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Review Article

Exploring the relationship between ABO blood groups and vulnerability to different diseases

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Abstract

The ABO grouping of blood, comprising the four main types A, B, AB, and O, has been widely recognized for its significance in establishing the suitability of organ transplants and blood transfusions. Recent research has revealed the potential influence of ABO blood types on susceptibility to certain diseases. The current study uses an extensive review of the body of literature and epidemiological investigations to explore the relationships between ABO blood types and disorders that impact various organ systems. The focus lies on chronic ailments, encompassing certain types of cancer as well as cardiovascular, gastrointestinal, and infectious disorders. For example, those with A blood group may exhibit a higher susceptibility to developing peptic carcinoma, whereas individuals with blood type O may demonstrate a lower propensity for cardiovascular issues. The fundamental mechanisms of these interactions remain incompletely understood. The potential causes for the impact of ABO antigens on immunological responses, coagulation factors, inflammation, and interactions with pathogens are still under investigation. The presence of genetic and molecular variations within ABO blood types may contribute to differing susceptibilities to illnesses. This review examines the correlation between ABO blood types and susceptibility to diseases.

Keywords: ABO blood groups, Cardiovascular disease, Cancer, Hypertension, Infectious disease, Malaria

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Introduction

An association between human ABO blood types and coronary problems has been shown in several epidemiological research. People with blood types other than O, such as A, B, or AB, have an elevated propensity of developing cardiovascular disease than those with blood type O (M. P. Reilly et al., 2011; Wu, Bayoumi, Vickers, & Clark, 2008). Additional investigation is necessary to elucidate the molecular underpinnings of this association (Chen et al., 2014). The structure and function of blood cells undergo modifications based on the existence or lack of antigens within a certain blood type. The present study investigates the correlation between blood type morphology and health outcomes, specifically focusing on the functions associated with different blood types regarding both well-being and illness (Ewald & Sumner, 2016). The production of most antigens is primarily governed by a solitary gene. Genetic alterations to this gene, including but not limited to deletion, addition of post-translational modifications, alternative splicing, or single-nucleotide polymorphisms (SNPs), might impact the immunogenicity of the antigen. Bladder and oral cancers have been seen to exhibit the partial or total removal of A- or B-antigen expression. (David et al., 1993). In addition, resistance to ABH antigens has been associated with the progression of numerous cancer types, including bladder and lung carcinomas(Lee et al., 1991). Following the elucidation of the molecular genetic underpinnings of the ABO system by Yamamoto et al.(F.-i. Yamamoto, Clausen, White, Marken, & Hakomori, 1990), numerous weak characteristics have been identified as outcomes of common allele combinations and single nucleotide polymorphisms in the coding exons and splicing sites. Nonetheless, reports have surfaced regarding feeble characteristics whose coding exons and splicing sites appear to be constant(Iwasaki, 2000). However, it is important to note that these factors might also potentially result in the emergence of novel antigens or even a total cessation of gene expression (Denomme, 2011).

The ABO blood type was the initial blood group system to be discovered, and its associated antigen has garnered significant importance and undergone extensive investigation (F. Yamamoto, Cid, Yamamoto, & Blancher, 2012). The RBC glycoconjugate structures on red blood cells provide a variety of tasks, encompassing the roles of receptors for external ligands, transporters, channels, structural proteins, integrin, and enzymes (Abegaz, 2021). How exactly adhesion molecules are involved in the relationship between blood type antigen and disease, however, remains elusive (Ahmad, Ilyas, Ahmad, Badshah, & Mateen, 2022). The creation of normal RBCs requires the contribution of a significant number of these structures; some of them serve as cell adhesion molecules (CAMs), while others have an impact on human sickness. The ABO, Hh, Sese (secretor), and Lele (Lewis) genes, each of which performs a unique role, affect the ultimate ABO antigen structure of a person's body tissues and secretions. This structure is determined by a person's blood type (Ewald & Sumner, 2016). Nevertheless, if novel data emerges, it is plausible for this foundational evidence to undergo revision (Abegaz, 2021).

The determination of an individual's ABO blood type is influenced by their genetic composition and has been associated with various illnesses. During the period spanning from 1960 to 1970, a multitude of epidemiological investigations were conducted on a global scale, leading to the formulation of widespread hypotheses on the potential correlations between the ABO blood type of individuals and their vulnerability to specific diseases. There exists a significant correlation between ABO blood types and a wide range of infectious and non-infectious diseases (Zhong, Wang, Xiao, Mo, & Luo, 2023). The potential influence of host genetics and environmental factors on the development of sickness is a subject of consideration. After the development of the ABO blood type system by Landsteiner in 1901, it was examined as a potential etiological factor in several ailments, such as stomach cancer and peptic ulcer (Abegaz, 2021). There is a prevailing belief that the evolution of ABO antigens is associated with conferring resistance against diseases. Nevertheless, research has demonstrated that specific ABO blood types are correlated with various medical conditions such as cancer, cardiovascular disease, infections, and hematologic disorders (Than et al., 2011). The predominant A and B antigens present in the human bloodstream are mostly derived from cellular secretions. Individuals who are non-secretors are hence prone to a range of diseases (Alireza, Mojtaba, & Sahar, 2010). There exists a multitude of organisms that are capable of adhering to polysaccharides present on the surfaces of cells. However, it is worth noting that the attachment process may be impeded by the presence of soluble blood-type antigens (Jefferys &

Kenneth, 2005). One theory holds that the ABO alternative phenotype protects its host species from illnesses that use a specific carbohydrate as a receptor (Legese et al., 2022). In contrast, the presence of ABO polymorphism leads to the production of anti-A and anti-B natural antibodies, resulting in the formation of several forms. These antibodies have the potential to provide individuals with protection against various pathogenic microorganisms that include A and B patterns (Abegaz, 2021). In light of the growing data indicating a possible connection between ABO blood types and illness outcomes, it is crucial to conduct a thorough assessment to evaluate the robustness and consistency of these correlations, identify areas where information is lacking, and provide guidance for future research and clinical practice.

Material and Methods

The researcher conducted an exhaustive evaluation of the issue and a comprehensive examination of current and pertinent literature in the same field. Through the deliberate omission of pivotal matters, a thorough examination of the subject was accomplished, encompassing a descriptive synopsis as well as lucidly presented counterarguments. Moreover, this investigation incorporated relevant scientific literature that had been previously published. A set of terms associated with a variety of disorders was correlated with the phrases blood types/groups to conduct the article search. The articles were subject to a filtering process.

Correlation between ABO blood type and certain diseases

Potential correlation between ABO blood group and cardiovascular disease

The ABO blood type has a high predictive association with plasma levels of factor VIII and von Willebrand factor (vWF) (Gill, Endres-Brooks, Bauer, Marks, & Montgomery, 1987). Those of blood type O have around 25% lower plasma levels of these glycoproteins compared to those of blood group A. Non-O blood groups elevate the risk and intensity of these illnesses by augmenting von Willebrand factor and plasma cholesterol levels, as well as triggering endothelial dysfunction and inflammation. Additionally, they have been associated with elevated levels of coronary artery calcification, greater complexity of coronary lesions, and inadequate collateral circulation. Blood groups have an impact on the prognosis of coronary artery disease and acute coronary syndrome, as well as the occurrence of complications and fatality rates also given in Table 1(Neshat et al., 2024). This connection is important from a therapeutic standpoint. Preston and Barr first reported a significant impact of ABO on plasma VWF: Ag levels in 1964(Preston & Barr, 1964), and this finding has been subsequently validated by several independent research involving diverse ethnic populations. Based on the findings of this research, it is evident that persons with blood type O who are in good health have plasma VWF: Ag levels that are around 20% to 30% lower compared to those who do not have blood type O(O'donnell & Laffan, 2001). While there may be some discrepancies in the non-O categories across various research, it is generally observed that persons with blood type AB had the greatest levels of plasma VWF: Ag. The ABO blood type has a comparable impact on plasma FVIII levels, with the main influence being dictated by changes in VWF levels(Ward, O'Sullivan, & O'Donnell, 2020). Ischemic heart disease and venous thromboembolism (VTE) may result from abnormally high plasma levels, whereas excessive bleeding can result from abnormally low plasma levels (O'donnell & Laffan, 2001; F. Yamamoto et al., 2012). The primary factors responsible for these effects are variations in the rates of vWF synthesis, secretion, and/or clearance, leading to differing levels of vWF in the plasma (F. Yamamoto et al., 2012). Epidemiological studies have consistently shown a positive association between non-O blood types and the incidence of myocardial infarction (MI). Nevertheless, there has been ongoing debate over the ABO blood group phenotypes that exhibit the highest susceptibility (Nydegger, Wuillemin, Julmy, Meyer, & Carrel, 2003). There was no observed impact of age, level of physical activity, alcohol consumption, smoking habits, or a prior diagnosis of diabetes on the relationships between blood type and the risk of coronary heart disease (CHD) (Zhang, Mooney, & Reilly, 2012). The results indicate that heightened inclination for thrombus development in individuals who are not blood type O may have conferred an evolutionary benefit to early human populations. The prothrombotic mutations factor V Leiden and prothrombin, that are often seen in persons of Caucasian descent, have been the focal point of a scholarly debate (Jokubaitis et al., 2022), that occurred around the conclusion of the last glacial epoch, around 20,000 to 24,000 years ago. There exists a hypothesis suggesting that genetic variations

such as factor V Leiden may decrease susceptibility to bleeding and/or severe infections, thereby reducing the likelihood of experiencing a miscarriage. The interaction between A and B antigens with von Willebrand factor (vWF) might potentially be elucidated using similar theoretical frameworks (Anstee, 2010).

Research was conducted by(Groot et al., 2020) that comprised a total of 406,755 unrelated people. The identification of blood types A, B, and O was determined by examining the combinations of alleles from the known single-nucleotide polymorphisms rs8176746 and rs8176719 in the ABO gene. Group AB was excluded because of its very limited sample size. A total of 187,387 persons, accounting for 46% of the population, were male. The mean age of these people was 57 years with a standard deviation of 8.1 years. The group's median overall exposure was 64 person-years, ranging from 57 to 70 person-years. Among the 406,755 individuals, 182,621 had blood type O, 182,786 had blood group A, and 41,348 had blood group B. The ABO blood type system is associated with several elements pertaining to the aging process and the development of illnesses as shown in figure 1(Groot et al., 2020).

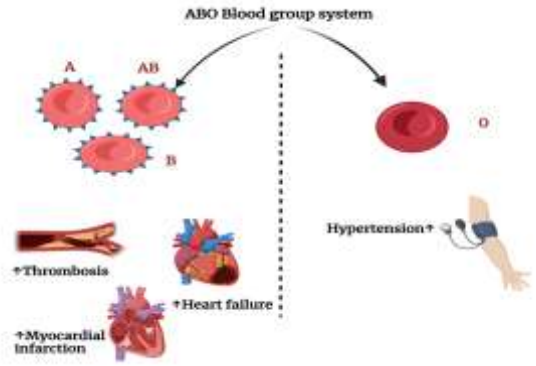

Figure-1. Correlation between ABO blood types and various cardiovascular disorders

Several studies examining the correlation of ABO blood types were conducted retrospectively, potentially introducing issues related to inadequately matched control groups (Wei, Yi, OuYang, & Wu, 2023). To address these limitations, a study conducted in the United Kingdom examined the correlation between the ABO blood type status of 7662 male participants and their susceptibility to ischemic heart disease (Whincup, Cook, Phillips, & Shaper, 1990). A random selection was made from a general registry of individuals aged 40 to 59, consisting only of men. These individuals were then observed for a period of 8 years in order to assess the occurrence of ischemic heart disease. While the frequency of ischemic heart disease did not vary across blood types A and O, those with blood type. Individuals with blood type A had a greater incidence of ischemic heart disease events as compared to individuals with blood type O (relative risk 1.21, 95% confidence limits 1.01 to 1.46). Furthermore, blood type O exhibited a decreased occurrence of ischemic heart disease in comparison to the other blood types (Parente et al., 2020). Two other prospective cohort studies were done over a span of 20 years: The Nurses' Health Study, which followed 62,073 women, and the Health Professionals Follow-up Study, which monitored 27,428 men. When considering age, those with blood type A had a hazard ratio of 1.06 for coronary artery disease (CAD), compared to individuals with blood group O. Similarly, persons with blood type B had a hazard ratio of 1.11, whereas those with blood group AB had a hazard ratio of 1.23 for CAD. In general, 6.27 percent of all cases of CHD were ascribed to the inheritance of a blood group other than O (M. He et al., 2012). Females with a BMI more than 25 kg/m2 and the ABO blood type were shown to be significantly related. However, further studies revealed that the association between ABO blood group status and coronary artery disease (CAD) remained unaffected by factors such as physical activity, alcohol use, smoking, or diabetes. Cardiovascular disease and their association with different diseases is given in Table 1.

Role of ABO in infectious diseases

The research conducted by Anstee (Anstee, 2010), has shown a correlation between ABO polymorphism and some viral diseases. The presence or absence of A/B antigens and anti-A/B antibodies determines the strength or weakness of defensive mechanisms against infection. The ABO gene is found in several vertebrate species, hence conferring benefits to them (O'Donnell, Zheng, Meric, & Marques, 2023). Nevertheless, the significance of sharing common A and B genes across species may be diminished when species eventually lose the capacity to make anti-A/B antibodies (Anstee, 2010). However, adaptation against microbial attacks might have been achieved by regular A/B specificity gene conversion that results in amino acid alterations or recombination with dormant incomplete genes (F. Yamamoto et al., 2014). The surfaces of red blood

cells that are glycoconjugated function as receptors for the attachment of parasites, bacteria, and viruses (F. Yamamoto et al., 2012). The presence of glycosylation polymorphisms within the ABO blood type has the potential to influence interactions between hosts and pathogens.

Table-1. Types of cardiovascular diseases and their association with different cardiovascular disease

Cardiovascular disease	Results	References
Coronary Heart Disease	Individuals with blood types other than O should be closely evaluated for cardiovascular risk factors, since taking preventive measures and receiving appropriate treatment for these risk factors will help reduce their chances of developing cardiovascular disease (CVD) and experiencing negative cardiovascular events	(Neshat et al., 2024)
Coronary artery disease	CAD was more prevalent among patients with blood group A. Patients with blood type A who had CAG (coronary angiography) showed a higher incidence of acute coronary syndrome (ACS), impaired function of the left ventricle, triple vessel disease, and severe coronary artery disease (CAD).	(Pai et al., 2023)
Coronary artery disease	The blood type alleles O1 and the B allele showed a substantial association with CAD, whereas the A1, A2, and O2 alleles were found to be insignificant. The presence of the O1 allele indicated a protective effect against atherosclerosis, but the B variation was associated with an increased risk of developing atherosclerosis. The BB genotype had a much higher susceptibility to developing CAD, with a 5-fold greater risk. In contrast, the O1O1 genotype had a lower risk, providing a protective effect that was at least 2-fold.	(Chawla, PC, Deshpande, & Ashavaid, 2020)
Cardiovascular disease	Blood type A had a stronger and statistically significant connection with IS, MI, and PVD than blood group O. Myocardial infarction risk is lowest for blood type B.	(Lilova et al., 2023)
Cardiovascular diseases	individuals with blood type A had a higher likelihood of experiencing major adverse cardiovascular events (MACE) compared to individuals with blood type O during the COVID-19 pandemic.	(Nauffal, Achanta, Goldhaber, & Piazza, 2021)
Cardiovascular diseases	The only variation seen across the four blood types was in the serum anti-Hsp27 titers of all 3 markers. The AB blood type had the greatest optical density (OD), whereas the O blood group showed the lowest OD. Patients with AB blood type who had Metabolic Syndrome (MetS), dyslipidemia, hypertension (HTN), and obesity exhibited higher levels of serum anti-Hsp27. Members with O blood type had reduced levels of serum anti-Hsp27. There was no variation in the levels of two other markers, serum PAB and hs-CRP, across different ABO blood types.	(Yaghooti-Khorasani et al., 2020)
Aortic disease	The incidence rates of aortic events were comparable for patients and blood type O donors and non-O donors. The assessment of aneurysms and aortic dissections was comparable across O and non-O blood types. Patients with blood type B were less likely than those with type O to develop aortic aneurysms.	(Zindovic, Edgren, Nozohoor, & Majeed, 2020)
Myocardial Infarction	A study conducted on a group of 6713 patients who did not have rheumatic heart disease, cardiomyopathy, myocarditis, constrictive pericarditis, or valvular heart disease revealed that individuals having blood type A had a higher likelihood of experiencing a myocardial infarction (MI).	(Pang, Zong, Hao, & Cao, 2020)
Primary hemostasis	Initial findings suggest that group O VWF and platelets may interact less. The exact chemical pathways that affect VWF due to ABO are unknown. The ABO(H) carbohydrate structures on VWF's N- and O-linked glycans may be their main effect. Multiple platelet glycoprotein receptors express ABO(H) determinants.	(Ward et al., 2020)
Carotid plaques	Carotid plaques were seen in 44% of individuals with ABO blood types. The prevalence of plaque and CIMT quartiles did not show a statistically significant difference between those with Non-O and O blood types.	(Mickelsson et al., 2023)

Consequently, individuals with different glycosylation profiles may exhibit varying levels of sensitivity to infectious agents. This is due to the fact that infections often use glycoconjugates as ligands for the purpose of adhesion as receptors for attachment (F. Yamamoto et al., 2012). There are other infectious illnesses in which the ABO phenotype has a strong correlation with the level of infection severity. Several investigations have shown that individuals with the O blood group phenotype had a higher susceptibility to severe infections in comparison with persons having non-O blood group morphologies when infected with cholera caused by Vibrio cholera strains O1 El Tor and O139 given in table 2 (Harris et al., 2005). Glass *et al.* (Glass et al., 1985) contend that cholera selection pressure is directly responsible for the low incidence of group O and the high prevalence of group B (Glass et al., 1985) The epidemiologic investigations were carried out at the field Hospital of the International Centre for Diarrheal Disease Research, Bangladesh. The ABO blood group was ascertained for a total of 1,346 individuals, consisting of 682 patients who had a diarrheal disease caused by a particular pathogen and 664 individuals who served as controls. Patients infected with *V. cholera* 01 had a higher likelihood of having blood type O (57%) compared to the control group (30%). Conversely, they had a lower likelihood of having blood group B (18% vs 35%). Furthermore, their likelihood of having blood group AB was one-ninth that of the control group(Glass et al., 1985). Recent cholera pandemics may be traced back to this area (Kaper, 1995). In a 1996 epidemic of gastrointestinal diseases caused by Escherichia coli O157 in Scotland with a sample size of 186, it was observed that patients belonging to group O had a higher susceptibility. The group O patients were responsible for 87.5% of the deaths (Blackwell et al., 2002).

There is a worldwide health catastrophe as a consequence of the SARS-CoV-2 virus, which has caused over 422 million illnesses and 5.8 million fatalities. Numerous investigations into the risk factors associated with the illness have shown a possible relationship between the patient's susceptibility and their ABO blood type. However, there are contradictory ideas at the moment about this matter. Banchelli et al. studied the relationship between ABO blood type and vulnerability to SARS-CoV-2 infection in 2022. He covered every study, including the ones with SARS-CoV-2 test controls. A cohort of 1,200,000 people is included in the meta-analysis; of these, 74,563 tested positive for SARS-CoV-2 and 1,166,717 tested negative. There were 487,985 people with blood type A, 151,879 people with blood group B, 52,621 people with blood group AB, and 548,795 people with blood group O overall. When comparing Group O's degree of connection with infection to the other three blood types, it was lower. Table 2 indicates that Group A had a much greater association with infection than the other three groups:(Banchelli et al., 2022).

Table-2. Connection between ABO and infectious diseases

Infectious disease	Results	References
COVID-19 Infection	The amount of connection between Group O and infection was slightly less than that of the other three blood groups. When compared to the other three groups, group A's link with infection was somewhat greater.	(Banchelli et al., 2022).
COVID-19 Infection	According to epidemiological statistics included in the findings, women who have blood type A are more susceptible to COVID-19.	(Fan et al., 2020)
COVID-19 Infection	Upon separate analysis of the four groups, it was shown that group 0 had a decreased susceptibility to infection in comparison to the groups that were not labelled as 0. In contrast, group A exhibited a higher susceptibility to infection compared to both the non-A groups and group 0. Regarding the danger of SARS-CoV-2 infection, our findings indicate that those with blood type O have a reduced risk, whereas those with blood type A have an elevated risk.	(Enguita-Germán et al., 2022)
Hepatitis B virus	People with blood type O were 12% more likely to get infected with HBV in areas where the illness was more common. The combined risk estimates for those with blood type B and HBV infection were consistent and dependable, as shown by the sensitivity analysis.	(Jing, Zhao, Liu, & Liu, 2020)

Hepatitis B infection	Individuals who have the B antigen but lack the Rh D antigen have a greater probability of acquiring HBV infection.	(Oladeinde et al., 2022)
Hepatitis C infection	The results revealed that persons with blood group 'O' had a greater viral load in comparison to those with other blood types among the patient population residing in Southern Punjab, Pakistan. Furthermore, the existence of the Rh-negative factor was shown to be associated with a greater viral load in comparison to those with the Rh-positive factor.	(Noreen et al., 2021)
Vibrio Cholera infection	Those with the O blood group phenotypic exhibited a greater vulnerability to severe infections when infected with cholera caused by Vibrio cholera, in contrast to those with non-O blood group morphologies.	(Harris et al., 2005).
Acute respiratory distress syndrome	The A1 genotype was more susceptible to moderate to severe ARDS than type O in all three groups. Sepsis and non-pulmonary infections correlated strongly. The association was found in non-secretors, suggesting a blood vessel mechanism. The A1 genotype enhanced thrombomodulin, von Willebrand factor, and disseminated intravascular coagulation risk. These variables enhanced acute respiratory distress syndrome risk. Blood type A also slowed ex vivo lung perfusion lung injury repair.	(J. P. Reilly et al., 2021)
Dengue fever	Of the 204 instances, 82 were O positive, 59 B positive, 38 A positive, 16 AB positive, 4 O negative, and 2 A negative. Dengue strongly correlated with ABO blood type. Compared to 16 controls (32%), 66 cases (42.9%) were O+. A research found that blood type O people are more likely to get DF. DF is strongly linked to blood type.	(Kouser, Abbas, & Naeem Effendi, 2020)

ABO blood group association with cancer incidence

Despite the comprehensive investigation of the relationship between cancer and ABO blood groups throughout the mid-20th century, new publications highlighting the correlation between ABO blood type and pancreatic cancer have sparked increased interest in this field of research (Simona, Patrick, Edoardo, Maria, & Albert, 2010). Evidence suggests that blood type antigens have a role in a wide variety of cellular processes, including recognition, signaling, adhesion, carcinogenesis, metastasis, and prognosis (Abegaz, 2021). The expression of ABH and associated antigens exhibits variability during cellular development, the aging process, and differentiation in the context of carcinogenesis and pathological processes (F. Yamamoto et al., 2012). The presence of ABH antigens has been observed in several tissues of epithelium, including GIT, breast, uterine cervix, oral cavity, pulmonary system, bladder, and prostate. The analysis of the prevalence of these carcinomas in ABO blood is given in table 2.

Nevertheless, the presence of these antigens has not been detected in the glycolipids and glycoproteins of malignant tissues in these locations (Daniels, 1999). One hypothesis suggests that DNA methylation occurring in the promoter region of the blood group A gene could potentially hinder the transcription process of the associated enzyme, leading to the absence of the A antigen. However, it is worth noting that several mechanisms contributing to the reduction of mRNA in A cancers have been identified, and these mechanisms seem to vary depending on the specific cell line (Hakomori, 1999). Metastasis occurs as a result of the downregulation of ABO transcription, leading to a decrease in A or B transferase activity.

Table-2. The ABO blood group system and its correlations with the risks of certain carcinoma (Abdollahi, Tavasolian, Esmaili, Broujeni, & Amini, 2014)

Blood group	Disease-associated	Type of Associated Risk
O	Squamous cell cancer of the skin	Low
O	Pancreatic carcinoma	Low
B	Ovary carcinoma	High
A and B	Peptic carcinoma	High/ low
O	Adenocarcinoma of breast	High
B	Lung carcinoma	High
A	Buccal carcinoma	High

This decrease in activity facilitates the accumulation of supplementary antigens, which serve as ligands for selectins and aid in the facilitation of the metastatic

process (Kronstein-Wiedemann et al., 2023). The development of cancer occurs when there is a loss of normal antigens and a gain of tumor antigens. The extent of tumor spreading potential may be inferred by the proportional decrease in A, B, and H antigens (Garratty, 2000).

The incidence of pancreatic cancer has a positive correlation with progressive age and exhibits a greater frequency among certain ethnic and racial groups, including African-Americans, Ashkenazi Jews, Pacific Islanders, and New Zealand Maori (Shaib, Davila, & El-Serag, 2006). The observed increase in vulnerability across different groups seems to be impacted by a confluence of environmental and genetic variables. While there are certain cancer syndromes and hereditary pancreatitis that increase individuals' susceptibility to pancreatic cancer, the identification of the primary genetic variables associated with the development of this disease remains elusive (Greer, Lynch, & Brand, 2009). Pancreatic cancer has been associated with many well-established risk factors, including tobacco use, chronic pancreatitis, type 2 diabetes, and obesity (Lowenfels & Maisonneuve, 2006). Based on the growing body of research, there seems to be a correlation between the ABO blood type and pancreatic cancer. The study conducted in Spain, which included 108 cases and 374 controls, found that those with blood type A exhibited a slightly higher but statistically insignificant risk of developing pancreatic cancer. A comparative study conducted by Italian researchers used a sample of 224 patients diagnosed with pancreatic cancer, whose histological confirmation was obtained. These patients were compared to two control groups: Group 1 consisted of 7086 individuals diagnosed with various medical ailments, while Group 2 comprised 7320 volunteer blood donors. The findings of this experiment demonstrate similar outcomes (Boyd et al., 2022).

A study was conducted by Wei, Yi et al. 2023 in China where he analyzed the association of Type1 endometrial cancer on 213 patients in which 43.7% were O blood group following B blood group with 27.7%, A blood group having 23.9% and AB having least prevalence of Type1 endometrial cancer that was 4.7%(Wei et al., 2023). Another study was conducted by Alexandra, Alexandru et al. 2022 in Romania for assesing the association of head and neck cancer with ABO blood groups. His study consists of larger population of 19,626 patients suffering from head and neck cancer in which A blood was prevalent with this type of carcinoma. About 44.39% patients of his study suffering from head and neck carcinoma were A blood group(Alexandra et al., 2022).

For analyzing the association of Prostate cancer with ABO blood groups, Porcaro, Amigoni et al. in 2022 conducted a study in Europe. He studied on 1149 patients who have prostate cancer. His findings indicated that O blood group indivdual were more prone to prostrate cancer followed by A blood group(Porcaro et al., 2022). Many other studies were conducted for analysing the prevelence of different cancers in different ABO blood group given in table 3.

Table-3. A meta review of different studies showing the prevalence of different types of carcinomas with their variability among different blood groups of ABO

Type of cancer	Authors, year, and country	No. of patients	A blood Group	B blood group	AB blood group	O blood group
Type1 endometrial cancer	Wei, Yi et al. 2023, China (Wei et al., 2023)	213	23.9 %	27.7 %	4.7 %	43.7 %
Head and neck cancer	Alexandra, Alexandru et al. 2022, Romania (Alexandra et al., 2022)	19,626	44.39%	17.28%	4.69%	33.64%
Prostate cancer	Porcaro, Amigoni et al. 2022, Europe (Porcaro et al., 2022)	1149	41.3%	11.1%	4.8%	42.8%
Colorectal cancer	Al-Sawat, Alswat et al. 2022, Taif and Saudia Arabia (Al-Sawat et al., 2022)	199	29.6%	13.1%	6.5%	50.8%
Epithelial ovarian cancer	Wang, Zhou et al. 2023, China (Wang et al., 2023)	1,870	30.6%	30.5%	11.7%	27.3%
Neural cancer	Patidar, Dhiman et al. 2022, India (Patidar, Dhiman, & Hazarika, 2022)	1970	20.91%	37.51%	8.83%	32.74%

Averaging nine million fatalities per year (Rawla, Sunkara, & Barsouk, 2019) colorectal carcinoma(CRC) is the fourth-most fatal malignancy. The second leading type of cancer in Saudi Arabia is CRC, which is more frequent in males and older individuals than other age group (Cossu, Saba, Minerba, & Mascalchi, 2018; Khoja et al., 2018). Genetic markers in the human blood grouping system have been linked in investigations to a greater likelihood of developing certain malignancies. Examining the connection involving blood type and CRC risk was the goal of investigation. From January 2017 to August 2021, record-based retrospective research was carried out. Individuals with CRC who were diagnosed throughout the study period were the focus of this investigation. The retrieved information contained the demographics, blood types, and associated risks of the patients, such as their medical history and any previous IBD or CRC. 199 individuals in all, ranging in age from 22 to 96, were examined. 101 (50.8%), 59 (29.5%), 26 (13.1%), and 13 (6.5%) patients had blood types O, A, B, and AB, respectively. The most common malignancy recorded was colon cancer (155/199, 77.9%), while individuals with blood type O had the highest incidence (74/155, 47.7%) (Al-Sawat et al., 2022).The deadliest neuroendocrine carcinoma, affecting males and females equally, is carcinoma of the thyroid, whose prevalence is rising more quickly than any other kind of carcinoma (L.-z. He et al., 2016). Several authorities ascribed this global rise to the increasing diagnostic techniques, whereas others hypothesized that this growth was actually caused by modifications to ecological conditions and people's lifestyles (Pellegriti, Frasca, Regalbuto, Squatrito, & Vigneri, 2013; Verkooijen et al., 2003).

Tam *et al.* 2020(Tam et al., 2020), conducted a study to evaluate the correlation between Rh and ABO blood types in individuals with thyroid cancer. Individuals with both benign and malignant thyroid disease had their cytological findings, ABO blood types, rh factor status, and medical history examined. Individuals with different ABO blood types as well as Rh positive and negative individuals had their thyroid cancer's histopathological characteristics were contrasted. 1,299 (63.5%) patients had a benign histologic diagnosis, whereas 744 (36.5%) patients had a malignant one. Age, sex, thyroid autoantibody positivity, and ABO blood types did not significantly vary between individuals with benign and malignant conditions (p >.05 for each variable). People with malignant sickness had a greater frequency of Rh positivity than people with benign diseases. Compared to those without B blood groups, individuals with B blood types exhibited a greater rate of extrathyroidal extension and advanced stage (3–4) thyroid cancer. In individuals with multifocal illness, the chance of extrathyroidal extension was 4.272 (95% CI: 1.816-10.049) times greater in B blood types than in non-B blood groups (p.001). Individuals with the blood group O experienced less capsular invasion than those with blood groups other than O (p =.018) (Tam et al., 2020).

The intriguing connection of ABO blood type with and malaria

In his study, Dhananjaya (DHANANJAYA, ROOPA, NAIK, & RAMESH, 2021) put out a hypothesis on the correlation between ABO blood type and malaria, positing that individuals with type B blood had a selective advantage in relation to susceptibility to malarial infection. By the year 1978, a notable number of patients with type A blood was successfully recognized using integrated data analysis, in contrast to those with type B and O blood types. In contrast, the many types of malaria were seldom referenced in the existing scholarly literature (F. Yamamoto et al., 2012). Differences in Lewis antigen levels may be seen among the A, B, and AB blood types, which can be attributed to the ABO phenotype. This discrepancy arises due to the lower presence of Le antigens in these blood types compared to O types. This distinction can be attributed to the use of equivalent precursors by the various transferases associated with these blood types (Loscertales et al., 2007). According to the latest hypothesis, it is suggested that the increased prevalence of the Le (a_b_) phenotype among individuals of African descent may be attributed to *P. falciparum* malaria (Cserti & Dzik, 2007). However, the importance of ABO blood types in the context of malaria defense has not been well-studied. Recent findings have demonstrated that individuals with O blood group may possess a certain level of resistance to severe P. falciparum malaria due to their ability to block rosetting mechanisms (Iyiola, Igunnugbemi, Raheem, & Anifowoshe, 2011). The occurrence of rosetting and sequestration has been linked to the development of severe malarial pathogenesis (Abegaz, 2021)

The evolutionary history of the ABO gene aligns well with the temporal context of malaria (Rattanapan, Duangchan, Wangdi, Mahittikorn, & Kotepui, 2023). The allele labelled O01, which is prevalent in group O,

exhibits complete similarity to the allele called A01, which is the most frequent allele in group A, for the foremost 261 nucleotides. At this particular site, a guanosine nucleotide is excised, leading to a frame-shift mutation that induces the occurrence of a premature stop codon and hampers the synthesis of a functional A or B transferase. The occurrence of a single nucleotide deletion in the otherwise intact group A gene indicates that individuals with the O01 allele in the group O blood type likely originated due to a mutation originating from the A01 allele (Roubinet et al., 2004). The allele O02, which is the second most common variant for blood type O, is an ancestral O allele that exhibits a shared deletion at position 261. Additionally, less often occurring group O alleles have been discovered, and it has been shown that almost all of them exhibit deletion 261. This observation has led (Roubinet et al., 2004) to the conclusion that the emergence of virtually all group O alleles coincided over the course of human evolution (Cserti & Dzik, 2007).

The prevalence of deletion 261 is seen throughout global populations, suggesting its emergence in Africa prior to the migratory movements of early humans. Consequently, the group O phenotype must have been subject to a selection pressure that was operative in Africa prior to 50,000 to 100,000 years ago. Given that *Plasmodium falciparum* was prevalent in Africa at the period when modern humans emerged, it is plausible to consider this parasite as a possible factor affecting human blood types. Undoubtedly, throughout around 150,000 years from the Homo sapiens' first appearance and their first migrations outside of Africa (Scerri, 2023), it is plausible that Group O may have seen a steady but consistent rise in prevalence, provided that Group O had even a marginal selective advantage in the context of *P. falciparum* infection. After the migratory event, it is possible that the presence of distinct group O mutations at position 261 might have contributed to an increased prevalence of group O genes among people residing in regions with endemic malaria, but outside of Africa. In summary, it can be inferred that for any infectious disease to have influenced the distribution of ABO blood types, it would have needed to be prevalent in Africa prior to human migration and possess a high fatality rate (Dobkin, Wu, & Mangalmurti, 2023), either before or during the reproductive years of individuals. *Plasmodium falciparum*, widely recognized as a significant entity in evolutionary history, happened to be situated in an opportune geographic region at a crucial period (Cserti & Dzik, 2007).

Influence of ABO blood type on hypertension

Multiple studies have shown correlations between blood type antigens and hypertension, a result that is unsurprising. Multiple research investigations have shown that individuals with blood type B have a greater vulnerability to hypertension in comparison to those with blood types A and AB, who have a significantly lower occurrence of this ailment. (Ghafar et al., 2022). The linkage between hypertension and the ABO gene has been established for the first time. Genetic studies have shown a correlation between hypertension and a variation in the ABO gene. The obtained data provide support for the hypothesis that this particular gene has a role in the regulation of ACE activity (Chung et al., 2010).Multiple studies have shown a positive association between a certain ABO blood type allele and an elevated vulnerability to cardiovascular diseases (Wu et al., 2008).

The presence of the A antigen has the potential to shield P-selectin and intercellular cell adhesion molecule 1 (ICAM1) from proteolytic degradation. This is achieved by facilitating a stronger and more prolonged attachment of leukocytes to these molecules in the vascular wall. Consequently, an increased number of adhesion molecules bound to endothelial cells would enhance adhesion and inflammation, while concurrently decreased blood flow (Paré et al., 2008). Type A carriers are more prone to developing cardiac difficulties and cumulative disease scenarios when exposed to redox stressors such as viral illnesses (Dai, 2020). Based on previous research, it was found that people of different blood types (AB, B, A, and O) had significant differences in their FVIII levels. (Chung et al., 2010). Furthermore, cognitive impairment was found to be linked to a wide range of chronic diseases, including diabetes mellitus, coronary heart disease, hypertension, obesity, hyperlipidemia, and adiposity, suggesting a multifactorial origin.

The risk of cardiovascular disease (CVD) is influenced by an individual's blood type, and it has been shown that variables associated with CVD are interconnected with the development of dementia and cognitive impairments (Abegaz, 2021).According to estimates, 5%–10% of conceptions across the world are complicated by hypertensive disorders of pregnancy (HDP). The study has shown an association between non-O blood group and the development of hypertensive disorders of pregnancy (HDP), including preeclampsia (PE). However, these assessments have

not always proven dependable. Mukhtar *et al*.2019(Mukhtar, Yakubu, Yakasai, Ahmed, & Mansur, 2019),sought to ascertain the association between HDP and blood type ABO within conceiving women undergoing prenatal care at Kano, Nigeria's Murtala Muhammad Specialist Hospital. For the research, 210 pregnant women with clinically confirmed HDP and an equivalent number of normotensive controls were included. With a mercury sphygmomanometer along with a Littman's stethoscope placed on the medial surface of the right bicep while the subject was seated, blood pressure was determined. A urine dipstick was used to do an evaluation of urine. Strong monoclonal anti-A, anti-B, and anti-D reagents were employed for assessing types of ABO blood by utilizing the tile agglutination technique. 90 of the 210 people in the HDP group (cases) had gestational hypertension (GH), 50 had preeclampsia, and 70 had it. Both in patients and controls, the type O blood group was the one that was most prevalent. Groups A, B, and AB, respectively, for cases and controls, followed next (Mukhtar et al., 2019).

Conclusion

Many studies have examined the potential correlation among ABO blood groups and illnesses, presenting logical mechanisms to support this relationship. However, contrasting findings from other studies have failed to corroborate these claims, leading to challenges in convincing others of a certain viewpoint owing to the lack of consistent evidence. The O blood group phenotype has a notable association with heightened vulnerability to severe infectious illnesses, such as cholera and gastrointestinal infections. Also the above research indicates a robust relationship amid blood group B and a higher vulnerability to certain types of carcinomas, such as ovarian, lung, buccal, and prostate cancers. There are several elements, both identified and unidentified, that might potentially influence the occurrence of an event, such as the ABO blood group system. The ABO blood types, as currently known, are not directly causative of diseases. However, they have been shown to potentially elevate an individual's susceptibility to illness or health-related complications. Those who possess blood group other than O exhibit a greater vulnerability to acquiring ailments when contrasted with those who have blood type O.

Limitations

The review may mostly consist of research with favorable findings, perhaps excluding studies with inconclusive or unfavorable results, resulting in an overestimation of the actual correlation between ABO blood types and illness outcomes. Also, some important confounding factors, such as genetic variations or environmental influences, may not have been sufficiently considered or accounted for in the research. This might have possibly affected the reported relationships between variables. Potential confounding variables that could affect the reported associations between ABO blood types and disease occurrence include age, gender, ethnicity, lifestyle factors, and comorbidities. These variables may not be adequately accounted for in the analysis under consideration.

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Contribution of Authors

M.I, R.Z, M.A.F, B.J and A.A conceived the focus of the study and reviewed the literature. K.J, M.U, and M.M contributed to the software and performed formal analysis. C.H.S, and M.S.F, provided resources and C.A.S and Z.K was involved in project administration. M.I R. Z and B.J wrote the original draft while M.A.F and A.A reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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