Original article

Impact of dexamethasone and tocilizumab on hematological parameters in COVID-19 patients with chronic disease

Haitham M.H. Qutob [a,b,*], Ramadan A. Saad [b,c], Hamza Bali [d], Abdulaziz Osailan [d], Jumana Jaber [d], Emad Alzahrani [d], Jamilah Alyami [d], Hani Elsayed [b,e], Raed Alserihi [f,g], Osama A. Shaikhomar [h]

[a] Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Rabigh, 25732, Saudi Arabia
[b] Medical Laboratory Sciences Department, Fakeeh College for Medical Sciences, Jeddah, Saudi Arabia
[c] Physiology Department, Faculty of Medicine, Ainshams University, Cairo, Egypt
[d] Internal Medicine Department, Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia
[e] Physics Department, Faculty of Science, Mansoura University, Mansoura, Egypt
[f] Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia
[g] 3D Bioprinting Unit, Center of Innovation in Personalized Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[h] Department of Physiology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

ARTICLE INFO

ABSTRACT

Background and aim: The most effective way to control severity and mortality rate of the novel coronavirus disease (COVID-19) is through sensitive diagnostic approaches and an appropriate treatment protocol. We aimed to identify the effect of adding corticosteroid and Tocilizumab to a standard treatment protocol in treating COVID-19 patients with chronic disease through hematological and lab biomarkers.

Materials and methods: This study was performed retrospectively on 68 COVID-19 patients with chronic disease who were treated by different therapeutic protocols. The patients were categorized into four groups: control group represented the patients' lab results at admission before treatment protocols were applied; group 1 included patients treated with anticoagulants, Hydroxychloroquine, and antibiotics; group 2 comprised patients treated with Dexamethasone; and group 3 included patients treated with Dexamethasone and Tocilizumab.

Results: The WBC and neutrophil counts were increased significantly in group 3 upon the treatment when they were compared with patients in group 1 ($p = 0.004$ and $p = 0.001$, respectively). The comparison of C-reactive Protein (CRP) level at admission was higher in group 3 than in group 1 with $p = 0.030$. After 10 days of treatment, CRP level was decreased in all groups, but in group 3 it was statistically significant ($p = 0.002$).

Conclusion: The study paves the way into the effectiveness of combining Dexamethasone with Tocilizumab in treatment COVID-19 patients with chronic diseases.

Impacto del tratamiento combinado de dexametasona y tocilizumab sobre parámetros hematológicos en pacientes con enfermedad crónica COVID-19

RESUMEN

Antecedentes y objetivo: La forma más eficaz de controlar la gravedad y la tasa de mortalidad de la enfermedad del nuevo coronavirus (COVID-19) es mediante enfoques de diagnóstico sensibles y un protocolo de tratamiento adecuado. Nuestro objetivo fue identificar el efecto de agregar corticosteroides y tocilizumab a un protocolo de tratamiento estándar en el tratamiento de pacientes con COVID-19 con enfermedad crónica a través de biomarcadores hematológicos y de laboratorio.

* Corresponding author.
E-mail address: hqutob@yahoo.com (H.M.H. Qutob).

Materiales y métodos: Este estudio se realizó de forma retrospectiva en 68 pacientes COVID-19 con enfermedad crónica que fueron tratados por diferentes protocolos terapéuticos. Los pacientes se clasificaron en cuatro grupos: el grupo de control representaba los resultados de laboratorio de los pacientes en el momento de la admisión antes de que se aplicaran los protocolos de tratamiento; el grupo 1 incluyó a pacientes tratados con anticoagulantes, hidroxicloroquina y antibióticos; el grupo 2 estaba compuesto por pacientes tratados con dexametasona; y el grupo 3 incluyó a pacientes tratados con dexametasona y tocilizumab.

Resultados: Los recuentos de glóbulos blancos y neutrófilos aumentaron significativamente en el grupo 3 tras el tratamiento cuando se compararon con los pacientes del grupo 1 ($p = 0,004$ y $p = 0,001$, respectivamente). La comparación del nivel de proteína C reactiva (CRP) al ingreso fue mayor en el grupo 3 que en el grupo 1, con $p = 0,030$. Después de 10 días de tratamiento, el nivel de CRP disminuyó en todos los grupos, pero en el grupo 3 fue estadísticamente significativo ($p = 0,002$).

Conclusión: El estudio allana el camino hacia la eficacia de la combinación de dexametasona con tocilizumab en el tratamiento de pacientes con COVID-19 con enfermedades crónicas.

Introduction

Coronavirus disease 2019 (COVID-19) is a serious pneumonia infection that was identified in Wuhan, Hubei Province, China, in late December 2019 and subsequently spread worldwide.[1,2] The causative virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the *Coronaviridae* family.[3] Currently, the number of people worldwide who have been infected with the virus has reached 194 million with approximately 4 million deaths; in Saudi Arabia, the total number of COVID-19 cases is 515,000 with 8141 deaths. The clinical characteristics of patients with COVID-19 vary from asymptomatic to the development of severe acute respiratory distress syndrome (ARDS), which can cause mortality in infected patients.[4]

The study of the pathophysiological process of COVID-19 has revealed the involvement of the host immune response. It has been found that inflammatory molecules, primarily interleukin (IL)-1, IL-6, and tumor necrosis factor, are elevated in patients with COVID-19.[5,6] These substances bind to host tissue, causing the development of ARDS, which is a serious causative factor in morbidity and organ dysfunction.[5,7] In patients with severe COVID-19 disease, it has been found that inflammatory factors such as C-reactive protein (CRP), ferritin, IL-1, and IL-6 are higher than in patients with mild disease.[7,8] Thus, it is suggested that elevated inflammatory markers are an indication of disease severity.

COVID-19 patients with chronic diseases such as diabetes mellitus, hypertension, and obesity are at high risk of developing severe ARDS and experiencing morbidity and mortality.[9] Studies in China have found that the patients with COVID-19 most likely to require hospitalization and have high mortality rates are individuals with cardiovascular disease, diabetes, and chronic respiratory diseases, with the ratio 10, 7, 6, and 6, respectively.[10–12] Moreover, the complications from COVID-19 associated with mortality were more often seen in patients suffering from hypertension, diabetes, ischemic heart disease, and chronic renal failure.[11–13]

Several therapeutic studies have been conducted with the goal of reducing the severity of the disease by targeting the inflammatory elements. Introducing treatment with corticosteroids such as Dexamethasone or hydrocortisone has shown a reduction in both inflammatory activity and mortality rate in severe patients.[14] Studies on the effect of such anti-inflammatory drugs have shown promising results in patients with COVID-19 who were on either mechanical oxygen support or noninvasive oxygen supplement.[15] Administration of Tocilizumab as an anti–IL-6 agent has shown a significant reduction in mortality and need for respiratory support.[16,17] In addition, patients who underwent treatment comprising a combination of steroids and Tocilizumab had a higher survival rate than patients treated with Tocilizumab or steroids alone (29%).[18]

The aim of our study was to evaluate the effect of steroid and Tocilizumab treatment on hematological and other laboratory results of COVID-19 patients with chronic diseases to establish predictive parameters for response to treatment protocols and expedite progress in the treatment of the disease.

Methods

Patients

The study was reviewed and approved by the institutional review board (IRB) at Fakeeh College for Medical Sciences and Dr. Soliman Fakeeh Hospital. The data of 68 patients with COVID-19 who were admitted to Dr. Soliman Fakeeh Hospital (DSFH) between April 24, 2020, and June 30, 2020 were collected following IRB waived the written informed consent for this retrospective data analysis. During this time, the Ministry of Health in Saudi Arabia published a treatment protocol that included steroid and/or Tocilizumab administration for patients with COVID-19 in moderate, severe, or critical conditions based on the World Health Organization disease severity classification as mild, moderate, severe, or critical illness (Table 1).[19]

COVID-19 detection test

The diagnosis of COVID-19 was confirmed by the presence of SARS-CoV-2 RNA in a nasopharyngeal swab. The RNA was extracted using the TANBead Nucleic Acid Extraction Kit and assayed using the PowerChek 2019-nCOV Real-Time PCR Kit.

Treatment protocols

The patients were categorized into the following four groups based on the treatment protocol: control group corresponded to the lab results of the patients at admission, before the treatment protocol was applied; group 1 comprised patients who were treated with the standard protocol of an anticoagulant (low molecular weight heparin – Enoxaparin) which was used as a prophylactic (40 mg subcutaneous once daily) or therapeutic (1 mg/kg twice daily), Hydroxychloroquine 400 mg/12 h on day one then followed with 200 mg/12 h for the next four days, and antibiotics in patients at high risk of developing an infection was as follow Ceftriaxone 2 g IV once daily for seven to ten days and Azithromycin 500 mg IV/PO once daily for three days; group 2 consisted of patients receiving Dexamethasone, and group 3 comprised patients receiving steroid and Tocilizumab (a monoclonal antibody against the IL-6 receptor) treatment. The dosages were as follows: 20 mg/day of Dexamethasone for groups 2 and 3 and

Table 1

COVID-19 disease severity classification according to World Health Organization guidelines.

Mild illness	Moderate illness	Severe illness	Critical illness
Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) $\geq$94% on room air at sea level.	Individuals who have $SpO_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Table 2

Distribution of patients with COVID-19 based on disease severity and history of chronic disease.

Type of chronic disease	Sample	COVID-19 disease severity			
		Mild	Moderate	Severe	Critical
Diabetes mellitus	14	5	2	3	4
Diabetes mellitus and other chronic diseases[a]	4	1	2	0	1
Hypertension	6	2	0	3	1
Hypertension and other chronic diseases[a]	5	0	1	4	0
Diabetes mellitus and hypertension	15	4	1	8	2
Diabetes mellitus, hypertension, and other chronic diseases[a]	13	4	0	6	3
Other chronic diseases[a]	8	2	1	4	1
Total	65	18	7	28	12

[a] Other chronic diseases include any disease other than diabetes mellitus and hypertension, such as obesity, chronic lung disease, hypothyroidism, bronchial asthma, and chronic kidney disease.

4–8 mg/kg of IV Tocilizumab by two consecutive IVs 12 h apart for group 3.

Identifying laboratory results

Laboratory result data at admission and after 10 days of treatment were collected retrospectively. The laboratory results investigated included red blood cell count, white blood cell (WBC) count, neutrophils, monocytes, platelets, and CRP. Coagulation profile and D-dimer tests were excluded because of the administration of anticoagulant therapeutics as part of the treatment protocol.

Statistical analysis

The statistical electronic platform SPSS version (v23) was used for data analysis comparing patient outcomes based on WBCs, neutrophils, monocytes, and lymphocytes. paired and unpaired t-test were used in the analysis. A p value <0.05 was considered statistically significant.

Results

There were 68 patients with COVID-19 and a history of chronic disease enrolled in the study. The distribution of chronic diseases and COVID-19 severity is summarized in Table 2. Among the patients, 64.6% were male and 35.4% were female, the mean age was 59.4 years (standard deviation = 14.1), and the median age was 61 years.

Severe and critical cases made up 38.5% (10/26) of group 1, 53.3% (8/15) of group 2, and 88% (22/25) of group 3. The mortality rate was 8% (1/26) in group 1, 6.7% (1/15) in group 2, and 21% (5/24) in group 3. The development of ARDS and acute kidney injury with or without septic shock was observed in patients with multiple preexisting chronic diseases such as hypertension and diabetes mellitus with chronic kidney disease or cardiopathy.

A comparison of hematological laboratory results showed a significant increase in WBC and platelet counts and a reduction in CRP in group 3 patients when compared with the laboratory results at admission, represented as control group ($p < 0.05$; Table 3). When group 1, treated with the standard protocol, and group 2, treated with Dexamethasone, were compared, the WBC count at admission for both groups was around $6.5 \times 10^3/\mu L$; WBC count increased in group 2 to $8.67 \times 10^3/\mu L$ after 10 days of treatment with Dexamethasone, though the difference between the two groups was nonsignificant ($p = 0.234$; Table 4). The neutrophil count in group 2 were higher than in group 1 after 10 days of treatment. In group 2, the neutrophil count increased to $6.79 \times 10^3/\mu L$, while the lymphocyte count slightly decreased to $1.85 \times 10^3/\mu L$. However, there were no significant differences between the groups in neutrophil count at admission or after 10 days of treatment ($p = 0.529$ and $p = 0.178$, respectively). Between-group comparisons of other hematological laboratory data showed nonsignificant results (Table 4).

Regarding group 3, which received both Tocilizumab and Dexamethasone as part of the therapeutic strategy, laboratory data revealed an improvement in WBC, neutrophil, and monocyte counts (Table 4). A similar pattern was observed in group 2 for WBCs and neutrophils, though monocytes and lymphocytes showed a slight reduction; all laboratory results were, however, within the normal range (Table 4). When comparing groups 1 and 3 before and after 10 days of treatment, only WBC and neutrophil counts showed significant differences. WBC and neutrophil counts increased by approximately 36.39% and 26%, respectively, after treatment, leading to a significant difference between groups 1 and 3 after treatment ($p = 0.004$ and $p = 0.001$, respectively; Table 5). Lymphocyte count was higher in group 1 than in group 3 at admission, though increased in both groups, by 12.8% in group 1 and 15.9% in group 3, after 10 days of treatment. The laboratory results of group 2 and group 3 showed nonsignificant differences after 10 days of treatment.

Furthermore, CRP levels in all groups were higher than the normal range. In group 3 patients, mean CRP level at admission was 130 mg/L (standard deviation = 80.42; Table 4). Comparison of CRP levels between groups 1 and 3 showed a significant difference ($p = 0.030$), while with group 2, the difference was non-significant ($p = 0.298$). After 10 days of treatment, CRP levels were reduced in all groups, though a significant difference was only seen in group 3 ($p = 0.002$).

Table 3

a comparison of laboratory results at admission in control group and 10 days after treatment in group 1, 2, and 3.

CBC markers	Control Group vs Group 1			Control Group vs Group 2			Control Group vs Group 3		
	Mean at admission (SD)	Mean after 10 days (SD)	p value	Mean at admission (SD)	Mean after 10 days (SD)	p value	Mean at admission (SD)	Mean after 10 days (SD)	p value
RBC count $\times 10^6$/μL	4.82 (0.75)	5.27 (0.88)	0.219	4.82 (0.75)	4.89 (0.59)	0.759	4.82 (0.75)	4.45 (0.65)	0.071
WBC count $\times 10^3$/μL	7.26 (3.61)	6.66 (2.13)	0.464	7.26 (3.61)	8.66 (3.78)	0.220	7.26 (3.61)	10.47 (4.79)	0.004*
Neutrophils $\times 10^3$/μL	5.58 (5.94)	3.94 (7.81)	0.180	5.58 (5.94)	6.36 (2.87)	0.645	5.58 (5.94)	7.59 (4.59)	0.184
Monocytes $\times 10^3$/μL	0.87 (1.84)	0.66 (0.20)	0.575	0.87 (1.84)	0.94 (3.63)	0.893	0.87 (1.84)	0.56 (0.35)	0.472
Lymphocytes $\times 10^3$/μL	1.55 (1.12)	1.93 (1.04)	0.253	1.55 (1.12)	1.85 (1.57)	0.423	1.55 (1.12)	1.44 (0.67)	0.707
Platelet count $\times 10^3$/μL	235.98 (75.96)	264.29 (83.73)	0.197	235.98 (75.96)	275.86 (89.01)	0.143	235.98 (75.96)	316.28 (54.59)	0.001*
C-reactive protein mg/L	97.13 (86.89)	19.6 (23.93)	0.063	97.13 (86.89)	75 (74.14)	0.622	97.13 (86.89)	23.85 (156.58)	0.024*

The p value represents the statistical significance between the mean values of the two groups.

* p value is statistically significance (< 0.05).

Table 4

Laboratory data of the three groups at admission and after 10 days of treatment.

Lab Parameters	Group 1 (Standard Protocol)				Group 2 (Steroid)				Group 3 (Steroid + Tocilizumab)			
	Sample	Mean at admission (SD)	Mean after 10 days (SD)	p value	Sample	Mean at admission (SD)	Mean after 10 days (SD)	p value	Sample	Mean at admission (SD)	Mean after 10 days (SD)	p value
RBC count $\times 10^6$/μL	26	4.96 (0.88)	5.27 (2.56)	0.562	15	4.85 (0.59)	4.89 (0.90)	0.875	24	4.62 (0.65)	4.45 (0.83)	0.479
WBC count $\times 10^3$/μL	26	6.64 (2.13)	6.66 (2.74)	0.970	15	6.84 (3.78)	8.66 (4.47)	0.257	24	8.39 (4.79)	10.47 (5.37)	0.216
Neutrophils $\times 10^3$/μL	26	5.56 (7.81)	3.94 (1.73)	0.316	15	4.03 (2.87)	6.36 (4.16)	0.097	24	6.75 (4.59)	7.59 (4.64)	0.580
Monocytes $\times 10^3$/μL	26	0.66 (0.20)	0.66 (0.73)	0.693	15	1.88 (3.63)	0.94 (1.62)	0.387	24	0.49 (0.35)	0.56 (0.42)	0.571
Lymphocytes $\times 10^3$/μL	26	1.65 (1.042)	1.93 (1.81)	0.508	15	1.96 (1.57)	1.85 (1.66)	0.851	24	1.12 (0.67)	1.44 (1.02)	0.254
Platelet count $\times 10^3$/μL	26	226.44 (83.73)	264.29 (116.71)	0.197	15	243.5 (89.01)	275.86 (136.86)	0.465	24	243.00 (54.59)	316.28 (112.68)	0.016*
C-reactive protein	5	37.31 (30.32)	19.6 (35.71)	0.280	5	96.2 (114.37)	75 (93.69)	0.757	9	130.89 (80.41)	23.85 (29.48)	0.002*

The p value represents the statistical significance between the mean values of the two groups.

* p value is statistically significance (< 0.05).

Table 5

Comparison of the different therapeutic strategies after 10 days of treatment.

Lab parameters	Group 1 vs Group 2				Group 1 vs Group 3				Group 2 vs Group 3			
	Sample	Group 1 mean after 10 days (SD)	Group 2 mean after 10 days (SD)	p value	Sample	Group 1 mean after 10 days (SD)	Group 3 mean after 10 days (SD)	p value	Sample	Group 2 mean after 10 days (SD)	Group 3 mean after 10 days (SD)	p value
RBC count ×10^6/μL	26	5.27 (2.56)	4.89 (0.90)	0.594	15	5.27 (2.56)	4.45 (0.83)	0.184	24	4.89 (0.90)	4.45 (0.83)	0.152
WBC count ×10^3/μL	26	6.66 (2.74)	8.66 (4.47)	0.092	15	6.66 (2.74)	10.47 (5.37)	0.004*	24	8.66 (4.47)	10.47 (5.37)	0.313
Neutrophils ×10^3/μL	26	3.94 (1.73)	6.36 (4.16)	0.015*	15	3.94 (1.73)	7.59 (4.64)	0.001*	24	6.36 (4.16)	7.59 (4.64)	0.439
Monocytes ×10^3/μL	26	0.66 (0.73)	0.94 (1.62)	0.449	15	0.66 (0.73)	0.56 (0.42)	0.617	24	0.94 (1.62)	0.56 (0.42)	0.331
Lymphocytes ×10^3/μL	26	1.93 (1.81)	1.85 (1.66)	0.895	15	1.93 (1.81)	1.44 (1.02)	0.300	24	1.85 (1.66)	1.44 (1.02)	0.389
Platelet count ×10^3/μL	26	264.29 (116.71)	275.86 (136.86)	0.784	15	264.29 (116.71)	316.28 (112.68)	0.155	24	275.86 (136.86)	316.28 (112.68)	0.367

The p value represents the statistical significance between the mean values of the two groups.

* p value is statistically significance (<0.05).

Discussion

In this retrospective study, the characteristics of hematological laboratory results were assessed in patients with COVID-19 with a history of chronic disease. We observed that WBC count, platelet count, and CRP level in patients in group 3 were significantly improved after treatment with Dexamethasone and Tocilizumab. In addition, WBC and neutrophil counts were higher in the patients administered Dexamethasone and Tocilizumab as well as patients treated with only Dexamethasone when compared to the patients treated with the standard treatment protocol. These parameters increased after administration of Dexamethasone alone or in combination with Tocilizumab. This result indicates that patients with COVID-19 and a history of chronic disease are more likely to benefit from treatment protocols that include Dexamethasone and Tocilizumab. In addition, the lymphocyte count in all groups was just above the lower cutoff while the inflammatory marker CRP was markedly high, which is consistent with other observations of COVID-19 cases at high risk of hospitalization.[20,21]

In our study, WBCs, neutrophils, and lymphocytes increased after steroid and Tocilizumab treatment but the level of lymphocytes is lower than the level observed in patients treated with the standardized protocol. Based on this, it is proposed that adding Tocilizumab, an IL-6 inhibitor, to the treatment may minimize the side effects associated with the administration of Dexamethasone by reducing the release of cytokines associated with chimeric antigen receptors redirecting T cells.[22] IL-6 levels have been identified in other studies and are used to monitor disease severity and progression during treatment.[20,23,17,24] IL-6 accumulates in the serum temporarily after Tocilizumab infusion before decreasing due to the inhibition of inflammatory activity, leading to an improvement in patients' clinical manifestation.[23,25] On the other hand, while an increase in platelet count was seen in all groups after treatment, the increase was only significant in group 3; this could be explained by the interaction of IL-6 with hematopoietic stem cells to enhance megakaryocyte production and release into the circulation. In addition, the over activation of hemostasis and related pathways is a hallmark in severe COVID-19 cases.[26] Thus, regulation of platelet adhesion, aggregation, and coagulation pathways during treatment leads to a reduction in platelet consumption, thus preserving platelet count.

Introducing Dexamethasone and Tocilizumab into the treatment of patients with COVID-19 elicited clinical improvements in patients with severe and critical conditions. Patients whose COVID-19 treatment protocol included Dexamethasone and Tocilizumab have been shown to have a 10.7% higher survival rate than patients not administered these therapeutics.[24] Furthermore, significant differences have been found between patients on steroid treatment and those without steroid treatment in oxygen support need ($p = 0.04$) as well as in mortality rate, with decreased mortality among patients undergoing steroid treatment ($p < 0.001$).[27,28] In another study performed on 100 patients treated with Tocilizumab, 58% of patients had improved clinical presentations and 37% were stabilized, and at day 10, the improvement in symptoms was 77%.[29]

Our study has some limitations that could reflect negatively on our conclusions regarding administering Tocilizumab with Dexamethasone to patients with COVID-19 and chronic disease. The primary limitations are the number of patients involved in the study and their laboratory results, such as lactate dehydrogenase, D-dimer, and ferritin. In addition, our patients' data were collected from a single tertiary hospital in the region. Increasing the number of patients and involving additional tertiary hospitals would strengthen our observation of the effectiveness of Dexamethasone and Tocilizumab in patients with COVID-19 and chronic disease. Moreover, IL-6 level was not reported in our study due to it not being tested at the time of diagnosis or during treatment. Thus, it is

recommended to consider testing IL-6 levels in routine laboratory tests to aid in categorizing disease severity, determining appropriate treatment protocols, and monitoring treatment progress.

Conclusion

An increase in CRP level and low lymphocyte count in patients with COVID-19 and a history of chronic disease could be a positive indication for the use of Dexamethasone with Tocilizumab as therapeutic strategies to improve clinical outcomes and prevent disease progression.

Ethics approval

The proposal of study was approved by IRB at DSFH.

Funding

Authors' contribution

Haitham MH. Qutob: Study plan, Methodology, data validation, and Writing – original draft. Ramadan A. Saad: Study plan, and Writing – original draft. Hamza Bali, Abdulaziz Osailan, Jumana Jaber, Emad Alzahrani, and Jamilah Alyami: Patients' data collection. Hani Elsayed: Data analysis, Raed Alserihi, and Osama A. Shaikhomar: Manuscript review and editing.

Consent for publication

I confirm that the study was carried out in accordance with relevant guidelines and regulations.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgments

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan. China, of novel coronavirus–inected pneumonia. N Engl J Med. 2020;382:1199–207.
2. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7:11.
3. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91–8.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395:497-506.
5. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. In: Paper presented at: Seminars in immunopathology. 2017.
6. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420–2.
7. Costanzo G, Cordeddu W, Chessa L, Del Giacco S, Firinu D. COVID-19: considerations about immune suppression and biologicals at the time of SARS-CoV-2 pandemic. World J Clin Cases. 2021;9:5352–7.
8. Fan Y, Wang Y, Yu S, Chang J, Yan Y, Wang Y, et al. Natural products provide a new perspective for anti-complement treatment of severe COVID-19: a review. Chin Med. 2021;16:67.
9. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323:1775–6.
10. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. MedRxiv. 2020.04.08.20057794.
11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan. China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475–81.
12. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan. China: a retrospective cohort study. Lancet. 2020;395:1054–62.
13. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan. China. Allergy. 2020;75:1730–41.
14. Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. 2004;31:304–9.
15. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. Jama. 2020;324:1317–29.
16. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18:1–5.
17. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020;117, 10970-5.
18. Ruiz-Antorán B, Sancho-López A, Torres F, Moreno-Torres V, de Pablo-López I, García-López P, et al. Combination of tocilizumab and steroids to improve mortality in patients with severe COVID-19 infection: a Spanish, multicenter, cohort study. Infect Dis Ther. 2021;10:347–62.
19. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. Geneva: World Health Organization; 2020.
20. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia. Italy Autoimmun Rev. 2020;19:102568.
21. Muñoz-Rodríguez JR, Gómez-Romero FJ, Pérez-Ortiz JM, López-Juárez P, Santiago JL, Serrano-Oviedo L, et al. Characteristics and Risk Factors Associated With Mortality in a Multicenter Spanish Cohort of Patients With COVID-19 Pneumonia. Arch Bronconeumol. 2021;57 Suppl 2:34–41.
22. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expert Rev Clin Immunol. 2019;15:813–22.
23. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020;92:814–8.
24. Mikulska M, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020;15, e0237831.
25. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008;112:3959–64.
26. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92:1533–41.
27. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020;324:1298–306.
28. Bauchner H, Fontanarosa PB. Randomized clinical trials and COVID-19: managing expectations. JAMA. 2020;323:2262–3.
29. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia. Italy. Autoimmun Rev. 2020;19, 102568.