Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

COVID-19–Associated Macrophage Activation Syndrome: Clinical Characteristics, Treatment Patterns, and Outcomes from a Hospitalized Cohort

Deniz İncaman

dr.denizincaman@researchersgroup.com

Başkent University

Research Article

Keywords: COVID-19, macrophage activation syndrome, hyperinflammation, cytokine storm, emerging infectious disease

Posted Date: June 22nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9817269/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

COVID-19–Associated Macrophage Activation Syndrome: Clinical Characteristics, Treatment Patterns, and Outcomes from a Hospitalized Cohort

Deniz İncaman

Department of Internal Medicine, Başkent University, Adana Dr. Turgut Noyan Hospital, Adana, Türkiye

ORCID: 0000-0002-5559-1093

Email: dr.denizincaman@researchersgroup.com

Corresponding author: Deniz İncaman

Email: dr.denizincaman@researchersgroup.com

Abstract

MacOS is a rare but severe hyperinflammatory complication of coronavirus disease 2019 (COVID-19), characterized by a cytokine storm, immune dysregulation, and multiorgan dysfunction. Even though immunomodulatory therapies have been extensively utilised in the context of the COVID-19 pandemic, clinical course and outcomes of the COVID-19-related MAS in the real world have not been well described. Our study was a retrospective cohort study conducted from March 2020 to 2023 at Kastamonu Education and Research Hospital, Türkiye, focusing on adults hospitalized with COVID-19-Related MAS. They included demographic factors, comorbidities that were measured using the Charlson Comorbidity Index (CCI), disease severity, which was measured by the World Health Organisation (WHO) ordinal scale, treatment patterns, and outcomes. The rate of mortality among 345 patients with COVID-19-related MAS was high, which is indicative of the severity of this hyperinflammatory phenotype. Comorbidity burden was high, and often rapid clinical deterioration occurred even with immunomodulatory

therapy after MAS diagnosis. COVID-19-related MAS is a high-risk hyperinflammatory phenotype in the conditions of a pandemic. The detection of cases at an early stage, use of a systematic assessment of their severity, and readiness to complications of an immune character are the essential elements of favourable management at the beginning of outbreaks of infectious diseases.

Keywords: COVID-19, macrophage activation syndrome, hyperinflammation, cytokine storm, emerging infectious disease.

Introduction

The coronavirus disease 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its discovery in Wuhan, China, at the end of 2019, it has caused unprecedented morbidity and mortality worldwide.[1] Even with the intensive campaigns at the health sector level, vaccination, and therapeutic innovations, COVID-19 has remained a major challenge to healthcare systems across the globe. Though most people infected with the disease succumb to mild or moderate illness, a significant percentage of them become severely ill and need hospitalisation, respiratory support, and intensive care.

Acute hypoxemic respiratory failure, systemic inflammation, and dysfunction of many organs are common features of severe COVID-19. There is growing evidence to support the idea that dysregulated host immune responses have a dominant role in the severity of disease, and not just viral replication. Specifically, hyperinflammation has been identified as a primary cause of respiratory failure and vascular damage, as well as organ dysfunction among critically ill patients.[2]

Macrophage activation syndrome (MAS) has emerged as one of the most severe immune-mediated complications associated with COVID-19. MAS is characterized by dysregulated activation of macrophages and cytotoxic lymphocytes, excessive cytokine release, systemic immune dysregulation, and progressive tissue injury. It shares important clinical and biological features

[1] National Institutes of Health (USA). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, <https://www.covid19treatmentguidelines.nih.gov/> (2021).

[2] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180:934 –43. doi: 10.1001/jamainternmed.2020.0994.

with secondary hemophagocytic lymphohistiocytosis and has been described in the context of severe infections and sepsis-related hyperinflammatory states.[3]

Hyperinflammatory syndromes like MAS pose special problems concerning the management of patients during large scale outbreak of infectious diseases. The disease can deteriorate rapidly, and it is not closely related to the viral load or time of infection. Consequently, the traditional antiviral-oriented treatment plans are not effective in preventing the development of a severe disease once the immune dysregulation is developed. The COVID-19 pandemic has highlighted the need to know the host's inflammatory responses and understand high-risk phenotypes that demand specific clinical care.

Immunomodulatory agents against important proinflammatory mediators have been integrated into the management of severe COVID-19. Specifically, interleukin-1 (IL-1) and interleukin-6 (IL-6) signaling inhibitors have been applied to inhibit cytokine storm and avoid additional tissue damage caused by immune-mediated responses.[4] Despite having shown promise in a few patient groups, the performance of these agents in practical contexts remains inconsistent, and patient outcomes in patients whose hyperinflammatory syndrome is already established, e.g., MAS, continue to be low.

Although the problem of MAS is becoming increasingly acknowledged as an essential complication of COVID-19, there are limited population-level data that reflect the clinical features, burden of comorbidities, severity of the disease, treatment patterns, and outcomes of MAS. The majority of the current research work has been based on short-lasting outcomes or certain interventions with minimal attention to the overall epidemiologic and clinical consequences of MAS in pandemic situations. A better understanding of COVID-19-related MAS will not only help with the better management of individual patients but also provide information on preparedness measures in cases of new outbreaks of infectious diseases.

---

[3] Tipirneni R, Schmidt H, Lantz PM, Karmakar M. Associations of 4 geographic social vulnerability indices with US COVID-19 incidence and mortality. Am J Public Health. 2022;112(11):1584–8.

[4] Y. Fujita, T. Hoshina, J. Matsuzaki, Y. Yoshioka, T. Kadota, Y. Hosaka, *et al.* Early prediction of COVID-19 severity using extracellular vesicle COPB2 J Extracell Vesicles, 10 (2021), Article e12092, 10.1002/jev2.12092

This research was aimed at characterising clinical presentation, comorbidity rate, severity of the disease, pattern of treatment, and outcomes of a large number of hospitalised patients with COVID-19-associated MAS. This study will present evidence that is applicable in the management of immune dysregulation in the context of the current and future emergent infectious diseases by describing this severe hyperinflammatory phenotype in a real-world clinical environment.

Materials and Methods

Study Design and Setting

Our study was a retrospective cohort study at the Kastamonu Education and Research Hospital, a tertiary care hospital in Türkiye, a referral hospital to the area during the COVID-19 pandemic. The inclusion was screening of adult patients who were hospitalised with laboratory-confirmed COVID-19 from March 2020 to July 2023. This timeframe included several tsunamis of the pandemic, and the treatment procedures and clinical practise changed due to the new evidence and changes in guidelines.

Patient Selection and Definition of Macrophage Activation Syndrome

Patients were also required to be included in case they were diagnosed with COVID-19-related macrophage activation syndrome when hospitalised. Clinical judgement with the help of hyperinflammatory presentation, laboratory results, and severity of the disease during the hospital course was used to diagnose MAS. The diagnosis of MAS was usually made with the first hospital admission to COVID-19, implying the development of the hyperinflammatory condition through the early viral disease.[5]

The clinical characteristics that were indicative of MAS were a high fever persistence, progressive respiratory failure, inflammation in the whole body, and signs of dysfunction of many organs. Laboratory results, which confirmed the diagnosis, were high markers of inflammation and other immune activation indicators, which are in line with clinical practise in the pandemic.

---

[5] M.O. Satici, M.M. Islam, C. Satici, C.N. Uygun, E. Ademoglu, İ. Altunok, *et al.* The role of a noninvasive index 'SpO_2/FiO_2' in predicting mortality among patients with COVID-19 pneumonia Am J Emerg Med, 57 (2022), pp. 54-59, 10.1016/j.ajem.2022.04.036

Data Collection and Variables

The demographic information was gathered via the hospital information system, such as age and sex. Each patient was documented to have comorbid conditions.[6] The Charlson Comorbidity Index (CCI) was calculated at hospital admission to quantify baseline comorbidity burden and estimate mortality risk, as it has been widely used and validated as a prognostic comorbidity measure in hospitalized and chronically ill populations.[7] The Charlson Comorbidity Index scoring system used to assess baseline comorbidity burden is presented in Table 1.

Table 1. Charlson Comorbidity Index used to assess baseline comorbidity burden in patients with COVID-19–associated macrophage activation syndrome[8]

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes mellitus	1

[6] P. Toniati, S. Piva, M. Cattalini, E. Garrafa, F. Regola, F. Castelli, *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, 19 (2020), Article 102568, 10.1016/j.autrev.2020.102568

[7] 1. Hsun Yang, Yi-Hsin Chen, Teng-Fu Hsieh, Shiun-Yang Chuang, Ming-Ju Wu, Prediction of Mortality in Incident Hemodialysis Patients: A Validation and Comparison of CHADS2, CHA2DS2, and CCI Scores. Journal.pone.0154627 May 5, 2016, 10.1371/journal.pone.0154627. t003

[8] Charlson Comorbidity Index scores were calculated at hospital admission to estimate baseline mortality risk and comorbidity burden.

Comorbidity	Score
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immunodeficiency syndrome (AIDS)	6

The severity of the disease was determined in terms of the World Health Organisation (WHO) ordinal scale of clinical improvement. The scores of the WHO ordinal scale were obtained at three moments: on the day of the administration of the biological agent, 48 to 72 hours after starting treatment, and on the 14th day. This methodology did enable assessment of early and short-term clinical outcomes after immunomodulatory therapy.

Treatment Patterns and Clinical Management

As part of pandemic-era clinical practice, patients received immunomodulatory therapy with either tocilizumab, an IL-6 pathway inhibitor, or anakinra, an IL-1 pathway inhibitor, in addition to routine treatment protocols during hospitalization. Tocilizumab has been evaluated in critically ill COVID-19 patients with hyperinflammatory features, although reported outcomes have varied according to disease severity, dose, and timing of administration.[9] Corticosteroids in the form of high-dose systemic therapy were commonly used in the two treatment groups, as was common clinical practise at times of acute disease.

[9] Hsun Yang, Yi-Hsin Chen, Teng-Fu Hsieh, Shiun-Yang Chuang, Ming-Ju Wu, Prediction of Mortality in Incident Hemodialysis Patients: A Validation and Comparison of CHADS2, CHA2DS2, and CCI Scores. Journal.pone.0154627 May 5, 2016, 10.1371/journal.pone.0154627. t003

It was based on clinical judgement, burden of comorbidity, and the changing institutional and national guidelines to influence treatment decisions. No standardised treatment algorithms were forced in the study, which allowed observing the results in the patient in the usual state of the clinic at various stages of the pandemic.

Outcomes and Follow-Up

The major outcome was 30-day all-cause mortality after the onset of biological therapy. Hospital length of stay and clinical progress based on change in WHO ordinal scale scores were the secondary outcomes.[10] Time to death following the start of treatment was also logged to describe the temporal dynamics of the disease progression in COVID-19 patients with MAS.

Ethical Considerations

The current study received the ethical approval of the Ethics Committee of Kastamonu University in 2022 with regard to performing activities that included participation in the study. The research was carried out in respect to the principles of the Helsinki Declaration. The requirement to use informed consent was raised under the exceptions of the institutional policies, due to the retrospective nature of the study and the use of anonymized clinical data.[11]

Results

Study Population and Baseline Characteristics

Baseline demographic characteristics and comorbidities of patients according to immunomodulatory treatment group are shown in Table 2.

---

[10] Jie Gao, Wenjing Zhang, Yaru Ding, Xinru Peng, *et al.* Evaluating the efficacy of different doses of tocilizumab in treating critically ill COVID-19 patients: a single-center retrospective cohort study Front Pharmacol. 2025 Jul 24:16:1571372. doi: 10.3389/fphar. 2025.1571372.

[11] Giulio Cavalli, Alessandro Larcher, Alessandro Tomelleri, Corrado Campochiaro, Emanuel Della-Torre et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. Lancet Rheumatol 2021 Apr;3(4): e253-e261. doi: 10.1016/S2665-9913(21)00012-6. Epub 2021.

Table 2. Demographic characteristics and comorbidities of hospitalized patients with COVID-19–associated macrophage activation syndrome, by immunomodulatory treatment group[12]

Characteristic	Tocilizumab (n = 259)	Anakinra (n = 86)
Sex, male/female	195 / 64	59 / 27
Age, median (IQR)*	72 (67–78)	69 (39–75)
Comorbidities		
Diabetes mellitus	131 (50.5%)	42 (48.8%)
Hypertension	121 (46.7%)	43 (50.0%)
Cerebrovascular disease	95 (36.7%)	34 (39.5%)
Cardiovascular disease	96 (37.1%)	35 (40.7%)
Chronic obstructive pulmonary disease	101 (39.0%)	31 (36.0%)
Chronic kidney disease	84 (32.4%)	20 (23.3%)
Chronic liver disease	61 (23.6%)	15 (17.4%)
Malignancy	75 (29.0%)	17 (19.8%)

*Age values reported according to available hospital records.

The number of hospitalised patients with COVID-19-associated macrophage activation syndrome who were identified in the study period was 345. A total of 259 such patients were treated with IL-6 pathway inhibition using tocilizumab, and 86 were treated with IL-1 pathway inhibition using anakinra. The cohort was also mostly older adults, as this represents the most impacted segment of the population by severe COVID-19 and its complications.

The patients in the anakinra group were younger compared to those in the tocilizumab group, and this is a result of clinical preferences towards anakinra in certain groups, like pregnant patients,

[12] Data are shown as number (%) unless otherwise indicated. Patients in the anakinra group were younger than those in the tocilizumab group, while comorbidity distribution was broadly similar between groups.

which is because anakinra is reported to be safe. There was no significant difference in sex, which was measured among treatments.

Comorbidity Burden

There was a great amount of comorbidity burden throughout the cohort. The most common comorbidities were diabetes mellitus, then hypertension, and chronic obstructive lung disease. There were also common cardiovascular diseases, cerebrovascular diseases, chronic kidney diseases, chronic liver diseases, and malignancies. Patients with COVID-19-associated MAS were vulnerable; this population was characterised by high scores on the Charlson Comorbidity Index, which serves to determine the risk of mortality.[13]

Clinical Course and Disease Severity

The disease progression after MAS diagnosis was usually fast and extreme. The assessment of the WHO ordinal scales showed the developed disease severity upon biological agent administration in most patients. Though immunomodulatory therapy was used, a significant percentage of patients did not improve significantly in the initial years after the treatment.[14] The accelerated evolution of the current cohort evidences the aggressiveness of MAS as a factor of COVID-19 and the difficulty of overcoming hyperinflammatory conditions once they are established.

Mortality and Outcomes

On the 30th day after biological therapy began, 205 deaths were registered, and this equated to the total mortality rate of 59 percent. The death rates were 61 and 53 percent in patients who were administered tocilizumab and anakinra, respectively. The median time of initial treatment to death was 15 days in the tocilizumab group as compared to 14 days in the anakinra group.

---

[13] Tocilizumab and COVID-19: Timing of Administration and Efficacy Emna Abidi, Wasim S El Nekidy, Eman Alefishat, Nadeem Rahman, *et al.* Front Pharmacol 2022 Feb 18:13:825749. doi: 10.3389/fphar. 2022.825749. eCollection 2022.

[14] Chen, Shunyao, Cong Zhang, Jialiu Luo, Zhiqiang Lin, Teding Chang, Liming Dong, Deng Chen, and Zhao-Hui Tang. "Macrophage activation syndrome in sepsis: from pathogenesis to clinical management." *Inflammation Research* 73, no. 12 (2024): 2179-2197.

Univariate logistic regression analysis showed no significant result in terms of association between the type of immunomodulatory treatment and 30-day mortality. These results indicate that in this real-world cohort of hospitalised patients, COVID-19-related MAS was a condition with high mortality despite extensive immunomodulatory treatment.

Discussion

The present research is a detailed report of clinical features, comorbidity burden, treatment trends, and outcomes of a large group of hospitalised patients with COVID-19-related macrophage activation syndrome. The results emphasise MAS as a serious hyperinflammatory phenotype that is fatal in the COVID-19 pandemic.

MAS as a vicious Hyperinflammatory Phenotype

The high mortality of this group of patients highlights the clinical severity of the MAS in COVID-19 patients. Hyperinflammatory syndromes are a vital feature of severe disease and are a result of dysregulated host immune responses and not a direct effect of viruses.[15] The high level of comorbidity that is witnessed among patients only increases the risk of adverse outcomes and makes it difficult to be managed clinically.

Emerging Infectious Disease Preparedness Implications

The COVID-19 pandemic confirmed that the complications that appear as a result of the immune response can also have a significant impact in the case of an emerging outbreak of an infectious disease. MAS is an example of the difficulties associated with hyperinflammatory syndromes, such as accelerated degradation, excessive use of resources, and a lack of therapeutic options once inflammatory dysregulation has developed. Risk stratification that is based on early recognition and methodical severity analysis can be valuable to inform prompt intervention in future outbreaks.[16]

---

[15] La-Beck, Ninh M., Young R. Lee, Jalpa Patel, Hui Yang, Michal Stout, Alanna Kologey, Amanda Ruesewald, Carlos A. Alvarez, and Carlos Alvarez. "Clinical characteristics and patterns of immune responses in COVID-19 patients from a rural community hospital." *Cureus* 16, no. 6 (2024).

[16] Chávez-Valencia, Venice, Citlalli Orizaga-de-la-Cruz, and Francisco Alejandro Lagunas-Rangel. "Acute kidney injury in COVID-19 patients: pathogenesis, clinical characteristics, therapy, and mortality." *Diseases* 10, no. 3 (2022): 53.

Patterns of Treatment and Clinical Practise

Real-world uses of the IL-1/IL-6 therapy against the pandemic involved wide usage of immunomodulatory therapies. Even though it was found that there were differences between the two treatments in terms of mortality, the differences were not found to be statistically significant.[17] The paper will not prove the superiority of treatment, but it illuminates the inconsistency of results and the drawbacks of the existing treatment methods to address the established hyperinflammatory syndromes in pandemic conditions.[18]

Study Limitations

There are various limitations of this study. The retrospective and single-centred design restricts the causal inference and generalisation. Diagnosis of MAS was not done according to the standardised diagnosis criteria, but according to the clinical evaluation, and the residual confounding about the severity of the disease and the choice of treatment cannot be ruled out. Also, there is the possibility that the developing treatment protocols during the course of the study period have affected results.

Conclusions

Macrophage activation syndrome is a life-threatening hyperinflammatory phenotype in patients with COVID-19 hospitalised, and it comes with high mortality rates. The results indicate the need to recognise the issue early, pay close attention to severity, and be ready to deal with immune-mediated complications in the case of outbreaks of infectious diseases. Developing a better insight into hyperinflammatory syndromes like MAS will be important in streamlining the clinical management and enhancing the response strategies to outbreaks in future pandemics.

---

[17] Albanji, Mohammed H., Ahmed A. Baghafar, Yasser A. Alghanmi, Mohammed M. Shaaban, Ebrahim A. Alkashlan, Haifa H. Sende, Mofareh S. Alzahrani, and Nuha N. Filfilan. "Clinical presentation and management of multisystem inflammatory syndrome in children with COVID-19: a systematic review." *Cureus* 15, no. 10 (2023): e46918.

[18] Kaddah, Safy Zahid, Samah Selim Abd El-Naeem, and Hala Ashraf. "PRELIMINARY STUDY: CLINICAL CHARACTERISTIC OF PATIENTS WITH MILD TO MODERATE COVID-19 PNEUMONIA EGYPTIAN EXPERIENCE REGARDING MANAGEMENT, MORBIDITY, MORTALITY."

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Kastamonu University in 2022. The study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective design of the study and the use of anonymized clinical data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional privacy and ethical restrictions but may be available from the corresponding author upon reasonable request and with appropriate institutional approval.

Competing interests

The author declares no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions

D.İ. conceived and designed the study, collected the data, analyzed and interpreted the findings, drafted the manuscript, critically revised the manuscript, and approved the final version for submission.

Acknowledgements

The author thanks the healthcare professionals and administrative staff involved in the care of hospitalized patients during the COVID-19 pandemic.

References

1. [1] National Institutes of Health (USA). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, <https://www.covid19treatmentguidelines.nih.gov/> (2021).
2. [1] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180:934 –43. doi: 10.1001/jamainternmed.2020.0994.
3. [1] Tipirneni R, Schmidt H, Lantz PM, Karmakar M. Associations of 4 geographic social vulnerability indices with US COVID-19 incidence and mortality. Am J Public Health. 2022;112(11):1584–8.
4. [1] Y. Fujita, T. Hoshina, J. Matsuzaki, Y. Yoshioka, T. Kadota, Y. Hosaka, *et al.* Early prediction of COVID-19 severity using extracellular vesicle COPB2 J Extracell Vesicles, 10 (2021), Article e12092, 10.1002/jev2.12092
5. [1] M.O. Satici, M.M. Islam, C. Satici, C.N. Uygun, E. Ademoglu, İ. Altunok, *et al.* The role of a noninvasive index 'SpO_2/FiO_2' in predicting mortality among patients with COVID-19 pneumonia Am J Emerg Med, 57 (2022), pp. 54-59, 10.1016/j.ajem.2022.04.036
6. [1] P. Toniati, S. Piva, M. Cattalini, E. Garrafa, F. Regola, F. Castelli, *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, 19 (2020), Article 102568, 10.1016/j.autrev.2020.102568
7. [1] Charlson Comorbidity Index scores were calculated at hospital admission to estimate baseline mortality risk and comorbidity burden.
8. [1] Hsun Yang, Yi-Hsin Chen, Teng-Fu Hsieh, Shiun-Yang Chuang, Ming-Ju Wu, Prediction of Mortality in Incident Hemodialysis Patients: A Validation and Comparison of CHADS2, CHA2DS2, and CCI Scores. Journal.pone.0154627 May 5, 2016, 10.1371/journal.pone.0154627. t003
9. [1] Jie Gao , Wenjing Zhang, Yaru Ding , Xinru Peng , *et al.* Evaluating the efficacy of different doses of tocilizumab in treating critically ill COVID-19 patients: a single-center

retrospective cohort study Front Pharmacol. 2025 Jul 24:16:1571372. doi: 10.3389/fphar. 2025.1571372.

10. [1] Giulio Cavalli , Alessandro Larcher , Alessandro Tomelleri , Corrado Campochiaro , Emanuel Della-Torre et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. Lancet Rheumatol 2021 Apr;3(4): e253-e261. doi: 10.1016/S2665-9913(21)00012-6. Epub 2021.
11. [1] Data are shown as number (%) unless otherwise indicated. Patients in the anakinra group were younger than those in the tocilizumab group, while comorbidity distribution was broadly similar between groups.
12. [1] Tocilizumab and COVID-19: Timing of Administration and Efficacy Emna Abidi , Wasim S El Nekidy , Eman Alefishat , Nadeem Rahman , *et al.* Front Pharmacol 2022 Feb 18:13:825749. doi: 10.3389/fphar. 2022.825749. eCollection 2022.
13. [1] Chen, Shunyao, Cong Zhang, Jialiu Luo, Zhiqiang Lin, Teding Chang, Liming Dong, Deng Chen, and Zhao-Hui Tang. "Macrophage activation syndrome in sepsis: from pathogenesis to clinical management." *Inflammation Research* 73, no. 12 (2024): 2179-2197.
14. [1] La-Beck, Ninh M., Young R. Lee, Jalpa Patel, Hui Yang, Michal Stout, Alanna Kologey, Amanda Ruesewald, Carlos A. Alvarez, and Carlos Alvarez. "Clinical characteristics and patterns of immune responses in COVID-19 patients from a rural community hospital." *Cureus* 16, no. 6 (2024).
15. [1] Chávez-Valencia, Venice, Citlalli Orizaga-de-la-Cruz, and Francisco Alejandro Lagunas-Rangel. "Acute kidney injury in COVID-19 patients: pathogenesis, clinical characteristics, therapy, and mortality." *Diseases* 10, no. 3 (2022): 53.
16. [1] Albanji, Mohammed H., Ahmed A. Baghafar, Yasser A. Alghanmi, Mohammed M. Shaaban, Ebrahim A. Alkashlan, Haifa H. Sende, Mofareh S. Alzahrani, and Nuha N. Filfilan. "Clinical presentation and management of multisystem inflammatory syndrome in children with COVID-19: a systematic review." *Cureus* 15, no. 10 (2023): e46918.
17. [1] Kaddah, Safy Zahid, Samah Selim Abd El-Naeem, and Hala Ashraf. "PRELIMINARY STUDY: CLINICAL CHARACTERISTIC OF PATIENTS WITH MILD TO

MODERATE COVID-19 PNEUMONIA EGYPTIAN EXPERIENCE REGARDING MANAGEMENT, MORBIDITY, MORTALITY."