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The Role of Vitamin C Supplementation in Preventing Severity Progression in Mild and Moderate COVID-19 Patients at Universitas Airlangga Hospital

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ABSTRACT

Introduction: Coronavirus disease (COVID-19) is an infectious disease that increases pro-oxidant elements and decreases antioxidants. Vitamin C functions as a potent antioxidant in humans due to its electron-donating properties. This study aimed to explain the impact of three distinct vitamin C supplementation dosages in preventing disease severity progression among mild and moderate COVID-19 patients.

Methods: This retrospective study used secondary data from 100 medical records (n=100). The subjects were classified into three categories based on the vitamin C dosage. The data were analyzed using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 26.0 for Windows.

Results: Most of mild and moderate COVID-19 patients (78%) did not experience increased disease severity. Vitamin C supplementation significantly demonstrated a different outcome in preventing disease severity progression among the three groups (p=0.018). However, it did not significantly show any difference in reducing the duration of hospital stay (p=0.680).

Conclusion: The impact of vitamin C supplementation on COVID-19 severity appeared to vary depending on the dosage administered. However, it did not affect the duration of the hospital stay.

Highlights:
1. The administration of different dosages of vitamin C significantly yields different outcomes in preventing the progression of disease severity.
2. Most patients with mild and moderate coronavirus disease (COVID-19) did not demonstrate an escalation in disease severity.

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Introduction

The World Health Organization (WHO) stated that globally, as of 30 June 2021, there have been 181,521,067 confirmed cases of coronavirus disease (COVID-19) with 3,937,437 deaths.[1] Meanwhile, in Indonesia, from 3 January 2020 to 30 June 2021, there were 2,178,272 confirmed cases of COVID-19 with 58,491 deaths.[1] As of 30 June 2021, there were 21,807 new cases.[1] The number of cases that continue to increase directly or indirectly impacts the availability of Intensive Care Unit (ICU) rooms. According to data from the Jakarta Health Office, as of 1 July 2021, the availability of ICU with negative pressure and ventilators was only 7%.[2] In addition, the emergence of a new variant of SARS-CoV-2 also had an effect. In the United Kingdom (UK), the emergence of the Delta variant led to a 79% increase in cases, which was said to be more contagious and increased the risk of hospitalization.[3–5]

Oxidative stress is a disturbance in the balance between pro-oxidant and antioxidant elements, which favors pro-oxidants and has the potential to cause damage.[6] In COVID-19 patients, reactive oxygen species (ROS) are imbalanced due to the nicotinamide adenine dinucleotide phosphate hydrogen/NADPH oxidase (NOX) activation pathway.[7] In addition to this mechanism, it is proven that in COVID-19 patients, the levels of antioxidants such as vitamin C, glutathione (GSH), porcine splenic hydrolysate (PSH), and vitamin E are far below the reference value.[8] Thus, the oxidative stress in these patients is even worse.[8]

COVID-19 has multiple manifestations ranging from mild to moderate disease, and some may lead to severe or even life-threatening conditions. Hence, there is a pressing demand for effective and targeted therapies. Foregoing treatment regimens such as antivirals and immunomodulatory drugs have been practiced amongst COVID-19 patients. Nevertheless, only remdesivir, an antiviral drug, received approval from the Food and Drug Administration (FDA) for COVID-19 treatment. Due to the availability and relatively high cost, the choice of treatment for COVID-19 remains supportive. Several supplements for supportive treatment, such as vitamin C, have been brought into clinical trials. Many show benefits in reducing the severity of COVID-19 disease through the antiviral properties, immunomodulatory, and antioxidant effects. Moreover, compared to other drugs used to treat COVID-19, oral and intravenous vitamin C supplementation is relatively cost-effective.[9]

Vitamin C is considered a reasonable adjunct treatment option for countering oxidative stress in COVID-19 patients due to its antioxidant properties.[10] Various recommendations exist regarding the dosage of vitamin C supplementation, which depend on different health perspectives and are based on specific rationales. The Food and Agricultural Organization (FAO)/WHO proposes a recommended nutrient intake for vitamin C of 45 mg per day for adults.[11] In COVID-19 currently, there is no specific guideline for vitamin C supplementation dosage to prevent disease severity progression, and research on this matter still varies in dosage.[12]

Oxidative stress conditions in the body can affect the severity of COVID-19 patients.[13] The Indonesian Society of Respirology (PDPI) classified the severity of COVID-19 into five, namely asymptomatic, mild, moderate, severe, and critical, according to symptoms and lung conditions.[7] The pathogenesis of COVID-19 in patients presenting with severe symptoms is believed to originate from ROS overproduction, resulting in oxidative stress. This heightened ROS generation disrupts cellular balance and contributes significantly to tissue damage. Furthermore, a subset of these patients exhibits an inadequate immune response, further complicating matters by promoting hyperinflammation. This hyperinflammatory state often manifests as a cytokine storm, where the immune system releases an overwhelming quantity of pro-inflammatory cytokines. The intricate interplay between oxidative stress and this dysregulated immune response ultimately leads to substantial tissue injury, exacerbating the severity of COVID-19. These complex pathological mechanisms underscore the multifaceted nature of disease progression in COVID-19 and emphasize the urgent necessity for targeted therapeutic approaches to mitigate these deleterious effects.[14] This is also supported by a study that found markers of damage caused by ROS in COVID-19 patients.[15]

The Centers for Disease Control and Prevention (CDC) classified disease prevention into primary, secondary, and tertiary prevention. This study is included in tertiary prevention because it treats disease after diagnosis to slow or stop its progression.[16] It aimed to explain the impact of three distinct vitamin C supplementation dosages in preventing disease severity progression among mild and moderate COVID-19 patients, which would be evaluated through oxygen saturation, respiratory rate, chest X-ray, and symptoms.

Methods

This was a descriptive-analytic observational study.[6] The dependent variable was the progression of disease severity, chest X-ray, and duration of hospital stay. Meanwhile, the independent variable was the dose of vitamin C received. This study had received ethical clearance from the ethics commission of the Faculty of Medicine, Universitas Airlangga, Surabaya (No. 202/KEP/2021).

This retrospective study was conducted using secondary data in the form of medical records. The medical records were obtained using a simple random sampling technique. The sample was part of the study population. Namely, all confirmed patients from the results of reverse transcription polymerase chain reaction (RT-PCR) COVID-19 swabs in June 2020-December 2020 at Universitas Airlangga Hospital, Surabaya, that met the inclusion criteria and were given oral or intravenous ascorbic acid. The statistical analysis was conducted using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 26.0 for Windows.[17]

Data Analysis

The data collected from this study were analyzed using descriptive analysis, normality test, and Mann-Whitney test with IBM SPSS version 26.0 for Windows with a 95% confidence level.[17]

Results

This study included 100 inpatients of Universitas Airlangga Hospital, consisting of 49 males (49%) and 51 females (51%). The age range was between 18 years old and 60 years old. The sample was then summarized in Table 1.

Table 1. Sample characteristics

Characteristics		n	%
Age	Mean	34.28	
	SD	10.83	
Gender	Male	49	49%
	Female	51	51%
Symptom	Cough	59	59%
	Fever	50	50%
	Headache	10	10%
	Sore throat	24	24%
	Rhinitis	18	18%
Severity	Mild	51	51%
	Moderate	49	49%
Progression	Worsen	22	22%
	Improved	78	78%
Mild Severity	Worsen	18	18%
	Improved	33	33%
Moderate Severity	Worsen	4	4%
	Improved	45	45%
Outcome	Recovered	99	99%
	Died	1	1%

Source: Research data, processed

As shown in Table 1, the mean age in the sample group was 34.28, with the highest number of patients from the 25-29 years old group (22%). The proportion of gender in this study sample was fairly proportional. Most of the patients (78%) did not progress into more severe forms of disease.

Table 2. Comparison between three vitamin C dosage groups to disease severity progression

Antioxidant	Severity Progression		p-value
	Worsen	Improved	
Vitamin C 50-750 milligrams	4 (10.9%)	33 (89.1%)	0.018
Vitamin C 751-1,500 milligrams	9 (23.7%)	29 (76.3%)	
Vitamin C 1,501-2,250 milligrams	9 (36%)	16 (64%)	

Source: Research data, processed

Table 2 shows the disease severity progression difference in mild and moderate COVID-19 patients who had been given vitamin C supplementation in three different dosage groups. The progression was determined by comparing the patients' disease severity the first time they were admitted to the hospital with the highest severity they experienced throughout their stay. Mann-Whitney analysis showed a significant difference between the three groups.

Table 3. Comparison between three vitamin C dosage groups and chest X-ray

Antioxidant	Chest X-Ray		p-value
	Worsen	Improved	
Vitamin C 50-750 milligrams	7 (18.9%)	30 (81.1%)	0.037
Vitamin C 751-1,500 milligrams	11 (28.9%)	27 (71.1%)	
Vitamin C 1,501-2,250 milligrams	11 (44%)	14 (56%)	

Source: Research data, processed

Table 3 compares the chest X-rays of patients with mild and moderate COVID-19 who had been given vitamin C supplementation in three different dosage groups. These results were obtained by comparing the chest X-rays of the patients when they first came into the hospital with those taken during their hospital stay. Mann-Whitney analysis showed a significant difference between the three groups.

Table 4. Comparison between three vitamin C dosage groups to duration of hospital stay

Antioxidant	Mean LoS (Days)	p-value
Vitamin C 50-750 milligrams	15.72	0.680
Vitamin C 751-1,500 milligrams	16.13	
Vitamin C 1,501-2,250 milligrams	13.64	

Source: Research data, processed
LoS: length of stay

The mean duration of hospital stay for patients was 15.38 days, ranging from 5 days to 44 days maximum. As shown in Table 4, there was no significant difference in the duration of hospital stay between the three dosage groups.

Discussion

As discussed previously, it is widely known that in healthy individuals, there is a balance between the formation of reactive species (RS) and the body's antioxidant defense mechanisms. Under normal physiological conditions, the production of RS is effectively counterbalanced by antioxidants, thereby maintaining cellular homeostasis and integrity. However, disruption of this balance, whether due to environmental factors, inadequate nutrition, or underlying health conditions, can lead to excessive accumulation of RS. This increase in concentration results in a condition known as oxidative stress, characterized by an abundance of potentially harmful molecules. Oxidative stress has significant implications, contributing to cell damage, inflammation, and the progression of various diseases. Therefore, understanding these complex interactions comprehensively is critical for designing strategies to reduce oxidative stress and improve overall health.[18]

As shown in Table 1, the mean age of the patients was 34.28 years old. This condition is similar to a previous study by Canning, *et al*. (2020), who found that the most age group that got infected were those who fell in the 30-39 years old group.[19] The different social distancing behaviors among age groups can explain this. Even though these people go out of their homes similarly, the older age group

seems to have less close contact with their household members compared to the younger age groups. This fact becomes necessary because, in a study, it was found that most of the patients who died were from the older age group (>64 years old).[20]

Regarding the gender of the infected patients, the result was fairly equal. This study is comparable to another study that found both genders had a similar prevalence of COVID-19, although men had a higher risk for death and worse outcomes.[20] Men have potentially worse outcomes for COVID-19 because they have been shown to express higher ACE2 compared to women.[20] Another explanation for this condition may be that men generally have a shorter life expectancy compared to women.[20]

COVID-19 caused many symptoms, including runny nose, anosmia, headache, and diarrhea, with cough and fever being the most common. It is similar to this study, which found cough and fever the most common symptoms. However, symptoms have a significant variant based on the country where the data was taken. Furthermore, about 12% of transmissions occurred before the initial case developed symptoms. Hence, better tracing and disease prevention methods are needed to combat COVID-19.[21]

Many factors influence COVID-19 outcomes. Aside from previously mentioned factors, variants, vaccination status, comorbidities, and care received also play a role. Although this study did not identify specific causes of these factors, it documented that 1% of mild and moderate COVID-19 patients had died. Wei et al. (2023) also stated a similar finding: 3.1% of the patients died.[22] Patients' age and comorbidities are considered risk factors for the worse outcomes.[22]

Numerous studies have shed light on the important role of oxidative stress in the initiation and progression of various diseases, especially viral infections such as COVID-19. In the early stages of infection, oxidative stress can activate immune cells, thereby increasing the body's defense mechanisms and inhibiting viral replication. However, in more severe cases, patients may experience uncontrolled oxidative stress, leading to increased inflammation, tissue damage, and potential organ failure. As the infection progresses, there is a depletion of antioxidants, such as vitamin C, coupled with increased oxidative damage. Postmortem analysis of lung tissue has revealed significant evidence of oxidative and nitrosative stress, underscoring the profound impact of these processes on the pathophysiology of this disease. In summary, oxidative stress is an important factor that significantly influences the clinical outcome of COVID-19, influencing the severity of symptoms and overall prognosis of affected individuals.[13]

This study was meticulously designed to systematically compare the effects of three different vitamin C supplementation dose groups on the progression of disease severity. It also aimed to assess the impact of vitamin C on chest X-ray findings and duration of hospitalization among patients diagnosed with mild to moderate COVID-19. The study group consisted of 100 patients, and the results showed a trend that the majority (78%) did not experience progression to more severe disease. These findings are consistent with a previous study, which consistently showed that only a small proportion (20%) of patients with mild to moderate COVID-19 ultimately experienced more serious manifestations, such as pneumonia, requiring advanced medical intervention.[23] Another study included 99 COVID-19 patients, where 17 of them developed acute respiratory distress syndrome (ARDS), and 11 of them died.[24] The underlying cause of these mortalities was heightened oxidative stress and the excessive production of cytokines, ultimately leading to the development of ARDS. Acute respiratory distress syndrome that is known to cause severe hypoxemia arises from uncontrolled inflammation, oxidative injury, and disruption of the alveolar-capillary barrier. Both ARDS and its precursor, acute lung injury (ALI), significantly contribute to morbidity and mortality in COVID-19 cases. In these patients, it was found that there were elevated levels of C-reactive protein (hs-CRP), which functions as a marker of inflammation and oxidative stress.[24]

Antioxidants can mitigate the effects of oxidants by neutralizing ROS and inhibiting enzymes that produce oxidants. The excessive production of ROS and the deficiency of antioxidant defenses play a crucial role in the frequency, progression, and severity of COVID-19.[25,26] Vitamin C is considered a viable treatment for COVID-19 infection among all available antioxidants due to its anti-inflammatory, antioxidant, and immunomodulating properties.[10] Vitamin C exerts its effects through several important pathways related to its antioxidant function. Primarily, it acts as a direct scavenger of free radicals, effectively neutralizing highly reactive molecules that can cause cell damage and contribute to oxidative stress. In addition to these direct actions, vitamin C plays an important role in modulating pro-inflammatory pathways. Vitamin C acts as a suppressant, thereby reducing the inflammatory response, which can reduce various diseases. Moreover, vitamin C activates important intracellular antioxidant systems, increasing the body's ability to fight oxidative stress from within cells. By supporting these diverse mechanisms, vitamin C maintains cellular integrity and significantly contributes to immune function and overall health. The importance of essential nutrients for preventing and managing conditions associated with oxidative stress cannot be overstated.[27] The evidence on the effectiveness of vitamin C supplementation against COVID-19 is based on studies with small sample sizes and varying doses.[12]

In this study, it was found that there was a significant difference in disease severity progression in vitamin C supplementation among three dose groups. This is consistent with a previous study that indicated a notable disparity between the effects of high-dose oral vitamin C, which shortens fever duration and accelerates viral clearance, and those of the group receiving the recommended dietary allowance dose.[28] Another study in China supported an improvement in COVID-19 patients treated with high-dose intravenous vitamin C compared to placebo.[28]

Respiratory tract disease associated with COVID-19 usually manifests clinically as pneumonia with radiological features. Therefore, radiological findings can be a good assessment in predicting the course of COVID-19 disease. Although chest X-rays are considered less sensitive for detecting lung lesions in the early stages of the disease, they help monitor the rapid development of lung defects in COVID-19, especially in critically ill patients admitted to intensive care.[29] A previous randomized controlled trial (RCT) evaluating the administration of vitamin C in critically ill COVID-19 patients showed a significant improvement in lung function and a higher ratio of PaO_2/FiO_2 following 7 days of 24 g/day of intravenous vitamin C administration.[30] Another study regarding the role of vitamin C supplementation in the prevention of COVID-19 patients exhibited positive outcomes in patients receiving high doses of vitamin C supplementation (0.5-1.6 g/day).[31] An improvement in chest X-rays alongside a reduction in hospital stay was shown in this group.[31] This study revealed a significant difference in the progression of chest X-rays among three vitamin C dosage groups.[31] Similar to this study, it was stated that more patients who had been treated with high-dose vitamin C developed abnormalities in chest X-rays than those in the non-high-dose vitamin C group.[32]

Different severity degrees of COVID-19 are present.[7] General ward-based care, high-dependency units with oxygen support, and intensive care where patients might be intubated for mechanical ventilation are all types of hospital care that can be provided. Due to different geographic conditions and the required degree of care, the length of hospital stay will likely depend on both factors.[33] Insight into COVID-19 patients' hospital duration of stay and associated risk factors was required in advance, and it might help with the appropriate distribution of medical resources.[34] This study showed that vitamin C supplementation in three different dose groups had a similar duration of hospital stay. This result is consistent with a previous study that stated there was no significant difference in hospital stay duration between the high-dose vitamin C supplementation group and lower-dose vitamin C supplementation.[35] Furthermore, there was no notable discrepancy in the duration of ICU stay between the high-dose vitamin C group and the control group. In contrast to these results, the median hospital length of stay in patients who were given vitamin C was shorter than those who were not given vitamin C. However, the two did not show a significant difference in mortality rates.[36]

Several factors could influence the outcome of this study. This could happen because the levels of vitamin C in mild and moderate COVID-19 patients might not be particularly low enough, even though this was not measured in this study. A previous study also stated that based on circulating vitamin C, which had been predicted genetically, did not show any association with severe COVID-19, hospitalization, infection, and pneumonia.[37] Furthermore, numerous factors, such as the patient's age, gender, and existing health background, could possibly influence the vitamin C requirement.[11]

Strength and Limitations

This study might have practical applications in preventing disease severity progression in mild and moderate COVID-19 patients by giving easily accessible antioxidants such as vitamin C. However, more detailed research is still needed. Moreover, this study has a limitation. The model's effect estimates rely on observational research. These model estimates may have been affected since they are susceptible to biases and confounding.

Conclusion

Antioxidant supplementation with vitamin C among the three dosage groups yielded significantly distinct outcomes in preventing disease severity progression. However, it did not demonstrate a significant difference in reducing the duration of hospital stay for mild and moderate COVID-19 cases. Further research remains necessary.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This research had received approval of ethical clearance from the ethics commission of the Faculty of Medicine Universitas Airlangga Surabaya (No. 202 /KEP/2021) on 23-11-2021.

Authors' Contributions

Conceived and designed the study: YAA. Gathered, analyzed, interpreted the data, and wrote the manuscript: YAA. Verified the analytical methods: ANR. Reviewed, revised, and approved the final version of the manuscript: ANR, DNI, and WIE.

References

1. World Health Organization (WHO). *Weekly Epidemiological Update on COVID-19 - 29 June 2021*. Geneva, (2021). [Website]
2. Jakarta Health Office (Dinas Kesehatan DKI Jakarta). Executive Information System Dinas Kesehatan Provinsi DKI Jakarta. *Executive Information System Dinas Kesehatan Provinsi DKI Jakarta*, (2021). [Website]

3. Mahase E. Delta Variant: What is Happening with Transmission, Hospital Admissions, and Restrictions? *BMJ* 2021; 373: n1513. [PubMed]
4. O'Dowd A. COVID-19: Cases of Delta Variant Rise by 79%, but Rate of Growth Slows. *BMJ* 2021; 373: n1596. [PubMed]
5. Torjesen I. COVID-19: Delta Variant is Now UK's Most Dominant Strain and Spreading through Schools. *BMJ* 2021; 373: n1445. [PubMed]
6. Ranganathan P, Aggarwal R. Study Designs: Part 3 - Analytical Observational Studies. *Perspect Clin Res*; 10, (2019). [Journal]
7. Burhan E, Susanto AD, Nasution SA, *et al*. *Pedoman Tatalaksana COVID-19*. 3rd ed. Jakarta: PDPI, PERKI, PAPDI, PERDATIN, IDAI, 2020. [Book]
8. Muhammad Y, Kani YA, Iliya S, Muhammad JB, Binji A, Ahmad AEF, *et al*. Deficiency of Antioxidants and Increased Oxidative Stress in COVID-19 Patients: A Cross-Sectional Comparative Study in Jigawa, Northwestern Nigeria. *SAGE Open Med* 2021; 9: 2050312121991246. [PubMed]
9. Abobaker A, Alzwi A, Alraied AHA. Overview of the Possible Role of Vitamin C in Management of COVID-19. *Pharmacol Reports* 2020; 72: 1517–1528. [PubMed]
10. Shahbaz U, Fatima N, Basharat S, Bibi A, Yu X, Hussain MI, *et al*. Role of Vitamin C in Preventing of COVID-19 Infection, Progression and Severity. *AIMS Microbiol* 2022; 8: 108–124. [PubMed]
11. Carr AC, Lykkesfeldt J. Discrepancies in Global Vitamin C Recommendations: A Review of RDA Criteria and Underlying Health Perspectives. *Crit Rev Food Sci Nutr* 2021; 61: 742–755. [PubMed]
12. Ahmad SR. Vitamin C for COVID-19 Treatment: Have We Got Enough Evidence? *Front Nutr*; 9, (2022). [Journal]
13. Georgieva E, Ananiev J, Yovchev Y, Arabadzhiev G, Abrashev H, Abrasheva D, *et al*. COVID-19 Complications: Oxidative Stress, Inflammation, and Mitochondrial and Endothelial Dysfunction. *International Journal of Molecular Sciences*; 24. 2023. [PubMed]
14. Avila-Nava A, Pech-Aguilar AG, Lugo R, Medina-Vera I, Guevara-Cruz M, Gutiérrez-Solis AL. Oxidative Stress Biomarkers and Their Association with Mortality among Patients Infected with SARS-CoV-2 in Mexico. *Oxid Med Cell Longev* 2022; 2022: 1058813. [PubMed]
15. Muhoberac BB. What Can Cellular Redox, Iron, and Reactive Oxygen Species Suggest about the Mechanisms and Potential Therapy of COVID-19? *Front Cell Infect Microbiol*; 10, (2020). [Journal]
16. Kisling LA, Das JM. Prevention Strategies. Treasure Island (FL), 2024. [PubMed]
17. Nie NH, Bent DH, Hull CH. Statistical Package for the Social Sciences (SPSS), (2018). [Website]
18. Sies H. Oxidative Stress: Concept and Some Practical Aspects. *Antioxidants*; 9. 2020. [PubMed]
19. Canning D, Karra M, Dayalu R, Guo M, Bloom DE. The Association between Age, COVID-19 Symptoms, and Social Distancing Behavior in the United States. *medRxiv : The Preprint Server for Health Sciences*. April 2020. [PubMed]
20. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, *et al*. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Heal* 2020; 8: 152. [PubMed]
21. Dabhekar S, Basagoudanavar S, Bidkar V, Prathipati K, Sujiv A, Rathod BS, *et al*. A Study of Symptomatology of COVID-19 Laboratory-Confirmed Cases at Tertiary Care Center: A Cross-Sectional Study. *Cureus* 2022; 14: e22186. [PubMed]
22. Wei Q, Mease PJ, Chiorean M, Iles-Shih L, Matos WF, Baumgartner A, *et al*. Risk Factors for Severe COVID-19 Outcomes: A Study of Immune-Mediated Inflammatory Diseases, Immunomodulatory Mmedications, and Comorbidities in a Large US Healthcare System. *medRxiv : The Preprint Server for Health Sciences*. June 2023. [PubMed]
23. Huang H, Cai S, Li Y, Li Y, Fan Y, Li L, *et al*. Prognostic Factors for COVID-19 Pneumonia Progression to Severe Symptoms Based on Earlier Clinical Features: A Retrospective Analysis. *Front Med*; 7, (2020). [Journal]
24. Boretti A, Banik BK. Intravenous Vitamin C for Reduction of Cytokines Storm in Acute Respiratory Distress Syndrome. *PharmaNutrition* 2020; 12: 100190. [PubMed]
25. DE Flora S, Balansky R, LA Maestra S. Antioxidants and COVID-19. *J Prev Med Hyg* 2021; 62: E34–E45. [PubMed]
26. Pincemail J, Cavalier E, Charlier C, Cheramy-Bien JP, Brevers E, Courtois A, *et al*. Oxidative Stress Status in COVID-19 Patients Hospitalized in Intensive Care Unit for Severe Pneumonia. A Pilot Study. *Antioxidants*; 10. 2021. [PubMed]
27. Gęgotek A, Skrzydlewska E. Antioxidative and Anti-Inflammatory Activity of Ascorbic Acid. *Antioxidants*; 11. 2022. [PubMed]
28. Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, *et al*. High-Dose Vitamin C Infusion for the Treatment of Critically Ill COVID-19. *Res Sq* 2020; 1–23. [Journal]
29. Yasin R, Gouda W. Chest X-Ray Findings Monitoring COVID-19 Disease Course and Severity. *Egypt J Radiol Nucl Med* 2020; 51: 193. [Springer]
30. Sadiq A, Sana A, Qamar F, Sadia H, Shahab S. Review Article on the Role of Vitamin C in the Prevention of COVID-19 or Viral Infection. *Int J Trends Heal Sci* 2023; 1: 11–16. [Journal]
31. Holford P, Carr AC, Jovic TH, Ali SR, Whitaker IS, Marik PE, *et al*. Vitamin C—An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19. *Nutrients*; 12. 2020. [PubMed]
32. Fleifel M, Mina J, Haykal T, Asmar R, El Hout G, Harb R, *et al*. Intravenous High Dose Vitamin C and Selected Antiviral Drugs in Hospitalized COVID-19 Patients: A Descriptive Cohort Study. *J Infect Dev Ctries* 2022; 16: 1542–1554. [PubMed]
33. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, Pearson CAB, *et al*. COVID-19 Length of Hospital Stay: A Systematic Review and Data Synthesis. *BMC Med* 2020; 18: 270. [PubMed]
34. Alahmari AK, Almalki ZS, Albassam AA, Alsultan MM, Alshehri AM, Ahmed NJ, *et al*. Factors associated with Length of Hospital Stay among COVID-19 Patients in Saudi Arabia: A Retrospective Study during the First Pandemic Wave. *Healthcare*; 10. 2022. [PubMed]
35. Wiboworini B, Ayusari A, Myrtha R, Rahayu D, Widardo W, Lanti Y, *et al*. Relationship between Vitamin C and Length of Hospital Stay for COVID-19 Patients with Comorbidities. *Maj Kedokt Bandung* 2022; 54: 14–19. [Journal]
36. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, *et al*. Safety and Effectiveness of High-Dose Vitamin C in Patients with COVID-19: A Randomized Open-Label Clinical Trial. *Eur J Med Res* 2021; 26: 20. [PubMed]
37. Hui LL, Nelson EAS, Lin SL, Zhao JV. The Role of

Vitamin C in Pneumonia and COVID-19 Infection in Adults with European Ancestry: A Mendelian Randomisation Study. *Eur J Clin Nutr* 2022; 76: 588–591. [PubMed]