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Original Research Article

A Study on Prognostic Outcome of Tocilizumab in Patients with COVID-19

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Abstract

Introduction: World Health Organization (WHO) received reports of above 149 million occurrences reported of COVID-19 as of April 29, 2022, including more than 3.1 million fatalities. Patients who have severe COVID-19 have significantly higher levels of interleukin (IL-6) and other proinflammatory cytokines. In COVID-19 individuals, elevated serum levels of cytokines such as interleukin-6 (IL-6), IL-10, tumor necrosis factor (TNF), and interferon may result in deadly ARDS and coagulation issues. Tocilizumab is a humanized recombinant monoclonal antibody being used in treating autoimmune and inflammation-related conditions. It was given FDA approval on January 8, 2010, primarily to treat several immune and inflammatory responses, including multiple types of arthritis, particularly cytokine release disorder.

Aims and Objectives: To evaluate the maximal benefit of tocilizumab over the standard treatment in COVID-19 and to determine the effect of tocilizumab on the outcome predictors.

Methods: This is a Retrospective and Observational Study which was conducted on 52 COVID-19 patients who were admitted to DCH of SCBMCH, Cuttack from June 2021 to November 2021. The patients were grouped into two, namely, the tocilizumab group and the control group. All the patients received standard treatment consisting of antibiotics and while, the tocilizumab group received a single intravenous dose of 400mg of tocilizumab. After the tocilizumab therapy, several outcome factors were determined for effective statistical analysis.

Results: The study showed that 38.46% of the Tocilizumab group died while 53.85% of the control group had died ($p<0.05$). It also showed that 46.15% % of the patients in the control group had died and their SpO_2 was less than 90% and CRP>200 mg/L. Most of the outcome predictors were significantly different ($p<0.05$) in the Tocilizumab group as compared to the control group, except clinical status after 1 week and IL-6>100 pg/ml.

Conclusion: The study concluded that tocilizumab can be beneficial in symptomatic improvement in outcome predictors and decrease death rates among patients with COVID-19.
Keywords: Tocilizumab, COVID-19, Coronavirus, Pandemic, Coronavirus treatment

Introduction:

In December 2019, Wuhan, China, reported the discovery of an entirely new coronavirus. It shared several clinical traits with the Middle East respiratory syndrome coronavirus (MERS-CoV) as well as the severe acute syndrome coronavirus-1 (SARS-CoV-1) [1]. The first incidence of a reported novel virus kind acknowledged as SARS-CoV-2, was found in Turkey on March 11, 2020, and it soon spread throughout the world. The 2019 coronavirus disease epidemic (COVID-19) has expanded quickly around of globe in addition to becoming an epidemic [2]. The World Health Organization (WHO) received reports of above 149 million occurrences reported of COVID-19 as of April 29, 2022, including more than 3.1 million fatalities [3].

The 2019 coronavirus disease consists of a first phase during which the virus replicates quickly, then a subsequent stage, which is regulated through the defence mechanism of the host [1]. Most seriously ill COVID-19 patients have been shown to have cytokine storms caused by proinflammatory cytokine overproduction [4]. Cardiovascular collapse, numerous organ malfunctions, and death are all results of cytokine storms. Patients who are in this stage of the disease show aberrant inflammatory markers, for example, elevated serum stages of ferritin, IL-6, in addition to CRP [5]. Improved SARS-CoV-2 viremia, protracted viral RNA detaching, transition onto respiratory support, and overall death has all been linked to higher serum IL-6 levels [6,7]. These results prompted us to postulate that by inhibiting the IL-6 receptor, the inflammatory procedure could be stopped at a crucial stage. Early cytokine storm detection, management, and prevention may therefore be crucial for patients. Further study of IL-6 signalling inhibitors is warranted given the importance of IL-6 in COVID-19 pneumonia [8,9].

The pathophysiology of COVID-19 is complex and includes, along with the direct viral impact and coagulopathy, an excess of proinflammatory cytokines known as a cytokine storm, which is thought to be a major factor in COVID-19-related mortality. Regrettably, the cytokine storm does not seem to be under control with conventional anti-inflammatory therapies. Patients who have severe COVID-19 have significantly higher levels of interleukin (IL-6) and other proinflammatory cytokines [8,9]. In COVID-19 individuals, elevated serum levels of cytokines such as interleukin-6 (IL-6), IL-10, tumor necrosis factor (TNF), and interferon may result in deadly ARDS and coagulation issues [10]. Serum interleukin-6 increase in particular is closely related to COVID-19 mortality and severity. Therefore, it is postulated that inhibiting IL-6 is a possible treatment approach to prevent the cytokine storm caused by COVID-19 and thereby alter the path of disease progression. It has been demonstrated that higher IL-6 concentrations are linked to a worse prognosis and a faster rate of illness development. Tocilizumab (TOC), an antagonist of the IL-6 receptors, was therefore thought of as a potential treatment [11-13].

Tocilizumab is a humanized recombinant monoclonal antibody being used to treat autoimmune and inflammation-related conditions. In 2003, once Roche subsidiary Chugai began making monoclonal

antibodies which suppress IL-6, it was first mentioned in the literature. Tocilizumab was given FDA approval on January 8, 2010, and primarily treats several immune and inflammatory responses, including multiple types of arthritis, particularly cytokine release disorder [10]. On April 30, 2010, Health Canada subsequently gave its approval. The European Commission authorized tocilizumab in December 2021 for the treatment of COVID-19 in patients who received systemic corticosteroid, and extra oxygen, including mechanical ventilation after it was investigated for the treatment of COVID-19 in critically ill patients. In October and December of 2022, respectively, Health Canada and the FDA approved it after that. Given typically every 4 weeks, tocilizumab has a longer duration of effect and a broad therapeutic index. The risks of infection, GI perforation, including liver toxicity should be discussed with patients [11].

Similar to other monoclonal antibodies, tocilizumab is anticipated to be broken down by proteolytic enzymes amino acids as well as smaller proteins. The half-life of tocilizumab is depending on the concentration. Patients with rheumatoid arthritis have a 21.5-day terminal half-life [12]. The IL-6 receptor alpha-targeting monoclonal antibody tocilizumab is utilized to cure inflammatory diseases, including giant cell arteritis, rheumatoid arthritis, as well as interstitial lung disease associated with systemic sclerosis [10,13]. Patients receiving tocilizumab for serious COVID-19 pneumonia demonstrated an instantaneous decrease in temperature, a decrease in the amount of supplemental oxygen as well as mechanical ventilation, as well as a recovery in pulmonary symptoms [14]. Evidence suggests that cytokine storms, which increase mortality, may be present in a subpopulation of individuals with severe symptomatology. Inhibitors of interleukin-6 (IL-6) may be used to manage the pathogenic immune reaction to the virus. For COVID-19 individuals exhibiting an inflammatory hyper-response, tocilizumab, a monoclonal antibody towards IL-6, is an optional treatment [12,14].

Materials and Methods

Research Design

This is a Retrospective and Observational Study conducted between June 2021 to Nov 2021 on 52 critically ill COVID-19 patients, who were admitted to DCH of SCBMCH, Cuttack from June 2021 to November 2021. Patients with COVID-19 disease, who met the inclusion criteria and were admitted to the ICU of our institution between Jun 21 to Nov 21 were recruited. All patients received standard treatment consisting of antibiotics (Piperacilin-Tzobactum or Meropenem/Teicoplanin given critical condition), low molecular weight heparin 1 mg/kg subcutaneously once daily (twice daily if D-dimer >3000 ng/mL), methylprednisolone 40 mg twice daily, and other supportive care as needed (Oxygen through non-rebreathing mask, High Flow Nasal Canula, Noninvasive or invasive ventilator support, inotropic support, renal replacement therapy). In addition to standard treatment, tocilizumab group (n=26) received a single intravenous dose of 400mg tocilizumab and the rest of 26 patients were classified as the control group. Arterial blood gases analysis, complete blood count, CRP, lactic dehydrogenase, D-dimer, ferritin, and inflammatory biomarkers were collected daily. The primary outcome was death or recovery.

Inclusion Criteria

1. Age ≥ 18 years.
2. Patients diagnosed as Covid -19 with Rapid Antigen Test and/or RTPCR for Covid -19.
3. Presence of severe disease (preferably within 24-48 hours of the onset of severe disease / ICU admission).
4. Persistent hypoxia (defined as saturation of 94% or less on

supplemental Oxygen of 15 L per minute through a non-rebreathing mask or PaO2/FiO2 ratio of less than 200).
5. Significantly raised inflammatory markers (CRP & / or IL6).
6. Not improving despite the use of steroids.
7. No active bacterial/fungal/tubercular infection.

Exclusion Criteria

1. Those, who did not give consent for Tocilizumab administration.
2. Any evidence of sepsis [high total leucocyte count (>15,000), raised serum procalcitonin].
3. Pregnancy
4. HIV / HBsAg / Anti-HCV positive.
5. Persons suffering from terminal malignancy.
6. Cardiomyopathy with ejection fraction less than 20.
7. Very low platelet count (< 20,000).
8. Deranged LFT (AST, ALT > 3times from baseline, bilirubin >2.5)

Statistical Analysis

The study used SPSS 25 for effective statistical analysis. The continuous variable was expressed as mean±standard deviation, while the discrete variable was expressed as counts and their respective percentages. The study used ANOVA for analyzing the data and $P<0.05$ was considered as the level of significance.

Ethical Approval

The study process was approved by the Ethical Committee of SCBMCH, Cuttack, India.

Results

The following research has been divided the patients into 2 groups, namely, Tocilizumab and control group. In addition, individual two groups Tocilizumab and the control group had 26 patients, who had been admitted to the hospital and the number of the Tocilizumab was 26 patients. The following results found that 2.6% were female and 3.1% were male patients. In addition, Hospitalized, requiring no oxygen supplementation, but requiring medical care were 3 out of 5 patients (Table 1).

Table 1: Baseline demographic and clinical characteristics of included patients

Characteristic	Tocilizumab n=26	Control group n= 26
Age		
Mean (SD)	61.2 (14.15)	62.85 (15.12)
Gender		
Female, *n* (%)	10 (38.46)	14(53.85)
Male, *n* (%)	16(61.54)	12(46.15)
Body mass index, mean (SD)	2 (7.69)	2 (7.69)
Disease severity at the baseline, *n*(%)		
Oxygen saturation 91–95%	8(30.77)	10(38.46)
Oxygen saturation ≤90%	18(69.23)	16(61.54)
Score on an ordinal scale, *n* (%)		
Hospitalized, requiring no oxygen supplementation, but requiring medical care	8 (30.77)	4 (15.38)
Hospitalized, requiring normal oxygen supplementation	10 (38.46)	8 (30.77)
Coexisting conditions, *n* (%)	8 (30.77)	14 (53.85)
Other medications related to COVID-19, *n*(%)		
Dexamethason	8 (30.77))	16(61.54)
Remdesivir	18 (69.23)	10 (38.46)

According to Table 2, the percentage of active treatment was significantly higher in those who did not receive Tocilizumab after 21 and 28 days. However, a statistically significant effect of the control group on death rates was observed and their condition deteriorated within the first week of hospitalization. The effect of Tocilizumab has been extensively studied. It was found that there was death in the Tocilizumab group who required high oxygen flow or $SpO_2 \leq 90\%$. About 46.15% of the patients in the Control group had died whose SpO_2 was less than 90%. About 46.15% of the control group died who had CRP>200 mg/L. Most of the outcome predictors were significantly different ($p<0.05$) in the Tocilizumab group as compared to the control group, except clinical status after 1 week and IL-6>100 pg/ml.

Table 2: Effects of Tocilizumab on various outcome predictors

Characteristic	Tocilizumab n=26	Control group n= 26	*p*-value
Overall			
Death, *n* (%)	10(38.46)	14(53.85)	0.0447
Mechanical ventilation, *n* (%)	6(23.08)	12(46.31)	
Required High Oxygen Flow			
Death, *n* (%)	0	4(15.38)	0.0488
Mechanical ventilation, *n* (%)	8(30.77)	14(53.85)	
Clinical improvement after 14 days, *n* (%)	10(38.46)	2(7.69)	
Clinical improvement after 21 days, *n* (%)	8(30.77)	3(11.54)	
Clinical improvement after 28 days, *n* (%)	0	3(11.54)	
Worsening clinical status after 1 week			
Death, *n* (%)	2(7.69)	6(23.08)	0.0589
Mechanical ventilation, *n* (%)	16(61.54)	8(30.77)	
Clinical improvement after 14 days, *n* (%)	4(15.38)	4(15.38)	
Clinical improvement after 21 days, *n* (%)	4(15.38)	4(15.38)	
Clinical improvement after 28 days, *n* (%)	0	4(15.38)	
$SpO_2 \leq 90\%$ at the baseline			
Death, *n* (%)	0	12(46.15)	0.0323
Mechanical ventilation, *n* (%)	4(15.38)	10(38.46)	
Clinical improvement after 14 days, *n* (%)	2(7.69)	4(15.38)	
Clinical improvement after 21 days, *n* (%)	2(7.69)	2(7.69)	
Clinical improvement after 28 days, *n* (%)	0	4(15.38)	
IL-6>100 pg/mL at baseline			
Death, *n* (%)	2(7.69)	4(15.38)	0.0554
Mechanical ventilation, *n* (%)	6(23.08)	8(30.77)	
Clinical improvement after 14 days, *n* (%)	4(15.38)	4(15.38)	
Clinical improvement after 21 days, *n* (%)	2(7.69)	2(7.69)	
Clinical improvement after 28 days, *n* (%)	12 (46.15)	8(30.77)	
CRP > 200 mg/L at the baseline			
Death, *n* (%)	4(15.38)	12(46.15)	0.0411
Mechanical ventilation, *n* (%)	4(15.38)	8(30.77)	
Clinical improvement after 14 days, *n* (%)	2(7.69)	4(15.38)	
Clinical improvement after 21 days, *n* (%)	2(7.69)	2(7.69)	
Clinical improvement after 28 days, *n* (%)	14 (53.85)	0	
D-dimers > 1000 µg/L at the baseline			

Death, *n* (%)	8(30.77)	12(46.15)	0.0498
Mechanical ventilation, *n* (%)	8(30.77)	12(46.15)	
Clinical improvement after 14 days, *n* (%)	6(23.08)	1(3.85)	
Clinical improvement after 21 days, *n* (%)	4(15.38)	1(3.85)	
Clinical improvement after 28 days, *n* (%)	0	0	

The predictive value was enhanced by analyzing a combination of several measures. As shown in Table 4, TOC administration is most effective in patients with D-dimers >1000 ug/L at the baseline. The risk of death, the need for mechanical ventilation, and clinical improvement after 21 and 28 days showed statistically significant effects. Although the adverse effects were more in the control group there was no significant difference between the two groups (Table 3).

Table 3: Findings of adverse effects of the patients in this study

Characteristic	Tocilizumab n=26	Control group n= 26	*p*-value
Prolonged QT interval	7(26.92)	3(11.54)	0.0629
Diarrhea	4(15.38)	5(19.23)	
ALT elevation	2(7.69)	3(11.54)	
Nausea or vomiting	8(30.77)	6(23.08)	
All adverse events	5(19.23)	9(34.62)	

Discussion

Tocilizumab was investigated and published by Goclu et al. in COVID-19 patients, comparing mortality results to those of conventional therapy. 364 patients in all were enrolled in this trial. 128 patients received Tocilizumab treatment in addition to regular therapy, while 233 patients received standard care. While 102 patients (79.7%) received an overall dose of 800 mg intravenously, 26 patients (20.3%) were only administered a dose of 400 mg parenteral once. Less noninvasive mechanical ventilation, less mechanical ventilation support, or fewer deaths were noted amongst participants, who received tocilizumab in the population with the same propensity scores. The multivariate-adjusted Cox regression model discovered, while compared to controls, tocilizumab participants had a significantly higher chance of surviving, with a hazard ratio (HR) of 0.157. The Tocilizumab group's mortality hazard ratio was 0.098. This study found that Tocilizumab therapy improved survival, and decreased mechanical ventilation is a requirement, because of decreased hospital-associated fatality among those who have COVID-19 [16].

Tocilizumab enhances the prognostic of COVID-19 in patients through elevated IL-6, according to research by Flisiak et al. from 2021. Having mild to serious conditions, 825 patients treated were included in the current investigation. Analysis was done on 655 patients receiving an alternative drug and 170 patients receiving TOC. The death rate and the necessity aimed at mechanical breathing, in addition to clinical progression served as the treatment's endpoints. In terms of gender, age, BMI, as well as the frequency of concomitant illnesses, TOC patients were evenly distributed in comparison to non-TOC patients. Patients with baseline IL-6 levels of more than 100 pg/mL showed that TOC has a major impact on mortality (hazard ratio: 0.21). Patients with baseline IL-6>100pg/mL as well as whichever $SpO_2 \leq 90\%$ (HR: 0.07) as well as

necessitating the addition of oxygen experienced the greatest benefits with TOC (HR: 0.18). During COVID-19, tocilizumab therapy decreases death besides accelerates scientific enhancement in individuals through a reference point concentration of IL-6 >100 pg/mL, especially if those patients require oxygen support due towards a subordinate $SpO_2 \leq 90\%$ value [17].

Tocilizumab effectively delivered results aimed at individuals through serious or acute COVID-19, according to Veiga et al. (2021) research. A total of 129 patients in total (mean age 57 years; 68% men) were included, as well as every single one of them completed a follow-up. Tocilizumab was administered to all patients in the tocilizumab group and two patients in the usual treatment group. In the tocilizumab group, 18 of 65 (28%) patients and in the usual care group, 13 of 64(20%) patients required mechanical breathing or passed away by day [15]. In the tocilizumab group, death occurred in 11(17%) patients at 15 days, compared to 2(3%) in the standard treatment group.29 of 67(43%) patients who got tocilizumab as well as 21 of 62(34%) individuals who did not report experiencing adverse events. In this experiment, which would include participants who were hospitalized with acute or severe COVID-19, tocilizumab standard care therapy was not better than traditional care alone for improving patients' clinical states at 15 days and could have amplified death [18].

Retrospective observational studies employing data from the COVACTA study were used by Tom et al. (2022) to research and present prognostic as well as predictive biomarkers found in patients hospitalized through severe COVID-19 pneumonia [15]. In the tocilizumab arm, 295 individuals underwent candidate biomarker testing, while 142 patients underwent a placebo test. Clinical status on a seven-category ordinal scale (1, discharge; 7, death), mortality, hospital stay length, and mechanical ventilation (if not already receiving it at randomization) today 28 were all evaluated as effectiveness outcomes. Continuous evaluation of prognostic and predictive biomarkers using proportional odds, binomial or Fine-Gray models, as well as additional sensitivity studies [14-16]. All potential biomarkers, except lactate dehydrogenase and d-dimer, were significantly predictive for the clinical outcomes of death, mechanical ventilation, clinical status, and delay to hospital discharge on day 28 in the placebo arm, according to modelling. Comparing ferritin versus placebo, modelling in the tocilizumab arm revealed a predictive value for day 28 clinical outcomes including fatality, mechanical ventilation, as well as clinical status [17]. In COVACTA, numerous biomarkers that predict clinical outcomes were confirmed. In the COVACTA patient cohort, ferritin was found to be a predictive biomarker for tocilizumab effects; high ferritin levels were associated with improved patient outcomes for tocilizumab compared to placebo at day 28.The primary cause of death in COVID-19 is pneumonia with respiratory failure, and lung damage caused by hyperinflammation is a significant factor in this [18]. Another study determined whether tocilizumab, a monoclonal antibody against the soluble IL-6 receptor [19], lowers patient mortality. Participants who received tocilizumab had a considerably higher survival rate than patients in the control group. In terms of improved survival and a favourable clinical course with Covid-19 pneumonia with the severe respiratory syndrome, tocilizumab has a positive effect when taken early [19-22].

Recently, research was carried out. a description of the first SARS-CoV2-related pneumonia cases within Australia that were treated successfully using tocilizumab, an interleukin-6 receptor antagonist Use of tocilizumab was linked

to good clinical results in our patients [23]. According to the study, tocilizumab should be tested in randomized controlled studies for the treatment of people suffering from severe COVID-19 pneumonia and should also be taken into consideration for compassionate use in these patients while these studies are still ongoing [21,23,24].

Conclusion

The study concluded that tocilizumab can be beneficial in symptomatic improvement in outcome predictors and decrease in death rates among the patients of COVID-19. The potential benefit of treating COVID-19 with tocilizumab is only attainable in certain subpopulations to maximize its potential effectiveness. Patients, who have a baseline concentration of interleukin 6 that is greater than 100 pg/mL and who require oxygen supplementation as a result of an oxygen saturation level that is less than 90 per cent may have a decreased risk of death and a decreased need for mechanical ventilation if they receive this regimen. Patients who experienced a worsening of their condition within the first seven days of hospitalization may still obtain some benefits from the administration of tocilizumab; however, this should be clarified in further studies conducted on a larger number of patients.

References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507–513.
2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020; 395:470–3.
3. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. https://covid 19.who.int. Accessed 10 Nov. 2022.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–1034.
5. Mangalmurti N, Hunter CA. Cytokine storms: Understanding COVID-19. Immunity. 2020;53(1):19–25.
6. Christensen J, Kumar D, Moinuddin I, et al. Coronavirus disease 2019 viremia, serologies, and clinical course in a case series of transplant recipients. Transplant Proc. 2020;52(9):2637–2641.
7. Zhu J, Pang J, Ji P, et al. Elevated interleukin-6 is associated with severity of COVID-19: A meta-analysis. J Med Virol. 2021;93(1):35–37.
8. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8(8):959–970.
9. Nasonov E, Samsonov M. The role of interleukin 6 inhibitors in therapy of severe COVID-19. Biomed Pharmacother. 2020;131:110698.
10. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;111:102452.
11. Antwi-Amoabeng D, Kanji Z, Ford B, Beutler BD, Riddle MS, Siddiqui F. Clinical outcomes in COVID-19 patients treated with tocilizumab: An individual patient data systematic review. J Med Virol. 2020;92(11): 251 6–2522.
12. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ProcNatlAcad Sci U S A. 2020;117(20):10970–10975.
13. Mastroianni A, Greco S, Apuzzo G, et al. Subcutaneous tocilizumab treatment in patients with severe COVID-19-related cytokine release syndrome: An observational cohort study. E Clinical medicine. 2020;24:10 0410.

14. Mert A, Vahaboğlu H, Arslan F, et al. Tocilizumab treatment in severe COVID-19: A multicenter retrospective study with matched controls. Rheumatol Int. 2022;42(3): 457–467.
15. Keske Ş, Tekin S, Sait B, et al. Appropriate use of tocilizumab in COVID-19 infection. Int J Infect Dis. 2020;99:338–343.
16. Güçlü ÖA, Önal U, Akalın H, et al. Tocilizumab treatment in COVID-19: A prognostic study using propensity score matching. AdvClinExp Med. 2022;31(11):1197–1206.
17. Flisiak R, Jaroszewicz J, Rogalska M, Łapiński T, Berkan-Kawińska A, Bolewska B, Tudrujek-Zdunek M, Kozielewicz D, Rorat M, Leszczyński P, Kłos K. Tocilizumab improves the prognosis of COVID-19 in patients with high IL-6. Journal of Clinical Medicine. 2021 Apr 9;10(8):1583.
18. Veiga VC, Prats JA, Farias DL, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LC, Avezum Á. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. bmj. 2021 Jan 20;372.
19. Tom J, Bao M, Tsai L, Qamra A, Summers D, Carrasco-Triguero M, McBride J, Rosenberger CM, Lin CJ, Stubbings W, Blyth KG. Prognostic and predictive biomarkers in patients with coronavirus disease 2019 treated with tocilizumab in a randomized controlled trial. Critical care medicine. 2022 Mar;50(3):398.
20. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, Cossi S. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020 Jun;76:31-35.
21. West TA, Malik S, Nalpantidis A, Tran T, Cannon C, Bhonagiri D, Chan K, Cheong E, Wan Sai Cheong J, Cheung W, Choudhury F, Ernest D, Farah CS, Fernando S, Kanapathipillai R, Kol M, Murfin B, Naqvi H, Shah A, Wagh A, Ojaimi S, Frankum B, Riminton S, Keat K. Tocilizumab for severe COVID-19 pneumonia: Case series of 5 Australian patients. Int J Rheum Dis. 2020 Aug;23(8):1030-1039.
22. Wei Q, Lin H, Wei RG, Chen N, He F, Zou DH, Wei JR. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty. 2021 May 18;10(1):71.
23. Tleyjeh IM, Kashour Z, Riaz M, Hassett L, Veiga VC, Kashour T. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis, first update. Clin Microbiol Infect. 2021 Aug;27(8):1076-1082.
24. Pyar K. P., Hla S. A., Lwin K. T. Y., Aung Z. N. H., Myat K., Maung L. M., Hein Y. M., Aung L. H., Thant M. M., Maung M. M., Zaw M. H., Mg Y. H., Maung N. L., Win T., Mg K. T., Phone S. S., Ya K. Z., Kyaw A. P., Aung Z. P., Kyaw M. T., Min S., Moe T. A., Oo K. M., & Ko M. K. Clinical and laboratory predictors for acquiring COVID-19 infections in patients on maintenance hemodialysis in 5th wave of epidemic in Myanmar. Journal of Medical Research and Health Sciences. 2022; 5(12): 2345–2354.