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THE IMPACT OF BLOOD GROUP VARIATIONS ON HUMAN HEALTH: A REVIEW OF CLINICAL AND EPIDEMIOLOGICAL EVIDENCE

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Abstract

Antigens of the blood groups are involved in predisposition to various infectious illnesses, such as malaria, COVID-19, cholera, Norovirus etc. and non-infectious diseases such as cardiovascular diseases, venous thromboembolism, diabetes mellitus, and various forms of malignancies, including gastric cancer. The purpose of the review is to establish the association in various disease outcomes and polymorphism of blood groups. The antigen's function in the development of numerous infectious and non-infectious diseases is achieved in various manners such as immune response, coagulation and adhesion. Finding out significance of blood type compatibility in transfusion medicine and maternal-fetal blood group incompatibility in various pregnancy outcomes, is the other objective of this review. Hence, it can be realized that the correlation between the genetic and medical importance of blood group differences can be applied to help in risk assessment of diseases and the creation of personalized medicine.

1. INTRODUCTION

Blood groups are the classifications of blood on the basis of presence and lack of the specific antigen on the erythrocyte surface, which play essential role in transfusion compatibility and immune reactions (Reid et al., 2012). International Society of Blood Transfusion recognized more than 48 systems of blood group. The primary system used in clinical transfusion is ABO blood group system, which classifies blood based upon presence of A and B antigens on the erythrocytes. The first person who distinguish the different ABO blood groups was Karl Landsteiner in 190 (Li & Guo, 2022). His discovery showed the blood from different individuals can agglutinate due to antigen-antibody reactions which leads to classification of the A, B and O blood groups. A fourth blood group AB discovered by his colleagues. This discovery of blood groups helps in safe blood transfusions and change the land scape of modern medicine (Abegaz, 2021). Blood group variations are very important for human health because blood group compatibility is crucial for safe blood transfusion and organ transplantation while the incompatible blood transfusions can cause severe immune reactions leading to hemolysis and potentially death (Richards, 1973). Blood group antigens also influence the person immunity and vulnerability to various diseases including pathogen infections, group of heart and blood vessel disorders and certain types of malignancies (Abegaz, 2021). Blood groups are also important in maternal fetal medicine particularly in Rh incompatibility during pregnancy (Cooling, 2015). This review focus on

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the classification of blood groups system, genetic mechanism underlying the blood group variation, function of antigens of the blood groups, and their clinical significances in disease susceptibility and transfusion medicine (Bitty Azachi & Mathias Dakop, 2022). This review analyze the various blood groups and impact of blood group variations on human health and also explores the global blood groups distribution and their evolutionary and population genetic implications (Abegaz, 2021).

2. Classification of the Human Blood Groups System

More than 48 blood group systems have been identified in humans by the International Society of blood transfusion (Daniels, 2013). Karl Landsteiner establish the base of modern blood group classification system and his research of ABO blood group system gives the concept of blood compatibility depends upon the antigen-antibody interactions (Franchini & Liumbruno, 2013). The most significant classification that is used in transfusion medicine is the ABO blood groups system, which is based upon the presence and absence of the A and B antigen on surface of the erythrocyte (Abegaz, 2021). After ABO system, Rh blood group system serves as the second blood group system that is clinically most important (Westhoff, 2004). The Rh system mainly characterized by the presence or lack of RhD antigen on the erythrocyte surface and those persons expressing the RhD antigen are categorizes Rh positive while those lacking it are classified as Rh negative (Westhoff, 2004). The other clinically important blood group systems are Duffy blood group system which includes antigen such as Fy^a and Fy^b located on cell membrane of erythrocyte (Daniels, 2013). These antigens have receptors for *Plasmodium vivax* that is responsible for malaria and those individuals who lacks this receptor are resistant to this infection. Beyond the primary systems, Kell blood group system consist of surface antigens network embedded in erythrocyte membranes (Daniels, 2013). Anti-Kell antibodies can trigger severe hemolytic disorders in infants and involve in transfusion reactions. MNS blood group system which include the M,N,S and s antigens that is located on Glycophorin molecules of erythrocytes and these antigens are also important in blood transfusions (Lopez et al., 2021). Kidd blood group system which include Jk^a and Jk^b antigens that associated with the urea transport across the red blood cell membranes, as given in the Table 01 (Olivès et al., 1997).

3. Genetic basis of the Human Blood Groups Variations

The ABO gene placed on the long arm of chromosome 9 serve as blueprint to determine blood group type. The alternation of red cell antigen caused by alleles of the ABO genes that codes for enzyme glycosyltransferases and this enzyme attaches the unique sugar molecules to precursor antigen. (Yamamoto et al., 2012). Mendelian inheritance pattern that is followed by the ABO blood group where alleles are transmitted biparentally (Daniels, 2013). Within ABO system, A and the B alleles exhibit co-dominance while O allele function as recessive allele and combination of these alleles produce 4 phenotypes A,B, AB and O (Daniels, 2013). Surface markers of blood group are carbohydrate or protein molecules which are located on surface of erythrocyte and these surface antigens are formed as a result of enzymatic changes of the precursor molecules on cell membrane of the red blood cells (Cooling, 2015). These structural modifications determine not only the blood group identity but also how the immune system recognizes the red blood cells as self or foreign (Cooling, 2015). Difference in the molecular structure of the antigens find the variations in blood types and also identify blood types, influence antibody formation, immunity recognition and important in transfusion reactions (Daniels, 2013). The blood groups distribution varies among different populations and geographical distribution and population genetics studies shows that this distribution is due to infectious diseases and evolutionary pressures (Cooling, 2015). For example B blood group remains very common in Asians and A in Europe whereas blood group O is most common across Africa (Mourant, 1950).

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Table 01: Major Human Blood Group System and their Key Antigens

Blood Group System	Major Antigens	Gene/Protein Involved	Key Characteristics	Clinical Importance	Reference
Karl Landsteiner-ABO Blood Groups System	A and B	ABO gene	Determines four blood types are A,B, AB,O defined by carbohydrate antigens on RBC,s	Most important system for blood transfusion compatibility	(Yamamoto et al., 1990)
Rh Blood Group System	D,C,c, E and e	RHD , RHCE genes	Rh system classifies blood as Rh-positive and Rh-negative based on presence of Rh(D) antigen	Important in hemolytic disease of newborns and transfusion reactions	(Daniels, 1995)
Duffy Blood Group System	Fy^a, Fy^b	ACKR1 gene	Chemokine receptor on RBC membrane	Duffy-negative phenotype provides resistance to malaria (*Plasmodium vivax*)	(Tournamille et al., 1995)
Kell Blood Group System	K, k	KEL gene	Membrane glycoprotein enzyme on RBCs	Results inhemolytic disease of newborns, intense hemolytic transfusion reactions	(Höher et al., 2017)
Kidd Blood Group System	Jk^a, Jk^b	SLC14A1 gene	Urea transporter protein on RBC membrane	Known for delayed hemolytic transfusion responses or reactions	(Dean, 2005)
MNS Blood Group System	M, N, S, s	GYPA and GYPB genes	Located on Glycophorin proteins of RBC membrane	May cause transfusion reactions and hemolytic disease in newborns	(Lopez et al., 2021)

4. Biological Functions of antigens of blood groups

Blood group antigen are critical for cell adhesion and cell recognition (Cooling, 2015). They are important for intercellular communication and tissue organization and also found across RBC's as well as on endothelial and epithelial cells (Eastlund & Warwick, 2012). Many pathogens also attach to the specific blood group antigens receptor on the host cell. For example, certain malaria parasites interact with specific blood group antigens for attack of disease during infection (Horuk et al., 1993). Antigens of blood groups are the immune system components that influence the susceptibility to infectious diseases (Cooling, 2015). When incompatible blood is transfused then the antibodies recognize foreign antigens and trigger immune reactions and these immune responses can lead to the hemolytic transfusion reactions (Strobel, 2008).

5. Impact of Blood Group on Infectious Diseases

The importance of blood group polymorphisms in the host, which predisposes to various infectious diseases, has become increasingly relevant. For example, malaria has been extensively investigated, and several epidemiological studies have demonstrated the

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effect of blood type O against the other various blood types. Reduction in erythrocyte due to the malaria parasite is credited to defense mechanism of type O blood. This is the process in which infected erythrocytes interact and aggregate with uninfected erythrocytes, causing serious manifestations of the disease (Asmerom et al., 2023). According to the study that used determine the blood group polymorphisms in malaria, patients are more inclined to suffer from some severe symptoms if they fall into A type, B type or AB category, at the same time type O patients have a reduced severity of the disease and parasitemia (Asmerom et al., 2023). Furthermore, the importance of blood group polymorphisms in the host, which predisposes to various infectious diseases, has become increasingly relative to current pandemic, known as COVID-19. Several studies have demonstrated the increased fragility of type A Blood to COVID-19 and the defensive action of type O (Khan et al., 2023). Similarly, the variation in blood groups also relates to the pathogenesis of cholera. People having O type blood have a higher chance of experiencing severe dehydrating symptoms of the disease caused by Vibrio cholerae. This proves that ABO system play some part in the attachment of bacterial toxins. In the case of Norovirus infection, a strong association exists between ABO blood groups. Histo-blood group antigens which are present in cells of the intestine act as attachment sites for the Norovirus. Different studies determined the effect of blood groups in the susceptibility to Norovirus infection, it showed that people having blood type O are more susceptible to Norovirus infection, on the other hand A type, B type, and AB type blood have a relatively low or negligible association (Bitty Azachi & Mathias Dakop, 2022). In addition to the above-mentioned infections, variations in ABO groups are also susceptible to other infections such as dengue virus, Escherichia coli, influenza virus, and Helicobacter pylori, as shown in the Fig.01 (Zarrar et al., 2024).

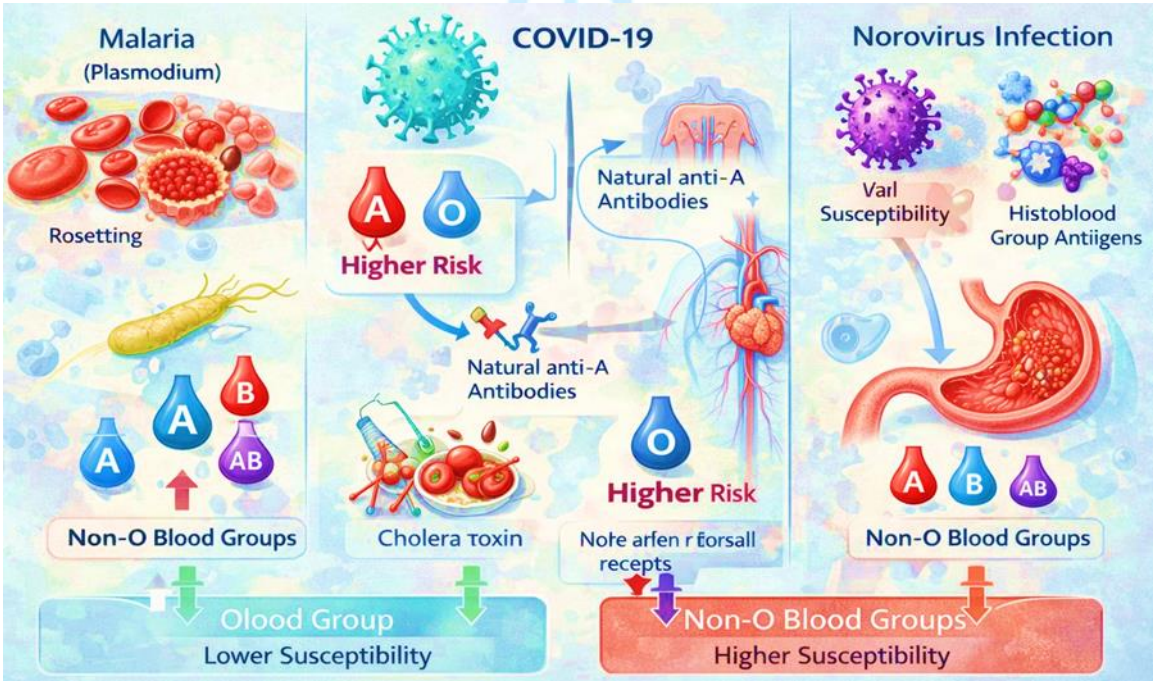


Fig. 01: Blood Groups and Susceptibility to Infectious Diseases

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6. Blood groups and Non-Communicable Diseases

In addition, the ABO blood group system has been related towards development and emergence of various kinds of non-communicable illnesses, like cardiovascular diseases, thrombotic diseases, metabolic diseases, and cancer. Epidemiological studies have revealed that people having A type, B type and AB type blood, as opposed to blood group O, is far more inclined to develop cardiovascular diseases like myocardial infarction, peripheral vascular diseases, and atherosclerosis. This might be due to the high plasma vWF and factor VIII, which show an important part in thrombogenesis (Mickelsson et al., 2024). According to study, type A blood and non-O type of blood phenotypes are related to the risk of venous thromboembolism, such as DVT and PE, as compared to blood group O phenotypes, as the odds ratio is greater than 1.6 (Liu et al., 2024). Apart from cardiovascular diseases, some studies have revealed that ABO system relates to development and progression of metabolic illnesses such as diabetes mellitus. Various studies have shown that there are different patterns of ABO phenotypes in diabetic patients. This implies that different pathways to metabolic diseases may be affected by blood groups. In cancer research, various studies have shown that gastric cancer and ABO system are linked. Various genetic studies have shown that A or AB type of blood has a moderately increased risk of gastric cancer (Mao et al., 2019). This link between ABO blood type and cancer is postulated to result from different host responses to Helicobacter pylori infection. In addition to gastric cancer, several investigations have found relation among type ABO polymorphisms and cancer of different malignancies, including pancreatic, breast, and esophageal cancers. Likelihood of cancer is greater in blood group type A, while O blood group has a relatively protective effect, as shown in the Table 02 (Liu et al., 2024).

7. Blood Groups and Pregnancy Outcomes

Another clinically important occurrence, which influences the outcome of pregnancy, is the blood group incompatibility between the mother and the fetus. It is transmitted by the immune responses to ABO and Rh types of blood. When the mother forms antibodies, red blood cells existing on developing fetus occurring as a result of parental inheritance, the maternal and fetal blood group becomes incompatible. ABO incompatibility is common that occurs in 15 to 25 percent of pregnancies. It arises when an O-positive mother is pregnant of a fetus with A type, B type and AB type blood. The maternal IgG antibodies that occur naturally are capable of passing through placenta to bind in the fetus's red cells, thus leading to hemolysis and complications in the newborn. However, in the fetus, the red blood cells contain lesser amounts of ABO antigens and since they also appear in other cells in the body, it is a mild form of hemolytic infection (Sahin et al., 2025). Severer type is called Hemolytic neonatal and fetal disorder, where fetus's red blood cells are in the case of untreated fetal jaundice and anemia, caused by maternal antibodies which leads to a range of complications such as hydrops fetalis and kernicterus. Due to the lower rate of Rh blood type incompatibility caused by the prophylaxis use of anti-D immunoglobulin, ABO Blood group immune activation is the cause of infant hemolytic diseases (Routray et al., 2023). Rh blood system and Rh-D antigen have significant influence on pregnancy complications when Rh+ fetus gets carried by Rh- mother, she is subjected to the risk of sensitization due to exposure to maternal and fetal blood cells. Maternal anti-D antibodies may cross the placenta in a later pregnancy where the fetus is Rh-positive, leading to severe cellular destruction of the fetus resulting in anemia, retarded growth or/and fetal fatality unless the mother receives progesterone therapy as shown in the Fig. 02.

The recent observational studies of the maternal blood groups and their distribution in pregnant population highlight the importance of blood typing and antibody screening to prevent unfavorable maternal and neonatal outcomes (Al-Kuran et al., 2023).

8. Blood Groups and Transfusion Medicine

It was shown in different research studies that by strictly observing and implementing blood typing

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and compatibility tests, it can help in reducing complications in real-world practice (Qiu et al., 2023). Indicatively, reports done in the transfusion center with incompatible cross-matched red cells have indicated that the cross-matching and antibody testing is important in identifying the alloantibodies and preventing reactions that happen due to transfusion. In another research carried out in the clinical laboratory on incompatible cross-match tests, it has been demonstrated that Rh antigens antibodies can result in incompatibility during blood transfusion (Bhattacharya et al., 2018).

Table 02: Interaction amongst ABO Blood group and Non-Communicable Diseases

Disease / Condition	Blood Group Association	Key Findings	Proposed Biological Mechanism	Reference
Cardiovascular diseases (Coronary artery disease, myocardial infarction)	Blood types A, B and AB indicated greater risk	Several cohort studies report increased incidence of coronary heart disease among them with blood types that are not O.	In non-O groups, greater levels in the blood of von Willebrand and factor VIII enhance the chance of thrombosis.	(Mickelsson et al., 2024)
Venous thromboembolism (VTE)	A type, B type and AB type bloods	People having blood type A, B and AB are much more inclined to suffer pulmonary embolism and deep vein thrombosis	Elevated vWF and factor VIII promote clot formation.	(Liu et al., 2024)
Diabetes mellitus	Blood group type B and AB slightly associated	Some epidemiological studies indicate higher prevalence of type 2 diabetes in individuals with B or AB blood groups.	Possible interaction between ABO antigens and inflammatory markers affecting insulin resistance.	(Mao et al., 2019)
Stomach cancer	A Blood group	Individuals having blood type A show more susceptibility to gastric carcinoma	ABO immune reaction gets influences by antigens and interaction with *Helicobacter pylori*.	(Mao et al., 2019)
Pancreatic cancer	A type, B type and AB type blood	Increased pancreatic cancer risk occurs in those having blood A, B and AB.	Genetic variation may influence inflammation and cell adhesion molecules.	(Liu et al., 2024)
Other malignancies (ovarian, colorectal)	Variable associations	Some studies report correlations between specific ABO blood groups and certain cancers, though results are inconsistent.	Changes in cell surface glycoproteins affecting tumor cell adhesion, immune surveillance, and metastasis.	(Sahin et al., 2025)

Besides red cell transfusion, even practice of platelet transfusion indicates the importance of ABO compatibility. Platelets have been demonstrated to be able to adsorb ABO antigens and that transfusion of ABO-incompatible platelets may cause hemolytic transfusion reactions and poor platelet recovery (Basu et al., 2019).

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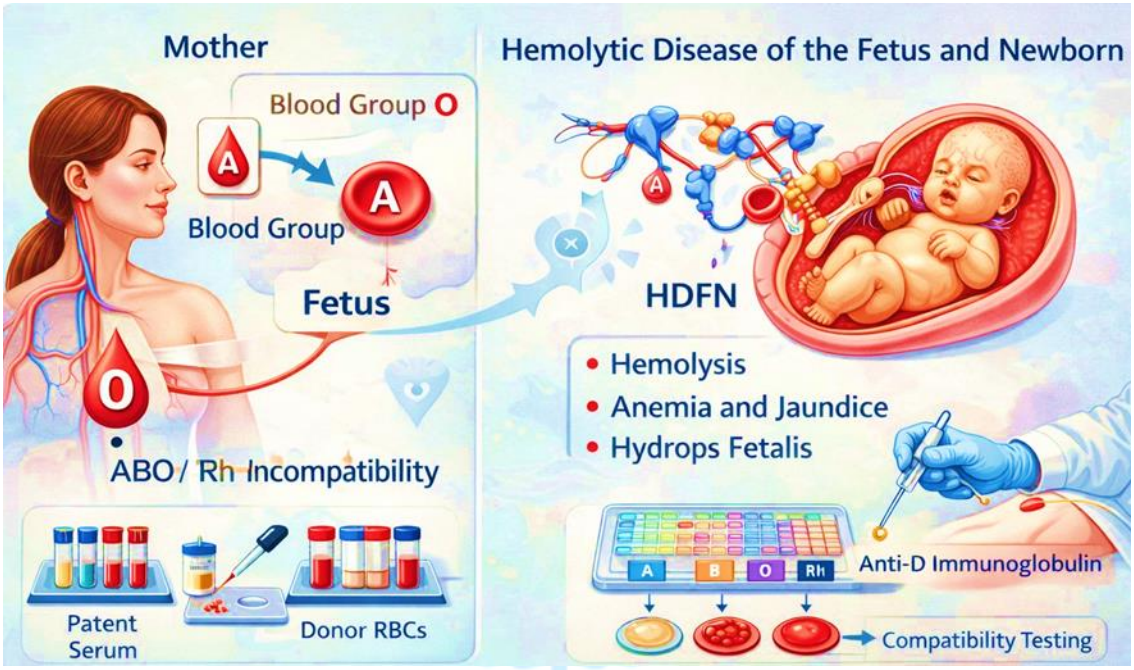


Fig. 02: Blood Groups and Pregnancy Outcomes

Moreover, case reports have also shown the presence of hemolytic reactions related to ABO-incompatible platelet transfusion that once again emphasize the fact that minor incompatibilities may have severe clinical outcomes in particular cases (Zulkeflee et al., 2023). Therefore, the precise techniques of blood group typing and cross-matching techniques are essential components of safe transfusion practice. The traditional techniques of transfusion practice include forward grouping, reverse grouping, antibody screening, and anti-globulin cross-matching techniques to ensure the compatibility of the transfused blood (as illustrated in the Fig. 03). In the research studies conducted to investigate the discrepancies concerning the ABO type of blood systems of transfused individuals, it is revealed that there was a potential for discrepancies in the transfused patients to the extent of 5.5%. It also opposes cross-matching of incompatible samples in the blood banks of hospitals through the retrospective study of samples that cannot be cross-matched and emphasizes that it is essential to define that precise compatibility and immune-hematologic testing is the key to understanding the underlying antibodies and to make a safe choice of transfusion units (Saha & Chowdhury, 2025).

9. Blood Groups in Personalized and Precision Medicine

Mainly in system of ABO blood group, variation in blood groups is recognized as potential tools in disease risk prediction, biomarker discovery and precision medicine. Research from large scale population studies suggest that conditions such as heart diseases, metabolic disorders and certain types of cancers may be affected by ABO blood types that highlight their potential role in predicting health outcomes (Li & Schooling, 2020). Studies show that elevated concentrations of proteins that clot blood such as factor VIII and Willebrand proteins are present in blood groups other than that of O blood group. Hence they are more likely to develop blood clots such as Venous Thromboembolism conditions (Vasan et al., 2016). Along with risk prediction blood group antigens are being studied as biomarkers for how likely it is that someone is going to get sick and how severe their illness might be. For instance, studies conducted during the COVID-19

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pandemic indicate that specific types of ABO blood groups might affect likelihood along with infection extent (Wu et al., 2020; Zietz et al., 2020). Additionally, the association of types of ABO blood with cancer like Gastric Cancer and Pancreatic Cancer shows that for early detection of disease and disease severity level, blood group antigens could be important biomarkers (Wolpin et al., 2010; Zhang et al., 2014). Combining hematological data with genomic data and clinical information may improve risk assessment and help in personalized healthcare supporting precision medicine.

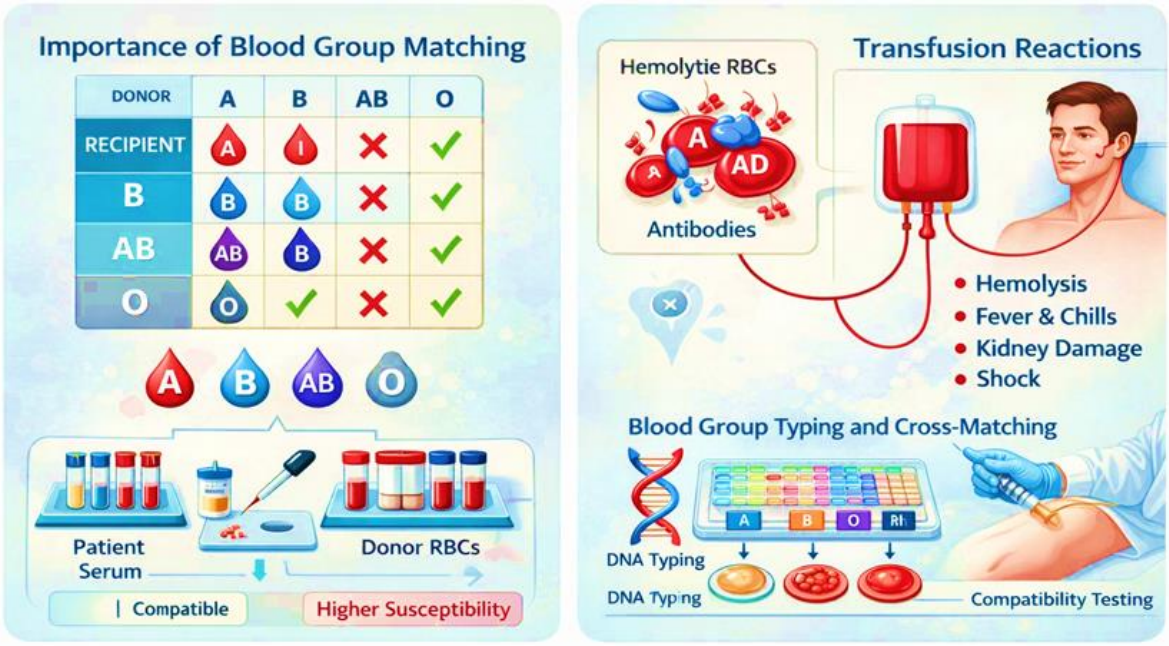


Fig. 03: Blood Groups and Transfusion Medicine

10. Epidemiological Studies on Blood Group Distribution and Health

In global health patterns, regional genetic diversity and vulnerability to diseases, epidemiological studies of blood group systems give important insights. Population based researches are being done on Rh systems of blood and ABO system of blood groups because of their medicinal importance along with genetic differences. Studies shows that ABO blood types distribution differs globally. It's due to the evolution pressure, migration history and population genetics. For example, blood type O is frequently found in populations of America and Africa while blood type A and B are more common in Europe and Asia, as shown in the Fig.04 (Cooling, 2015). Regional research studies shows considerable variations in blood groups within the countries. For example, in South Asia and Middle East surveys of blood donor communities show clear ABO and Rh blood types frequencies affected by ethnicity and demographic factors (Goktas, 2024; Jamil et al., 2024). Many population studies show relationship between blood groups and health conditions. These studies suggest that there is possible connection between blood groups and metabolic and heart-related diseases. Research in Pakistan has found certain diseases like hypertension and diabetes are linked with blood types. Another research reported connection of blood groups with hemoglobin level in different groups of people (Mahjour et al., 2024; Shaikh et al., 2024). Also, there is possibility that ABO blood types are connected with the possibility of infection and extremity of the disease, as suggested in large studies conducted during pandemic of COVID-19 (Asad et al., 2024; Dahlén et al., 2023). Overall, these studies shows that regional disease

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patterns may be affected by blood group variations in the populations. These studies provide useful information for global monitoring, blood transfusion planning, and public health research.

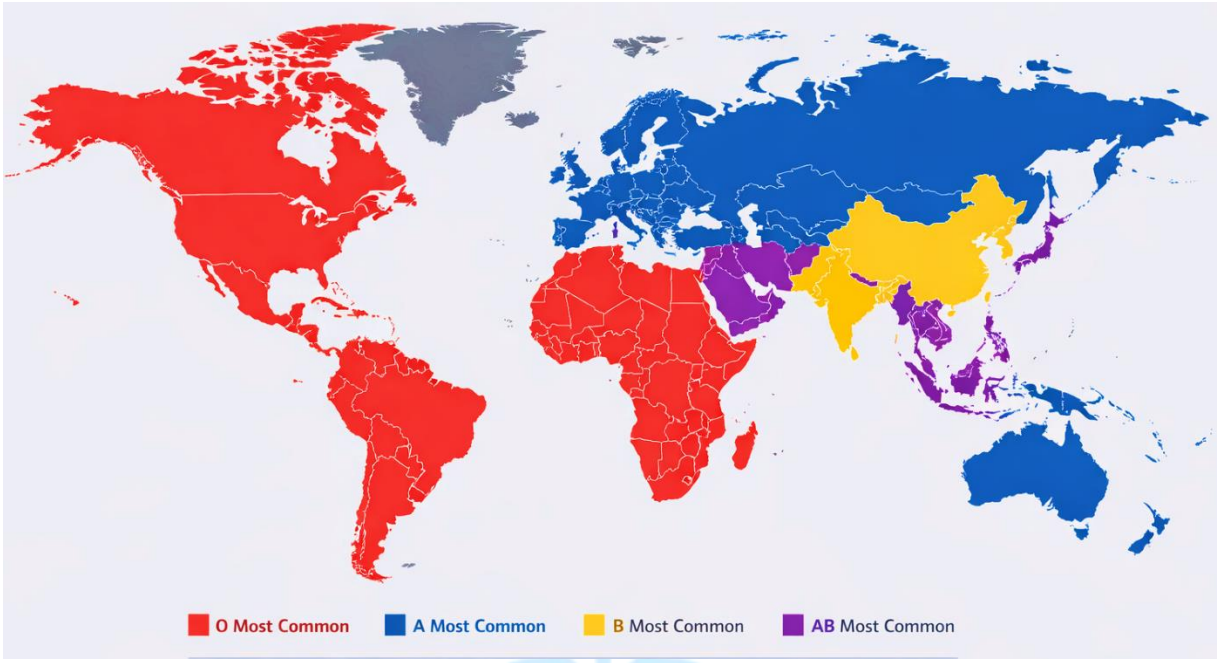


Fig.04: Prevalence of the most common ABO blood group by region

11. Challenges and Research Gaps

Various researches have been conducted to detect the association of blood types with various diseases. However, many research gaps and methodological challenges still exist. Limitations are present in existing literature as they are observational or reviewed and many studies are of small sample size and potential bias. Hence, it is difficult to confirm that either blood group types directly influence chance of disease occurrence and severity of disease (Liu et al., 2024). Large umbrella reviews shows that there are some links that are reported between non-O blood group types and Venous Thromboembolism. However, evidence quality is still moderate and varies in different studies (Imran et al., 2024). Confounding variable factors like age, gender, race, lifestyle and existing health conditions are also challenges because these factors influence blood group distribution disease risks. Hence, it is difficult to interpret observed relationships (Imran et al., 2024). For example, many researches have produced conflicting results in investigating the connection of types of blood group with infection caused by COVID-19 virus. Some researches shows link between certain blood types and severity of disease while many studies find no significant relationship. This highlights the need for more reliable and well-designed researches (Halawani et al., 2024).

12. Future Perspectives

Future research on blood group variations is likely to get help from advancements in genomic technologies and bioinformatics. It will allow more accurate identification of blood group alleles and there role in chance of disease occurrence. In ABO blood group systems, genetic variants are identified with the help of sequencing techniques and large scale genetic studies, influencing cardiovascular, infectious, and metabolic diseases possibility. These progresses signifies the potential of combining blood group genetic data into large models for predicting the risk of diseases (Groot et al., 2020). Combining large bio bank datasets with bioinformatics tools helps in doing phenome-wide analysis that link the blood group antigens with various clinical traits. This provide new

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understandings of biological mechanisms that are involved in blood clotting pathways (Li & Schooling, 2020) In personalized medicine knowing blood group types is very important because it helps in preventing and early detection of diseases. It is very important especially in blood clotting diseases and infectious diseases, for example in COVID-19 (Dahlén et al., 2023). By combining blood group type data with genetic data, lifestyle, and medical history, researchers can help in precision medicine and public health strategies.

Conclusion

Based on extensive investigations, variations in the types of bloods are related to a variety of illnesses, most results derive out of observational information, and thus, they point to the correlation, not necessarily to causation. It is probable that the impact of blood group on the disease susceptibility is acted through intricate systems that may include immune response, as well as, inflammation and pathways of coagulation. Moreover, population genetic variations, environmental exposures, and lifestyle changes can influence the population distribution of blood groups and disease prevalence and understanding of these changes can be difficult. Consequently, although the blood group systems could offer valuable epidemiological information, more large-scale genetic and mechanistic research on the topic in question are necessary to understand what part the systems of blood type serve in health effects.

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