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ORIGINAL ARTICLE

The Incidences of S and s Antigens of the MNS Blood Group System in the Western Region of Saudi Arabia

Amr J. Halawani [1], Sahal A. Jamalallail [2]

[1] *Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia*
[2] *King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Jeddah, Saudi Arabia*

SUMMARY

Background: **Various issues can arise during blood transfusion, including red blood cell alloimmunization due to incompatible blood units. For example, anti-S and anti-s antibodies can lead to hemolytic transfusion reactions. Therefore, extended phenotyping is necessary for various blood groups other than ABO and RhD antigens, especially for multiply transfused patients such as patients with sickle cell disease. This study aimed to analyze the frequencies of the S and s antigens and phenotypes among the healthy blood donors.**
Methods: **A cross-sectional observational study was conducted by retrieving the registries of healthy blood donors. Blood donations were performed at the blood bank of King Abdulaziz Medical City - Western Region (KAMC-WR), Jeddah, Saudi Arabia. Serological analysis was performed for S and s antigens based on solid phase technique.**
Results: **A total of 27,027 healthy blood donors were enrolled in this study. Out of these, Saudi and non-Saudi blood donors accounted for 83.64% and 16.36%, respectively. The rates of S and s antigens among Saudis were 59.70% and 84.07, respectively. In contrast, the frequencies in non-Saudis were 54.53% and 87.11%, respectively. Regarding the phenotypes, S+s+ was the most prevalent among Saudi Arabians, with 43.89%, followed by S-s+ (40.18%), S+s- (15.81%), and S-s- (0.12%). The distribution in non-Saudis was as follows: S-s+ at 45.22%, S+s+ at 41.89%, S+s- at 12.64%, and S-s- at 0.25%. The frequencies of the phenotypes showed a statistically significant difference between Saudis and non-Saudis ($p < 0.01$).**
Conclusions: **The incidences of the S and s antigens and phenotypes have been reported in both populations. We highly recommend to extend the transfusion screening panel to include the S and s antigens to preclude the red blood cell alloimmunization to these antigens.**
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Correspondence:
Amr J. Halawani
Department of Clinical Laboratory Sciences
Faculty of Applied Medical Sciences
Umm Al-Qura University
Makkah
Saudi Arabia
Email: ajjhalawani@uqu.edu.sa

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INTRODUCTION

Blood transfusion helps patients with anemia to maintain sufficient oxygen supply to the tissues. Moreover, it can be used in other clinical settings including cardiothoracic surgeries, acute upper gastrointestinal bleeding, and hip fracture repairs [1]. Karl Landsteiner discovered the first antigens of the ABO blood group system, and by that enabling the safe delivery of blood transfusions

[2]. To date, 48 blood group systems have been recognized according to the International Society of Blood Transfusion (ISBT) [3].

The MNS blood group system was discovered following the ABO system. In 1927, Karl Landsteiner and Levine conducted an experiment by immunizing a rabbit with human red cells, and after the absorption, they identified the antibodies to the first two antigens in the system, M and N [4]. In 1947, Walsh and Montgomery described the S antigen in an Australian female from Sydney, a patient who developed the anti-S antibody. The antithetical antigen "s" was then identified four years later, and after that, the fifth antigen "U" was identified [5].

This system is extremely complex, like the RH; however, it is the only system that is represented by three homologous genes (GYPA, GYPB, and GYPE) encoding 50 antigens on the red cell surface [3]. Two single nucleotide variants (SNV) distinguish between the M and N antigens (p.Ser1Leu and p.Gly5Glu on GPA), while one SNV differentiates between the S and s antigens (p.Thr29Met on GPB) [6].

Glycophorin A (GPA) is the carrier molecule for the M and N antigen, whereas the S and s antigens are carried by glycophorin B (GPB). Both glycophorins are sialoglycoproteins that traverse the red cell membrane once and their amine-terminals extracellular to the red cells and the carboxy-terminals are intracellular. O-glycan is carried on the amine-terminal GPA and GPB, while there is an N-glycan on the GPA only, linked to amino acid at position 26 [7]. These glycans are carbohydrate molecules that provide the red cells potent net negative charge on the red cell surface, precluding red cell clumping and supporting the blood flow in the circulation [8].

The anti-M and anti-N antibodies are clinically benign, because they are normally naturally occurring IgM antibodies and do not react at 37 °C. However, some studies reported that both antibodies can be involved in causing immediate or delayed hemolytic transfusion reaction (HTR) as well as hemolytic disease of the fetus and newborn (HDFN) [9-12]. IgG forms of the anti-M and anti-N have been reported [13]. Regarding the anti-S and anti-s, both are IgG antibodies and cause immediate and delayed HTR and HDFN [14–18].

Given the clinical importance of the anti-S and anti-s antibodies and their impact on transfusion practices, this study aimed to screen the prevalence of the S and s antigens as well as of the four phenotypes among Saudi and non-Saudi blood donors at King Abdulaziz Medical City - Western Region (KAMC-WR).

MATERIALS AND METHODS

Blood samples

Ethical approval was obtained from the Institutional Review Board at King Abdullah International Medical Research Center (no. 0000086124), Ministry of National Guard Health Affairs, Kingdom of Saudi Arabia. A cross-sectional observational study was conducted by retrieving the data of the blood donor registry from January 2020 through May 2024. A total of 27,027 healthy blood donors visited the blood bank center of KAMC-WR, Saudi Arabia, to donate blood. This study followed the principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of this study.

Immunohematology

Serological investigations, based on a solid phase technique, were conducted using two different types of assays employing different types of antisera. The first protocol was PhenH7: Polyspecific anti-S and anti-s (from January 1, 2020, through October 22, 2023). The second protocol was switched to use PhenH11, monospecific antisera (anti-S and anti-s) (from October 23, 2023, through May 31, 2024).

When agglutination occurs with these antibodies, it indicated the presence of the corresponding antigen on the red blood cells, showing a positive test assay. However, lack of agglutination meant that the related antigen is missing on the red cell surface.

Statistics

The sample size was calculated to 664 samples, with 99% confidence level and 5% margin of errors.

The distributions of the S and s antigens and phenotypes were identified and demonstrated as percentages. A chi-squared test was conducted to observe any statistical significance. A p-value of < 0.01 demonstrated a highly significant difference.

The frequencies of the JK blood group for Saudi and non-Saudi donors were determined and standardized as percentages. A chi-squared test was used to detect statistically significant outcomes. A p-value of < 0.01 indicated a highly significant difference.

RESULTS

A total of 27,027 blood donations were included in this study, with 22,606 from Saudi blood donors (83.64%) and 4,423 from non-Saudi blood donors (16.36%). Table 1 represents the frequencies of the donation types at the blood bank center of KAMC-WR. The most common donation type was the whole blood donations, accounting for 95.30% and 96.43% in Saudis and non-Saudis, respectively. Plateletpheresis was the second most prevalent, with 4.41% in Saudis compared to 3.26% in non-Saudis. Donations using red cell apheresis were 0.27% and 0.29% in Saudis and non-Saudis, respectively. The least common type of blood donations was plasma apheresis, comprising 0.02% for both Saudi and non-Saudi blood donors.

This study demonstrated the frequencies of the ABO and RhD antigens (Table 2). Among the Saudi population, the most prevalent blood group was the O blood

Table 1. Donation types according to nationality.

Donation types	Saudis		Non-Saudis	
	n	%	n	%
Whole blood	21,543	95.30	4,265	96.43
Plateletpheresis	997	4.41	144	3.26
Red cell apheresis	61	0.27	13	0.29
Plasma apheresis	5	0.02	1	0.02
Total	22,606	100	4,423	100

Table 2. Frequencies of ABO and RhD blood groups of the study population.

Blood group		Saudis		Non-Saudis	
System	Antigen	n	%	n	%
ABO	A	4,735	20.95	937	21.18
	B	2,177	9.63	630	14.24
	AB	487	2.15	194	4.39
	O	15,207	67.27	2,662	60.19
	Total	22,606	100	4,423	100
RH	D+	20,227	89.48	3,980	89.98
	D-	2,379	10.52	443	10.02
	Total	22,606	100	4,423	100

Table 3. Rates of S and s antigens among Saudis and non-Saudis.

	Saudis (n = 22,606)		Non-Saudis (n = 4,423)		chi-squared	p-value
Antigen	observation	frequency (%)	observation	frequency (%)		
S	13,496	59.70	2,412	54.53	19.87	0.001 [a]
s	19,005	84.07	3,853	87.11		

[a] highly significant ($p < 0.01$).

Table 4. Comparison of frequencies of the Ss phenotypes between Saudi Arabian population versus non-Saudi Arabians.

	Saudis (n = 22,606)		Non-Saudis (n = 4,423)		chi-squared	p-value
phenotype	observation	frequency (%)	observation	frequency (%)		
S+s-	3,574	15.81	559	12.64	55.02	0.001 [a]
S-s+	9,083	40.18	2,000	45.22		
S+s+	9,922	43.89	1,853	41.89		
S-s-	27	0.12	11	0.25		
Total	22,606	100	4,423	100		

[a] highly significant ($p < 0.01$).

group (67.27%) followed by A (20.95%), B (9.63%), and AB (2.15%). Likewise in non-Saudis, O blood group was the most common (60.19%), followed by A (21.18%), B (14.24%), and AB (4.39%). Regarding the RhD antigen, similar observations were found in Saudis and non-Saudis, with 89.48% and 89.98%, respectively. With regard to the S and s antigens, the frequencies in Saudis were observed at 59.70% and 84.07, respectively, while the distributions of these antigens among non-Saudis were 54.53% and 87.11%, respectively. Table 3 demonstrates the frequencies of the S and s antigens in the study population.

Regarding the Ss phenotypes, the highest phenotype expressed among Saudis was the S+s+ at 43.89%, followed by S-s+ (40.18%), and S+s- (15.81%). The least common phenotype was S-s-, which was observed at 0.12%. On the other hand, the most common phenotype among non-Saudis was S-s+ at 45.22%, followed by S+s+ (41.89%), S+s- (12.64%), and S-s- (0.25%). Table 4 shows the rates of the S and s phenotypes among Saudi and non-Saudi Arabian populations.

DISCUSSION

Blood transfusion is extremely crucial for patients with blood loss. Some patients tend to produce new alloantibodies due to exposure of unprecedented antigens that results from the donor's blood and require frequent blood transfusion units.

It has been reported in Jeddah City that sickle cell disease (SCD) patients developed anti-S and anti-s antibodies after receiving blood transfusion units that matched for ABO and RhD antigens [19]. Hence, extended phenotyping of various blood groups is required for patient safety and reduces risks of red blood cell alloimmunization. Knowledge about the distribution of blood groups in a given population is essential, especially in countries lacking a national blood group database [20].

In this study, the distribution of the ABO blood groups ranked as O > A > B > AB in both populations. The most common blood group was O, and the rate in Saudis (67.27%) was higher in comparison with non-Saudis (60.19%). The B and AB phenotypes in non-Saudis were almost double the amount in Saudis, as demonstrated in Table 2.

Furthermore, we investigated the prevalence of the S and s antigens in Saudi and non-Saudi Arabians at KAMC-WR. A highly significant difference was seen for the prevalence of S and s between Saudi and non-Saudi populations ($p < 0.01$). The prevalence of the S antigen was higher in Saudis, at 59.70%, compared to non-Saudis (54.53%). The Saudi population in the present study demonstrated a similar rate to the Eastern Province (59%) and a slightly lower one than Saudis living in the Jazan Province (61%) [21,22].

The expression of the s antigen was 87.11% in non-Saudis, compared to the Saudi population (84.07%). The antigen prevalence among the Saudis of the current study was in line with other provinces, which were 82.55% and 83% in Jazan and Eastern provinces, respectively [21,22].

We observed a higher frequency of the S antigen than the reported frequencies in Caucasians and Africans, which were 55% and 31%, respectively. However, the outcome in Saudis regarding the s antigen was lower than in the observed incidences in Caucasians and Africans, which were 89% and 93%, respectively [23].

Regarding the Ss phenotypes, there was a high statistically significant difference ($p < 0.01$) between Saudis and non-Saudis. The most common phenotype observed among Saudis was S+s+ at 43.89%. Individuals with other phenotypes (S+s-, S-s+, and the least prevalent S-s-) accounted for 56.11% in total, more than double the Saudi population. They are prone to produce anti-S and anti-s antibodies. Therefore, the screening panel for blood transfusions is highly recommended to be updated to include the S and s antigens to reduce the risk of red blood cell alloimmunization [24,25].

A key limitation of the present study is lack of the main antigens (i.e. M and N) of the MNS blood group system. However, the blood bank center focuses on highly immunogenic antigens (S and s) due to the fact that anti-M and anti-N rarely shifted from benign to clinically significant antibodies. Moreover, another limitation is the absence of some demographic data of the blood donors, including age and gender.

In conclusion, this study reports the frequencies of the S and s antigens as well as of the phenotypes among healthy blood donors in Jeddah City, Saudi Arabia. We highly recommend to include these antigens in the transfusion screening panel for both blood donors and patients, as this will ensure safety of the blood transfusion units provided to the patients, especially to the transfusion-dependent patients.

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Declaration of Interest:
The authors have no conflicts of interest to declare.

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