

The effect of ABO blood group on COVID-19 in pregnancy

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ABSTRACT

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Background: The COVID-19 virus has spread throughout the world and has been declared as a global pandemic by WHO. Some population groups are more susceptible to COVID-19, and one of them is pregnant women. Pregnancy increases risks of the COVID-19, especially thrombotic complications. The SARS-CoV-2 infection may vary widely from asymptomatic to severe infection. Some studies have shown that ABO blood group can be a marker of susceptibility to some disease progression.

Objective: This study aims to investigate relationships between the ABO blood group, the COVID-19 infection and its complications in pregnant women at Dr. Moewardi Hospital, Surakarta.

Methods: This study was an observational analytic study with a cross-sectional study design involving 40 pregnant women infected with COVID-19 at Dr. Moewardi Hospital, Surakarta. COVID-19 PCR swabs on the women were administered on their oropharynx and nasopharynx, and laboratory examination of the ABO blood group in all samples was performed. Comparative data distribution of blood groups in the population and the global population distribution were calculated by Chi Square Goodness of Fit. Comparative data between ABO blood group distributions, blood parameters and complications (respiratory, thrombotic, other infections, and death) were calculated by Chi square test and then by One-Way ANOVA. Next, correlation tests for the complications of the blood group and the ages applied a multinomial regression.

Results: There were significant differences of thrombotic complications on the blood group of pregnant women infected with COVID-19 ($p=0.027$). Blood type B significantly tended to experience thrombotic complications when compared to other blood groups ($p=0.022$).

Conclusion: The ABO blood group could affect the complication levels in the pregnant women infected with the COVID 19.

Latar Belakang: Infeksi virus COVID-19 telah menyebar ke seluruh dunia dan telah dinyatakan sebagai pandemi global oleh WHO. Beberapa kelompok populasi lebih rentan mengalami infeksi COVID-19, salah satunya adalah ibu hamil. Kehamilan semakin meningkatkan risiko COVID-19, terutama komplikasi trombotik. Infeksi SARS-CoV-2 secara klinis sangat bervariasi dari tanpa gejala hingga kondisi klinis yang parah. Beberapa penelitian menunjukkan bahwa golongan darah ABO dapat menjadi penanda kerentanan perkembangan penyakit.

Tujuan: Pada penelitian ini kami meneliti hubungan penggolongan darah ABO dengan infeksi COVID-19 dan komplikasinya pada ibu hamil di RSUD Dr Moewardi Surakarta.

Metode: Penelitian ini merupakan penelitian analitik observasional dengan rancangan studi cross-sectional yang melibatkan 40 pasien ibu hamil yang dicurigai terinfeksi COVID-19 di RSUD Dr. Moewardi, Surakarta. Dilakukan swab PCR COVID 19 pada orofaring dan nasopharing serta pemeriksaan laboratorium darah golongan darah ABO pada seluruh sampel. Data perbandingan distribusi golongan darah pada populasi penelitian dengan distribusi populasi global dihitung menggunakan Chi Square Goodness of Fit. Data perbandingan antara distribusi golongan darah ABO dengan parameter darah serta komplikasi (respiratorik, trombotik, infeksi lain, dan kematian) dihitung dengan uji Chi square untuk kategorik, dan kontinu dengan Kruskal Wallis dan One-Way ANOVA. Sedangkan uji korelasi komplikasi terhadap golongan darah dan umur menggunakan regresi multinomial.

Hasil: Terdapat perbedaan signifikan pada komplikasi trombotik terhadap golongan darah ibu hamil terinfeksi COVID-19 ($p=0,027$). Golongan darah B secara signifikan lebih sering mengalami komplikasi trombotik jika dibandingkan golongan darah lainnya ($p=0,022$).

Kesimpulan: Golongan darah ABO berpengaruh terhadap tingkat komplikasi yang ditimbulkan dari infeksi COVID 19 yang diderita oleh ibu hamil

INTRODUCTION

Coronavirus 2019, also known as COVID-19, is a variant of new coronavirus known as SARS-CoV-2. This disease was first discovered in Wuhan, Hubei Province, Republic of China in December 2019. Previously, diseases caused by Coronavirus (CVs) were included in SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East respiratory syndrome) that had been a threat to global health.^{1,2}

Currently the COVID-19 has spread throughout the world and has been declared as a global pandemic by WHO as it has significant impacts, especially on the respiratory system.³ COVID-19 pneumonia is characterized by generalized inflammation of endothelial cells that affects multiple organ systems and contributes to vascular thrombosis.³

Immunocompromised conditions, pregnant women, age and obesity were risk factors of the COVID-19.⁴ In addition, Black, Asian and Minority Ethnic (BAME) groups in the UK were at increased risks of complications from the COVID-19.⁵

Pregnant women are more susceptible to the COVID-19 than normal people. This is due to changes of physiological conditions of the pregnant women. These physiological changes include changes in respiratory, cardiovascular, blood coagulation and immune systems.⁶ Pregnant women have fewer maternal and neonatal effects in the COVID-19 than in the SARS and MERS.⁵ In China, 154 pregnant women were reported to be infected with the COVID-19 with a maternal morbidity rate of 1%, and without maternal deaths. In America, maternal morbidity rates were 4-10%, and there were no reported deaths of the pregnant women with COVID-19.⁷ This may be related to special immunological adaptation that develop in them. This immunological adaptation was physiological and was required to maintain tolerance for a foetus which is a semi-allograft entity.⁸ Activation of the immune system occurs because of an interaction of maternal immune cells with foetal trophoblast cells. This interaction causes a pro-inflammatory state that is dominated by T helper 1 (Th1) cells in the first and third trimesters of pregnancy. However, in the second trimester, the anti-inflammatory condition is dominated by T helper 2 (Th2) cells considering that pregnancy at this age is quite stable and the foetus is experiencing rapid development.⁹ This condition serves to protect the foetus, so the pregnant women tend to be more susceptible to viral infections.¹⁰ COVID-19 infection is often associated with cytokine storm condition. This condition is characterized by an increase in plasma concentrations of interleukin 2 (IL-2), IL-7, IL-10, granulocyte-colony stimulating factor, interferon--protein induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha and tumour necrosis factor (TNF- α).¹¹ Pregnant women in the first and third trimesters

are in a proinflammatory state, so the cytokine storm induced by COVID-19 infection can cause severe inflammatory state in them.¹² Pregnancy also increases risks of thrombotic complications associated with the COVID-19 infection. These complications are often associated with blood groups. People with blood type O have biological activities and low circulating concentrations of von Willebrand factor, a protein that carries coagulation factor VIII which is important for blood clotting; therefore, the risk of thromboembolic disease was lower.

The ABO blood group system by Karl Landsteiner classifies blood groups based on the presence of A and B antigens on the surface of red blood cells.⁵ An individual with A antigen has blood type A; an individual with B antigen has blood group B; an individual with A and B antigens has blood type AB; and an individual with blood type O do not have antigens. Blood type A has antibodies against antigen B (anti-B); blood type B has anti-A; blood type AB has neither anti-A nor anti-B; and type blood O has anti-A and anti-B antibodies. Since the ABO blood group system has been discovered, some studies have investigated the relationship between the ABO blood group system and disease incidence.⁵ From some of these studies, it was found that there was a relationship between ABO blood type and risks of developing acute diseases to become severe. There was also an association between ABO blood type and the respiratory syndrome known as SARS, which is caused by SARS-CoV-1 infection and associated with the severity and complications of the disease.

Some genetic factors affect an individual's susceptibility of the COVID-19. One of the genes that play a role is the gene that codes for the presence of ABO antigens in erythrocytes. Susceptibility to certain viral infections was often associated with ABO blood group antigens. Cheng et al. reported an association of SARS-CoV infection with the ABO blood group system, in which individuals with blood type O were less likely to be infected than individuals with other blood types. Data from Wuhan, China

also showed a link between the ABO blood type and the incidence of the COVID-19 infection.¹³ A study conducted by Zhao et al. compared the ABO blood group of the global population and 2173 patients of COVID-19 from three hospitals in Wuhan. Its results obtained that blood type A was associated with a higher risk of COVID-19 ($P=0.027$) than other blood types, while blood type O was associated with a very low risk of COVID 19 ($P<0.001$) compared with blood groups other than O 11. Another study on 1550 patients of COVID-19 conducted in Presbyterian, New York also found similar results.¹⁴

The study of Zhao et al. also stated that blood type A had a higher risk of death than blood type O (OR=1.482; $P=0.008$), and blood type O had a lower risk of death than other blood types (OR=0.660; $P=0.014$).¹¹ Zietz & amp, Tatonetti said that this relationship only applies to positive Rhesus blood types. However, the association with this blood type has not excluded other risk factors such as obesity, diabetes mellitus and other comorbid diseases.¹⁵ Based on discussion above, this study focuses on effects of the ABO blood type on the severity of COVID 19 in pregnant women. In this study, the authors specifically examine the pregnant women, and it is a novelty because some previous studies focus on COVID-19 patients who are not pregnant. so that we can further study the effect of ABO blood group on pregnant and non-pregnant with COVID-19 infection.

METHODS

Study design

This study was an observational analytic study with a cross-sectional study design involving 40 pregnant women infected with COVID-19 at Dr. Moewardi Hospital, Surakarta, Central Java, as a main referral hospital for pregnant women with COVID-19. This study was conducted from March to May 2021. The dependent variable in this study was pregnant women with COVID-19, and the independent variable was the ABO blood group.

Research subject

The subjects of this study were all pregnant women with suspected symptoms of COVID-19 who were hospitalized at Dr Moewardi Hospital Surakarta. Nasopharyngeal and oropharyngeal swabs were administered for them, and laboratory tests for the ABO blood group were performed.

The inclusion criteria of this study were pregnant women with COVID-19 symptoms and were confirmed with the COVID-19 infection with positive PCR swab results. Then, its exclusion criteria were the patients with underlying diseases related to blood type, thalassemia. The number of samples calculated by a Lameshow formula obtained 40 samples.

Data measurement

The ABO blood group system was used to indicate the presence of A and B antigens in erythrocytes. This blood group system is the most important of the 36 currently recognized blood group classification systems. Determination of the patient's blood group used blood laboratory tests. The blood laboratory examination was conducted by taking venous blood samples from the median cubital vein, and then they were examined at the Clinical Pathology Laboratory, Dr. Moewardi Hospital, Surakarta. To detect the status of the COVID-19, nasopharyngeal and oropharyngeal swabs of RT-PCR were conducted at the Clinical Pathology Laboratory, Dr. Moewardi Hospital.

Statistical analysis

The obtained data were analysed by univariate, bivariate and multivariate statistics using IBM-SPSS version 25. Comparison of distributions of the blood group in this

studied population and the global population distribution was calculated by using Chi Square Goodness of Fit. Categorical variables included respiratory complications, thrombotic complications and other infections; the blood group variables were tested by using the Chi Square Likelihood Ratio. Meanwhile, relationships between continuous variables (age, lymphocytes, neutrophils, NLR, Hb, leukocytes, platelets, D-Dimer, respiratory complications, thrombotic complications, other infections, death) and the blood type were tested by using One-Way ANOVA test for normally distributed data and Kruskal-Wallis test for abnormally distributed data. The correlation between respiratory complications, thrombotic complications, other infections, blood type distributions and ages were tested by using Multinomial logistic regression.

Ethical clearance

This study was approved by Health Research Ethics Committee of dr. Moewardi Hospital, Surakarta, Central Java with No. 344/III/HREC/2021.

RESULTS

In this study, there were 40 pregnant women who met the inclusion and exclusion criteria, which were then analysed. Table 1 demonstrated the comparison of the blood group distributions in the studied population and in the global population. Based on the Chi square Goodness of Fit Test, there was no a significant difference in the distributions of the blood group in the studied population and in the global population. There was a high percentage in groups A and B, but the results were not significant.

Table 1. Comparison of blood group distributions in the studied population and in the global population

Group	COVID positive (%)	Global population (%)	OR (95% CI)	Global p value
A	8 (20.5%)	78,402 (43.0%)	1.56 (0.76, 1.24)	0.556
AB	2 (6.8%)	4,652 (2.6%)	0.05 (0.95, 123.41)	
B	9 (22.7%)	11,725 (6.4%)	1.96 (0.66, 3.04)	
O	21 (50%)	87,605 (48.0%)	0.82 (0.99, 1.92)	

Table 2 portrayed the relationships between continuous variables (age, lymphocytes, neutrophils, NLR, Hb, leukocytes, platelets, and D-Dimer) and the blood types. Meanwhile, table 3 described the categorical variables (respiratory complications, thrombotic complications, other infections). The distributions according to the

ages, the number of lymphocytes, neutrophils, NLR, Hb, leukocytes, platelets and D-dimer did not show statistically significant results. A significant relationship could be observed in the thrombotic complications with the blood group of the pregnant women with p value = 0.027 (Table 3).

Table 2. Characteristics of the subjects

Variable	Blood type A	Blood type AB	Blood type B	Blood type O	p value
Age (year)	28.56 (±5.525)	28.67 (±1.528)	30.20 (±5.959)	28.45 (±6.131)	0.881 ^a
Lymphocyte (/μl)	1360.578 (±711.2675)	1605.567 (±388.5427)	1784.294 (±557.7994)	1444.145 (±1416.000)	0.358 ^a
Neutrophil (/μl)	9031.556 (±3365.4186)	7206.700 (±3576.3187)	10393.214 (±5669.5383)	9407.127 (±4058.5472)	0.686 ^b
NLR	7.84236049 (±4.396855570)	4.92726087 (±3.440792272)	6.84170791 (±5.452773404)	7.37113889 (±4.268101707)	0.469 ^b
Hb (mg/dL)	11.622 (±1.1904)	10.967 (±0.3512)	30.800 (±60.5121)	10.850 (±1.4774)	0.176 ^b
Leukocytes (/μl)	10977.78 (±3676.200)	9300.00 (±3269.557)	13060.00 (±5570.797)	11659.09 (±4571.720)	0.628 ^b
Platelets (/μl)	274.22 (±81.510)	246.67 (41.187)	241.90 (±109.817)	236.82 (±74.572)	0.729 ^a
D-dimer (μg)	1504.67 (±432.049)	3026.67 (±2427.804)	2222.60 (±872.486)	2146.91 (±1209.079)	0.259 ^b

a One-Way ANOVA test mean data (standard deviation)

b Kruskal-Wallis test mean data (standard deviation)

Table 3. The relationship between complications and blood types

Variable	Blood type A (%)	Blood type AB (%)	Blood type B (%)	Blood type O (%)	p value
Respiratory complications (use of ventilation devices)					
Yes	2 (22.2%)	1 (33.3%)	2 (20.0%)	5 (22.7%)	0.974
no	7 (77.8%)	2 (66.7%)	8 (80.0%)	17(77.3%)	
Thrombotic complications					
Yes (D-Dimer >500)	1 (11.1%)	1 (33.3%)	7 (70.0%)	5 (22.7%)	0.027
No (D-Dimer <500)	8 (88.9%)	2 (66.7%)	3 (30.0%)	17 (77.3%)	
Other infections (premature rupture of membranes)					
Yes	3 (33.3%)	0 (0.0%)	2 (20.0%)	2 (9.1%)	0.297
No	6 (66.7%)	3 (100.0%)	8 (80.0%)	20 (90.0%)	
Death					
Yes	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0.385
No	9 (100.0%)	3 (100.0%)	9 (90.0%)	22 (0.0%)	

Table 4. Risks of complication types based on the blood types

Respiratory					
Variable	Age (year)	Blood type A	Blood type B	Blood type AB	Blood type O
OR	0.996 (0.776-1.278)	Ref	0.812 (0.087-7.533)	1.763 (0.096-32.424)	1.037 (0.158-6.805)
P value	0.976		0.854	0.703	0.97
Thrombotic					
Variable	Age (year)	Blood type A	Blood type B	Blood type AB	Blood type O
OR	0.996 (0.876-1.209)	Ref	18.268 (1.521-219.437)	4.018 (1.176-133.103)	2.371 (0.235-23.900)
P value	0.973		0.022	0.392	0.464
Other infections					
Variable	Age (year)	Blood type A	Blood type B	Blood type AB	Blood type O
OR	1.071 (0.903-1.269)	Ref	0.392 (0.044-3.503)	0.289 (0.33-2.503)	1.031 (0.878-1.210)
P value	0.433		0.402	0.26	0.71

Table 4 illustrated the risks of developing respiratory, thrombotic and other complications based on the distributions of the blood types and the ages. There was no a significant relationship between the complications, the ages and the blood types, except for the thrombotic complications for blood type B as it had a significant relationship. Pregnant women with blood type B had 18 times greater risks of experiencing thrombotic complications if infected with the COVID-19 [OR 18.268 (1.521-219.437); $p = 0.022$]. The level of denominator (blood type A) was known as a reference level (Ref).

DISCUSSION

In this study, there were no significant results on the overall blood parameters with the blood groups of pregnant women infected with the COVID-19. Respiratory complications, other infections and death also did not show a significant relationship with the blood types of the pregnant women. However, there was a significant difference between the significant thrombotic complications of the blood group of the pregnant women infected with COVID-19 ($p=0.027$). Blood type B was significantly more likely to experience thrombotic complications

when compared to other blood groups ($p=0.022$).

Coronavirus Disease (COVID-19) is now a main concern of the world because it has the potential to be fatal to global public health.² The respiratory system is a system that indicates the most common manifestation of the COVID-19 because it is in accordance with the route of its transmission, through inhalation of the virus through the respiratory tract. Some retrospective studies have reported pulmonary manifestations in patients with COVID-19, including cough, shortness of breath, sputum production, more severe respiratory failure and ARDS. Cough and fever are the most dominant symptoms, and these symptoms lead to severe pneumonia.¹⁶

The COVID 19 not only has pulmonary manifestations but also has haematological manifestations, such as coagulation disorders or coagulability. The prothrombotic state may be caused by endothelial damage and activation of the coagulation cascade and is likely to contribute to the thromboembolic phenomenon. This coagulopathy is associated with decreased PT, increased D-dimer and aPTT. The COVID-19 is usually associated with the increased D-Dimer.¹⁷ Thus, the increase of D-Dimer also causes increased risks of blood clotting diseases such as pulmonary embolism and deep vein

thrombosis. The majority of D-Dimer values in patients with SARS-CoV-2 is usually above the normal limit (>500 ng/ml) although there is no potential of thrombotic complications. Therefore, the use of the D-Dimer cut-off that has been studied (>2903 ng/ml) can be a limiting value of whether a patient with a certain D-Dimer value will lead to thrombotic complications or not.¹⁸ In pregnant women, prothrombic factors also play an important role related to changes in the physiological condition of them.

The ABO blood group system explains the phenomenon of agglutination in erythrocytes. There is substantial evidence by experimental analysis supporting the association between the ABO blood group, susceptibility and resistance to infectious and communicable diseases. For example, natural antibodies to antigen A had been shown to have protective factors against certain infections, and blood type O also had protective factors for severe malaria infections.^{19,20}

The influence of the ABO blood group on the COVID-19 included the following. Firstly, the blood type was affected by sugar molecules, and the surface of the COVID-19 had proteins binding sugar molecules. Meanwhile, the surface of erythrocytes in blood type A had an additional sugar molecule, namely N-acetyl galactosamine which was not present in blood type O.¹⁵ Secondly, the adhesion of the Spike protein to the COVID-19 with the ACE2 receptor on the surface of the host cell could be inhibited by the presence of antibodies against the A antigens belonging to the blood type B and O. However, the blood type AB which did not have Anti-A antibodies did not susceptible of the COVID-19 infection.¹⁰

The COVID-19 virus replicates in the respiratory and gastrointestinal epithelium.²¹ This virus can synthesize Glycan A or B antigens, depending on the phenotype. If the S protein from blood type A, B, or AB carries glycan antigens, each of these antigens will bind to other antibodies and block the interaction of the S protein with the ACE2 protein to be a protective factor against the COVID-19.²² Thus, transmission of a viral infection can be predicted according to the ABO blood system. For example, a viral

infection that occurs in an individual with blood type B will carry the B antigen and have a greater risk of infecting a person with blood type B or AB, compared to blood type A or O. This can also explain the low incidence of infection in the blood type B. Blood type O has A and B antibodies.²³

A recent study that had documented the association between the ABO blood group and the COVID-19 susceptibility concluded that individuals with blood type O were at lower risks for the COVID 19 infection. This was because the virus replicated in epithelial cells in the respiratory and gastrointestinal tracts. This virus had the ability to synthesize the carbohydrate epitope ABH (the H antigen was found in blood type O), so that the S virion protein could bind to the carbohydrate epitope A or B.^{19,24}

In this study, a significant correlation was found for differences in blood group with thrombotic complications. The pregnant women with blood type B (22.7%) had a greater risk of thrombotic complications with an OR of 18.268 (1.521-219.437). This is in line with a study by Marcos et al. (2020) showing that the women with blood type B infected with SARS-CoV-2 had a higher incidence of thrombotic complications than other blood groups²⁶. There are no other studies that have found a relationship between the blood type B and greater thrombotic complications in COVID-19 patients. In this study, the authors found that there were some differences of the ABO blood group effects on the covid 19 infection in pregnant and non-pregnant women. In the pregnant women, there were no significant effects of the ABO blood group on respiratory or infectious complications.

CONCLUSION

The ABO blood group could affect the complication levels caused by the COVID 19 infection in pregnant women. There was a significant relationship between the ABO blood group, especially in the B blood type at thrombotic complications.

CONFLICT OF INTEREST

The author declared that there was no conflict

of interest related to the process and the writing of this study.

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