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ORIGINAL ARTICLE

Rh and Kell Blood Group Antigen Frequencies in Saudi Arabia: a Review

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SUMMARY

Background: **Effective blood transfusion services rely heavily on comprehending the distribution of blood antigens among populations. Saudi Arabia's unique genetic and evolutionary influences require thorough comprehension of these antigen frequencies as they are crucial for patient care. This systematic analysis aimed to explore the frequencies of Rh and Kell blood group antigens across various regions of Saudi Arabia.**
Methods: **An exhaustive literature search was conducted using PubMed, Embase, and the Cochrane Library, focusing on studies from 2019 through 2024 that report Rh and Kell blood antigen frequencies within the Saudi population.**
Results: **Analysis of seven selected studies provided data from locales including Samtah, Jazan, Hail, Riyadh, the Eastern region, Taif City, and Najran. The DCcee (R1r) Rh phenotype was the most prevalent throughout these regions. However, the frequencies of individual Rh (D, C, E, c, e) and Kell (K) antigens demonstrated regional variability. Notably, the K antigen was found to be less common in Jazan compared to other regions. The observed variations in antigen frequencies suggest that factors beyond geography may influence the distribution of Rh and Kell blood groups. Comprehending these findings is critical for enhancing blood transfusion services, including refining donor recruitment strategies, managing blood inventory, and developing personalized transfusion protocols. Additionally, understanding similarities and variations is essential for managing pregnancies affected by Rh incompatibility and improving care for patients with conditions like sickle cell disease that require frequent transfusions. Further investigation is needed to explore the underlying causes of regional similarities or variations.**
Conclusions: **Further studies are necessary to investigate the genetic and environmental factors influencing the regional similarity and differences in blood group antigen frequencies. Expanding the scope of data collection throughout Saudi Arabia is also imperative to provide a comprehensive understanding that supports optimal transfusion practices and enhanced healthcare outcomes.**
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INTRODUCTION

Blood transfusion is a critical medical procedure that saves lives and improves patient outcomes [1,2]. Successful and safe blood transfusions require donor and recipient blood compatibility, which is determined by blood group antigens [3]. Among the numerous blood group systems identified, ABO and Rhesus (Rh) sys-

tems are the most clinically significant, although other systems, such as the Kell blood group system, are also immunogenic and contribute to donor-recipient incompatibility and adverse transfusion reactions. Understanding the distribution and frequencies of blood group antigens is fundamental for maintaining safe and efficient blood banking systems. In 1900, Karl Landsteiner discovered the first blood group system, the ABO blood group system, when he observed how red blood cells of some individuals agglutinated when mixed with serum collected from other individuals [4,5]. These observations provided the basic knowledge for every future blood transfusion.

The ABO blood group system comprises three primary alleles: A, B, and O. Inheritance of ABO blood groups follows Mendelian principles, with individuals possessing two ABO alleles, where one is inherited from each parent. A and B alleles are codominant, so individuals carrying A and B alleles will express A and B antigens on their red blood cells, producing the AB blood type [4]. The O allele is recessive, so O blood type only occurs when an individual inherits two O alleles (OO). Accordingly, if a person inherits one O and one A or B allele, they will have blood type A or B, respectively. Possible ABO genotypes and their corresponding phenotypes are as follows: AA or AO - blood type A, BB or BO - blood type B, AB - blood type AB, and OO - blood type O. Compared to the ABO blood group system, the Rh blood group system is more complex and contains 61 antigens. The D antigen is the most immunogenic and determines whether an individual is Rh positive or negative. Other clinically relevant antigens in the Rh system are C, c, E, and e, and the combination of these antigens produces different rhesus phenotypes with different prevalences. Understanding how prevalence varies across different populations is important for managing national blood supplies to ensure donor-recipient blood compatibility.

Inheritance of the Rh system involves two major genes located on chromosome 1: RHD and RHCE, as proposed by Tippett [4]. Type D locus of the RHD gene encodes the Rh protein (Rh is D antigen) and CE or ce locus of the RHCE gene encode homologous chromophilic antigens e, E, c, and C [6]. Both genes are 97% identical and have a 10-exon structure. Another gene located on chromosome 6, the RHAG gene, encodes Rh-associated glycoprotein (RhAG); necessary for assembling and expressing Rh antigens [4]. Mutations in the RHAG gene can modify or fully knock out Rh proteins, as observed in the rare erythrocyte phenotype Rhnull that lacks Rh antigens.

The Kell system is the third most clinically important blood group after ABO and Rh. This system is less complex with a limited number of alleles (36) [7]. The Kell (or K) system is clinically important, because its immunogenicity is almost as high as the D antigen in Rh system. Kell antibodies can cause severe hemolytic transfusion reactions and hemolytic disease of the fetus and newborn (HDFN). Therefore, understanding the prevalence of Kell antigens in a population is crucial for predicting the risk of Kell sensitization and managing pregnancies in Kell-negative women. The inheritance of the Kell system involves the KEL gene on chromosome 7, which has 19 exons. Mutations result in different Kell antigens, and some cause the rare null phenotype, Ko [4]. Each haplotype encodes one low-prevalence antigen, with dual positives having alleles on separate chromosomes. The XK gene, independent of KEL, encodes the Kx antigen and is located on the X chromosome at Xp21.1.

Saudi Arabia has a unique genetic pool, influenced by historical migration patterns and traditional consanguineous marriages, that exhibits distinctive blood group antigen frequencies. These variations can significantly impact blood banking practices and transfusion strategies. Therefore, understanding the precise frequencies of Rh and Kell blood group antigens within the Saudi Arabian population is essential, not only for optimizing donor recruitment strategies to ensure adequate blood type supplies, but also for improving blood inventory management to meet the specific needs of the population, enhancing cross-matching protocols to reduce the risk of alloimmunization, guiding prenatal screening and management strategies, particularly for Rh and Kell incompatibilities, and informing the development of local guidelines for transfusion practices.

Several studies have investigated blood group antigen frequencies in Saudi Arabia, but the data remains fragmented and geographically limited. There is a lack of nationwide data that accurately represents potential regional variations in blood groups within Saudi Arabia. This knowledge gap impacts the development of optimized, population-specific transfusion strategies and blood banking practices in Saudi Arabia. Subsequently, a systematic review of published research could help collate available data and provide a more comprehensive picture of Rh and Kell antigen frequencies across Saudi Arabia. Subsequently, findings from this review could significantly improve current blood inventory management by informing more reliable donor population selection or developing personalized transfusion programs. Importantly, insights from this review could enhance patient care and reduce transfusion-related complications.

MATERIALS AND METHODS

A comprehensive literature search was performed using PubMed, Embase, and Cochrane Library databases. To identify all relevant studies about the frequency or distribution of Rh and Kell blood group systems within the Saudi Arabian population, search terms included the ‘Rh blood group system’, ‘Kell blood group system’, ‘blood group antigens’, ‘prevalence’, and ‘Saudi Arabia’. Following identification of relevant studies, the following inclusion and exclusion criteria were applied: Inclusion criteria: studies that reported the frequency,

prevalence, or distribution of Rh and Kell blood group antigens within the Saudi Arabian population. Research that reported the frequency and phenotypes of Rh (D, C, E, C, and e) and Kell blood group systems in Saudis. Exclusion criteria: studies that did not focus on the Saudi Arabian population, such as studies that involved non-Saudi participants. Case reports and conference abstracts were also excluded to ensure that collected data was from peer-reviewed, published research.

After inclusion and exclusion criteria were applied, the following data were extracted from the selected studies: study setting, sample size, and detailed frequencies or prevalence rates of Rh and Kell blood group antigens. Data extraction enabled the distribution and patterns of Rh and Kell blood group systems across the different regions and localities within Saudi Arabia to be collated. The extracted and collated data was synthesized narratively, providing a detailed overview of the key findings and emerging trends observed across the included studies. Importantly, this narrative approach provided a comprehensive analysis of the geographic variations and distinct characteristics of Rh and Kell blood group systems across different regions and localities in Saudi Arabia.

RESULTS

The current review analyzed the prevalence of Rh and Kell blood group phenotypes among blood donors across different cities and regions in Saudi Arabia. Findings from this review are summarized in Table 1. Overall, this review extracted and collated the frequencies of Rh and Kell blood group antigens in several locations, including Samtah, Jazan, Hail, Riyadh, the Eastern region, Taif City, and Najran (Table 1).

Samtah exhibited a high prevalence of the Rh phenotype R1r, with 94.9% for the D antigen and 79.2% for the c antigen. Lower frequencies of C (69.7%) and E (27.0%) antigens were found. The K antigen was present in 11.9% of the population, indicating strong dominance of the Rh DCcee phenotype among donors in Samtah.

The most common Rh phenotype recorded in Jazan was R1r. Frequencies of D, C, E, e, and c antigens were 93.3%, 71.0%, 18.9%, 98.0%, and 75.4%, respectively. The K antigen was present in only 4.5% of the donors. This study region exhibited a varied distribution of phenotypes with lower prevalence of E and K antigens.

Phenotype R1r was the most commonly recorded phenotype in Hail, particularly in RhD-positive individuals. Frequency of the D antigen was 81.7%, and again, the e antigen was comparatively higher at 96.2%. Lower frequencies of C and E antigens were observed. The Hail study revealed a high frequency of Rh antigens, with a notable variation in E antigen prevalence.

In Riyadh, the R1r phenotype was the most common phenotype with frequencies of D, C, E, e, and c antigens being 86.4%, 65.9%, 25.8%, 97.2%, and 78.1%, respectively. The K antigen was present in 13.9% of study participants. Data showed a high prevalence of the e antigen with a moderate distribution of other Rh antigens. The DCcee phenotype was observed in the Eastern region with high frequencies of D, e, and c antigens. The C and E antigens were present at 59% and 21%, respectively. The K antigen was recorded in 8% of the population, indicating a high prevalence of the DCcee phenotype.

In Taif City, the most prevalent phenotype was the DCcee phenotype with high frequencies of D, e, and c antigens. Study data suggest high prevalence of D and e antigens with variable frequencies of C, E, and K antigens. Rh phenotypes, like DCcee (R1r), were commonly observed across the regions, reflecting a broader trend in blood group antigen distribution among donors in Saudi Arabia.

Table 2 provides an overview of various research studies that focused on blood group phenotypes and antigens among different populations in Saudi Arabia. Study timeframes ranged from November 2022 to 2024 and employed mostly cross-sectional and retrospective cross-sectional designs. Study sample sizes varied greatly from 100 to 4,675 participants. Importantly, all included studies have either been published in clinical laboratory science, immunogenetics, hematology, and medical pharmacology journals. Study regions included Samtah, the Southwestern region (Jazan) , Hail, Riyadh, the Eastern region, Taif, and Najran. Each study investigated Rh and Kell blood group systems and aimed to elucidate the prevalence and distribution of these blood types among the Saudi population to better inform medical and transfusion practices.

DISCUSSION

A review of seven studies that focused on prevalence of Rh and Kell blood group antigens in Saudi Arabia revealed similar regional patterns in the distribution of Rh and Kell blood group antigens. This review analyzed data from multiple cities and regions within the kingdom, revealing similar patterns in the prevalence of these clinically significant blood group systems. Findings highlight that even though Rh phenotypes DCcee (R1r) were more commonly observed in certain geographical areas, prevalence of individual Rh and Kell blood group antigens, like D, C, E, e, c, and K, varied considerably across different locations within Saudi Arabia. Subsequently, review findings showed single or consistent pattern(s) in the prevalence of Rh and Kell blood group antigens throughout different regions in Saudi Arabia. For example, the DCcee (R1r) phenotype was highly frequent in the seven studies. While K antigens showed lower frequencies in the Jazan area compared to other antigens, it was not tested in Hail [6,9]. The similar regional distribution of these clinically significant blood group systems suggests antigen prevalence may be influenced by factors beyond geographical

Table 1. Distribution and frequencies of Rh and Kell blood group phenotypes among blood donors across various regions in Saudi Arabia.

City/Region	D (%)	C (%)	E (%)	e (%)	c (%)	K (%)	Rh phenotypes	Reference
Samtah	94.9	69.7	27.0	96.7	79.2	11.9	DCcee (R1r) most common	[7]
Jazan	93.3	70.9	18.9	97.9	75.4	4.5	DCcee (R1r) most common	[8]
Hail	81.7	67.5	30.9	99.2	76.2	NS	DCcee (R1r) most common	[9]
Riyadh	86.4	65.9	25.8	97.2	78.1	13.9	DCcee (R1r) 31%, DCCee (R1R1) 22%	[10]
Eastern region	80.0	59.0	21.0	97.0	86.0	8.0	DCcee (R1r)	[11]
Taif city	87.8	62.3	31.3	95.8	81.7	22.1	DCcee (R1r) most prevalent	[12]
Najran	99.9	67.1	25.8	98.5	77.9	NS	DCcee ((R1r) most common in RhD+) with 33.40%, dce (rr) most common in RhD- with 19.25% presence	[13]

NS - not studied.

location.

Regional consistencies in the distribution of clinically relevant blood group antigens reflect local population genetics, highlighting how important it is for healthcare providers to understand the unique characteristics of local populations for appropriate blood product selection and transfusion safety. This knowledge is also crucial for minimizing the risk of alloimmunization, delivering personalized transfusion services to patients and anticipating the availability of compatible blood products. By leveraging regionally-specific data, healthcare providers can optimize transfusion practices, improve patient outcomes, and contribute to the overall quality and safety of the nation's blood banking system. For example, high incidence of D blood type within a population infers that supplies of D-negative blood may be more in demand, requiring careful donor screening and management. Similarly, variable frequencies of C, E, and K antigens highlight the need for maintaining appropriately diverse blood inventories to meet the needs of patients with corresponding alloantibodies.

Understanding Rh and Kell antigen frequencies in Saudi Arabia can also inform management of pregnancies, particularly for Rh incompatibility between mother and fetus. Knowledge of blood group antigen prevalence is also essential for pregnancy management of Rh alloimmunization. High frequency of the D antigen in Saudi Arabia highlights the need for comprehensive Rh typing and implementing anti-D prophylaxis for D-negative pregnant women to prevent maternal alloimmunization and development of hemolytic disease of the newborn - a potentially life-threatening condition. Early Rh typing and appropriate administration of anti-D immunoglobulin during pregnancy (antenatal) and in the postpartum period can significantly reduce alloimmunization risk and improve maternal outcomes. All healthcare providers in Saudi Arabia ensure that all D-negative pregnant women receive an appropriate Rhesus prophylaxis to protect the mother and child's health and alleviate morbidity or mortality associated with RhD alloimmunization.

Understanding how prevalence of Rh variants varies among different Saudi Arabian populations can also effectively inform management of certain hematological conditions, like sickle cell disease, that disproportionately affect populations in Saudi Arabia. For example, reported interactions between genetic factors, such as sickle cell trait and glucose-6-phosphate dehydrogenase (G6PD) deficiency in Saudi Arabia, further complicate transfusion requirements of those patients, compromising clinical outcomes. Understanding the frequency of clinically significant blood group antigens, particularly the Rh and Kell blood group systems, can help healthcare providers predict compatible units available, minimizing the risk of alloimmunization among individuals with sickle cell disease or other than rare hereditary conditions that require long-term transfusion support. Importantly, this knowledge will enhance the quality of care for patients with rare hematological conditions at risk for complications.

Limitations of this review include the small sample sizes of to date studies selected for review and their spe-

Table 2. Characteristics of Rh and K antigen studies in Saudi Arabia.

Study	Journal/Year	Region/City	Participants	Sample size	Study design	Time of collection
Prevalence of Rh and K phenotypes among blood donors from different ethnicities in Samtah (Southwestern region) Saudi Arabia	International Journal of Immunogenetics/ 2022	Samtah	Saudi and non-Saudi	3,863	Cross-sectional study	January 2019 through August 2020
ABO, RH, and KEL1 antigens, phenotypes and haplotypes in Southwestern Saudi Arabia	Clinical Laboratory Publications/2021	Southwestern	Saudi	3,563	Experimental research project	NS
The frequencies of ABO and Rh phenotypes among male blood donors in Northwestern Saudi Arabia	Clinical Laboratory Publications/ 2022	Hail	NS	126	Cross-sectional study	NS
Frequency of Rh and K antigens in blood donors in Riyadh	Hematology, Transfusion and Cell Therapy/2022	Riyadh	Saudi and non-Saudi blood donors	4,675	Retrospective cross-sectional study	January 4, 2019, through February 28, 2019
Phenotype frequencies of major blood group systems (Rh, Kell, Kidd, Duffy, MNS, P, Lewis, and Lutheran) among blood donors in the Eastern region of Saudi Arabia	Journal of Blood Medicine/2020	Eastern region	Saudi	100	Cross-sectional study	NS
ABO, Rh, and Kell blood group antigen frequencies in blood donors of Taif city, Saudi Arabia	Clinical Laboratory Publications/2023	Taif city	Saudi	2,073	Retrospective cross-sectional study	From May 2016 through May 2019
Prevalence of ABO, Rh and KELL blood group types and transfusion- transmissible infections	Biomedical & Pharmacology Journal/2021	Najran	Saudi	966	Cross-sectional study	NS
(TTI) among blood donors in Najran city, Saudi Arabia						

cific regions or cities within Saudi Arabia that do not represent the full diversity of the kingdom. Further research with larger, more representative samples across the entire kingdom would provide a more comprehensive understanding of national Rh and Kell blood group antigen distribution. In addition, investigating the genetic and environmental factors contributing to observed regional variations could provide valuable insights into population health and transfusion medicine and produce evidence-based research to inform policies in transfusion medicine.

CONCLUSION

This review provides a comprehensive analysis of Rh and Kell blood group antigen distribution throughout Saudi Arabia. Findings showed that certain Rh phenotypes, such as DCcee (R1r), were more prevalent in Saudi Arabia, revealing significant regional similarity and highlighting the importance of understanding local population characteristics for effective blood product management, reducing alloimmunization risk, and enhancing transfusion safety. Subsequently, insights from this review have important implications for transfusion medicine, blood banking practices, and pregnancy management in Saudi Arabia. Healthcare providers can use

this information to develop appropriate strategies for donor recruitment, blood inventory optimization, and region-specific transfusion protocols. This review also highlights the need for further research into other regions and cities as well as genetic and environmental factors that contribute to regional similarities or variations in either pattern or frequency in blood group antigens, emphasizing the importance of population-specific approaches for improving transfusion services and patient outcomes across the kingdom.

Declaration of Interest:
None.

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