collection and Processing

Five millilitres of blood were aseptically collected from each subject. About 2.7 mL was dispensed into 3.2% tri-sodium citrate-containing tubes and the remaining 2.3 mL into ethylene-diamine-tetraacetate (EDTA) tubes. The samples were then inverted gently about 6 times to ensure that the blood was adequately mixed with the anticoagulant. The EDTA blood was used for full blood count (FBC), ABO, and Rh (D) blood grouping. The tri-sodium citrate sample was immediately centrifuged at 4000 rpm for 15 minutes to obtain platelet-poor plasma (PPP) for the vWF: Ag assay. The plasma was aliquoted into Eppendorf tubes and stored at -20°C for analyses of vWF: Ag using a sandwich enzyme-linked immunosorbent assay (ELISA).

2.4. Full Blood Count Measurement

Full blood count for each participant was estimated using a three-part Mindray haematology analyzer (Mindray, BC-2800, China) following the manufacturer's protocol. The analyzer works on the principles of impedance for the

measurement of red blood cells and platelets, flow cytometry for the assessment of white blood cells and differentials, and colorimetry for the estimation of haemoglobin (Hb). The procedure for the measurement of CBC parameters was adopted from the Mensah et al. [18] study. The procedure was carried out at the Haematology Laboratory of TTH.

2.5. ABO and Rh Typing

The blood group of each participant was determined using commercially produced anti-A, anti-B, and anti-D sera (Medsource Ozone Biomedicals Pvt. Limited., India). For each individual, the red blood cell ABO phenotype was determined by routine serological testing with the use of monoclonal anti-A, anti-B, and anti-D blood grouping reagents. The standard tube method was used for the determination of the ABO blood groups. The red cells were washed three times in normal saline to get rid of plasma proteins that may interfere with the agglutination process. A 2-5% cell suspension was then prepared. Two drops each of anti-A, anti-B, and anti-D were added to three different tubes and appropriately labelled. A drop of the cell suspension was added to each of the tubes (ratio of 2:1), mixed, and centrifuged at 1500 rpm for 1 minute. After centrifugation, the tubes were shaken to disperse the cell button at the bottom of the tube and checked for agglutination.

2.6. Plasma vWF Assay Using ELISA

Plasma vWF was assayed by the sandwich ELISA method using commercially prepared ELISA kits (Biobase, China). The ELISA procedures were performed according to the manufacturer's instructions. The ELISA plates were washed and read using a separate automated microplate washer and reader (Poweam, China) at the Postgraduate Laboratory, University for Development Studies, Tamale, Ghana. The protocols for the ELISA were adopted from the Nkansah et al. [19] study. The processes involved in the methodology have been summarized in Figure 1 below.

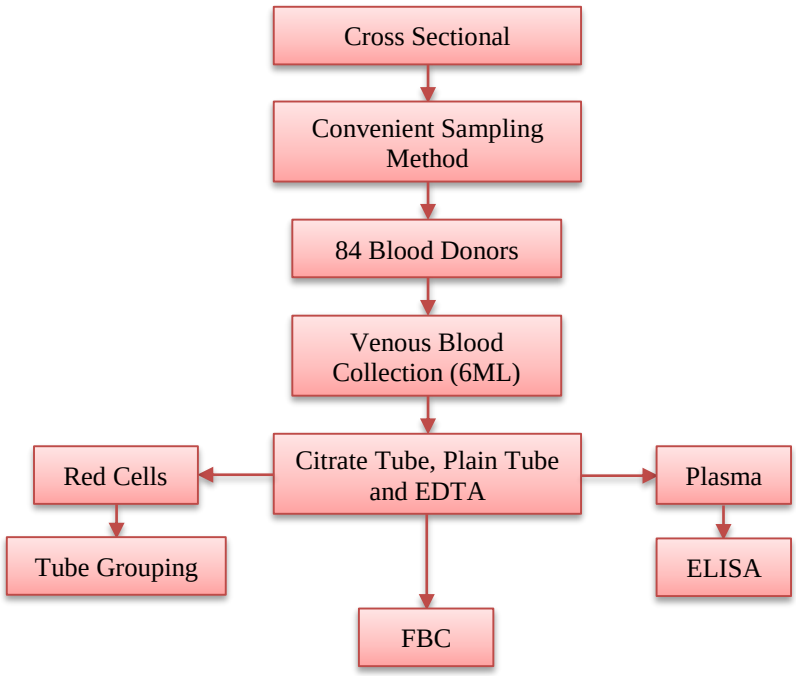

Figure 1. Overview of the study design

2.7. Data Analysis

Data were entered into Microsoft Excel 2013 and analyzed using IBM Statistical Packages for the Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as frequencies with corresponding percentages. The Mann-Whitney U-Test was used to compare the median vWF: Ag levels between group O and non-group O individuals, as well as male and female participants. Kruskal Wallis test was used to compare the median vWF: Ag levels within the various ABO blood group phenotypes. Correlation between age and plasma vWF: Ag levels were assessed by the Spearman rank correlation test. Statistical significance was set at $p<0.05$ at a 95% confidence interval.

3. Results

3.1. Sociodemographic Characteristics of the Study Subjects

This study recruited 84 participants, comprising 45 males (53.6%) and 39 females (46.4%). The majority of the participants (53/63.1%) were between the ages of 18 to 29 years with only 4.8% (4) between 40 to 49 years. Most

(34/40.5 %) of the participants were blood group O, 25 (29.8%) were group B, 20 (23.8 %) were blood group A, and 5 (6.0 %) of the participants were blood group AB. The blood group phenotypes were further categorized as group O (34/40.5%) and non-O group (50/59.5%) individuals (Table 1).

Table 1. Demographic Characteristics of the Study Participants

Variables	Categories	Frequency	Percentage (%)
Sex	Male	45	53.6
	Female	39	46.4
Age categories (Years)	18-29	53	63.1
	30-39	27	32.1
	40-49	4	4.8
O and Non-O Blood Group	O Group	34	40.5
	Non-O Group	50	59.5
ABO Group	O	34	40.5
	A	20	23.8
	B	25	29.8
	AB	5	6.0

Data are represented in frequencies with corresponding percentages.

3.2. Plasma vWF: Ag Levels between Blood Group O and Non-O Participants

Figure 2 shows the variation in plasma vWF: Ag levels between group O and non-group O participants. The median plasma vWF level of the participants was 111.45 (78.19–143.05) U/L. The median plasma vWF level was significantly higher among non-O blood group individuals as compared to blood group O [123.05 (92.15-147.40) U/L vs. 86.68 (68.09-139.30) U/L, $p = 0.008$].

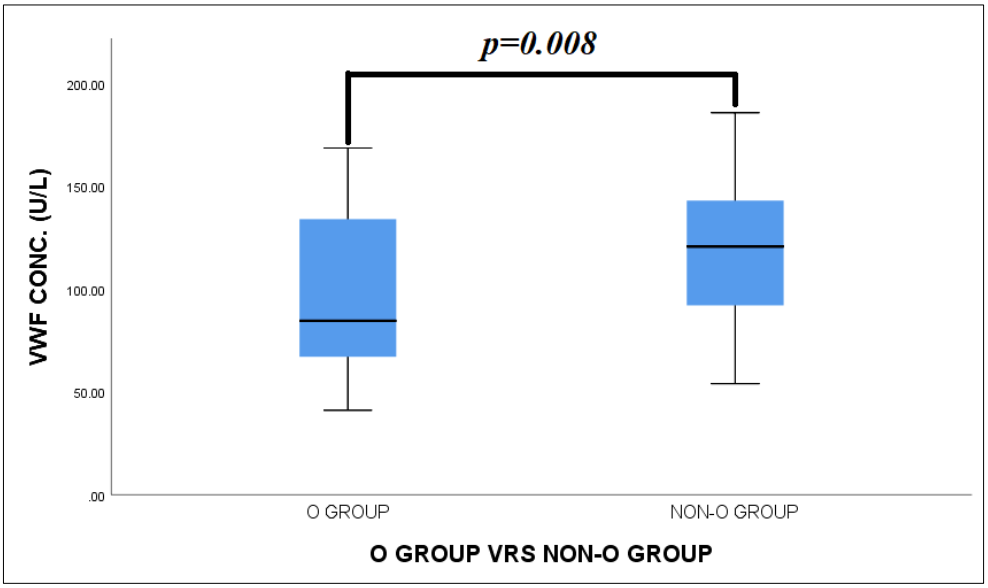

Figure 2. Plasma vWF: Ag levels between blood group O and non-O participants. U/L=Units per Liter, vWF=von Willebrand Factor, CONC=Concentration. Data were compared with Mann-Whitney U-Test and p<0.05 was considered statistically significant.

3.3. Plasma Concentrations of vWF: Ag within the ABO Blood Group Phenotypes

Figure 3 shows the distribution of VWF: Ag levels among the ABO blood group phenotypes. The median plasma vWF (U/L) among the blood groups were O: 86.68 (68.01–139.30), A: 128.60 (108.30–149.15.40), B: 111.80 (92.15–139.70), and AB: 140 (130.00–150.00). The vWF levels were significantly lower in group O individuals compared to AB ($p = 0.015$) and A ($p = 0.013$). No significant difference was found in the levels of vWF between group B and group O as well as other blood types ($p>0.05$).

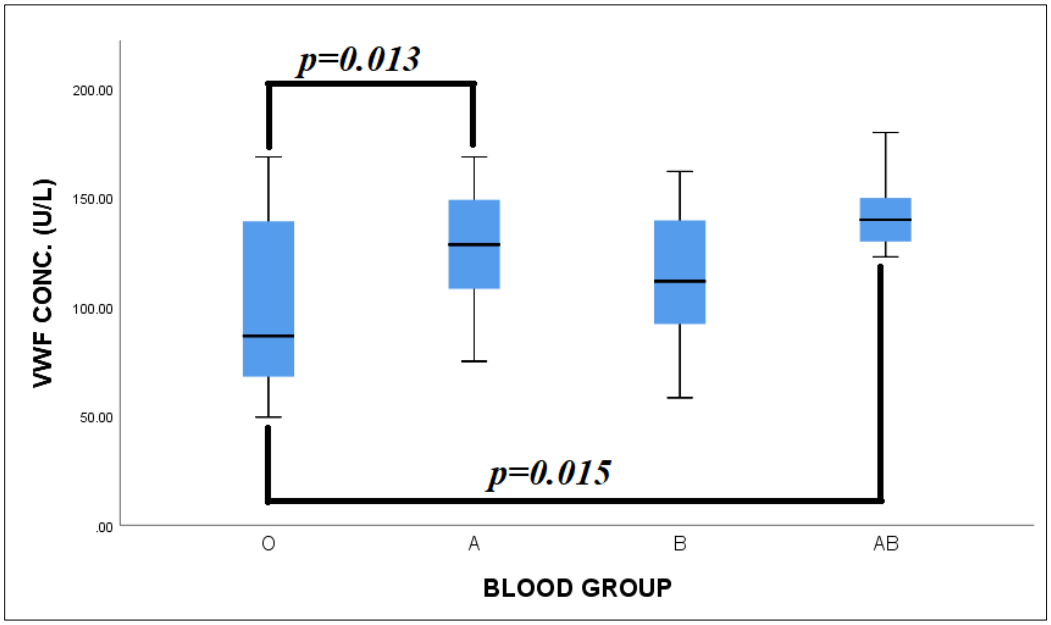

Figure 3. Plasma concentrations of vWF: Ag within the ABO blood group phenotypes. vWF= von Willebrand Factor, CONC=Concentration. Data were compared with Kruskal Wallis Test, and p<0.05 was considered statistically significant

3.4. Plasma vWF: Ag Levels between Male and Female Participants

Figure 4 shows the variation of plasma vWF levels between male and female participants. The median plasma vWF: Ag level was significantly higher among male participants as compared with their female counterparts [132.30 (115.50–143.80) U/L vs. 91.64 (68.89–126.07) U/L, p = 0.002].

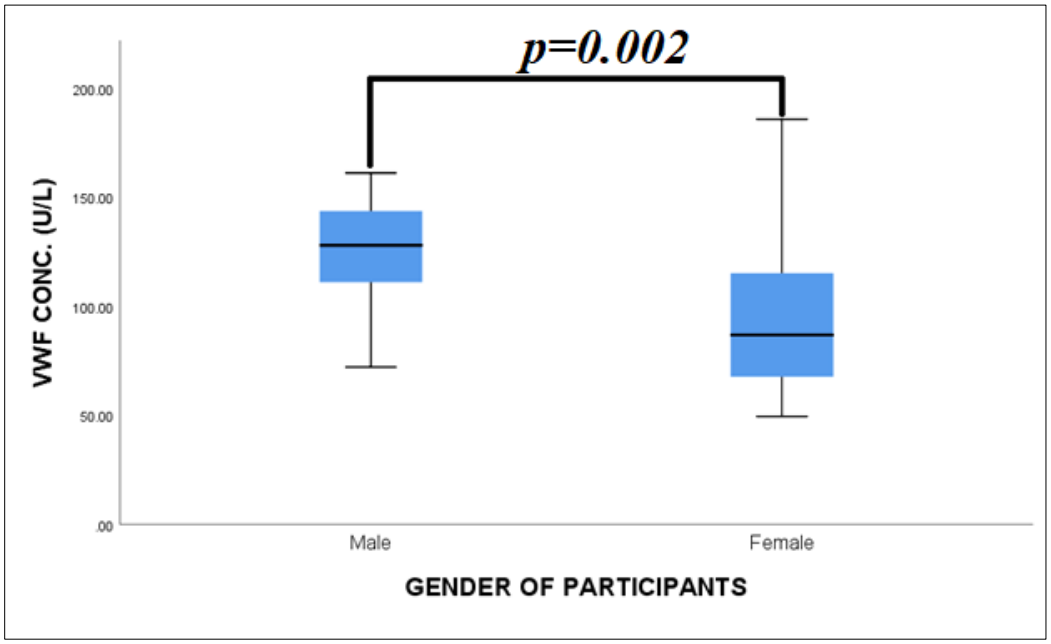

Figure 4. Plasma vWF: Ag levels between male and female participants. vWF= von Willebrand Factor, CONC=Concentration. Data compared with Mann-Whitney U-Test, and p<0.05 was considered statistically significant

3.5. Correlation between Age and Plasma vWF: Ag Levels among the Study Participants

Figure 5 illustrates the correlation between age and plasma vWF: Ag levels among the study participants. A moderately positive correlation was observed between age and plasma vWF: Ag levels among the blood donors (r = 0.497, p<0.001).

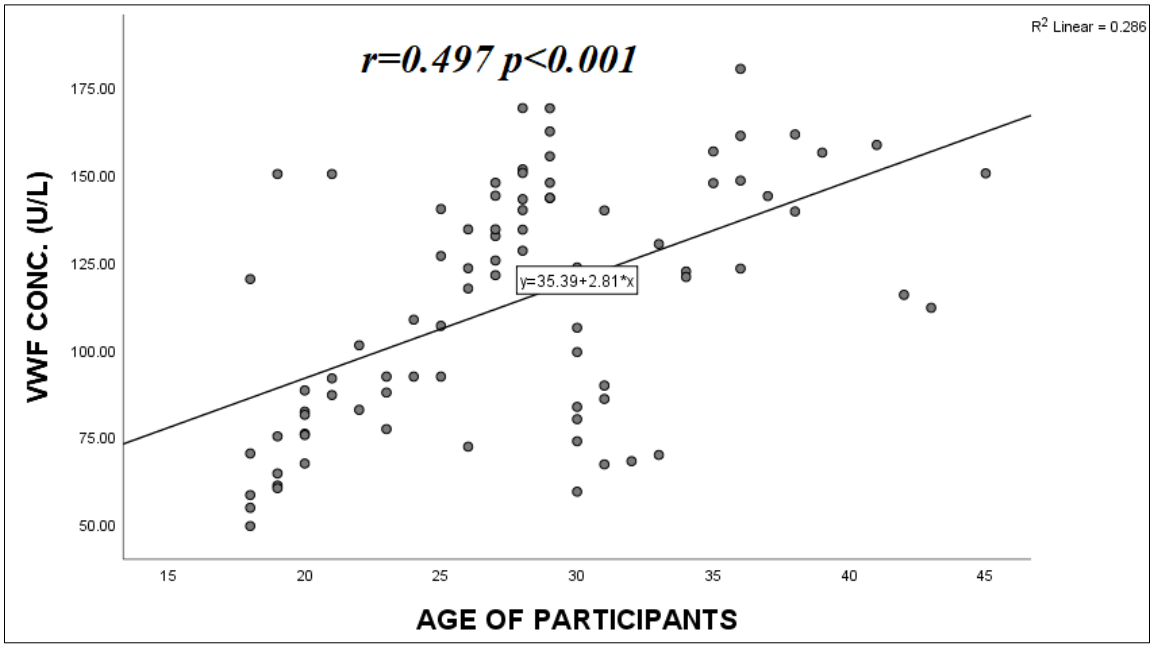

Figure 5. Correlation between age and plasma vWF: Ag levels among the Study Participants. r=Correlation coefficient, U/L=Units per litre, VWF=Von Willebrand Factor, CONC=Concentration. The correlation was assessed by the Spearman rank correlation test and p<0.05 was considered statistically significant.

3.6. Comparison of Blood Cell Indices between O and Non-O Blood Groups

Table 2 shows the comparison of haematological parameters between O and Non-O blood groups. The neutrophil number was significantly higher in Non-group O than in group O participants [Abs Neut. x10^9/L: 1.292 (0.683-1.719) vs 0.707 (0.42-1.531), *p*=0.039], but RDW SD was reduced in the Non-group O compared with the group O individuals [45.60 (42.40-47.70) vs 47.40 (44.70-49.10), *p*=0.045]. However, other FBC parameters were not different between the O and non-O blood groups.

Table 2. Comparison of Blood Cell Indices between O and Non-O Blood Groups

FBC Parameters	O GROUP and NON-O GROUP		P-value
	O GROUP	NON-O GROUP	
WBC x10^9/L	4.55 (3.28 - 5.60)	4.44 (3.47 - 5.11)	0.949
LYM. ABS x10^9/L	2.702 (2.44 - 4.101)	2.567 (2.024 - 3.299)	0.210
MON. ABS x10^9/L	0.120 (0.08 - 0.300)	0.253 (0.154 - 0.337)	0.079
NEUT. ABS x10^9/L	0.707 (0.42 - 1.531)	1.292 (0.683 - 1.719)	**0.039**
EOS. ABS x10^9/L	0.044 (0.03 - 0.096)	0.075 (0.036 - 0.120)	0.299
BASO. ABS x10^9/L	0.004 (0.003 - 0.005)	0.005 (0.003 - 0.006)	0.346
RBC x10^{12}/L	5.05 (4.24 - 5.26)	4.74 (3.95 - 5.29)	0.452
HGB, g/dL	15.05 (13.10 - 15.80)	13.65 (13.10 - 15.30)	0.161
HCT%	45.95 (38.50 - 48.20)	42.40 (36.80 - 46.90)	0.084
MCV, fL	88.70 (86.00 - 93.00)	88.80 (81.90 - 93.10)	0.541
MCH, pg	30.70 (28.70 - 31.30)	29.50 (27.80 - 32.40)	0.682
MCHC, g/dL	33.60 (33.10 - 34.80)	33.75 (32.60 - 35.50)	0.736
RDW-SD, fL	47.40 (44.70 - 49.10)	45.60 (42.40 - 47.70)	**0.045**
RDW-CV%	10.60 (9.80 - 11.50)	10.55 (8.20 - 10.90)	0.144
PLT x10^9/L	240.50 (218.0 - 310.0)	239.00 (210.0 - 275.0)	0.480
MPV, fL	6.75 (6.30 - 7.60)	7.10 (6.10 - 7.70)	0.616
PDW%	7.90 (7.20 - 8.60)	8.30 (7.00 - 9.00)	0.677

HGB=Haemoglobin, HCT=Haematocrit, MCV=Mean Cell Volume MCH=Mean Corpuscular Haemoglobin, MCHC=Mean Corpuscular Haemoglobin Concentration, RDW_CV=Red Cell Distribution Width-Coefficient of Variation, WBC=White Blood Cell, MPV=Mean Platelet Volume, L=litre, g/dl=Grams per decilitre, fL=Femtolitre, pg=Picogram. Non-parametric data [presented in medians (25^{th}-75^{th} percentiles)] were compared with Mann-Whitney U Test, and p<0.05 was considered statistically significant.

4. Discussion

The plasma levels of von Willebrand factor (vWF) may be influenced by several factors, including heredity, hormonal changes, and environmental influences [20]. The ABO blood group is one important determinant of the wide variations in plasma vWF: Ag levels in normal individuals. This study determined the levels of vWF: Ag and its relation with the ABO blood antigens, age, and sex among healthy adults in Northern Ghana.

In this study, there were predominantly more males than females, which is consistent with studies by Alharbi et al. [21] and Asuquo et al. [22]. This may be due to the false cultural perception that only men are healthy enough to donate blood, possibly because they do not menstruate [23]. The age range of participants was between 18 and 50 years, with the majority of participants (63.1%) between the ages of 18 and 30 years. This is consistent with a study by Souto et al. [24], but at variance with a study by Asuquo et al. [22]. Similar to the Souto et al. [24] study, the current study recruited only blood donors as participants. Blood group O being the predominant blood type among the participants in this study is consistent with previous studies [5, 7, 16, 23, 25]. O blood type has the highest frequency despite being a recessive gene, probably because it is more highly expressed in the gene pool than the others [21].

The significantly lower vWF: Ag levels among blood group O compared to non-O individuals recorded in this study corroborate with previous studies in Nigeria [16, 22], southern India [5], and Saudi Arabia [21, 26]. Variations in the levels of vWF: Ag were observed among the ABO blood groups. AB individuals had the highest vWF: Ag levels, followed by blood groups A, B, and O. These findings in the present study agree with previous studies by Alharbi et al. [21] and Asuquo et al. [22]. The variation in the levels of vWF: Ag could be a result of the nature of carbohydrates in ABO blood group antigens, affecting the rate of vWF: Ag proteolysis in the various ABO blood groups. Individuals of the non-O blood group have more complex carbohydrate antigens and, hence, have a slower rate of proteolysis as compared to blood group O individuals [21]. The levels of vWF: Ag were significantly higher in males than females in the current study, and this is consistent with findings from previous studies [12, 27, 28]. This may be due to the estrogenic effect and increased bleeding in females as a result of menstruation, as most of the female subjects were within the menopausal age.

The positive correlation observed between age and plasma vWF: Ag levels among the study participants corroborated earlier studies [28, 29]. The positive correlation between age and plasma vWF: A levels could probably be linked to the associated molecular and anatomical abnormalities with aging. Anatomical processes such as increased diameter and thickness of vessel walls, fragmentation of the internal elastic lamina, and hypertrophy of vascular smooth muscle cells within the vessel walls result in endothelial injury. Consequently, these processes alter the levels of various circulating and vessel wall-associated factors, such as vWF, thereby displaying an age-associated increase in circulation [30]. Conversely, the studies by Asuquo et al. [22] and Biguzzi et al. [31] found no significant association between vWF levels and age. This disparity could be because the majority of the participants in the study by Asuquo et al. [22] were younger. Also, von Willebrand disease patients were included as participants in the study by Biguzzi et al. [31], which could account for the discrepancy, contrary to the current study.

In the present study, blood group O participants had lower absolute neutrophil counts but higher RDW-SD compared with the non-O individuals, and this is similar to the findings from the study by Ajayi et al. [32]. The exact reason for this occurrence remains unclear. Other blood cell indices were not different between group O and non-O participants in this study, and this agrees with earlier findings [32, 33]. The study was limited to only healthy adults, and cannot be inferred for children and the aged. Also, the study could not assess the link between the entire endothelial parameters and the blood antigens.

5. Conclusion

The predominant blood group was O, followed by the other groups in the order: O>A>B>AB. Plasma vWF: Ag levels were higher in non-group O than in group O individuals. Males had higher vWF: Ag levels compared to females, and a positive correlation between age and plasma vWF: Ag levels was observed. Again, blood group O participants had lower absolute neutrophil counts but higher RDW-SD. The relationship between ABO blood phenotypes and plasma vWF: Ag should be considered in clinical practice. The establishment of separate reference intervals for vWF: Ag for the various phenotypes of ABO is recommended. Also, the study recommends further multicenter studies to assess the link between ABO phenotypes and all the endothelial cell parameters.

6. Declarations

6.1. Author Contributions

Conceptualization, S.K.A., C.N., A.B.S., M.D.A-R.Y., K.M., S.B.B., and G.A.; methodology, S.K.A., C.N., A.B.S., M.D.A.Y., Y.Q., V.K. and G.A.; validation, C.N., K.M., S.K.A., V.K., D.S., and F.O-B.; data curation, A.B.S., M.D.A-R.Y., Y.Q., V.K., and A.M.; writing—original draft preparation, S.K.A., C.N., K.M., A.B.S., M.D.A-R.Y., F.O-B., D.S., C.A.D. and S.D.; writing—review and editing, S.K.A., C.N., K.M., A.B.S., M.D.A.Y., F.O-B., D.S., C.A.D., S.B.B., V.K., Y.Q., G.A., and S.D. All authors have read and agreed to the published version of the manuscript.

6.2. Data Availability Statement

The data presented in this study are available on request from the corresponding author.

6.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

6.4. Acknowledgements

Authors appreciate the efforts of the staff of Tamale Teaching Hospital Haematology Laboratory, and the Department of Biomedical Laboratory Sciences, School of Allied Health Sciences, University for Development Studies, Tamale, Ghana. We are also grateful to all the subjects who willingly participated in the study.

6.5. Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the Research and Ethics Committee of the University for Development Studies, Tamale, Ghana (UDS/RB/100/22). Permission was sought from the management of Tamale Teaching Hospital. Written or oral informed consent was taken from the study participants.

6.6. Informed Consent Statement

Not applicable.

6.7. Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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