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COVID-19 patients with blood group A have a higher risk of becoming severe cases compared to non-A blood groups

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** The risk factors associated with COVID-19 disease severity are still being investigated. Individual susceptibility to viral infections has been known to be associated with the ABO blood group.
Objectives. This study aims to determine the association between the ABO blood group and disease severity in COVID-19.
Material and methods. This is an observational study with a prospective design. Patients were followed during treatment, and clinical outcomes were recorded, being severe or mild-moderate cases. A total of 207 confirmed COVID-19 patients who underwent treatment from November 2020 to January 2021 were included in this study. Chi-square analysis was used to determine the association between blood group A and other blood groups with the occurrence of severe cases. Multiple logistic regression analysis was used to obtain the adjusted odds ratio (OR) and determine the effect of confounding variables.
Results. We found a significant association between blood group A and disease severity, though not for any other blood group. By using multiple logistic regression analysis, blood group A was independently associated with disease severity with an adjusted OR (95% confidence interval (CI)) of 2.36 (1.07–5.23) (p = 0.034).
Conclusions. COVID-19 patients with blood group A have a higher risk of becoming severe cases compared to non-A blood groups.
Key words: blood group antigens, COVID-19, patients.

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Background

Coronavirus disease 2019 (COVID-19) has become a global health problem. The increasing number of infections and deaths due to the COVID-19 pandemic causes anxiety in each individual [1]. Various risk factors have been identified associated with disease severity in COVID-19 patients, including old age, male gender and the presence of comorbidities [2]. Individual susceptibility to viral infections such as Hepatitis B, Hepatitis C, West Nile and Norwalk viruses have been known to be associated with the ABO blood group [3–6]. Blood group antigens can also function as receptors in infections by some microorganisms, parasites and viruses [7]. Studies by Fujitani et al. have found that antigens in the blood group system are not only expressed on the surface of erythrocytes but also on epithelial cells in the alveolar [8]. Other investigations have shown that the ABO blood group is associated with plasma angiotensin-converting enzyme (ACE) activity [9].

The association between the ABO blood group and COVID-19 has been shown by several studies. A person with blood group O was reported to have a lower risk of being infected with the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [10]. A study by Fan et al. found that the ABO blood group is associated with SARS-Cov-2, i.e. blood group A has a higher susceptibility [11]. However, whether the ABO blood group is associated with disease severity in COVID-19 patients is not well known. More aggressive treatment is needed in patients with certain blood groups who are more at risk of developing severe cases in order to reduce mortality.

Objectives

This study aims to determine the association between the ABO blood group and disease severity in patients with COVID-19.

Material and methods

Study design and samples

This is an observational study with a prospective design. COVID-19 patients who were treated at the Udayana University Hospital, Bali, Indonesia, from November 2020 to January 2021 were included in this study. The sample in this study was obtained by the consecutive sampling method. Patients were diagnosed with COVID-19 based on examination of nasopharyngeal swab samples with the real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) method. Patients over 18 years of age were included in this study. Patients who experienced clinical deterioration or died during treatment caused by conditions unrelated to COVID-19 progress, such as haemorrhagic stroke, were excluded from this study. A total of 207 patients were included in this study.

Instruments and procedures

The patient's ABO blood group was determined by standard examination methods performed for clinical purposes, such as blood transfusions. The Roche Diagnostic Cobas 6800 SARS-CoV-2 test, Basel, Switzerland, was used for examination of nasopharyngeal swab samples. Demographic, clinical, laboratory and blood group data was obtained when the patient was

admitted to hospital. A follow-up was performed while the patient was hospitalised, and clinical outcomes (severe or mild-moderate cases) were recorded.

The blood group was transformed into dichotomous variables, blood group A and non-A blood group, as well as blood groups B, AB and O. The case severity was divided into severe and mild-moderate cases based on World Health Organization (WHO) criteria. The criteria for severe cases included patients with fever or symptoms of respiratory tract infection plus one of the following conditions: respiration rate > 30 breaths/minute, signs of respiratory distress or oxygen saturation in room air ≤ 90% [12]. This condition was not found in mild-moderate cases.

Data analysis

Categorical variables are presented as percentages, while continuous variables are presented in the median and interquartile range. To compare a continuous variable, we used the Mann-Whitney U-test, while to compare a categorical variable, we used chi-square analysis. We calculated the odds ratio (OR) with a 95% confidence interval (CI) to determine the association between blood group A and other blood groups with the occurrence of severe cases in COVID-19. Multiple logistic regression analysis was used to obtain the adjusted OR and determine the effect of confounding variables such as age and comorbidity. All statistical analyses were performed using SPSS version 25.0 software. The value obtained was statistically significant if $p < 0.05$.

Ethical considerations

This study received approval from the Ethics Committee of the Faculty of Medicine, Udayana University (number of approval: 1010/UN1422.VII.14/LT/ 2020).

Results

The median age of the patients was 51 years of age, and 59.9% were male. Diabetes was the most common comorbidity in patients (15.5%). The majority of the patient's blood group was blood group O (42.5%), as shown in Table 1.

Table 1. Demographic, comorbidity and blood group characteristics

Variable	All patients (*n* = 207)
Age, years, median (interquartile range)	51 (18 – 84)
Gender (%)	
male	124 (59.9)
female	83 (40.1)
Comorbidity (%)	
without comorbidity	125 (60.4)
hypertension	26 (12.6)
diabetes	32 (15.5)
congestive heart failure	9 (4.3)
coronary artery disease	9 (4.3)
asthma	4 (1.9)
chronic kidney disease	2 (1.0)
Blood group (%)	
A	41 (19.8)
B	67 (32.4)
AB	11 (5.3)
O	88 (42.5)

Table 2 shows that there was a significant association between age and the presence of comorbidities with case severity in COVID-19 patients ($p < 0.001$). There was a significant association between blood group A and case severity ($p = 0.016$), but this association was not found for blood groups B, AB and O.

The OR for blood group A to the occurrence of severe cases was 2.55 (95% CI: 1.23–5.27) ($p = 0.010$). By including the age and comorbidity variables in the multiple logistic regression analysis, blood group A was independently associated with the occurrence of severe cases with an adjusted OR of 2.36 (95% CI: 1.07 – 5.23) ($p = 0.034$) (Table 3).

Table 2. Association between age, gender, presence of comorbidities and blood group with disease severity in COVID-19 patients

Variable	Mild – Moderate (*n* = 103)	Severe (*n* = 104)	*p*
Age, years, median (interquartile range)	43 (18 – 75)	54.5 (19 – 84)	< 0.001
Gender, *n* (%)			
male	55 (53.4)	69 (66.3)	0.079
female	48 (46.6)	35 (33.7)	
Comorbidities, *n* (%)			
yes	24 (23.3)	58 (55.8)	< 0.001
no	79 (76.7)	46 (44.2)	
Blood group, *n* (%)			
A	13 (12.6)	28 (26.9)	0.016
non-A	90 (87.4)	76 (73.1)	
Blood group, *n* (%)			
B	38 (36.9)	29 (27.9)	0.216
non-B	65 (63.1)	75 (72.1)	
Blood group, *n* (%)			
AB	6 (5.8)	5 (4.8)	0.987
non-AB	97 (94.2)	99 (95.2)	
Blood Group, *n* (%)			
O	46 (44.7)	42 (40.4)	0.630
non-O	57 (55.3)	62 (59.6)	

Table 3. Odds ratio and adjusted odds ratio of blood group A, age and comorbidities

Variable	Odds ratio (95% CI)	*p*	Adjusted odds ratio (95% CI)	*p*
Blood group A	2.55 (1.23 – 5.27)	0.010	2.36 (1.07 – 5.23)	0.034
Age	5.26 (2.78 – 9.97)	< 0.001	3.54 (1.78 – 7.05)	< 0.001
Comorbidities	4.15 (2.28 – 7.55)	< 0.001	4.37 (2.23 – 8.55)	< 0.001

Discussion

Our study found that patients with blood group A had a higher risk of developing a severe case compared to patients with non-A blood groups. This finding is in accordance with a meta-analysis study by Wu et al. which found that patients with blood group A are more susceptible to COVID-19 infection [13]. Patients with blood group A are also more at risk of becoming critical cases compared to other blood groups [14, 15]. Several studies can theoretically explain this finding, although further study is needed to prove this. Studies by Guillon et al. found that the anti-A antibody can inhibit the adhesion of the spike protein of SARS-CoV to the angiotensin-converting enzyme 2 (ACE2) receptor, thus inhibiting the invasion of the virus into the cell [16]. Anti-A antibodies may play the same role in COVID-19 as there are similarities between SARS-CoV and SARS-CoV-2, both of which bind to ACE2 receptors [17, 18]. The two viruses also have similar nucleic acid sequences [19]. Another study found that A-antigen can prevent the enzymatic breakdown of the intercellular cell adhesion molecule 1 (ICAM1) and P-selectin in the endothelium. These molecules can stimulate the strong binding of leukocytes in the vascular wall. Furthermore, activated leukocytes can form aggregates and attract more adhesion molecules attached to the vascular wall that increase the incidence of thrombosis and also inflammation [20].

In this study, we did not find a significant association between blood group O and disease severity. These results differ from previous studies which found that individuals with blood group O had a lower susceptibility to SARS-CoV-2 infection [21, 22]. This result is also different from the study by Leaf et al., which found that patients with blood group O have a lower risk of becoming critical cases [15]. This difference may be due to differences in sample sizes.

Although it is too early to implement these findings into official guidelines, based on these findings, it can, however, be suggested that COVID-19 patients with blood group A may need more aggressive therapy to prevent severe cases. This study has limitations, including: a single centre study with a relatively small sample size.

Conclusions

Patients with blood group A have a higher risk of becoming severe cases compared to other blood groups. Further multicentre studies, as well as studies that can explain the association between blood groups and SARS-CoV-2 infection, are needed to confirm the existing findings.

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