Pharmaceutical Sciences Asia

Pharm Sci Asia 2023; 50(3), 204-210

DOI:10.29090/psa.2023.03.22.331

Research Article

# ABO blood group and effectiveness of tocilizumab in clinical response to COVID-19: A single center, retrospective study

Izza Aulia Rizqika Nasution[1], Retnosari Andrajati[1,2*], Nadia Farhanah Syafhan[1,2], Rania Imaniar[2]

[1] Graduate Program, Division of Clinical Pharmacy, Faculty of Pharmacy, Universitas Indonesia, Depok, West Java, Indonesia
[2] Universitas Indonesia Hospital, Jl. Prof. DR. Bahder Djohan, Pondok Cina, Beji, Depok, West Java, Indonesia

## ABSTRACT

As an anticytokine therapy, tocilizumab has been recommended for the management therapy in patients with severe and serious COVID-19 cases. The association between the severity of COVID-19 and blood groups has been the subject of prior research. Therefore, it is important to analyze the relationship between blood types and the effectiveness of tocilizumab (TCZ) therapy in COVID-19 patients. This research involved 68 patients diagnosed with severe and critical COVID-19 receiving Tocilizumab (TCZ) therapy at Universitas Indonesia Hospital. Blood type O was associated with a significantly improvement in CRP levels ($P$=0.014) and has better favorable outcomes compared to other blood type in terms of WHO Clinical Progression Scale (OR: 1.254, 95% CI: 0.457-3.443; $P$=0.797), length of stay (OR: 5,333, 95% CI: 0.495-3,734; $P$=0.614), and improvement in CRP levels (OR: 5,333, 95% CI: 1.385-20,541; $P$=0.014).

**Keywords:**
Blood Types, COVID-19, Interleukin-6 Inhibitors, SARS-CoV-2, Tocilizumab

## 1. INTRODUCTION

People all around the world have been affected significantly by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The prognosis in elderly with comorbidities like diabetes, lung disease, liver injury, or cardiovascular disease often lead to poor clinical outcomes, which has a significant impact on morbidity and mortality rates. Data on comorbidities that potentially make patients more susceptible to COVID-19 infection must be analyzed in order to identify potential risk factors for the onset and severity of symptoms in SARS-CoV-2 patients[1].

Many disease processes, including malignancy venous and arterial thromboembolism have been linked to blood type as a risk factor. Nonetheless, correlations with viral disorders have received the greatest attention. Blood group antigens contribute to infection directly through a number of methods. They can act as coreceptors and receptors for pathogens at the molecular level, and they can also promote viral particle absorption inside cells[2].

Certain blood group antigens have been implicated as disease susceptibility markers. For example, HBGA (Histo-blood group antigen), which is regulated by the gene FUT2, is regarded as a sign for susceptibility. In FUT2, A gene that expresses the alpha-1, 2-L-fucosyltransferase enzyme also causes the expression of HBGA in the gut, which contributes to the composition of the phenotypical profile found in various groups with particular histories.

It is a product of evolution and serves as a genetic population marker. It is discovered to have an association with many disease. Its function is known to be inhibited and diminished by polymorphic mutations, which are population-specific. It is necessary to have a thorough understanding of its role in the development and prevention of numerous diseases. Due to its link to respiratory illnesses and the ABO blood group, FUT2 may also play a role in the COVID-19 case as a susceptibility sign[3].

ABO and FUT2 are polymorphic genes and epithelial

***Corresponding author:**
*Retnosari Andrajati Email: andrajati@farmasi.ui.ac.id

cells in association with the environment frequently contain their products. They are most highly expressed in mucins, which are located in the body's exposed surfaces including the lungs and the gastrointestinal system and are assumed to play a protective role in binding to bacteria. These characteristics imply that ABO antigens may play a role in the interaction with pathogens. Carbohydrates are widely distributed on the surfaces of cells and have a variety of structural variations, making them important molecules with potential for cell recognition. In fact, pathogenic microbes and toxins may need to attach to particular carbohydrate antigens in order to cause infection and illness. It has been thoroughly researched and reviewed how ABO polymorphism and infectious illness are related. For example, associations with West Nile Virus, HIV, hepatitis B, malaria. As a result, it has been suggested that the ABO polymorphism is an adaptive characteristic that may limit the transmission of illnesses within a particular species[4]

Human pre-immune serum containing anti-A or anti-B antibodies partially neutralized the viruses produced in A- or B-type cells in a complement-dependent manner, but not the viruses produced in type O cells. Moreover, type O plasma and anti-A monoclonal antibodies prevented transfected CHO cells from adhering to Vero cells expressing ACE2 and co-expressing the A antigen and the Spike (S) protein of SARS-CoV[5].

A systematic review and meta-analyses study conducted by Liu et al. Collected 715 articles taken from seven databases. Ten articles were selected for meta-analysis after going through two levels of screenings. Overall, individuals with blood groups A (OR=1.33; CI=95% 1.14-1.56) and B (OR=1.06, 95% CI 1.00 to 1.13) have a higher risk of developing much higher infection of COVID-19, blood type AB (OR=1.07, 95% CI 0.88-1.30) and blood type O (OR=0.71, 95% CI 0.60 to 0, 84) that are not susceptible to unfavorable outcome. This study showed the results that patients with blood type A were associated with a significantly increased risk of death by COVID-19 infections (OR=1.25, 95% CI 1.02-1.52). Conclusions from this study indicate that blood groups A and B can be risk factors for the incidence of COVID-19 infection, while blood group O is protective, while blood group A is associated with poor clinical outcomes[6].

Another Systematic-review and Meta-analyses study collected publications through several databases such as PubMed, Google Scholar, Scopus, and EMBASE from January 1 to March 21 2021, 16 relevant papers were found and included in final analysis. For blood groups A, O, B, and AB, the respective incidence rates (95% CI) were 0.459 (95% CI: 0.358-0.441), 0.342 (95% CI: 0.298-0.374), 0.180 (95% CI: 0.150-0.214), and 0.076 (95% CI: 0.055-0.127). This study shows that individuals with blood group A > O > B > AB have a higher rate of COVID-19 infection. The overall statistical significance of the susceptibility of the ABO blood group to COVID-19 infection was 0.001 (significantly different). This study shows the results, that susceptibility of individuals with blood type A to COVID-19 infection is higher compared to patients with blood type AB who have a lower risk of infection with COVID-19[7].

In patients with severe SARS-CoV-2 infection, hypoxia, shock, multiorgan failure, acute respiratory distress syndrome (ARDS), and mild respiratory failure were a few indicators of major complications. The clinical signs and symptoms of COVID-19 could be brought on by cytokine release syndrome (CRS), for example. Overproduction of inflammatory cytokines is the cause of CRS. TCZ as an IL-6 receptor antagonist, which has been approved by the US Food and Drug Administration, is one of the therapies associated with CRS in COVID-19 patients[8] and has the potential to improve clinical outcomes and reduce mortality. Anti-cytokine therapies have been suggested as a COVID-19 treatment to increase potential outcomes in patients with severe and critical COVID-19[9]. Prior research has highlighted concerns about its population-level effectiveness and safety, nevertheless.

There has never been research on the effectiveness of anti-IL-6 medication, TCZ in COVID-19 patients, or the association between blood type variations to COVID-19, particularly in Indonesia. As a result, it's crucial to evaluate the associations between blood types and effectiveness of TCZ therapy in COVID-19.

## 2. MATERIALS AND METHODS

This research has received ethical clearance approval from Research Ethics Committee of Universitas Indonesia Hospital Number S-027/KETLIT/RSUI/VII/2022. This is an observational study with cross-sectional design. Data collection was carried out retrospectively using medical records of Covid-19 patients at Universitas Indonesia Hospital in 2020-2021. Patients who were confirmed positive for COVID-19 with Tocilizumab therapy were included in this study. Patient's history, clinical findings, diagnostic test results, patient's progress and medication were reviewed. Patients under 18 years old, incomplete medical record data, and referred to other hospitals were excluded. There were 68 COVID-19 patients who received Tocilizumab therapy at Universitas Indonesia Hospital and met the inclusion and exclusion criteria in this study. The sampling technique used was total sampling, nall patients who met the inclusion criteria were include as research samples. Chi-square test was used to analyze the relationship between the relationship of blood groups and effectiveness of TCZ based on WHO Clinical Progression Scale, CRP and Length of Stay.

## 3. RESULTS

A total of 2,338 medical data patients with confirmed COVID-19 in 2020-2021 were analyzed for this research. TCZ was administered to 72 patients, and 68 of them met the requirements for inclusion. A total of 30 (44.1%) patients survived, while 38 (55.9%) passed away.

TCZ was administered in 68 COVID-19 patients, 28 (41.2%) were females and 40 (58.8%) were males. The proportion of adult patients between the ages of 18-59 were 44 patients (64.7%), while the proportion of patients over 60 were 24 patients (35.3%). Patients with blood type A, B, AB, and O were 16 (23.5%), 23 (33.8%), 6 (8.8%), and 23 (33.8%) patients, respectively.14 patients (20.6%) were comorbid free, 12 patients (17.6%) had one comorbidities, and 42 (60.3%) patients had more than one comorbidities. According to Table 1, the most prevalent comorbidity is hypertension 32 patients (47.1%), followed by diabetes mellitus, which affects 25 patients (36.8%), CVD 12 patients (17.6%), Kidney disease 9 patients (13.2%), Obesity 20 patients (29.4%), and others comorbidities 32 patients (47.1%) such as asthma, pneumonia, dyspepsia, anemia, and gartritis. According to Table 1, Remdesivir is the most frequently used therapy for COVID-19 patients in this study, had been used in 47 patients (69.1%). Corticosteroid therapy was used in 36 patients (52.9%), Levofloxacin in 33 patients (48.5%), Ceftriaxone in 21 patients (30.9%), Azithromycin in 11 patients (16.2%). According to the WHO Clinical Progression Scale, 30 patients (44.1%) shows improvement after receiving TCZ medication, while 38 patients (55.9%) shows no improvement. According to laboratory tests of CRP (C-Reactive Protein), 45 patients (66.2%) shows improvement, while 23 patients (33.8%) shows no improvement. According to the Length of Stay (LOS), 33 patients (48.5%) had LOS more than 20 days, while 35 patients (51.5%) less than 20 days.

Based on Table 2, the effectiveness of TCZ therapy is 1.364 times in blood type A (OR: 1.364, 95% CI: 0.443-4.195; *P*=0.774), 0.735 times in blood type B (OR: 0.735, 95% CI: 0.264-2.041; *P*=0.613), 0.607 times in patients with blood type AB (OR: 0.607, 95% CI: 0.103-3.563; *P*=0.687) and 1.254 times in patients with blood type O (OR: 1.254, 95% CI: 0.457-3.443; *P*=0.797). Compared with other blood types in improving clinical outcomes based on the WHO Clinical Progression Scale, there is no significant relationship between each blood type and the WHO Clinical Progression Scale.

Based on Table 3, the effectiveness of TCZ treatment reaches 1.165 in patients with blood type A (OR: 1.165, 95% CI: 0.350-3,873; *P*=1,000), 0.703 in patients with blood type B (OR: 0.703, 95% CI: 0.246-2005; *P*= 0.591), 3.647 in patients with blood type AB (OR: 3,647, 95% CI: 2,433-5,468; *P*=0.001) and 5.333 in patients with blood type O (OR: 5,333, 95% CI: 1.385-20,541; *P*=0.014). Compared with another blood type in improving clinical outcomes based on CRP levels, there is a significant relationship between blood types AB and O in the improvement of CRP levels. Prior observational study demonstrates a strong correlation between the elevation in IL-6 and the use of invasive mechanical ventilation (IMV) in patients with severe and serious COVID-19, which may contribute to provide information for early TCZ administration decisions[10]. It was not possible to use IL-6 as a clinical outcome in this study since not all patients at Universitas Indonesia Hospital had their IL-6 levels checked. The improvement is based on CRP levels, which can be used as an early indicator in addition to IL-6 to predict whether COVID-19 patients would respond to TCZ treatment ultimately. A study was conducted in Pakistan established a substantial correlation between CRP levels and TCZ medication. Patients receiving TCZ treatment showed a 50% improvement in CRP levels within 48 hours[11].

Based on Table 4, TCZ treatment in patients with blood type A with LOS of less than 20 days and more than 20 days were 8 (50%) patients, respectively with 0.926 times LOS reduction (OR: 0.926, 95 % CI: 0.302-2.840; *P*=1000) when compared with other blood type groups. A total of 12 (52.2%) patients with blood type B were treated for less than 20 days and 11 (47.8%) patients in blood type B were treated for more than 20 days in which TCZ treatment is proven to reduce LOS 1.043 times (OR: 1.043, 95% CI: 0.382-2.852; *P*=1.000) when compared to other blood types. Meanwhile, 2 (33.3%) patients with blood type AB were hospitalized for less than 20 days and 4 (66.7%) patients of blood type AB were hospitalized for more than 20 days with 0.439 times LOS reduction (OR: 0.439, 95% CI: 0.075-2,577; *P*=0.421). Patients with blood type O respectively, 13 (56.5%) patients hospitalized for less than 20 days and 10 (43.5%) patients were hospitalized for more than 20 days with 1.359 times LOS reduction (OR: 5,333, 95% CI: 0.495-3,734; *P*=0.614) compared with COVID-19 patients with other blood types received TCZ treatment. There is no statistical significantly between each blood type and LOS.

## 4. DISCUSSION

The majority of the patients are male, representing 40 (58.8%) patients, whereas the proportion of female patients were 28 (41.2%). Men are substantially more likely than women to have poor clinical outcomes from COVID-19, according to Italian studies on the subject rate of case deaths are 16.1% vs. 10.4%. Women take an average of 14.5±14.4 days from diagnosis to death, while men take an average of 10.6±10.7 days (P<0.01). The risks of hospitalization, chronic infection, and death are higher in male patients over the age of 55 who have at least one comorbidity[12].

**Table 1.** Patient Characteristics during COVID-19 therapy with TCZ treatment at Universitas Indonesia Hospital, Depok, Indonesia.

| Patient Characteristic | Category | Tocilizumab Therapy (n=68 ) n (%) |
|---|---|---|
| Gender | Female | 28 (41.2) |
| | Male | 40 (58.8) |
| Age, years | Median (IQR) | 57 (46-63.75) |
| | Adult (18-59) | 44 (64.7) |
| | Elderly (≥ 60) | 24 (35.5) |
| Blood type | A | 16 (23.5) |
| | B | 23 (33.8) |
| | AB | 6 (8.8) |
| | O | 23 (33.8) |
| Number of comorbid diseases | None | 14 (20.6) |
| | One | 12 (17.6) |
| | More than one | 42 (60.3) |
| Comorbidities | DM | 25 (36.8) |
| | CVD | 12 (17.6) |
| | Hypertension | 32 (47.1) |
| | Kidney diseases | 9 (13.2) |
| | Obesity | 20 (29.4) |
| | Others Comorbidities | 32 (47.1) |
| Previous or simultaneous therapies | Remdesivir | 47 (69.1) |
| | Corticosteroids | 36 (52.9) |
| | Levofloxacin | 33 (48.5) |
| | Ceftriaxone | 21 (30.9) |
| | Azithromycin | 11 (16.2) |
| WHO Clinical Progression | Improvement | 30 (44.1) |
| | No Improvement | 38 (55.9) |
| CRP | Improvement | 45 (66.2) |
| | No Improvement | 23 (33.8) |
| Length of Stay | <20 days | 35 (51.5) |
| | ≥20 days | 33 (48.5) |

Notes: CVD= Cardiovascular Disease, DM= Diabetes Mellitus, IQR = Interquartile Range, CRP = C-Reactive Protein

**Table 2.** TCZ Treatment Effects on WHO Clinical Progression Scale outcomes with different blood type groups.

| Blood Type | WHO Clinical Progression | | OR | 95% CI | *P* value |
|---|---|---|---|---|---|
| | Improvement | No Improvement | | | |
| A | 8 (50.0) | 8 (50.0) | 1.364 | 0.443-4.195 | 0.774 |
| B | 9 (39.1) | 14 (60.9) | 0.735 | 0.264-2.041 | 0.613 |
| AB | 2 (33.3) | 4 (66.7) | 0.607 | 0.103-3.563 | 0.687 |
| O | 11 (47.8) | 12 (52.2) | 1.254 | 0.457-3.443 | 0.797 |

**Table 3.** TCZ Treatment Effects on CRP outcomes with different blood type groups.

| Blood Type | CRP | | OR | 95% CI | *P* value |
|---|---|---|---|---|---|
| | Improvement | No improvement | | | |
| A | 11 (68.8) | 5 (31.2) | 1.165 | 0.350-3.873 | 1.000 |
| B | 14 (60.9) | 9 (39.1) | 0.703 | 0.246-2.005 | 0.591 |
| AB | 6 (100.0) | 0 | 3.647 | 2.433-5.468 | 0.001 |
| O | 20 (87.0) | 3 (13.0) | 5.333 | 1.385-10.541 | 0.014 |

**Notes**: CI=Confidence Interval, OR=Odds Ratio

**Table 4.** TCZ Treatment Effects on Length of Stay outcomes with different blood type groups.

| Blood Type | Length of Stay | | OR | 95% CI | *P* value |
|---|---|---|---|---|---|
| | < 20 days | > 20 days | | | |
| A | 8 (50.0) | 8 (50.0) | 0.926 | 0.302-2.840 | 1.000 |
| B | 12 (52.2) | 11 (47.8) | 1.043 | 0.382-2.852 | 1.000 |
| AB | 2 (33.3) | 4 (66.7) | 0.439 | 0.075-2.577 | 0.421 |
| O | 13 (56.5) | 10 (43.5) | 1.359 | 0.495-3.734 | 0.614 |

**Notes**: CI=Confidence Interval, OR=Odds Ratio

Obesity and diabetes mellitus are substantial contributors to unfavorable outcomes of COVID-19 patients who received TCZ therapy, according to the current study. Overeating can result in adipocyte hypertrophy and hyperplasia as well as blood vessel compression, which prevents the body from getting the oxygen it needs to counter hypoxia. The formation of tissuespecific macrophages in response to hypoxia results in the excessive production of adipokines, including pro-inflammatory mediators like TNF-α, IL-1, IL-6, CRP, and adipokines. Infiltrating macrophages also form a crown-like structure around adipocytes. Obesity plays a significant role in generating systemic inflammation to the initiation and development of metabolic diseases[13]. Patients with obesity and diabetes mellitus, which are often associated with insulin resistance, exhibit higher non-steroidal fatty acid release. Insulin can stimulate and mobilize macrophages in adipose tissue, which causes the release of pro-inflammatory cytokines and chemokines such monocyte chemoattractant protein-1 and CRP. Insulin can also increase adipocytes and glucose uptake. As a result, in COVID-19 patients, serum levels of IL-6 and TNF-α become important predictors of disease severity and mortality. These factors might make it more likely for COVID-19 individuals to develop endothelial dysfunction and platelet aggregation, which cause occlusive thrombus development in the heart and lungs[13]. An observational, single-center cohort study conducted in Kuwait investigate the correlation between diabetes and higher BMI and the incidence of ICU admission in accordance to the severity of COVID-19 disease[14].

One of the co-morbidities that significantly influences how severely COVID-19 patients undergoing TCZ treatment are affected is hypertension. Patients with COVID-19 may become more severe if they have hypertension. Millions of individuals worldwide have been affected by this condition, which carries a high risk of developing cardiovascular disease. Recent research has shown that hypertension regulates the RAAS, inflammation, immunological response, urinary tract, and digestive system, which worsen COVID-19 patients' conditions[15]. A retrospective cohort research comparing hypertension and non-hypertensive participants reveals that hypertensive patients have lower lymphocyte counts and eGFR and higher CRP, NT-proBNP, serum amyloid A, and neutrophil counts. According to observations, COVID-19 individuals who have high blood pressure are more likely to experience significant inflammatory reactions, substantial internal organ damage, and worsening of their condition[16].

Significant comorbidities for the severity of the state of COVID-19 patients following TCZ treatment include liver and kidney illnesses. According to a US study, individuals with CKD have a considerably higher COVID-19 mortality rate (23.1% vs. 10.2%), with a 1.51 times higher mortality rate (95% CI: 1.19). -1.90), which is a significant independent predictor of mortality in COVID-19 patients, when compared to COVID-19 patients who do not have coexisting CKD[17]. In COVID-19 individuals, liver disease is significantly associated with a poor prognosis. In order to prevent liver failure, it is crucial to assess impairment using biomarkers in individuals with comorbid liver dysfunction. Hepatobiliary problems brought on by COVID-19 with a hepatic disease that is already present become a major issue[18].

Remdesivir therapy is one of the most frequently used treatments in this study. Remdesivir has an excellent safety profile and is effective when used in COVID-19 patients, based on a retrospective analysis of the prior study. According to clinical findings, there is an 84% prevalence of recovery and improvement rates, with a larger percentage of patients who are under 60 years old, are receiving standard low-flow oxygen, and have a death rate of 6.77%[19]. In a cohort study conducted in Germany, patients taking corticosteroids and/or Remdesivir in addition to conventional therapy were contrasted. The results showed that Remdesivir administered early could increase the prevalence of improvement in clinical outcomes[20].

Among COVID-19 patients, corticosteroids have also appeared as one of the most common treatments. The probability of worse progression for COVID-19 patients receiving corticosteroid therapy and TCZ compared to TCZ and control groups is 0.74 (95% (CI): 0.36-1.50) and 0.48 (95% CI: 0.31-0.74), respectively, based on a meta-analysis of the topic. According to this study, TCZ combined with corticosteroids reduces the risk of mortality in COVID-19 patients' cases more than TCZ alone[21]. This is consistent with a prior retrospective study that found that using IV TCZ therapy along with corticosteroids improved clinical outcomes in 65 years and older patients with a hyperinflammatory status brought on by SARS-CoV-2 infection more effectively than using only corticosteroids[22].

According to the WHO Clinical Progression Scale, blood type A has a higher proportion of clinical improvement than other blood types. These findings are consistent with an observational study on 14,112 patients in USA that determines the association between blood types ABO with intubation, infection, and mortality. It was discovered that people with blood types other than O had a slightly higher rate of infection. The risk of death is higher in blood type AB patients and lower in blood types A and B, whereas the risk of intubation lowers in patients with A types and increases in patients with types AB and B if compared to type O[23]. However, this finding is different from a study conducted in Bangladesh where clinical indications of infection can be significantly evident in patients with blood type A ($P$<0.05). The peak serum ferritin levels and WBC counts in blood type A patients differ, and both differences are statistically significant ($P$<0.001). Those with blood type A

required more oxygen and are significantly more susceptible to death than patients with the other blood group ($P$<0.05)[24].

Compared to other blood types, blood type AB has a higher possibility of elevated CRP levels. In contrast to a study done in Nepal, which discovered that people with blood type AB are more likely to get SARS-CoV-2 virus infections. Blood types A, B, and O don't appear to be more susceptible to SARS-CoV-2 infection. The probability of acquiring SARS-CoV-2 is lowest in blood type B[25]. According to estimates, patients with blood type AB have a slightly higher infection risk than other blood types, but blood type O patients are thought to have the lowest infection risk[25]. Due to the small sample size, particularly among people with blood type AB, the findings of this study may not be comparable to those of other studies.

Blood type O has a relatively smaller susceptibility for LOS than other blood types. The LOS of blood types A and AB is higher than that of other blood types. According to Shibeeb et al., blood type O is thought to be protective against SARS-CoV-2 infection while blood type A is more at risk and more likely to manifest the possibility of poor clinical outcomes[26]. The relative risk of SARS-CoV-2 infection in patients with blood type O is estimated to be 0.74 in a study investigating the comparative distribution of convalescent donors among blood types (0.6-0.90). It appears that blood type O is protected from acquiring the SARS-CoV-2 virus[27]. However, Nasiri et al. demonstrate that patients with blood type A do not differ substantially from those with blood type B (8.8± 7.2 days) in terms of mean LOS (8.4±6.1 days). Blood type O (7.8±5.4 days) and blood type AB (7.4±4.4 days) are not significantly different from one another. In terms of length of stay, patients with positive or negative rhesus have no significant differences. Blood type is not related to COVID-19 mortality rates or the length of hospitalization, however, blood type B has a significant relationship with the duration it takes for oxygen levels to return to normal[28].

## 5. CONCLUSION

Observing clinical outcome based on length of stay, WHO Clinical Progression Scale, and improvement in CRP levels in this study with COVID-19 patients receiving TCZ therapy showed blood type O was associated with a significantly improvement in CRP levels ($P$=0.014) and has better favorable outcomes compared to other blood type in terms of WHO Clinical Progression Scale (OR: 1.254, 95% CI: 0.457-3.443; $P$=0.797), length of stay (OR: 5,333, 95% CI: 0.495-3,734; $P$=0.614), and improvement in CRP levels (OR: 5,333, 95% CI: 1.385-20,541; $P$=0.014). Large-scale randomized controlled trials are warranted to ascertain the relationship between blood type and clinical improvement in patients receiving TCZ therapy.

## 6. ACKNOWLEDGEMENT

We acknowledge the numerous beneficial discussions we had with our supervisor and the medical records department at the Universitas Indonesia Hospital for their contributions to this study.

### Conflict of interest

The authors confirm that there were no substantial competing financial, professional, or personal interests that could have compromised how the research reported in this manuscript was performed or presented.

### Funding

None to declare.

### Ethics approval

Universitas Indonesia Hospital Ethics Committee provided the study protocol approval (number S-027/ KETLIT/RSUI/VII/2022). The Ethics Committee ruled out the need for consent because there is no direct interference with the patients.

### Article info:

Received October 28, 2022
Received in revised form February 24, 2023
Accepted March 8, 2023

### Author contribution

The study was designed and implemented by IA, RA, NF, and RI. IA acquired, assessed, and comprehended the information. The manuscript was written by IA, RA, NF, and RI. All of the authors participated with the critical review of the manuscript for significant intellectual substance and decided to give their approval to the final draft.

## REFERENCES

1. Latz CA, DeCarlo C, Boitano L, Png CYM, Patell R, Conrad MF, et al. Blood type and outcomes in patients with COVID-19. Ann Hematol. 2020;99(9):2113-8.
2. Kim Y, Latz CA, DeCarlo CS, Lee S, Png CYM, Kibrik P, et al. Relationship between blood type and outcomes following COVID-19 infection. Semin Vasc Surg. 2021;34(3):125-31.
3. Kaur P, Gupta M, Sagar V. FUT2 gene as a genetic susceptible marker of infectious diseases: A review. Int J Mol Epidemiol Genet. 2022;13(1):1-14.
4. Pereira E, Felipe S, de Freitas R, Araújo V, Soares P, Ribeiro J, et al. ABO blood group and link to COVID-19: A comprehensive review of the reported associations and their possible underlying mechanisms. Microb Pathog. 2020;169:105658.
5. Guillon P, Clément M, Sébille V, Rivain JG, Chou CF, Ruvoën-Clouet N, et al. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology. 2008;18(12):1085-93.
6. Liu N, Zhang T, Ma L, Zhang H, Wang H, Wei W, et al. The impact of ABO blood group on COVID-19 infection risk and mortality: A systematic review and meta-analysis. Blood Rev. 2021;48:100785.
7. Kabrah SM, Kabrah AM, Flemban AF, Abuzerr S. Systematic

review and meta-analysis of the susceptibility of ABO blood group to COVID-19 infection. Transfus Apher Sci. 2021;60(4): 103169.
8. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: A cautionary case report. Chest. 2020;158(1):e15-9.
9. Rezaei S, Fatemi B, Karimi Majd Z, Minaei H, Peikanpour M, Anjidani N, et al. Efficacy and safety of tocilizumab in severe and critical COVID-19: A systematic review and meta-analysis. Expert Rev Clin Immunol. 2021;17(5):499-511.
10. Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, et al. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study. J Allergy Clin Immunol. 2021;147(1):72-80.e8.
11. Khurshid S, Rehman N, Ahmed S, Ahmad B, Khurshid M, Muhammad A, et al. Early fall in c-reactive protein (CRP) level predicts response to tocilizumab in rapidly progressing COVID-19: Experience in a Single-Arm Pakistani Center. Cureus. 2021; 13(11):e20031.
12. Fortunato F, Martinelli D, Lo Caputo S, Santantonio T, Dattoli V, Lopalco PL, et al. Sex and gender differences in COVID-19: An Italian local register-based study. BMJ Open. 2021;11(10):1-7.
13. Alberti A, Freiberger V, Ventura L, Grigollo L, Dias P, Comim CM, et al. Obesity in people with diabetes in COVID-19 times: Important considerations and precautions to be taken. World J Clin Cases. 2021;9(20):5358-71.
14. Al-Sabah S, Al-Haddad M, Al-Youha S, Jamal M, Almazeedi S. COVID-19: Impact of obesity and diabetes on disease severity. Clin Obes. 2020;10(6):e12414.
15. Peng M, He J, Xue Y, Yang X, Liu S, Gong Z. Role of hypertension on the severity of COVID-19: A review. J Cardiovasc Pharmacol. 2021;78(5):e648-55.
16. Xia F, Zhang M, Cui B, An W, Chen M, Yang P, et al. COVID-19 patients with hypertension are at potential risk of worsened organ injury. Sci Rep. 2021;11(1):1-10.
17. Mohamed NE, Benn EKT, Astha V, Okhawere KE, Korn TG, Nkemdirim W, et al. Association between chronic kidney disease and COVID-19-related mortality in New York. World J Urol. 2021;39(8):2987-93.
18. Sivandzadeh GR, Askari H, Safarpour AR, Ejtehadi F, Raeis-Abdollahi E, Lari AV, et al. COVID-19 infection and liver injury: Clinical features, biomarkers, potential mechanisms, treatment, and management challenges. World J Clin Cases. 2021;9(22): 6178-200.
19. Gupte V, Hegde R, Sawant S, Kalathingal K, Jadhav S, Malabade R, et al. Safety and clinical outcomes of remdesivir in hospitalised COVID-19 patients: a retrospective analysis of active surveillance database. BMC Infect Dis. 2022;22(1):1-8.
20. Marx K, Gončarova K, Fedders D, Kalbitz S, Kellner N, Fedders M, et al. Clinical outcomes of hospitalized COVID-19 patients treated with remdesivir: a retrospective analysis of a large tertiary care center in Germany. Infection. 2023;51(1):97-108.
21. Moosazadeh M, Mousavi T. Combination therapy of tocilizumab and steroid for COVID-19 patients: A meta-analysis. J Med Virol. 2022;94(4):1350-6.
22. López-Medrano F, Pérez-Jacoiste Asín MA, Fernández-Ruiz M, Carretero O, Lalueza A, Maestro de la Calle G, et al. Combination therapy with tocilizumab and corticosteroids for aged patients with severe COVID-19 pneumonia: A single-center retrospective study. Int J Infect Dis. 2021;105:487-94.
23. Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. Nat Commun. 2020;11(1):1-27.
24. Halim MR, Saha S, Haque IU, Jesmin S, Nishat RJ, Islam ASMDA, et al. ABO blood group and outcomes in patients with COVID-19 admitted in the intensive care unit (ICU): A retrospective study in a tertiary-level hospital in Bangladesh. J Multidiscip Healthc. 2021;14:2429-36.
25. Gurung S, Mahotra NB, Shrestha L, Sherpali A, Joshi SP, Shrestha G, et al. Association of ABO blood group with susceptibility to SARS-CoV-2 infection in Rupandehi district of Nepal. SAGE Open Med. 2022;10:20503121221095413.
26. Shibeeb S, Khan A. ABO blood group association and COVID-19. COVID-19 susceptibility and severity: A review. Hematol Transfus Cell Ther. 2022;44(1):70-5.
27. Franchini M, Glingani C, Del Fante C, Capuzzo M, Di Stasi V, Rastrelli G, et al. The protective effect of O blood type against SARS-CoV-2 infection. Vox Sang. 2021;116(2):249-50.
28. Nasiri M, Khodadadi J, Hajrezaei Z, Bizhani N. The probable association between blood groups and prognosis of covid-19. Iran J Public Health. 2021;50(4):825-30.