Association of ABO blood groups with SARS-COV-2 infection

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Research Article

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Abstract

In view of the influence of ABO blood group antigens on infectious diseases, we explore the effect of ABO blood types on SARS-COV-2 infection. In this report, demographic data of 80 COVID-19 patients and 26 SARS-COV-2 asymptomatic carriers were collected based on electronic medical records. The results indicated that the distribution of ABO blood group in the confirmed patients was significantly different from asymptomatic carriers; importantly, antigen A carrier have significantly higher risk of developing into severe or critically cases than other types. These data present further evidence for the association of the blood groups to susceptibility to SARS-COV-2 infection.

Background

Since the Austrian physiologist Carl Landsteiner discovered the ABO blood type in 1901, scientists have continued to study the theory of blood types for more than 100 years[1]. With the development of technology, it has been found that human blood group has at least more than 30 systems such as ABO group, Rh group, HLA and Lewis, which has important application in clinical transfusion and organ transplantation [1]. More and more studies have found that the ABO blood group antigen system is closely related to human microbial infections such as bacteria, viruses, and parasites [2]. Researchers have presented findings showing that natural antibodies to human red blood cell type B antigens can directly react with some E. coli strains; therefore in a large-scale retrospective report demonstrating that patients with type B and AB have a higher risk of E. coli-related sepsis than those with type O and A[3]. At the same time, research on the relationship between ABO blood group and malaria also found that the prognosis of patients with blood type O was significantly better than that of patients with blood type A[4]. In addition, the research related to ABO blood group antigen and virus infection is also very extensive, such as Norovirus, E-B virus, HBV, HIV, influenza virus[5–10]. Most common respiratory virus infections are characterized by family clustering, which may be related to the transmission mechanism of the virus itself, but it also suggests that genetic factors may affect the disease[11]. In 2003, Hong Kong scholars found that patients with SARS infection without protective measures were mostly individuals with non-O antigen when the SARS epidemic broke out; on the contrary, people with type O had better resistance to the virus[12]. In short, diversity of ABO antigen causes significant differences in host susceptibility to pathogens, yet the mechanism is still not completely clear[4].

Human ABO blood group antigens are divided into four types: A, B, AB, and O, the difference among them lies in the glycosyl structure of the antigen terminal which are determined by the three genes A, B, and O locating at the end of chromosome 9[13]. Among them, gene A and B are dominant alleles with the same advantages and encode different glycosyltransferases, whereas O gene allele acting as a stealth gene does not have the ability to encode functional enzymes[4]. Except for red blood cells, ABO antigen it is expressed in epithelial cells, vascular endothelial cells, platelets and other parts, moreover, these antigens can be distributed in a variety of body fluids in free form[1].

In recent years, studies have found that blood group antigens also play an important role in the immune system. For example, Blood A antigen can directly act as a receptor for rotavirus subtype HAL1166, and the pathogenic ability of the subtype may also be related to the strength of the binding to type A antigen[14]. In addition, type O plasma significantly inhibits the binding of SARS-COV spinous protein to host cell receptor ACE2, and this inhibitory effect has a clear dose-dependent relationship[15]. These suggest that the ABO blood group antigen system has an important role in the process of virus invasion into the human body, for the reason that blood group antigens are likely to cause large differences in individual sensitivity to pathogens.

Of late, the outbreak of 2019 new coronavirus pneumonia (COVID-19) which was characterized as a pandemic by the World Health Organization (WHO) have occurred in many countries around the world, but we still know little about the pathogenesis of the disease. In order to explore the susceptibility factors for the occurrence of COVID-19, we analyzed the association between the blood type of the patients diagnosed with COVID-19 and the asymptomatic carriers of SARS-COV-2 to the occurrence of the disease.

Materials And Methods

Subjects

The study subjects were locally diagnosed from January 20, 2020 to February 22, 2020 in Zhuzhou City, including 80 patients diagnosed with new-type coronavirus pneumonia and 26 asymptomatic carriers. The diagnostic criteria and disease classification criteria are based on the diagnosis and treatment guidelines issued by the National Health and Health Committee. Eligible patients were meeting epidemiological history, clinical manifestation(match any 2)and etiology evidence that listed in table1, and confirmation criteria for asymptomatic carriers were both of epidemiological history and etiology evidence. Data of asymptomatic carriers came from the active detection of some people with epidemiological history and the isolation test of history of residence in Wuhan and surrounding areas.

Data Sources

Basic information and clinical data according to electronic medical records, including: age, gender, blood group test, nucleic acid test results, classification of clinical infection condition and outcome were collected. Nucleic acid negative time is the time from the first detection to the virus clearance which was defined as 2 continuous negatives of nucleic acid tests.

Statistical methods

Continuous variables were expressed as the medians and interquartile ranges (IQR). comparison between groups was conducted by Mann-Whitney test. Categorical variables were summarized as the counts and percentages in each category. R × C list comparison between groups was made by χ^2 test, and $P < 0.05$ was considered statistically significant. The Odds ratio, which is one of the familiar statistical measures,

was used to know the likelihood of possessing the risk of COVID-19. SPSS 19.0 software was used for statistics.

Results

Demographic characteristics of COVID-19 confirmed patients and asymptomatic carriers

From January 20 to February 22, 2020, a total of 106 cases of SARS-COV-2 nucleic acid positives were detected in the region, including 80 COVID-19 confirmed patients and 26 asymptomatic infection cases. Because the age of the subjects showed a skewed distribution, the median and interquartile range were used to describe their characteristics(Table 2). Comparing the age and sex distribution of the COVID-19 patient group and the asymptomatic group, it was found that there was no significant statistical difference in gender between the two groups which may be caused by the small sample size, but the age difference was statistically significant.

Blood group distribution of COVID-19 confirmed patients and asymptomatic carriers

To understand the effect of blood group antigens on virus pathogenicity, we performed a statistical analysis for blood type data of COVID19 patients and asymptomatic carriers. Based on existing literature, the proportion of blood group A was highest (30.54%), followed by O (30.37%), B (29.42%) and AB (9.66%) among 3.8 million Chinese[16].In contrast, the proportion of blood group distribution of all SARS-COV-2 infected cases was basically consistent with these data(Table 2). We found that patients with blood type A occupied the mainly proportion among COVID19 patients, while individuals with blood type B accounted for 50% in asymptomatic Group (Table 3). Surprisingly, the distribution of blood types was significantly different between the two groups ($\chi^2 = 9.245$, $p = 0.026$), implying that ABO blood antigens can affect the occurrence of COVID-19. It can be inferred from Table 3 that blood type A patients have the highest risk of developing the COVID group, and blood type B individuals are relatively resistant. In order to elaborate the effect of type A antigen on the occurrence of disease, we divided the subjects into two groups: A antigen carrier and no A antigen group. The results showed that the risk of COVID-19 (type A and type AB blood) was much higher than non-A individuals ($\chi^2 = 3.942$, $p = 0.047$), the risk index $OR_{A+AB/O+B}$ was 2.727 (95% confidence interval 0.99-7.511). Then, we analyzed the differences between type B antigen carriers to non B individuals , and found that type B antigen has a significant protective effect ($\chi^2 = 6.757$, $p = 0.009$), which leaded to the risk of disease significantly reduced with $OR_{B+AB/A+O}$ value of 0.305 (95% confidence interval 0.122-0.764).

Influence of blood type on the prognosis and outcome of SARS-COV-2 infection

Of the 80 COVID patients diagnosed locally, 17 patients were in condition with severe and critically who have undergone systematic treatment, and all were finally discharged from the hospital(Table 4). It is a concern that patients with type A antigen may be at high risk of severe illness. In line with this, we found that the risk of severe and critical with blood type A carried patients increased almost 3.9 times (95%

confidence interval 1.22-12.45) compared with non A antigen blood types(χ^2 =5.711, p = 0.017).Consistent with the above results, these data indicated that patients with type A antigen have more susceptible to develop into severe conditions than patients with other antigen types. In addition, we also analyzed the average time for the viral nucleic acid to become negative in the respiratory specimens of patients with COVID. Patients with blood type A had the longest time, with an average of 14.5 days and a maximum time of 41 days. In contrast, patients with blood type B had a shorter time with an average of 9.5 days and a minimum of 5 days. These data further confirmed the susceptibility of blood antigen A to SARS-COV-2 infection, while blood group B or O has stronger immunity to SARS-COV-2 infection.

Discussion

As of 8 Apr 2020, more than 1,282,931 new coronavirus pneumonia cases have been reported worldwide, causing more than 72,776 deaths, which has brought severe tests to the world's public health security system[17]. In order to effectively control the spread of the epidemic, China has incorporated the coronavirus-infected pneumonia into a Class B infectious disease, and adopted measures for the prevention and control of Class A infectious diseases. In the face of this new infectious disease, exploring the morbidity characteristics of the susceptible factors related to the occurrence of the disease will help to early identify the risks and take corresponding preventive measures.

In the aftermath of the SARS epidemic, a lot of research on new coronavirus were carried out and gradually deepened our understanding. However, SARS-COV-2 that act as the third human pathogenic coronavirus, is significantly different from previous SARS-COV and MERS-COV on nucleic acid sequence [18]. Although belonging to the genus Coronavirus β, the transmission ability of SARS-COV-2 is significantly higher than SARS-COV and MERS-COV, and yet a large gap still remains in our knowledge regarding the cause[19]. Recently, much more asymptomatic carriers have been found on the Diamond Princess cruise ship in Japan, and we also observed that COVID-19 does not occur in all SARS-COV-2 infected persons, which suggests that individual genetic factors may affect the occurrence of disease [20]. At the time of the SARS epidemic in 2003, scholars in Hong Kong had found that individuals of blood group O were significantly less susceptible to SARS-COV than other blood groups, but only 42 patients were studied in the report[21]. Since then, no reports of the effect of ABO blood group on the pathogenicity of coronavirus have been found. In present paper, we analyzed the effect of ABO blood type on the occurrence of COVID-19 in 106 SARS-COV-2-positive people, and confirmed that individuals of different blood types resulting in completely different immunity to SARS-COV-2. Among the four blood types, carriers of type B antigens, including type B and type AB, have significantly better resistance to SARS-COV-2 than individuals with type A and type O blood. Regardless of the onset of COVID-19 patients or severe COVID-19 patients, the proportion of carriers of type B antigens was significantly lower than that of individuals of other blood types. More importantly, we have found that the risk of developing severe and critically conditions for type A antigen blood was significantly higher than that with other blood types in patients with COVID-19. In addition, the time during which the SARS-COV-2 nucleic acid of the patient turned negative also verified that the blood type A population has a higher susceptibility risk of SARS-

COV-2 infection, indicating that genetic factors have an important impact on the occurrence and development of the disease.

In the past 10 years, researches related to ABO blood group and virus infection have been frequently reported. For example, in a large-scale study on susceptibility factors of Chikungunya virus also confirmed that carriers of type A antigens are more sensitive than those of type O and B individuals[22]. Research on Norwalk virus infection found that individuals with type B antigens have better resistance to the virus, however it reported that individuals with type O blood are more susceptible which was different from our observation[23]. In addition, it was also found that type B antigens have a better protective effect on viral infections when exploring the susceptibility factors of norovirus[24]. These evidences have confirmed that ABO blood group antigens have a significant effect on virus infection, and some scholars have studied the mechanism of action [25, 26]. It has been reported that blood group antigens can be used as direct receptors or co-receptors for norovirus. Norovirus recognizes non-secretory blood group antigens through the capsid protein VP1, in which the nucleic acid sequence is different among subtypes of the virus. As well as the crystallographic studies have shown that there are significant differences in the VP1 recognition structure among subtypes, justly the differences that make the virus and blood group antigen recognizable[27]. In addition to Norovirus, rotavirus has also been found to recognize blood group antigen[14]. However, in SARS-COV-2 infection, whether the effect of ABO blood group antigen disease infection is also due to the virus recognizing different blood group antigens requires further research to confirm.

Conclusions

A significant effect of ABO blood group antigens on the occurrence of COVID-19 was reported in our study, and profoundly affect the outcome of infected cases. However, this was a retrospective study, and the number of cases included was limited which need more cases to be confirmed. Importantly, the influence of blood group antigens on the body's immunity still needs further research to better understand the pathophysiology of SARS-COV-2 infection.

Abbreviations

COVID-19: 2019 Coronavirus infectious diseases; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; COV: Coronavirus; ACE2: Angiotensin converting enzyme2; OR: Odds ratio.

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

Y-z.L designed the study and contributed to data interpretation. J. Z as lead investigators drafted the manuscript. Y-z.T, L.H, D. L, X-j.H, T. Y, H-h.L collected and analyzed field data. All authors have read the manuscript and provided final approval of the manuscript.

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Ethics approval and consent to participate

This study was a retrospective study and approved by the ethics committee of the affiliated Zhuzhou hospital Xiangya medical college(ref. 2020029). All clinical data used in this study were anonymized prior to analysis, and informed consent was waived.

Availability of data and materials

All data analyzed during this study were included in this published article.

Consent for publication

Not applicable.

Competing Interest

We have no conflict of interest.

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Tables

1 Criteria for COVID-19 diagnostic

:ondition	content
lemiological history:	a. Travel or residence history in Wuhan and surrounding areas, or other communities with case reports within 14 days before the onset of illness; b. Have a history of contact with a new coronavirus infection (positive nucleic acid test) within 14 days before onset;
	c. Contact with patients who have fever or respiratory symptoms from Wuhan and surrounding areas or communities with case reports within 14 days before the onset of illness;
	d. Cluster onset.
cal manifestation:	a. Fever and / or respiratory symptoms;
	b. With the imaging characteristics of pneumonia;
	c. The total number of white blood cells is normal or decreased in early onset, or the lymphocyte count is reduced.
ogical evidence	a. Real-time fluorescent PCR detection for New coronavirus positive in respiratory or blood specimens; b. Respiratory or blood specimens are genetically sequenced and find highly homologous to known new coronaviruses.

2 Basic situation of COVID-19 patients and asymptomatic carriers

	Male（%）	Minimum age (years)	Maximum age (years)	Median age (P_{25}, P_{75})
VID Group	42（52.5）	3	90	47.5(34.5, 64)*
mptomatic Group	10（38.5）	3	80	37(26.25, 49.5)
Total	51（50）	3	90	45(31, 58.75)

)33（contrast to Asymptomatic Group.

3 Distribution of blood types in patients with COVID-19 and asymptomatic carriers

	Type A（%）	Type B（%）	Type AB（%）	Type O（%）
VID Group	31（38.8）	16（20）	5（6.2）	28（35）
mptomatic Group	5（19.2）	13（50）	1（3.9）	7（26.9）
Total	36(34.0)	29(27.4)	6(5.6)	35(33.0)

4 Distribution of blood types in disease classification of patients with COVID19

Group	Type A（%）	Type B（%）	Type AB（%）	Type O（%）
non Patients	20（31.7）	16（25.4）	4（6.3）	23（36.5）
evere and ally Patients	11（64.7）	0（0）	1（5.9）	5（29.4）
Total	31	16	5	28