Relationship Between the Prevalence of Blood Groups and Severity of Leptospirosis: A Case-Control Study

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Infectious Diseases: Research and Treatment
Volume 13: 1–5

DOI: 10.1177/1178633720936273
SAGE

ABSTRACT

INTRODUCTION: The correlation between the prevalence and severity of leptospirosis with blood groups has not been investigated so far, but several studies have been conducted to link the infectious diseases with blood groups. The aim of this study was to investigate the prevalence of blood type in patients with leptospirosis and its association with disease severity.

METHODS: This is a case-control study performed on hospitalized patients with the diagnosis of leptospirosis in Mazandaran province, Iran, in 2018. The control group was selected from among the families of patients. Blood groups (ABO and Rh) and severity of the disease were assessed. Data were analyzed by SPSS 22.

RESULTS: A total of 300 people (150 in the case and 150 in the control) enrolled in the study. The mean age was 44.35 ± 15.39 years and 81.3% were men. The highest frequency of blood type in both groups was O+, A+, and B+, respectively. There was a statistically significant difference in the frequency of blood groups ($P = .037$). Comparison between severity of disease and blood types (ABO, Rh) showed no significant difference ($P > .05$).

CONCLUSIONS: According to our study, O+ was the most common among patients with leptospirosis. The frequency of O in patients was significantly higher than in the control group, but there was no significant relationship between leptospirosis and Rh. The prevalence of this blood type was higher in people with a severe form of the disease. Finally, there is no statistically significant difference between the severity of the disease and ABO and Rh.

KEYWORDS: Leptospirosis, ABO blood groups, Rh blood group

RECEIVED: January 27, 2020. **ACCEPTED:** June 1, 2020.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Leptospirosis, also known as field fever, is a common disease between humans and animals with the highest prevalence in the world, the source of which are rodents and dogs. The disease is transmitted by skin scraping smeared with contaminated water containing the urinary waste of animals, including mammals.[1] Leptospirosis is an occupational disease in developing countries such as Iran and occurs mostly in farmers, ranchers, butchers, slaughterhouse staff, and fishermen in hot seasons.[2,3] The disease is characterized by a wide range of clinical manifestations, ranging from nonspecific infection to flashy and fatal illness. Leptospirosis, in its mild form, can present as a flu-like illness with headaches and myalgia, and its severe form is characterized by jaundice, kidney dysfunction, and a bleeding disorder called "Weil disease."[4,5]

As leptospirosis has no specific pathognomonic symptoms to make a clinical diagnosis, its laboratory diagnosis is of particular importance. Laboratory diagnosis of leptospirosis is by conventional serological methods including PCR (polymerase chain reaction) and MAT (microscopic agglutination test); the culture of bacteria from blood, urine, or tissue; and confirmation of the presence of *Leptospira* in the tissue using antibodies conjugated with fluorescent dyes. The PCR-restriction fragment length polymorphism method is useful for determining the identity and studying the structures of a species in such a way that it can be used directly for clinical specimens and for rapid diagnosis and identification. Nested PCR is also a fast and simple method to differentiate between pathogenic and nonpathogenic leptospires.[3,6,7]

Leptospirosis-related mortality rates worldwide have been reported to be less than 5% to 30%.[8] According to the World Health Organization, the annual incidence varies from 0.1 to 1 person per 100 000 in temperate regions to 10 to 100 persons per 100 000 in tropical and humid areas and occurs sporadically in industrialized countries.[3,9] The incidence of the disease is higher in men than in women, and so far, according to information available in Iran, this disease has been mainly confined to the north of the country, especially Gilan province.[3]

The correlation between the prevalence and severity of leptospirosis with blood groups has not been investigated so far,

but several studies have been conducted to link the prevalence and severity of infectious diseases with blood groups. In many studies, blood group O has been associated with increased prevalence of plague, cholera, mumps, and tuberculosis. Type A blood group is associated with an increased incidence of smallpox and *Pseudomonas aeruginosa* infection. Type B blood group is associated with an increased incidence of gonorrhea, tuberculosis, *Streptococcus pneumoniae, Escherichia coli*, and *Salmonella* infections, and type AB blood group is associated with an increased incidence of smallpox, *E coli*, and *Salmonella* infections.[10] In many studies, malaria cases are lower in group O patients and more severe in group A, and people with group O appear to be relatively resistant to the severe disease caused by malaria infection.[11] *Streptococcus pyogenes* M1T1, or group A streptococcus (M1T1 GAS), has been shown to have a greater tendency in oral epithelial cells to bind to cells with H antigen than to cells with A, B, or AB antigens.[12]

We must also consider the fact that some diseases such as periodontal diseases,[13] *Helicobacter pylori* infectiom,[14] and tuberculosis[15] are relatively more prevalent in certain blood groups and due to the climatic conditions of Mazandaran province and rural population and common occupations including cultivation, agriculture, and fishing, as well as endemic disease in neighboring provinces such as Gilan, Golestan, and Mazandaran province and the incidence and hospitalization of large numbers of farmers, ranchers, and especially paddy farmers in the spring and summer and acute and severe complications, along with mortality, The aim of this study was to investigate the prevalence of blood type in patients with leptospirosis and its association with disease severity.

Methods

Study design and setting

This is a case-control study performed in patients admitted with the diagnosis of leptospirosis in Razi Hospital of Ghaemshahr, Mazandaran Province, Iran, from January to December 2018. Due to the lack of previous studies, considering the significance level of .05, the sample size of 150 people was estimated for each group. In all hospitalized patients with the diagnosis of leptospirosis, randomly 150 patients were assigned to the case group based on simple randomization. The control group was selected from among the families of patients who were exposed but not infected.

Demographic data, clinical symptoms, laboratory tests, and blood group (ABO, Rh) were extracted from the patient's records. In the absence of blood group information, the patient was called for a blood group test. The control group was called in to check their blood group.

Eligibility criteria

Patients with acute flu-like symptoms, such as fever, diarrhea, headache, myalgia, and conjunctival suffusion, were identified as mild to moderate, and patients with jaundice/icteric sclera, abdominal pain, nausea, vomiting and diarrhea, oliguria/anuria, organ involvement, sepsis/septic shock, altered mental states, and hemorrhage (pulmonary and gastrointestinal) were identified as those with severe leptospirosis. All patients with symptoms and positive laboratory tests were enrolled in the study. The MAT was considered positive by a 4-fold increase or a single titer above 400. In ELISA, the criterion of positive or negative was first measured by the kit manufacturer's standard and then standardized by MAT and PCR. Patients with incomplete records were excluded.

Ethical consideration

This study was conducted after approval from the Ethics Committee in Biomedical Research of Mazandaran University of Medical Sciences (Code: IR.MAZUMS.REC.1397.2985) was obtained. All patients consented (written consent) to contribute data to the database. Privacy and confidentiality were guaranteed by excluding patient identifiers and coding them. Only the researcher or data collectors had access to the data.

Statistical methods

Data normality was assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Central and dispersion (mean and standard deviation) indices were used to express quantitative data and frequency (percentage), and charts were used to express qualitative data. The Mann-Whitney test was used to evaluate the relationship between the ages of the 2 groups, and the χ^2 test was used to evaluate the qualitative data. Data were analyzed by Statistical Package for the Social Sciences (SPSS) version 22. *P* values below .05 were considered statistically significant.

Results

A total of 300 individuals, 150 each in both case and control groups, were studied. The mean age was 44.35 ± 15.39 years. The minimum and maximum ages were 11 and 82 years, respectively. The number of men (244, 81.3%) was higher than women (56, 18.7%). About half of the people (51%) were farmers and 30 people had underlying diseases (hypertension, diabetes, and ischemic heart disease). Only 2 patients had a previous history of leptospirosis (Table 1). The mean number of days of onset of symptoms until admission was 4.24 ± 1.76, and the mean number of hospitalization days was 5.50 ± 3.54.

Among symptoms of cases, fever and chills (98%), myalgia (91.3%), headache (76.7%), nausea (64%), and vomiting (42%) were the most frequent. Two people died of the disease. There was a significant correlation between increasing white blood cell count, creatinine, bilirubin, liver enzymes, creatine phosphokinase (CPK), and inflammatory biomarkers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) and decreasing hemoglobin, platelets, and serum sodium and potassium levels with symptoms ($P < .05$).

Table 1. Demographic information of groups, No. (%).

VARIABLES		GROUPS		*P* VALUE
		CASE	CONTROL	
Age (mean ± SD)		45.05 ± 15.87	43.65 ± 14.92	.434[a]
Sex	Male	127 (84.7)	117 (78)	.138[b]
	Female	23 (15.3)	33 (22)	
Job	Farmer	63 (42)	90 (60)	.621[b]
	Self-employment	51 (34)	37 (24.7)	
	Employee	10 (6.7)	9 (6)	
	Unemployed	26 (17.3)	17 (11.3)	
Underlying diseases		22 (14.67)	8 (5.34)	.352[b]

$P < .05$ was considered significant.
[a]Mann-Whitney *U* test.
[b]χ^2 test.

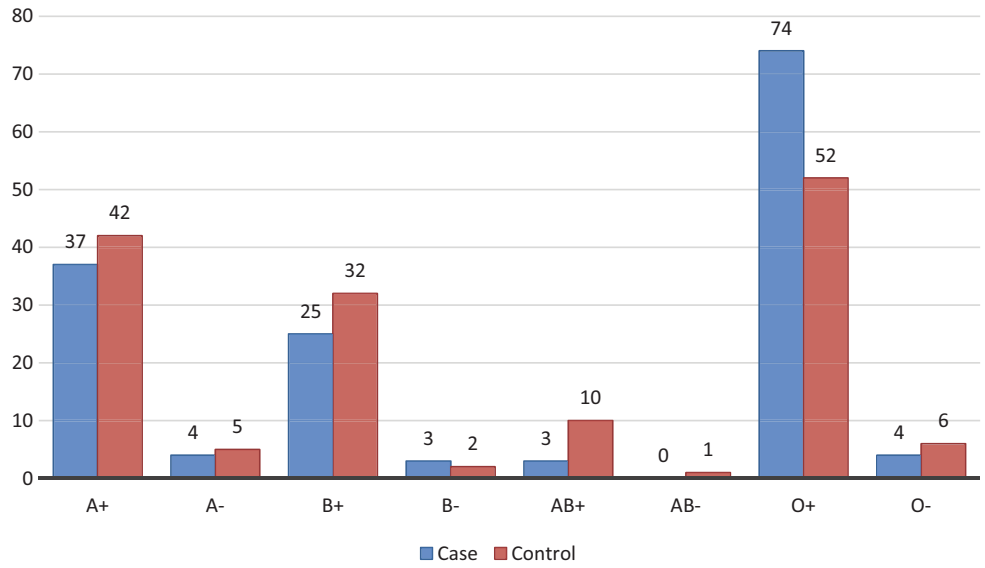

Chart 1. The frequency of blood type in case and control groups.

The highest frequency of blood type in both groups was O+, A+, and B+, respectively (Chart 1). There was a statistically significant difference in the frequency of blood groups between the 2 groups ($P = .037$). Comparison of Rh frequency between groups showed no significant difference between the 2 groups ($P = .531$), and Rh-positive was the most frequent in both groups (92.7% in the case group vs 90.7% in the control group) (Table 2).

Regarding the severity of disease in all patients (case group), 113 (75.3%) and 37 (24.7%) had mild to moderate and severe leptospirosis, respectively. Frequency of O+ in both groups was significantly higher than the other blood groups ($P < .05$). A Comparison between severity of disease and blood types (ABO, Rh) showed no significant difference ($P > .05$) (Table 3).

Discussion

Blood group antigens represent polymorphic traits that are inherited in a population. There are currently 34 known human blood groups, and there are hundreds of individual blood group antigens and alleles. Differences in the expression of blood group antigens increase or decrease the susceptibility of the host to many infections. Blood groups can play an attributive role in the transmission of infection in microorganisms, parasites, and viruses as coreceptors or receptors.[16] Leptospirosis is one of the most common human and animal diseases in the world caused by a pathogen called *Leptospira*.[17] In our study, the number of men in both groups was higher, and most were farmers. In our study area, which is one of the northern regions of Iran, people whose main occupation was not agriculture were farming in their spare

Table 2. Comparison of frequency of blood and Rh groups in case and control groups, No. (%).

VARIABLE		CASE	CONTROL	*P* VALUE[a]
Blood groups	A	41 (27.3)	47 (31.3)	.037
	B	28 (18.7)	34 (22.7)	
	AB	3 (2)	11 (7.3)	
	O	78 (52)	58 (38.7)	
Rh	Positive	139 (92.7)	11 (7.3)	.531
	Negative	136 (90.7)	14 (9.3)	

$P < .05$ was considered significant.
[a]χ^2 test.

Table 3. Comparison of the frequency of blood groups based on the severity of leptospirosis, No. (%).

VARIABLES		MILD TO MODERATE	SEVERE	*P* VALUE[a]
Blood groups	A	32 (28.3)	9 (24.3)	.915
	B	20 (17.7)	8 (21.6)	
	AB	2 (1.8)	1 (2.7)	
	O	59 (52.2)	19 (51.4)	
Rh	Positive	107 (94.7)	32 (86.5)	.097
	Negative	6 (5.3)	5 (13.5)	

$P < .05$ was considered significant.
[a]χ^2 test.

time. In many studies, sex and occupational exposure play an important role in the development of leptospirosis. The role of sex in the possibility of leptospirosis infection has been investigated in humans so that the prevalence of this disease in men is higher than that in women, possibly due to occupational exposure.[17,18] Leptospirosis is more common in temperate and tropical climates.[19] Pathogenic *Leptospira* can be found in ponds, rivers, pits, sewers, agricultural fields, and moist soils,[20] which is why agricultural occupations are so important in terms of occupational exposure. Thus, most people with the disease have been involved in agriculture as their mainoccupation.[21-23] In many surveys,[17,18,24,25] including our study, leptospirosis was most common in middle-aged people (40-60 years). In our patients, the mean hospitalization days were lower than in the study by Goris et al,[26] which could be due to the fact that in the study by Goris et al,[26] people with severe forms of the disease were examined. The most common and typical symptoms of this disease are fever and chills, muscle aches, and headaches, respectively,[27] which were the same in our patients. In general, we expect patients with leptospirosis to have leukocytosis and increased bilirubin, creatinine, CPK, liver enzymes (alanine transaminase and aspartate transaminase), and inflammatory indicators (CRP and ESR), as well as decreased hemoglobin, platelets, and serum sodium and potassium levels,[17,22,25] which was true in our study.

To date, no study has been conducted on the relationship between the prevalence and severity of leptospirosis with blood groups, and this is the first study to examine this issue. In our survey, we found that O+ and A+ blood groups had the highest prevalence in patients with leptospirosis. Comparisons between O and A blood groups between case and control groups showed a significant relationship, but this relationship was not significant in the Rh blood group system. According to the Blood Transfusion Research Center of Iran, among blood donors in Mazandaran province, blood groups A (28.98%) and O (39.25%) had the highest frequency. These percentages decreased by 6.87% and 2.53%, respectively, after 19 years, but O blood type was still the most common blood group. Also, more than 90% of people donating blood in this province were Rh-positive.[28] Although some evidence suggests that N-acetylglucosamine, which is a basic element of antigen H in ABO blood groups and is expressed in mucosal membrane cells, could transmit bacterial infection into cells as a ligand and as a result the prevalence of these infections in the blood type O will be higher,[29] but with attention to these statistics,[28] in our study, it is not possible to conclude from the high frequency of O that these people are more likely to affected by this disease. In other words, this high frequency is probably due to a large number of people with O blood type in Mazandaran province. In this study, we measured the relationship between blood type and disease severity and found no association between the 2, but almost half of the people with severe leptospirosis had O.

Various studies have been performed on the effect of blood groups on the incidence and severity of different infectious diseases. A study examining the link between malaria and blood types in China found that blood type O (38.38%) had the highest prevalence among patients with malaria, but no statistically significant relationship was found between blood groups and malaria prevalence,[30] whereas in another study on the issue, the most common blood type was B.[31] In an epidemiological study of 34 hospital staff who became infected with the severe acute respiratory syndrome (SARS) after being exposed to a single patient, most of the infected people (23/34) had non-O blood types (A, B, and AB), and group O individuals are more resistant to SARS-CoV due to ABO antibodies.[16]

Due to the fact that our study for the first time investigates the relationship between blood groups with the prevalence and severity of leptospirosis, there are limitations to this study. For example, our statistical population was small and the members of the control group were selected based solely on the family relationship with the members of the case group and occupational exposures. It is suggested that further studies be conducted in a prospective and cohort manner in a larger statistical community.

Conclusion

According to our study, the O+ blood group was the most common among patients with leptospirosis. The frequency of O in patients was significantly higher than in the control group, but there was no significant relationship between leptospirosis and Rh. The prevalence of O was higher in people with a severe form of the disease. Finally, there is no statistically significant difference between the severity of the disease and ABO and Rh.

Acknowledgements

The authors wish to express their appreciation to all study participants and study staff.

Author Contributions

AR, LD, MH, and HJ participated in the design of the study. ES and HJ carried out the immunoassays. LD and RG performed the statistical analysis. AR, LD, HJ, and RG contributed reagents/materials/analysis tools. AR, LD, and HJ wrote the initial draft of the manuscript. LD and RG critically revised the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study may be made available from the corresponding author on a reasonable request.

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REFERENCES

1. Davoodi L, Kazeminejad A, Jafarpour H, et al. Leptospirosis presented with erythema nodosum on four limbs: an unusual presenting. *Oxford Medical Case Reports*. 2020;2020:omz130.
2. Kasper D, Fauci A, Hauser S, et al. *Harrison's principles of internal medicine*. New York: McGraw-Hill; 2018.
3. Rafiei A, Hedayati Zadeh-Omran A, Babamahmoodi F, Alizadeh Navaei R, Valadan R. Review of leptospirosis in Iran. *J Mazandaran Univ Med Sci*. 2012;22:102-110.
4. Bharti AR, Nally JE, Ricaldi JN, et al. Leptospirosis: a zoonotic disease of global importance. *Lancet Infect Dis*. 2003;3:757-771.
5. Abdollahpour G, Shafighi ST, Sattari Tabrizi S. Serodiagnosis of leptospirosis in cattle in north of Iran, Gilan. *Iran J Veter Med*. 2009;3:7-10.
6. Marchiori E, Lourenço S, Setúbal S, Zanetti G, Gasparetto TD, Hochhegger B. Clinical and imaging manifestations of hemorrhagic pulmonary leptospirosis: a state-of-the-art review. *Lung*. 2011;189:1-9.
7. Obiegala A, Woll D, Karnath C, et al. Prevalence and genotype allocation of pathogenic Leptospira species in small mammals from various habitat types in Germany. *PLoS Neglect Trop Dis*. 2016;10:e0004501.
8. Babamahmoodi F, Salmani Mojaveri M, Babamahmoodi A. Seroepidemiology of leptospirosis in workers of high risk occupation in Mazandaran province—Iran 2007-2008. *J Mazandaran Univ Med Sci*. 2009;19:10-15.
9. Costa F, Hagan JE, Calcagno J, et al. Global morbidity and mortality of leptospirosis: a systematic review. *PLoS Neglect Trop Dis*. 2015;9:e0003898.
10. Ewald DR, Sumner SC. Blood type biochemistry and human disease. *Wiley Interdiscip Rev Syst Biol Med*. 2016;8:517-535.
11. Hegde S, Sinha R, Chakraborti S, et al. Relationship between malaria and ABO blood group types. *Int J Sci Res*. 2015;5:1041-1044.
12. De Oliveira DM, Hartley-Tassell L, Everest-Dass A, et al. Blood group antigen recognition via the group A streptococcal M protein mediates host colonization. *Mbio*. 2017;8:e02237-16.
13. Vahabi S, Aslani M. Relationship between periodontal diseases and ABO blood groups and Rh system in pregnant women. *Iran J Obstetr Gynecol Infert*. 2013;15:7-12.
14. Kanbay M, Gür G, Arslan H, Yilmaz U, Boyacioglu S. The relationship of ABO blood group, age, gender, smoking, and Helicobacter pylori infection. *Dig Dis Sci*. 2005;50:1214-1217.
15. Liumbruno GM, Franchini M. Beyond immunohaematology: the role of the ABO blood group in human diseases. *Blood Transfus*. 2013;11:491-499.
16. Cooling L. Blood groups in infection and host susceptibility. *Clin Microbiol Rev*. 2015;28:801-870.
17. Abbasi A, Jafarpour H, Khodavandegari Z, et al. Report of the clinical features of patients with leptospirosis in Golestan, Iran, 2011-2015: based on information available at the provincial health center. *Chron Dis J*. 2018;6:165-170.
18. Puca E, Pipero P, Harxhi A, et al. The role of gender in the prevalence of human leptospirosis in Albania. *J Infect Develop Count*. 2018;12:150-155.
19. Evangelista KV, Coburn J. Leptospira as an emerging pathogen: a review of its biology, pathogenesis and host immune responses. *Future Microbiol*. 2010;5:1413-1425.
20. Karpagam KB, Ganesh B. Leptospirosis: a neglected tropical zoonotic infection of public health importance—an updated review. *Eur J Clin Microbiol Infect Dis*. 2020;39:835-846.
21. Davoodi A, Najafi N, Tayebi A, et al. Pulmonary involvement in leptospirotic patients. *J Mazandaran Univ Med Sci*. 2011;21:69-74.
22. Alian S, Davoudi A, Najafi N, et al. Clinical and laboratory manifestation and outcome of icterohemorrhagic leptospirosis patients in Northern Iran. *Medical Journal of the Islamic Republic of Iran*. 2015;29:308.
23. Garshasbi V, Naddaf SR, Aghighi Z, Hassan N, Pooya M, Mostafavi E. Leptospirosis in Caspian Sea littoral, Gilan Province, Iran. *Acta Trop*. 2018;181:11-15.
24. Ghasemian R, Shokri M, Makhlough A, Suraki-Azad MA. The course and outcome of renal failure due to human leptospirosis referred to a hospital in North of Iran; A follow-up study. *Caspian J Intern Med*. 2016;7:7-12.
25. Najafi N, Davoudi AR, Alian S, et al. Clinical and laboratory findings on complication in patients with leptospirosis in Mazandaran Province, Iran. *Arch Clin Infect Dis*. 2015;10:e24695.
26. Goris MG, Kikken V, Straetemans M, et al. Towards the burden of human leptospirosis: duration of acute illness and occurrence of post-leptospirosis symptoms of patients in the Netherlands. *PLoS ONE*. 2013;8:e76549.
27. Haake DA, Levett PN. Leptospirosis in humans. *Curr Top Microbiol Immunol*. 2015;387:65-97.
28. Pourfathollah A, Oody A, Honarkaran N. Geographical distribution of ABO and Rh (D) blood groups among Iranian blood donors in the year 1361 (1982) as compared with that of the year 1380 (2001). *Sci J Iran Blood Transfus Organ*. 2004;1:11-17.
29. Chen J-K, Shen C-R, Liu C-L. N-acetylglucosamine: production and applications. *Marine Drugs*. 2010;8:2493-2516.
30. Zhang X, Yang M, Zhao H, Hu J, Li L. Relationship between malaria and ABO blood types in East China. *Biomed Res Int*. 2017;2017:8163762.
31. Deepa AV, Alwar VA, Rameshkumar K, Ross C. ABO blood groups and malaria related clinical outcome. *J Vector Borne Dis*. 2011;48:7-11.