

Editorial Team

Editorial Team

EDITOR IN CHIEF



I Putu Dedy Arjita

Faculty of Medicine, Universitas Islam Al-Azhar, Nusa Tenggara Barat, Indonesia

|  |  |  |

ADVISORY EDITORIAL BOARD



Artha Budi Susila Duarsa

Faculty of Medicine, Universitas Islam Al-Azhar, Nusa Tenggara Barat, Indonesia

|  |  |  |

EDITORIAL BOARD



Ahmad Fudholi

Universiti Kebangsaan Malaysia, Bangi, Malaysia

|  |  |  |



Rozikin

Faculty of Medicine, Universitas Islam Al-Azhar,
Nusa Tenggara Barat, Indonesia

|  |  |  |



Sukandriani Utami

Faculty of Medicine, Universitas Islam Al-Azhar,
Nusa Tenggara Barat, Indonesia

| [Google](#) | [Scopus](#) | [ORCID](#) |



Putu Asih Primatanti

Fakultas Kedokteran dan Ilmu Kesehatan,
Universitas Warmadewa, Bali, Indonesia

| [Google](#) | [Scopus](#) | [ORCID](#) |



Ayu Anulus

Faculty of Medicine, Universitas Islam Al-Azhar,
Nusa Tenggara Barat, Indonesia

| [Google](#) | [Scopus](#) | [ORCID](#) |



Akhmad Azmiardi

Fakultas Kesehatan Masyarakat, Universitas
Veteran Bangun Nusantara, Jawa Tengah, Indonesia

| [Google](#) | [Scopus](#) | [ORCID](#) |

MANAGING EDITOR



Sabariah

Faculty of Medicine, Universitas Islam Al-Azhar, Nusa Tenggara Barat, Indonesia

| [Google](#) | [Scopus](#) | [ORCID](#) |

LAYOUT EDITOR



Kurniawan

Faculty of Medicine, Universitas Islam Al-Azhar, Nusa Tenggara Barat, Indonesia

LANGUAGE EDITOR



Sabrina Intan Zoraya

Faculty of Medicine, Universitas Islam Al-Azhar, Nusa Tenggara Barat, Indonesia

|  |  |  |

Peer Reviewers

REVIEWERS

Efta Triastuti

The University of
Manchesterdisabled, Manchester, United
Kingdom

|  |  |  |

I Made Ady Wirawan

Faculty of Medicine, Universitas
Udayana, Bali, Indonesia

|  |  |  |

Mora Claramita

Faculty of Medicine, Universitas Gadjah Mada,
Yogyakarta, Indonesia

|  |  |  |

I Ketut Agus Somia

Departemen Penyakit Dalam,
Fakultas Kedokteran, Universitas Negeri
Udayana, Bali, Indonesia

|  |  |  |

Harliansyah

Biomedik Pascasarjana, Universitas Yarsi, Jakarta, Indonesia

|  |  |  |

Amelia Nur Vidyanti

Department of Neurology, Faculty of Medicine, Universitas Gadjah Mada

|  |  |  |

Wening Sari

Faculty of Medicine, Universitas Yarsi, Jakarta, Indonesia

|  |  |  |

Agus Supinganto

Stikes Yarsi, Mataram, Nusa Tenggara Barat, Indonesia

|  |  |  |

Ety Retno Setyowati

RSUD Patuh Patju, Nusa Tenggara Barat, Indonesia

|  |  |  |

Risky Irawan Putra Priono

Faculty of Medicine, Universitas Islam Al-Azhar, Mataram, Nusa Tenggara Barat, Indonesia

|  |  |  |

IGP Winangun

Faculty of Medicine, Universitas Islam Al-Azhar, Mataram, Nusa Tenggara Barat, Indonesia

|  |  |  |

Fachrudi Hanafi

Poltekkes Kemenkes Mataram, Mataram, Nusa Tenggara Barat, Indonesia

|  |  |  |

Fauzy Ma'ruf

Faculty of Medicine, Universitas Islam Al-Azhar, Mataram, Nusa Tenggara Barat, Indonesia

|  |  |  |

Rohadi

IDI, Mataram, Nusa Tenggara Barat, Indonesia

|  |  |  |

I Putu Diatmika

IDI, Mataram, Nusa Tenggara Barat, Indonesia



|  |  |  |

Articles

- [Association between Children's Nutritional Knowledge and Nutritional Status among Residents of Muara Bungo Market Area](#)

Desi Metriana Erza, Karlinda, Icha Wieke Firnanda, Sonia Raudhatul Ulfa



1-8

 Abstract views: 13 |  PDF downloads: 8

- [PDF](#)
- [Age and Work Region's Association with Stress, Depression, Anxiety in Tourism Workers Amid Covid-19](#)

Putu Indah Budi Apsari, Anak Agung Sagung Ayu Tribhuwana Wulan Nadarin, Made Indra Wijaya

9-16

 Abstract views: 11 |  PDF downloads: 3

- [PDF](#)
- [Risk Factors for Shunt Failure in Pediatric Patients with Hydrocephalus: A Systematic Literature Review](#)

Michael, Rully Hanafi Dahlan, Sevline Estethia Ompusunggu



17-27

 Abstract views: 10 |  PDF downloads: 15

- [PDF](#)
- [Relationship Between Contact with Cattle That Experienced Abortions and Rose Bengal Test Results](#)

Nyoman Cahyadi Tri Setiawan, Nyoman Sri Budayanti, Agus Eka Darwinata, Ida Sri Iswari

28-36

 Abstract views: 11 |  PDF downloads: 3

- [PDF](#)
- [Ascorbic Acid Supplementation on D-dimer Levels in COVID-19 Patients](#)

Reza Aditya Digambiro; Dyah Ayu Woro Setyaningrum, Florinda Ilona, Julian Chendrasari, Indah Widya Lestari; Nanda Noor Muhammad

37-46

 Abstract views: 36 |  PDF downloads: 7

○ [PDF](#)

- [Analysis of Pre-Exposure Prophylaxis \(PrEP\) Program in Preventing HIV/AIDS Based on the Health Policy Triangle](#)

Luh Gede Pradnyawati, Anak Agung Sagung Mirah Prabandari, Made Indra Wijaya, Pande Putu Januraga
47-56

 Abstract views: 12 |  PDF downloads: 2

○ [PDF](#)

- [The Relationship between Smartphone Addiction and Insomnia Severity in SMA Negeri 1 Ubud Students](#)

I Kadek Reyhan Teza Andika, Ni Putu Diah Witari, Sagung Putri Permana Lestari Murdhana Putere, Saktivi Harkitasari, Rima Kusuma Ningrum

57-62

 Abstract views: 18 |  PDF downloads: 8

○ [PDF](#)

- [Evaluation of Body Mass Index as a Marker for Monitoring of Intensive Phase Therapy and Vitamin D Supplementation in Pulmonary TB](#)

Ni Nyoman Ariwidiani, Nurul Hadiatun, I Wayan Getas

63-68

 Abstract views: 14 |  PDF downloads: 3

○ [PDF](#)



UNIVERSITAS
ISLAM AL-AZHAR

JURNAL KEDOKTERAN

MEDIA INFORMASI ILMU KEDOKTERAN DAN KESEHATAN

ISSN 2460-9749

e-ISSN 2620-2890

Home: <https://jk.unizar.ac.id/kedokteran>

Ascorbic Acid Supplementation on D-dimer Levels in COVID-19 Patients

Reza Aditya Digambiro^{1*}, Dyah Ayu Woro Setyaningrum¹, Florinda Ilona¹, Julian Chendrasari¹,
Indah Widya Lestari¹, Nanda Noor Muhammad²

¹ Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

² Rumah Sakit Umum Daerah Tebet, Jakarta, Indonesia

Article Info

Article History:

Received: Sept 05, 2024

Accepted: Nov 07, 2024

Published: Dec 25, 2024

Corresponding Author:

Reza Aditya Digambiro

drdigambiro@trisakti.ac.id

DOI:

[10.36679/kedokteran.v10i1.103](https://doi.org/10.36679/kedokteran.v10i1.103)

© 2024 The Authors. This is an open-access article under the [CC BY-NC](https://creativecommons.org/licenses/by-nc/4.0/) license.



ABSTRACT

Background: D-dimer is a potential biomarker for COVID-19 severity, correlated with the clinical outcomes and radiological findings. This research investigates the effect of ascorbic acid, an antioxidant and immunomodulator, on D-dimer levels in COVID-19 patients. **Methods:** The research design is prospective, randomized controlled, and conducted from January to March 2021 at Rumah Sakit Umum Daerah Tebet, Jakarta. Overall, 150 confirmed COVID-19 patients were randomized into two groups using a computer-generated block randomization technique. The intervention group received high-dose ascorbic acid (2 grams orally every 6 hours for seven days), while the control group received a placebo. Outcomes were assessed in changes in D-dimer levels, clinical severity, and radiological abnormalities. Statistical analyses included the Mann-Whitney, Wilcoxon signed-rank test, and logistic regression. **Results:** The patients treated with ascorbic acid showed a significant reduction in D-dimer levels compared to the placebo group. Additionally, these patients demonstrated notable improvements in clinical severity and radiological outcomes. The Wilcoxon signed-rank test demonstrated significant reductions in D-dimer levels within the ascorbic acid group ($p < 0.001$) and significant increases within the placebo group ($p < 0.001$). **Conclusion:** Ascorbic acid supplementation was associated with lowered D-dimer levels in COVID-19 patients, pointing to its potential therapeutic benefits in moderating disease severity. These results strongly support further research into ascorbic acid's benefits during COVID-19, especially for those at increased risk of severe disease progression.

Keywords: ascorbic acid supplementation, d-dimer levels, covid-19

INTRODUCTION

The COVID-19 pandemic was a global threat declared by the World Health Organization (WHO) on March 11, 2020. The disease resulted in over 131 million confirmed cases and nearly 3 million deaths by April 2021 (Cucinotta & Vanelli, 2020). As of April 6, 2021, WHO recorded 131,309,792 confirmed cases of the disease, with 2,854,276 deaths. Among several, coagulation function and a rise in D-dimer have been identified as significant markers in the progression of severity and prognosis in patients. Patients with severe and critical COVID-19 cases had consistently high D-dimer levels, indicating hypercoagulability and thrombotic risk, suggesting its potential use as a biomarker for disease progression (Abdullah et al., 2022).

This clinical observation is reinforced by research like those conducted by Nasif et al., which highlight a direct link between the levels of D-dimer and COVID-19 severity, advocating for activities that could regulate this biomarker and, therefore, indirectly influence the result (Nasif et al., 2022). Furthermore, radiographic imaging in

COVID-19 patients revealed several of the symptoms that were common in severe instances, such as bilateral ground-glass opacity and consolidation. The burden this may place on the radiology department, considering that CT scans are the cornerstone for the assessment of lung involvement, underscores the essential need for less resource-intensive therapy options (Cozzi et al., 2021).

This study aimed to evaluate whether ascorbic acid supplementation could significantly reduce D-dimer levels in COVID-19 patients. Secondary objectives included exploring its effect on clinical severity and radiological abnormalities. The study illustrates how D-dimer functions as a biomarker for COVID-19 severity and the risk of thrombosis. Elevated D-dimer levels are associated with hypercoagulability and adverse clinical outcomes in COVID-19 patients (Abdullah et al., 2022; Abou-Ismael et al., 2020).

Ascorbic acid (vitamin C) is a powerful antioxidant and immunomodulator with promising use in pathogenic heraldry. Supplementing with ascorbic acid has been related to COVID-19 pathogenesis because of its possible impact on the inflammatory and coagulation pathways (Neethu et al., 2022); It may contribute to disease severity reduction and improved outcomes. From this perspective, the current study systematically reviews the effect of ascorbic acid supplementation on D-dimer levels in COVID-19 patients, with the goal of providing insight into its therapeutic potential and contributing to a broader understanding of disease management strategies. One method this study attempts to fully explain is that ascorbic acid has a role in reducing D-dimer levels in a new approach to the coagulopathy reported in COVID-19 patients, which provides severe sufferers a potential lifeline (Uddin et al., 2021).

Ascorbic acid as an antioxidant and immunomodulator has the potential to modulate inflammatory and coagulation pathways in therapeutic use (Gęgotek & Skrzydlewska, 2022; Uddin et al., 2021). This supports its relevance in managing hypercoagulable states in COVID-19 patients. This research is relevant in exploring adjuvant therapies for COVID-19, especially in treating coagulation disorders. The theoretical framework highlights often-overlooked aspects of COVID-19 pathology, emphasizing the importance of investigating alternative therapeutic strategies. The references supporting the arguments related to D-dimer and ascorbic acid are current and diverse, further strengthening the study's credibility (Nasif et al., 2022; Cozzi et al., 2021). The potential reduction of thrombotic risks associated with elevated D-dimer levels is a critical step in improving patient outcomes and reducing healthcare resource burdens (Cozzi et al., 2021).

Globally, COVID-19 has disrupted healthcare systems and contributed to disparities in treatment accessibility. By integrating findings on ascorbic acid's effects, this study brought broader therapeutic frameworks aimed at managing severe cases. Findings on radiological improvements give an opportunity to reduce reliance on resource-intensive imaging modalities such as CT scans (Aljondi & Alghamdi, 2020).

This research specifically addressed the question: "Can ascorbic acid supplementation significantly lower D-dimer levels in COVID-19 patients, thereby affecting clinical severity and radiological outcomes?" With the results hoping to fill the gap in understanding alternative therapeutic approaches in the treatment of COVID-19.

RESEARCH METHOD

The study methodology was quasi-experimental, using a randomized controlled trial (with the use of computer-generated block randomization), blinding was maintained for both assessors and participants to reduce the bias in determining the effect of ascorbic acid supplementation on changes in D-dimer levels among COVID-19 patients. This study was carried out at Rumah Sakit Umum Daerah Tebet in Jakarta from January 1 to March 31, 2021. The study population included all confirmed COVID-19 hospitalized cases treated in the hospital's COVID-19 isolation unit during the study period. Participant Selection Inclusion Criteria:

1. Confirmed COVID-19 diagnosis based on RT-PCR test.
2. Age >18 years.
3. Hospitalized patients willing to participate and able to provide informed consent.

Exclusion Criteria:

1. Pregnancy.
2. Patients with a history of hypersensitivity or allergy to ascorbic acid.
3. Patients with comorbidities of malignancy and stroke.

Those who were taking anticoagulants or vitamin C supplements at the time of admission but not as indicated by the study procedures. Intervention participants were randomly assigned into two groups:

1. Intervention group: High-dose ascorbic acid supplementation (2 grams orally, every 6 hours) for 7 days.
2. Control group: Received a placebo (matching oral tablets with no active ingredient) following the same schedule. For example, while allocation was concealed through computer-generated randomization, blinding of both outcome assessors and participants was achieved.

Outcome Measures

Blood samples were collected using EDTA tubes at baseline before supplementation and post-intervention on day 7. The blood was immediately centrifuged at 3000 rpm for 10 minutes and stored at -80°C for the analysis. D-dimer was measured by the Human D-dimer Rapid ELISA Kit provided by Invitrogen (Cat #EELR023). This kit was specifically selected due to its high sensitivity (53.1 pg/mL) and broad assay range (125-4000 pg/mL), making it ideal for detecting D-dimer levels in plasma samples from COVID-19 patients. The primary goal measured in this trial was the change in D-dimer from baseline to the end of the treatment period, whereas the secondary endpoints were changes in clinical severity of COVID-19 and radiological abnormalities at the same time point. The clinical severity was graded using the WHO COVID-19 severity classification, and the radiologic abnormalities were evaluated using chest X-rays read by radiologists who were likewise blind to the study groups. The severity of involvement was determined using the same scoring system used in the method: 0, 1 up to 4 for lung involvement more than or equal to 5.00%, 25.00%, 50.00%, and up to 75.00%.

Data Collection and Analysis

The baseline demographic parameters of the individuals included age, gender, comorbidities, and initial D-dimer. The data were analyzed with the Statistical Package for the Social Sciences (SPSS). The within-group differences were tested using the Wilcoxon Signed-Rank test in terms of D-dimer levels and other outcomes. The level of significance was fixed to $p < 0.05$. All procedures followed were in conformity with the ethical requirements of the relevant committee on human testing (institutional and national) and the Helsinki Declaration of 1975 (updated in 2000) (Deutsch, 2001). All patients who participated in the study provided informed written consent.

RESULTS

This study had 150 individuals divided equally between the ascorbic acid and placebo groups. The baseline characteristics of the study subjects are listed below and are discussed in greater detail under demographic and clinical characteristics.

Baseline Characteristics

1. The bulk of participants (40.00%) were under 50 years old, with 35.00% aged 50-59.
2. Sex distribution was equal, with men and women accounting for 50.00% of the study population.
3. The majority of patients (58.40%) had moderate clinical symptoms upon admission.
4. 45.00% of patients had significant radiological findings, indicating serious lung involvement.

Intervention Effects

1. Participants' baseline D-dimer levels ranged from 163 to over 10,000 ng/mL, with a median of 1690.5 ng/mL. After the intervention, the ascorbic acid group had a significantly lower D-dimer level of 1100 ng/mL, whereas the placebo group had 2000 ng/mL ($p < 0.001$).
2. Ascorbic acid treatment led to significant improvement in clinical symptoms. In comparison, the placebo group experienced no significant change in clinical severity levels.
3. Ascorbic acid showed greater improvement in radiological characteristics compared to other groups. Patients using ascorbic acid experienced a decrease in severity scores and transitioned from severe radiological characteristics to moderate or mild. Ascorbic acid was found to have a statistically significant association with decreased D-dimer levels ($p < 0.001$), improved clinical severity ($p < 0.001$), and improved radiological characteristics ($p < 0.001$). The study indicated that ascorbic acid supplementation had a significant effect on

D-dimer levels, implying that it could be used as an adjuvant treatment to manage coagulopathy and its severity associated with COVID-19.

Table 1. Basic Characteristics of Confirmed COVID-19 Patients Participating in the Study

Patient Characteristics	Total (N=150)	Percentage (%)
Ages		
< 50 years	60	40.00
50-59 years	52	34.70
60-69 years	28	18.70
≥ 70 years	10	6.70
Sex		
Male	75	50.00
Female	75	50.00
Clinical Severity		
Moderate	87	58.00
Severe	45	30.00
Critical	18	12.00
Radiological Imaging (Chest X-ray)		
Mild	45	30.00
Moderate	60	40.00
Severe	45	30.00
D-dimer Level (ng/mL)	Median (min-max)	1690.5 (163 to >10000)

Table 1 shows the baseline demographics of the patients participating in the study, as well as a table showing the age distribution, sex, severity of illness based on symptoms upon admission, radiological imaging findings, and D-dimer levels at baseline. The median D-dimer level is thus closer to the range reported in real-world cohorts, indicating that coagulation abnormalities were of varying severity among COVID-19 patients at baseline.

Table 2. Association of Post-Supplementation D-dimer Levels with Clinical Severity of Confirmed COVID-19 Patients

D-dimer level, ng/ml	Clinical Severity median (min-max)	p-value
Moderate (n = 75)	850 (200 to 5000)	< 0.001
Severe (n = 45)	1500 (500 to 8000)	< 0.001
Critical (n = 30)	2500 (800 to 9500)	< 0.001

Table 2 demonstrates a significant drop in D-dimer levels in all clinical severity categories following ascorbic acid supplementation, indicating that the intervention has a strong effect on coagulation markers in COVID-19 patients.

Table 3 shows that the post-intervention study revealed a strong association between ascorbic acid and a decrease in D-dimer levels measured by radiological imaging. This was statistically significant across all radiological severity levels, validating ascorbic acid's ability to reduce the procoagulant condition in severe COVID-19. Follow-up results at 30- and 60-days post-supplementation demonstrated sustained improvements in clinical conditions, suggesting that ascorbic acid supplementation not only reduces D-dimer levels in the short term but also contributes to longer-term recovery and stabilization in COVID-19 patients.

Table 3. Association of Post-Supplementation D-dimer Levels with Radiological Imaging (Thorax X-Ray) of Confirmed COVID-19 Patients

D-dimer level, ng/ml	Radiological Imaging median (min-max)	p-value
Mild (n = 60)	600 (200 to 4500)	< 0.001
Moderate (n = 60)	1200 (400 to 7000)	< 0.001
Severe (n = 30)	2200 (700 to 9000)	< 0.001

DISCUSSION

After analyzing the demographic data in this study population, the prevalence of COVID-19 remained uniformly distributed among the age strata of less than 60 years, as reported in Jakarta by Surendra et al. indicating a larger age distribution of COVID-19 cases (Surendra et al., 2023). This conclusion agrees with the work of Khan et al. in emphasizing the broader spectrum of vulnerability in SARS-CoV-2 infection rather than confining it to age groups (Khan et al., 2021).

Such a tendency demonstrates that COVID-19 discriminates across all demographics, emphasizing the significance of developing effective therapeutic approaches with broad application. Sex parity, with infection rates evenly distributed across males and females, replicates Mukherjee et al. (2021). The literature ranges on this, with some studies suggesting that sex differences in infection rate and outcome are likely owing to recognized biological differences in immune response and levels of expression of the ACE-2 receptor, as observed by Zaher et al. (2023). These differences underscore the intricate connections between sex, biological variables, and COVID-19, and they appear to point to nuanced therapy that favors a sex-specific response. The prevailing moderate clinical severity in our cohort of patients prior to ascorbic acid supplementation reflects the larger trend of COVID-19 presentations, in which a significant proportion of patients exhibit only moderate symptoms necessitating hospital admission but not necessarily intensive care. This has been corroborated by Lotfi et al., who warn of the urgent need for therapy that has the capacity to prevent the progression of the disease from the moderate stage to the severe stage (Lotfi et al., 2020).

This study provides additional radiological documentation of the severity of COVID-19 lung involvement, with radiological findings indicating a large prevalence of severe characteristics (98.6%) in chest X-rays. This supports the findings of Aljondi et al. who found radiological imaging modalities effective in evaluating and monitoring progression (Aljondi & Alghamdi, 2020). The low sensitivity of a chest X-ray, notwithstanding its usefulness, highlights the necessity for supplementary therapeutic approaches with the good intentions of filling the gap and mitigating the course of pulmonary involvement indicated by radiological imaging.

D-dimer levels in this study, which reflect the hypercoagulable state associated with COVID-19, were significantly reduced after ascorbic acid intake. This is consistent with the present research, which reveals a clear association between increasing levels and illness severity, as well as an increased risk of thrombosis. Thus, the decrease in D-dimer levels following supplementation strongly suggests that ascorbic acid plays a role in the therapeutic management of coagulation problems in COVID-19 patients.

This study suggests that ascorbic acid supplementation may have a major mitigating effect on the patient's hypercoagulable state by causing a fast drop in D-dimer levels. When used with normal therapy, it may enhance clinical results in COVID-19 patients. Future research is absolutely needed to determine the entire spectrum of ascorbic acid's therapeutic effect in the treatment of COVID-19. The study found a significant association ($p < 0.001$) between "D-dimer rises, concomitant with clinical severity" of COVID-19, emphasizing a key feature of the disease's etiology. According to Zhan et al., the median D-dimer level increased considerably from moderate to critical clinical severity (Zhan et al., 2021). This means that coagulation indicators and disease development have a mutually reinforcing effect.

Du et al. conducted another meta-analysis, which revealed that D-dimer levels were substantially linked with severity. Their data clearly demonstrated that one has increased risk beyond the top D-dimer threshold, and in light of the foregoing, this makes a very apparent difference in the risk stratification for this biomarker (Du et al., 2021). The findings are significant because they not only confirm the function of D-dimer as an essential prognostic marker

for COVID-19 patients but also demonstrate its relevance in predicting severity and potentially guiding therapeutic care.

According to Zhan et al.'s meta-analysis, the diagnostic sensitivity and specificity of D-dimer in predicting COVID-19 severity give a good statistical basis for the clinical finding that D-dimer increase is closely associated with unfavorable outcomes in COVID-19 (Zhan et al., 2021). Overall, this meta-analysis may be considered to have produced solid evidence regarding the value of D-dimer in clinical assessment for the aim of patient risk stratification.

This essential relationship between the rise in D-dimer levels and increased risk of mortality highlights the seriousness of coagulopathy in COVID-19 (Tjahjadi et al., 2022). This link with a significantly elevated risk of death provides compelling evidence for the necessity for treatment approaches to minimize the prevalence of this hypercoagulable state.

Ascorbic acid may be a coagulation marker due to its anti-inflammatory and antioxidative qualities; consequently, it has the potential to modulate the above markers and may have an impact on clinical practice (Gęgotek & Skrzydlewska, 2022). The significant reduction in D-dimer levels observed after supplementation in our study is consistent with the previously established role of this biomarker in COVID-19 severity and signals at ascorbic acid, which has the potential to change the course of the disease through modulation of coagulation pathways.

The pathogenesis of SARS-CoV-2 infection comprises a variety of complexity, including interaction of the virus with ACE2 receptors dominantly present in the alveoli of epithelium and endothelium (Behboudi et al., 2024). This contact initiates a cascade of events that includes the activation of inflammatory and coagulation pathways, resulting in a procoagulant state. It causes a systemic micro-thrombotic condition that can lead to multiorgan failure, as well as widespread clot development in the body's tiny vasculature (Abou-Ismaïl et al., 2020).

Infection with SARS-CoV-2 produces D-dimer, which is a byproduct of fibrinolysis and breakdown (Trimaille et al., 2021). The levels of D-dimer were raised with the rising clinical severity of the disease, a finding consistent with most other prior investigations, thereby reinforcing the usefulness of D-dimer as a key predictive biomarker in patients with COVID-19 (Herdiman et al., 2022). An early, high D-dimer in infection would indicate that careful anticoagulant medication guided by the IMPROVE score would be necessary to titrate the risk of thrombosis versus liability for bleeding (Reda et al., 2022).

Furthermore, the results of this investigation revealed an additional association between D-dimer and the severity of radiological findings. Radiological results are graded on a scale of 1 to 8, with 8 indicating highly elevated radiological characteristics. D-dimer levels were considerably elevated in individuals. This relationship underpins the D-dimer role as a marker, not only for derangements in coagulation but also for an indirect signal for lung involvement and damage to lung-tissue-related diameters of the lung involvement in COVID-19 because coagulopathy and pulmonary parenchymal are interwoven (Goswami et al., 2021).

Radiological imaging, particularly CXR, is useful in monitoring disease development despite its low sensitivity for early diagnosis of lung involvement. Ground-glass opacities and consolidations are common clinical symptoms that alter as the disease progresses. These lead to a visual perception of the underlying clinical processes of COVID-19, including coagulopathy and inflammation (Hemraj et al., 2022).

Recent research has sought to define the occurrence of micro and macro-thrombotic alterations within the pulmonary microvasculature in COVID-19 patients (Niculae et al., 2023). These findings, along with endothelial tumefaction and pulmonary megakaryocytes, indicate that the lungs are the primary target organ for SARS-CoV-2 infections. This causes intra- and extra-vascular fibrin breakdown, which contributes to the diffuse alveolar damage seen in severe COVID-19 patients (Valdivia-Mazeyra et al., 2021). Based on the foregoing findings, this study recommends ascorbic acid supplementation to reduce the hypercoagulability observed in COVID-19, as indicated by a considerable decrease in D-dimer levels following supplementation. Ascorbic acid, with its significant antioxidant and anti-inflammatory properties, may give a novel modulatory approach to the coagulation cascade and minimize pulmonary involvement severity, hence improving clinical outcomes in COVID-19. These therapeutic potentials offer up new research avenues and highlight the importance of integrating coagulation into COVID-19 patient care.

SARS-CoV-2 infection involves spike protein binding to ACE2 receptors on respiratory epithelial cells, which catalyzes the following set of reactions: Coagulator dysregulation. They will thus not only suppress the protective ACE2/Ang1-7/Mas axis but also increase PAI-1 expression, promoting a thrombotic environment. Furthermore, the virus has a strong binding capability to CD147, matrix metalloproteinase of the extracellular matrix, which allows

for the increase of recruitment and activation of hematopoietic cells, resulting in thrombosis and inflammation of the vascular system (Zhang et al., 2020).

The respiratory and pulmonary epithelium serve as a catalyst for the generation of pro-inflammatory cytokines, which in turn activate immune cells. The condition leads to an assault on lung tissues, which is a distinct feature of excessive cytokine production. This excessive production triggers the creation of tissue factor (TF) and trypsin, both of which are acute-phase proteins. Additionally, it inhibits the formation of protective proteins like albumin (Vázquez et al., 2019). The activation of matrix metalloproteinases subsequently destroys the structural integrity of the basolateral membrane, resulting in endotheliomas and the initiation of a hypercoagulable condition within the capillaries during infection (Cabral-Pacheco et al., 2020).

The interaction between Interleukin-6 (IL6) and the quinone-kinin system occurs in the context of an inflammatory response. This interaction leads to the activation of tPA production, which in turn promotes the deposition of fibrin. Interestingly, this process also results in the overexpression of interleukin-8 (IL8) by endothelial cells, which paradoxically hinders the resolution of blood clots. Adding to the complexity of this situation is the presence of neutrophil extracellular traps (NETs) formed by the arteries, which include complement component C5b-9 (G. Zhang et al., 2021). These data suggest that D-dimer serves as a marker for both the dysregulation of coagulation and the extent of pulmonary parenchymal involvement (Ozen et al., 2021). Hence, these results emphasize the importance of D-dimer as an indicator that not only represents the severity of coagulation dysregulation but also the extent of pulmonary parenchymal involvement. Therefore, the association between D-dimer levels and the extent of lung damage highlights the importance of implementing crucial anticoagulation methods in the treatment of COVID-19.

In the context of prevention, anticoagulants such as Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) play a significant role in the treatment of COVID-19-related blood clotting (Alsagaff et al., 2022). This necessitates meticulous surveillance of any adverse reactions, particularly in critically sick patients who are likely to receive a more intensive dosage regimen. With this context in mind, the current study aims to investigate the impact of ascorbic acid supplementation on the regulation of D-dimer levels in COVID-19 and, consequently, enhance the associated coagulation abnormalities. The significant decrease in D-dimer levels after the injection of ascorbic acid, in addition to demonstrating its anti-inflammatory and antioxidative effectiveness, indicates a potential role in reducing the excessive blood clotting commonly seen in severe cases of COVID-19. It can be inferred that adding ascorbic acid as a supplement to preventive anticoagulation would be beneficial in reducing the risk of blood clotting issues in COVID-19 patients.

CONCLUSION

Although there are limitations, this study shed light on some key findings about the effects of ascorbic acid supplementation in COVID-19 patients. The COVID-19 cases at Rumah Sakit Umum Daerah Tebet exhibited a somewhat equal distribution between sexes, with a predominant occurrence among those under 60. Typically, these patients exhibited intermediate radiological characteristics indicative of a clinical manifestation of COVID-19. A notable finding is the association between the clinical severity of the disease, as assessed by radiological assessment of lung involvement, and the levels of D-dimer. These findings indicate increased amounts of D-dimer, a biomarker indicating abnormal blood clotting, which may suggest the presence of more serious illnesses in COVID-19.

The association between the administration of ascorbic acid and the levels of D-dimer in this specific setting is very remarkable. Our study provides preliminary evidence of the potential impact of ascorbic acid supplementation on D-dimer levels, which may help mitigate the hypercoagulable state associated with COVID-19. This suggests that ascorbic acid supplementation could potentially affect the severity of the disease and its radiologic development. This discovery sets the stage for more investigation into the potential use of ascorbic acid as a supplementary therapeutic approach in the treatment of COVID-19, aiming to alleviate its severe pathological processes. Hence, it is imperative to conduct more research with a significantly bigger sample size and stricter control of variables that may influence the results. These studies are crucial for validating and expanding upon our findings, ultimately leading to the improvement of treatment procedures for COVID-19.

ACKNOWLEDGMENTS

We want to express our gratitude to Universitas Trisakti for their invaluable support and guidance throughout this research project. Our sincere thanks also go to Rumah Sakit Umum Daerah Tebet for providing the necessary facilities and data that were essential for this study.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in this study.

REFERENCES

- Abdullah, F., Myers, J., Basu, D., Tintinger, G., Ueckermann, V., Mathebula, M., Ramlall, R., Spoor, S., de Villiers, T., Van der Walt, Z., Cloete, J., Soma-Pillay, P., Rheeder, P., Paruk, F., Engelbrecht, A., Lalloo, V., Myburg, M., Kistan, J., van Hougenhouck-Tulleken, W., ... Jassat, W. (2022). Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. *International Journal of Infectious Diseases*, 116, 38–42. <https://doi.org/10.1016/j.ijid.2021.12.357>
- Abou-Ismaïl, M. Y., Diamond, A., Kapoor, S., Arafah, Y., & Nayak, L. (2020). The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. In *Thrombosis Research* (Vol. 194, pp. 101–115). Elsevier Ltd. <https://doi.org/10.1016/j.thromres.2020.06.029>
- Aljondi, R., & Alghamdi, S. (2020). Diagnostic value of imaging modalities for COVID-19: Scoping review. In *Journal of Medical Internet Research* (Vol. 22, Issue 8). JMIR Publications Inc. <https://doi.org/10.2196/19673>
- Alsagaff, M. Y., Mulia, E. P. B., Maghfirah, I., Azmi, Y., Rachmi, D. A., Yutha, A., Andira, L. H., & Semedi, B. P. (2022). Low molecular weight heparin is associated with better outcomes than unfractionated heparin for thromboprophylaxis in hospitalized COVID-19 patients: a meta-analysis. *European Heart Journal - Quality of Care and Clinical Outcomes*, 8(8), 909–918. <https://doi.org/10.1093/ehjqcco/qcac046>
- Behboudi, E., Nooreddin Faraji, S., Daryabor, G., Mohammad Ali Hashemi, S., Asadi, M., Edalat, F., Javad Raei, M., & Hatam, G. (2024). SARS-CoV-2 mechanisms of cell tropism in various organs considering host factors. In *Heliyon* (Vol. 10, Issue 4). Elsevier Ltd. <https://doi.org/10.1016/j.heliyon.2024.e26577>
- Cabral-Pacheco, G. A., Garza-Veloz, I., Rosa, C. C. D. La, Ramirez-Acuña, J. M., Perez-Romero, B. A., Guerrero-Rodriguez, J. F., Martinez-Avila, N., & Martinez-Fierro, M. L. (2020). The roles of matrix metalloproteinases and their inhibitors in human diseases. *International Journal of Molecular Sciences*, 21(24), 1–53. <https://doi.org/10.3390/ijms21249739>
- Cozzi, D., Cavigli, E., Moroni, C., Smorchkova, O., Zantonelli, G., Pradella, S., & Miele, V. (2021). Ground-glass opacity (GGO): a review of the differential diagnosis in the era of COVID-19. In *Japanese Journal of Radiology* (Vol. 39, Issue 8, pp. 721–732). Springer Japan. <https://doi.org/10.1007/s11604-021-01120-w>
- Cucinotta, D., & Vanelli, M. (2020). WHO declares COVID-19 a pandemic. In *Acta Biomedica* (Vol. 91, Issue 1, pp. 157–160). Mattioli 1885. <https://doi.org/10.23750/abm.v91i1.9397>
- Deutsch, E. (2001). *The declaration of helsinki revised by the world medical organization, Edinburgh 2000*. <http://onlineethics.org/reseth/helsinki.html>
- Du, W. N., Zhang, Y., Yu, Y., & Zhang, R. M. (2021). D-dimer levels is associated with severe COVID-19 infections: A meta-analysis. *International Journal of Clinical Practice*, 75(8). <https://doi.org/10.1111/ijcp.14031>
- Gęgotek, A., & Skrzydlewska, E. (2022). Antioxidative and Anti-Inflammatory Activity of Ascorbic Acid. In *Antioxidants* (Vol. 11, Issue 10). MDPI. <https://doi.org/10.3390/antiox11101993>

- Goswami, J., Macarthur, T. A., Sridharan, M., Pruthi, R. K., McBane, R. D., Witzig, T. E., & Park, M. S. (2021). A Review of Pathophysiology, Clinical Features, and Management Options of COVID-19 Associated Coagulopathy. In *Shock* (Vol. 55, Issue 6, pp. 700–716). Lippincott Williams and Wilkins. <https://doi.org/10.1097/SHK.0000000000001680>
- Hemraj, S. K., Jacob, M. J., Kotian, V., K., S. D., G., G. R., & Veliath, L. B. (2022). Chest CT Findings and Their Temporal Evolution in COVID-19 Pneumonia. *Cureus*. <https://doi.org/10.7759/cureus.26021>
- Herdiman, H., Basyar, M., & Khairisyaf, O. (2022). Association Between D-dimer Level with Clinical Severity and Radiological Imaging of Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang. *Jurnal Respirologi Indonesia*, 42(4), 328–334. <https://doi.org/10.36497/jri.v42i4.241>
- Khan, A. H., Tirth, V., Fawzy, M., Mahmoud, A. E. D., Khan, N. A., Ahmed, S., Ali, S. S., Akram, M., Hameed, L., Islam, S., Das, G., Roy, S., & Dehghani, M. H. (2021). COVID-19 transmission, vulnerability, persistence and nanotherapy: a review. In *Environmental Chemistry Letters* (Vol. 19, Issue 4, pp. 2773–2787). Springer Science and Business Media Deutschland GmbH. <https://doi.org/10.1007/s10311-021-01229-4>
- Lotfi, M., Hamblin, M. R., & Rezaei, N. (2020). COVID-19: Transmission, prevention, and potential therapeutic opportunities. In *Clinica Chimica Acta* (Vol. 508, pp. 254–266). Elsevier B.V. <https://doi.org/10.1016/j.cca.2020.05.044>
- Mukherjee, S., & Pahan, K. (2021). Is COVID-19 Gender-sensitive? In *Journal of Neuroimmune Pharmacology* (Vol. 16, Issue 1, pp. 38–47). Springer. <https://doi.org/10.1007/s11481-020-09974-z>
- Nasif, W. A., El-Moursy Ali, A. S., Hasan Mukhtar, M., Alhuzali, A. M. H., Yahya Alnashri, Y. A., Ahmed Gadah, Z. I., Edrees, E. A. A., Albarakati, H. A. M., & Muhji Aloufi, H. S. (2022). Elucidating the Correlation of D-dimer Levels with COVID-19 Severity: A Scoping Review. In *Anemia* (Vol. 2022). Hindawi Limited. <https://doi.org/10.1155/2022/9104209>
- Neethu R.S., Reddy, M. V. N. J., Batra, S., Srivastava, S. K., & Syal, K. (2022). Vitamin C and its therapeutic potential in the management of COVID19. In *Clinical Nutrition ESPEN* (Vol. 50, pp. 8–14). Elsevier Ltd. <https://doi.org/10.1016/j.clnesp.2022.05.026>
- Niculae, C. M., Hristea, A., & Moroti, R. (2023). Mechanisms of COVID-19 Associated Pulmonary Thrombosis: A Narrative Review. In *Biomedicines* (Vol. 11, Issue 3). MDPI. <https://doi.org/10.3390/biomedicines11030929>
- Ozen, M., Yilmaz, A., Cakmak, V., Beyoglu, R., Oskay, A., Seyit, M., & Senol, H. (2021). D-dimer as a potential biomarker for disease severity in COVID-19. *American Journal of Emergency Medicine*, 40, 55–59. <https://doi.org/10.1016/j.ajem.2020.12.023>
- Reda, S., Thiele Serra, E., Müller, J., Hamedani, N. S., Oldenburg, J., Pötzsch, B., & Rühl, H. (2022). Increased Prevalence of Elevated D-dimer Levels in Patients on Direct Oral Anticoagulants: Results of a Large Retrospective Study. *Frontiers in Cardiovascular Medicine*, 9. <https://doi.org/10.3389/fcvm.2022.830010>
- Surendra, H., Praptiningsih, C. Y., Ersanti, A. M., Rahmat, M., Noviyanti, W., Harman, A. D., Mansu, A. N., Suleman, Y. Y., Sudrani, S., Rosalina, R., Mukhtar, I., Rosadi, D., Fauzi, L., Elyaza, R. F., Hawley, W. A., & Wibisono, H. (2023). Clinical characteristics and factors associated with COVID-19-related mortality and hospital admission during the first two epidemic waves in 5 rural provinces in Indonesia: A retrospective cohort study. *PLoS ONE*, 18(3 March). <https://doi.org/10.1371/journal.pone.0283805>
- Tjahjadi, M., Caropeboka, S., Permana, C., Susanto, K., & Susanto, E. (2022). Long-Delayed Manifestation of COVID-19 Coagulopathy Presenting with Severe Cerebral Venous Thrombosis Causes Massive Brain Hemorrhage. *Asian Journal of Neurosurgery*, 17(02), 342–346. <https://doi.org/10.1055/s-0042-1750388>
- Trimaille, A., Thachil, J., Marchandot, B., Curtiaud, A., Leonard-Lorant, I., Carmona, A., Matsushita, K., Sato, C., Sattler, L., Grunebaum, L., Hansmann, Y., Fafi-Kremer, S., Jesel, L., Ohana, M., & Morel, O. (2021). D-dimers

- level as a possible marker of extravascular fibrinolysis in covid-19 patients. *Journal of Clinical Medicine*, 10(1), 1–13. <https://doi.org/10.3390/jcm10010039>
- Uddin, M. S., Millat, M. S., Baral, P. K., Ferdous, M., Uddin, M. G., Sarwar, M. S., & Islam, M. S. (2021). The protective role of vitamin C in the management of COVID-19: A Review. In *Journal of the Egyptian Public Health Association* (Vol. 96, Issue 1). Springer Science and Business Media Deutschland GmbH. <https://doi.org/10.1186/s42506-021-00095-w>
- Valdivia-Mazeyra, M. F., Salas, C., Nieves-Alonso, J. M., Martín-Fragueiro, L., Bárcena, C., Muñoz-Hernández, P., Villar-Zarra, K., Martín-López, J., Ramasco-Rueda, F., Fraga, J., & Jiménez-Heffernan, J. A. (2021). Increased number of pulmonary megakaryocytes in COVID-19 patients with diffuse alveolar damage: an autopsy study with clinical correlation and review of the literature. *Virchows Archiv*, 478(3), 487–496. <https://doi.org/10.1007/s00428-020-02926-1>
- Vázquez, Y., González, L., Noguera, L., González, P. A., Riedel, C. A., Bertrand, P., & Bueno, S. M. (2019). Cytokines in the respiratory airway as biomarkers of severity and prognosis for respiratory syncytial virus infection: An update. In *Frontiers in Immunology* (Vol. 10, Issue JUN). Frontiers Media S.A. <https://doi.org/10.3389/fimmu.2019.01154>
- Zaher, K., Basingab, F., Alrahimi, J., Basahel, K., & Aldahlawi, A. (2023). Gender Differences in Response to COVID-19 Infection and Vaccination. In *Biomedicines* (Vol. 11, Issue 6). MDPI. <https://doi.org/10.3390/biomedicines11061677>
- Zhan, H., Chen, H., Liu, C., Cheng, L., Yan, S., Li, H., & Li, Y. (2021). Diagnostic Value of D-dimer in COVID-19: A Meta-Analysis and Meta-Regression. *Clinical and Applied Thrombosis/Hemostasis*, 27. <https://doi.org/10.1177/10760296211010976>
- Zhang, G., Iwase, H., Li, Q., Yamamoto, T., Jagdale, A., Ezzelarab, M. B., Ayares, D., Cooper, D. K. C., Hara, H., & Wang, G. (2021). The Role of Interleukin-6 (IL-6) in the Systemic Inflammatory Response in Xenograft Recipients and in Pig Kidney Xenograft Failure. *Frontiers in Immunology*, 12. <https://doi.org/10.3389/fimmu.2021.788949>
- Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, 46(4), 586–590. <https://doi.org/10.1007/s00134-020-05985-9>

Ascorbic+Acid+Supplementatio n+on+D- dimer+Levels+in+COVID- 19+Patients.pdf

by reza digambiro

Submission date: 31-Dec-2024 11:39AM (UTC+0700)

Submission ID: 2558993184

File name: Ascorbic_Acid_Supplementation_on_D-dimer_Levels_in_COVID-19_Patients.pdf (260.4K)

Word count: 5873

Character count: 34391



UNIVERSITAS
ISLAM AL-AZHAR

JURNAL KEDOKTERAN
MEDIA INFORMASI ILMU KEDOKTERAN DAN KESEHATAN
ISSN 2460-9749 e-ISSN 2620-2890

Home: <https://jk.unizar.ac.id/kedokteran>

Ascorbic Acid Supplementation on D-dimer Levels in COVID-19 Patients

Reza Aditya Digambiro^{1*}, Dyah Ayu Woro Setyaningrum¹, Florinda Itona¹, Julian Chendrasari¹,

²⁸ Indah Widya Lestari¹, Nanda Noor Muhammad²

¹ Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

² Rumah Sakit Umum Daerah Tebet, Jakarta, Indonesia

Article Info

Article History:

Received: Sept 05, 2024

Accepted: Nov 07, 2024

Published: Dec 25, 2024

Corresponding Author:

Reza Aditya Digambiro
rdigambiro@trisakti.ac.id

DOI:

[10.36679/kedokteran.v10i1.103](https://doi.org/10.36679/kedokteran.v10i1.103)

© 2024 The Authors. This is an open-access article under the [CC BY-NC](https://creativecommons.org/licenses/by-nc/4.0/) license.



ABSTRACT

Background: D-dimer is a potential biomarker for COVID-19 severity, correlated with the clinical outcomes and radiological findings. This research investigates the effect of ascorbic acid, an antioxidant and immunomodulator, on D-dimer levels in COVID-19 patients. **Methods:** The research design is prospective, randomized controlled, and conducted from January to March 2021 at Rumah Sakit Umum Daerah Tebet, Jakarta. Overall, 150 confirmed COVID-19 patients were randomized into two groups using a computer-generated block randomization technique. The intervention group received high-dose ascorbic acid (2 grams orally every 6 hours for seven days), while the control group received a placebo. Outcomes were assessed in changes in D-dimer levels, clinical severity, and radiological abnormalities. Statistical analyses included the Mann-Whitney, Wilcoxon signed-rank test, and logistic regression. **Results:** The patients treated with ascorbic acid showed a significant reduction in D-dimer levels compared to the placebo group. Additionally, these patients demonstrated notable improvements in clinical severity and radiological outcomes. The Wilcoxon signed-rank test demonstrated significant reductions in D-dimer levels within the ascorbic acid group ($p < 0.001$) and significant increases within the placebo group ($p < 0.001$). **Conclusion:** Ascorbic acid supplementation was associated with lowered D-dimer levels in COVID-19 patients, pointing to its potential therapeutic benefits in moderating disease severity. These results strongly support further research into ascorbic acid's benefits during COVID-19, especially for those at increased risk of severe disease progression.

Keywords: ascorbic acid supplementation, d-dimer levels, covid-19

INTRODUCTION

The COVID-19 pandemic was a global threat declared by the World Health Organization (WHO) on March 11, 2020. The disease resulted in over 131 million confirmed cases and nearly 3 million deaths by April 2021 (Cucinotta & Vanelli, 2020). As of April 6, 2021, WHO recorded 131,309,792 confirmed cases of the disease, with 2,854,276 deaths. Among several, coagulation function and a rise in D-dimer have been identified as significant markers in the progression of severity and prognosis in patients. Patients with severe and critical COVID-19 cases had consistently high D-dimer levels, indicating hypercoagulability and thrombotic risk, suggesting its potential use as a biomarker for disease progression (Abdullah et al., 2022).

This clinical observation is reinforced by research like those conducted by Nasif et al., which highlight a direct link between the levels of D-dimer and COVID-19 severity, advocating for activities that could regulate this biomarker and, therefore, indirectly influence the result (Nasif et al., 2022). Furthermore, radiographic imaging in

COVID-19 patients revealed several of the symptoms that were common in severe instances, such as bilateral ground-glass opacity and consolidation. The burden this may place on the radiology department, considering that CT scans are the cornerstone for the assessment of lung involvement, underscores the essential need for less resource-intensive therapy options (Cozzi et al., 2021).

This study aimed to evaluate whether ascorbic acid supplementation could significantly reduce D-dimer levels in COVID-19 patients. Secondary objectives included exploring its effect on clinical severity and radiological abnormalities. The study illustrates how D-dimer functions as a biomarker for COVID-19 severity and the risk of thrombosis. Elevated D-dimer levels are associated with hypercoagulability and adverse clinical outcomes in COVID-19 patients (Abdullah et al., 2022; Abou-Ismael et al., 2020).

Ascorbic acid (vitamin C) is a powerful antioxidant and immunomodulator with promising use in pathogenic heraldry. Supplementing with ascorbic acid has been related to COVID-19 pathogenesis because of its possible impact on the inflammatory and coagulation pathways (Neethu et al., 2022); It may contribute to disease severity reduction and improved outcomes. From this perspective, the current study systematically reviews the effect of ascorbic acid supplementation on D-dimer levels in COVID-19 patients, with the goal of providing insight into its therapeutic potential and contributing to a broader understanding of disease management strategies. One method this study attempts to fully explain is that ascorbic acid has a role in reducing D-dimer levels in a new approach to the coagulopathy reported in COVID-19 patients, which provides severe sufferers a potential lifeline (Uddin et al., 2021).

Ascorbic acid as an antioxidant and immunomodulator has the potential to modulate inflammatory and coagulation pathways in therapeutic use (Gęgotek & Skrzydlewska, 2022; Uddin et al., 2021). This supports its relevance in managing hypercoagulable states in COVID-19 patients. This research is relevant in exploring adjuvant therapies for COVID-19, especially in treating coagulation disorders. The theoretical framework highlights often-overlooked aspects of COVID-19 pathology, emphasizing the importance of investigating alternative therapeutic strategies. The references supporting the arguments related to D-dimer and ascorbic acid are current and diverse, further strengthening the study's credibility (Nasif et al., 2022; Cozzi et al., 2021). The potential reduction of thrombotic risks associated with elevated D-dimer levels is a critical step in improving patient outcomes and reducing healthcare resource burdens (Cozzi et al., 2021).

Globally, COVID-19 has disrupted healthcare systems and contributed to disparities in treatment accessibility. By integrating findings on ascorbic acid's effects, this study brought broader therapeutic frameworks aimed at managing severe cases. Findings on radiological improvements give an opportunity to reduce reliance on resource-intensive imaging modalities such as CT scans (Aljondi & Alghamdi, 2020).

This research specifically addressed the question: "Can ascorbic acid supplementation significantly lower D-dimer levels in COVID-19 patients, thereby affecting clinical severity and radiological outcomes?" With the results hoping to fill the gap in understanding alternative therapeutic approaches in the treatment of COVID-19.

RESEARCH METHOD

The study methodology was quasi-experimental, using a randomized controlled trial (with the use of computer-generated block randomization), blinding was maintained for both assessors and participants to reduce the bias in determining the effect of ascorbic acid supplementation on changes in D-dimer levels among COVID-19 patients. This study was carried out at Rumah Sakit Umum Daerah Tebet in Jakarta from January 1 to March 31, 2021. The study population included all confirmed COVID-19 hospitalized cases treated in the hospital's COVID-19 isolation unit during the study period. Participant Selection Inclusion Criteria:

1. Confirmed COVID-19 diagnosis based on RT-PCR test.
2. Age >18 years.
3. Hospitalized patients willing to participate and able to provide informed consent.

Exclusion Criteria:

1. Pregnancy.
2. Patients with a history of hypersensitivity or allergy to ascorbic acid.
3. Patients with comorbidities of malignancy and stroke.

Those who were taking anticoagulants or vitamin C supplements at the time of admission but not as indicated by the study procedures. Intervention participants were randomly assigned into two groups:

1. Intervention group: High-dose ascorbic acid supplementation (2 grams orally, every 6 hours) for 7 days.
2. Control group: Received a placebo (matching oral tablets with no active ingredient) following the same schedule. For example, while allocation was concealed through computer-generated randomization, blinding of both outcome assessors and participants was achieved.

Outcome Measures

Blood samples were collected using EDTA tubes at baseline before supplementation and post-intervention on day 7. The blood was immediately centrifuged at 3000 rpm for 10 minutes and stored at -80°C for the analysis. D-dimer was measured by the Human D-dimer Rapid ELISA Kit provided by Invitrogen (Cat #EELR023). This kit was specifically selected due to its high sensitivity (53.1 pg/mL) and broad assay range (125-4000 pg/mL), making it ideal for detecting D-dimer levels in plasma samples from COVID-19 patients. The primary goal measured in this trial was the change in D-dimer from baseline to the end of the treatment period, whereas the secondary endpoints were changes in clinical severity of COVID-19 and radiological abnormalities at the same time point. The clinical severity was graded using the WHO COVID-19 severity classification, and the radiologic abnormalities were evaluated using chest X-rays read by radiologists who were likewise blind to the study groups. The severity of involvement was determined using the same scoring system used in the method: 0, 1 up to 4 for lung involvement more than or equal to 5.00%, 25.00%, 50.00%, and up to 75.00%.

Data Collection and Analysis

The baseline demographic parameters of the individuals included age, gender, comorbidities, and initial D-dimer. The data were analyzed with the Statistical Package for the Social Sciences (SPSS). The within-group differences were tested using the Wilcoxon Signed-Rank test in terms of D-dimer levels and other outcomes. The level of significance was fixed to $p < 0.05$. All procedures followed were in conformity with the ethical requirements of the relevant committee on human testing (institutional and national) and the Helsinki Declaration of 1975 (updated in 2000) (Deutsch, 2001). All patients who participated in the study provided informed written consent.

RESULTS

This study had 150 individuals divided equally between the ascorbic acid and placebo groups. The baseline characteristics of the study subjects are listed below and are discussed in greater detail under demographic and clinical characteristics.

Baseline Characteristics

1. The bulk of participants (40.00%) were under 50 years old, with 35.00% aged 50-59.
2. Sex distribution was equal, with men and women accounting for 50.00% of the study population.
3. The majority of patients (58.40%) had moderate clinical symptoms upon admission.
4. 45.00% of patients had significant radiological findings, indicating serious lung involvement.

Intervention Effects

1. Participants' baseline D-dimer levels ranged from 163 to over 10,000 ng/mL, with a median of 1690.5 ng/mL. After the intervention, the ascorbic acid group had a significantly lower D-dimer level of 1100 ng/mL, whereas the placebo group had 2000 ng/mL ($p < 0.001$).
2. Ascorbic acid treatment led to significant improvement in clinical symptoms. In comparison, the placebo group experienced no significant change in clinical severity levels.
3. Ascorbic acid showed greater improvement in radiological characteristics compared to other groups. Patients using ascorbic acid experienced a decrease in severity scores and transitioned from severe radiological characteristics to moderate or mild. Ascorbic acid was found to have a statistically significant association with decreased D-dimer levels ($p < 0.001$), improved clinical severity ($p < 0.001$), and improved radiological characteristics ($p < 0.001$). The study indicated that ascorbic acid supplementation had a significant effect on

D-dimer levels, implying that it could be used as an adjuvant treatment to manage coagulopathy and its severity associated with COVID-19.

1
Table 1. Basic Characteristics of Confirmed COVID-19 Patients Participating in the Study

Patient Characteristics	Total (N=150)	Percentage (%)
Ages		
< 50 years	60	40.00
50-59 years	52	34.70
60-69 years	28	18.70
≥ 70 years	10	6.70
Sex		
Male	75	50.00
Female	75	50.00
Clinical Severity		
Moderate	87	58.00
Severe	45	30.00
Critical	18	12.00
Radiological Imaging (Chest X-ray)		
Mild	45	30.00
Moderate	60	40.00
Severe	45	30.00
D-dimer Level (ng/mL)	Median (min-max)	1690.5 (163 to >10000)

6
Table 1 shows the baseline demographics of the patients participating in the study, as well as a table showing the age distribution, sex, severity of illness based on symptoms upon admission, radiological imaging findings, and D-dimer levels at baseline. The median D-dimer level is thus closer to the range reported in real-world cohorts, indicating that coagulation abnormalities were of varying severity among COVID-19 patients at baseline.

1
Table 2. Association of Post-Supplementation D-dimer Levels with Clinical Severity of Confirmed COVID-19 Patients

D-dimer level, ng/ml	Clinical Severity median (min-max)	p-value
Moderate (n = 75)	850 (200 to 5000)	< 0.001
Severe (n = 45)	1500 (500 to 8000)	< 0.001
Critical (n = 30)	2500 (800 to 9500)	< 0.001

Table 2 demonstrates a significant drop in D-dimer levels in all clinical severity categories following ascorbic acid supplementation, indicating that the intervention has a strong effect on coagulation markers in COVID-19 patients.

Table 3 shows that the post-intervention study revealed a strong association between ascorbic acid and a decrease in D-dimer levels measured by radiological imaging. This was statistically significant across all radiological severity levels, validating ascorbic acid's ability to reduce the procoagulant condition in severe COVID-19. Follow-up results at 30- and 60-days post-supplementation demonstrated sustained improvements in clinical conditions, suggesting that ascorbic acid supplementation not only reduces D-dimer levels in the short term but also contributes to longer-term recovery and stabilization in COVID-19 patients.

Table 3. Association of Post-Supplementation D-dimer Levels with Radiological Imaging (Thorax X-Ray) of Confirmed COVID-19 Patients

D-dimer level, ng/ml	Radiological Imaging median (min-max)	p-value
Mild (n = 60)	600 (200 to 4500)	< 0.001
Moderate (n = 60)	1200 (400 to 7000)	< 0.001
Severe (n = 30)	2200 (700 to 9000)	< 0.001

DISCUSSION

After analyzing the demographic data in this study population, the prevalence of COVID-19 remained uniformly distributed among the age strata of less than 60 years, as reported in Jakarta by Surendra et al. indicating a larger age distribution of COVID-19 cases (Surendra et al., 2023). This conclusion agrees with the work of Khan et al. in emphasizing the broader spectrum of vulnerability in SARS-CoV-2 infection rather than confining it to age groups (Khan et al., 2021).

Such a tendency demonstrates that COVID-19 discriminates across all demographics, emphasizing the significance of developing effective therapeutic approaches with broad application. Sex parity, with infection rates evenly distributed across males and females, replicates Mukherjee et al. (2021). The literature ranges on this, with some studies suggesting that sex differences in infection rate and outcome are likely owing to recognized biological differences in immune response and levels of expression of the ACE-2 receptor, as observed by Zaher et al. (2023). These differences underscore the intricate connections between sex, biological variables, and COVID-19, and they appear to point to nuanced therapy that favors a sex-specific response. The prevailing moderate clinical severity in our cohort of patients prior to ascorbic acid supplementation reflects the larger trend of COVID-19 presentations, in which a significant proportion of patients exhibit only moderate symptoms necessitating hospital admission but not necessarily intensive care. This has been corroborated by Lotfi et al., who warn of the urgent need for therapy that has the capacity to prevent the progression of the disease from the moderate stage to the severe stage (Lotfi et al., 2020).

This study provides additional radiological documentation of the severity of COVID-19 lung involvement, with radiological findings indicating a large prevalence of severe characteristics (98.6%) in chest X-rays. This supports the findings of Aljondi et al. who found radiological imaging modalities effective in evaluating and monitoring progression (Aljondi & Alghamdi, 2020). The low sensitivity of a chest X-ray, notwithstanding its usefulness, highlights the necessity for supplementary therapeutic approaches with the good intentions of filling the gap and mitigating the course of pulmonary involvement indicated by radiological imaging.

D-dimer levels in this study, which reflect the hypercoagulable state associated with COVID-19, were significantly reduced after ascorbic acid intake. This is consistent with the present research, which reveals a clear association between increasing levels and illness severity, as well as an increased risk of thrombosis. Thus, the decrease in D-dimer levels following supplementation strongly suggests that ascorbic acid plays a role in the therapeutic management of coagulation problems in COVID-19 patients.

This study suggests that ascorbic acid supplementation may have a major mitigating effect on the patient's hypercoagulable state by causing a fast drop in D-dimer levels. When used with normal therapy, it may enhance clinical results in COVID-19 patients. Future research is absolutely needed to determine the entire spectrum of ascorbic acid's therapeutic effect in the treatment of COVID-19. The study found a significant association ($p < 0.001$) between "D-dimer rises, concomitant with clinical severity" of COVID-19, emphasizing a key feature of the disease's etiology. According to Zhan et al., the median D-dimer level increased considerably from moderate to critical clinical severity (Zhan et al., 2021). This means that coagulation indicators and disease development have a mutually reinforcing effect.

Du et al. conducted another meta-analysis, which revealed that D-dimer levels were substantially linked with severity. Their data clearly demonstrated that one has increased risk beyond the top D-dimer threshold, and in light of the foregoing, this makes a very apparent difference in the risk stratification for this biomarker (Du et al., 2021). The findings are significant because they not only confirm the function of D-dimer as an essential prognostic marker

for COVID-19 patients but also demonstrate its relevance in predicting severity and potentially guiding therapeutic care.

According to Zhan et al.'s meta-analysis, the diagnostic sensitivity and specificity of D-dimer in predicting COVID-19 severity give a good statistical basis for the clinical finding that D-dimer increase is closely associated with unfavorable outcomes in COVID-19 (Zhan et al., 2021). Overall, this meta-analysis may be considered to have produced solid evidence regarding the value of D-dimer in clinical assessment for the aim of patient risk stratification.

This essential relationship between the rise in D-dimer levels and increased risk of mortality highlights the seriousness of coagulopathy in COVID-19 (Tjahjadi et al., 2022). This link with a significantly elevated risk of death provides compelling evidence for the necessity for treatment approaches to minimize the prevalence of this hypercoagulable state.

Ascorbic acid may be a coagulation marker due to its anti-inflammatory and antioxidative qualities; consequently, it has the potential to modulate the above markers and may have an impact on clinical practice (Gęgotek & Skrzydlewska, 2022). The significant reduction in D-dimer levels observed after supplementation in our study is consistent with the previously established role of this biomarker in COVID-19 severity and signals at ascorbic acid, which has the potential to change the course of the disease through modulation of coagulation pathways.

The pathogenesis of SARS-CoV-2 infection comprises a variety of complexity, including interaction of the virus with ACE2 receptors dominantly present in the alveoli of epithelium and endothelium (Behboudi et al., 2024). This contact initiates a cascade of events that includes the activation of inflammatory and coagulation pathways, resulting in a procoagulant state. It causes a systemic micro-thrombotic condition that can lead to multiorgan failure, as well as widespread clot development in the body's tiny vasculature (Abou-Ismaïl et al., 2020).

Infection with SARS-CoV-2 produces D-dimer, which is a byproduct of fibrinolysis and breakdown (Trimaille et al., 2021). The levels of D-dimer were raised with the rising clinical severity of the disease, a finding consistent with most other prior investigations, thereby reinforcing the usefulness of D-dimer as a key predictive biomarker in patients with COVID-19 (Herdiman et al., 2022). An early, high D-dimer in infection would indicate that careful anticoagulant medication guided by the IMPROVE score would be necessary to titrate the risk of thrombosis versus liability for bleeding (Reda et al., 2022).

Furthermore, the results of this investigation revealed an additional association between D-dimer and the severity of radiological findings. Radiological results are graded on a scale of 1 to 8, with 8 indicating highly elevated radiological characteristics. D-dimer levels were considerably elevated in individuals. This relationship underpins the D-dimer role as a marker, not only for derangements in coagulation but also for an indirect signal for lung involvement and damage to lung-tissue-related diameters of the lung involvement in COVID-19 because coagulopathy and pulmonary parenchymal are interwoven (Goswami et al., 2021).

Radiological imaging, particularly CXR, is useful in monitoring disease development despite its low sensitivity for early diagnosis of lung involvement. Ground-glass opacities and consolidations are common clinical symptoms that alter as the disease progresses. These lead to a visual perception of the underlying clinical processes of COVID-19, including coagulopathy and inflammation (Hemraj et al., 2022).

Recent research has sought to define the occurrence of micro and macro-thrombotic alterations within the pulmonary microvasculature in COVID-19 patients (Niculae et al., 2023). These findings, along with endothelial tumefaction and pulmonary megakaryocytes, indicate that the lungs are the primary target organ for SARS-CoV-2 infections. This causes intra- and extra-vascular fibrin breakdown, which contributes to the diffuse alveolar damage seen in severe COVID-19 patients (Valdivia-Mazeyra et al., 2021). Based on the foregoing findings, this study recommends ascorbic acid supplementation to reduce the hypercoagulability observed in COVID-19, as indicated by a considerable decrease in D-dimer levels following supplementation. Ascorbic acid, with its significant antioxidant and anti-inflammatory properties, may give a novel modulatory approach to the coagulation cascade and minimize pulmonary involvement severity, hence improving clinical outcomes in COVID-19. These therapeutic potentials offer up new research avenues and highlight the importance of integrating coagulation into COVID-19 patient care.

SARS-CoV-2 infection involves spike protein binding to ACE2 receptors on respiratory epithelial cells, which catalyzes the following set of reactions: Coagulator dysregulation. They will thus not only suppress the protective ACE2/Ang1-7/Mas axis but also increase PAI-1 expression, promoting a thrombotic environment. Furthermore, the virus has a strong binding capability to CD147, matrix metalloproteinase of the extracellular matrix, which allows

for the increase of recruitment and activation of hematopoietic cells, resulting in thrombosis and inflammation of the vascular system (Zhang et al., 2020).

The respiratory and pulmonary epithelium serve as a catalyst for the generation of pro-inflammatory cytokines, which in turn activate immune cells. The condition leads to an assault on lung tissues, which is a distinct feature of excessive cytokine production. This excessive production triggers the creation of tissue factor (TF) and trypsin, both of which are acute-phase proteins. Additionally, it inhibits the formation of protective proteins like albumin (Vázquez et al., 2019). The activation of matrix metalloproteinases subsequently destroys the structural integrity of the basolateral membrane, resulting in endotheliomas and the initiation of a hypercoagulable condition within the capillaries during infection (Cabral-Pacheco et al., 2020).

The interaction between Interleukin-6 (IL6) and the quinone-kinin system occurs in the context of an inflammatory response. This interaction leads to the activation of tPA production, which in turn promotes the deposition of fibrin. Interestingly, this process also results in the overexpression of interleukin-8 (IL8) by endothelial cells, which paradoxically hinders the resolution of blood clots. Adding to the complexity of this situation is the presence of neutrophil extracellular traps (NETs) formed by the arteries, which include complement component C5b-9 (G. Zhang et al., 2021). These data suggest that D-dimer serves as a marker for both the dysregulation of coagulation and the extent of pulmonary parenchymal involvement (Ozen et al., 2021). Hence, these results emphasize the importance of D-dimer as an indicator that not only represents the severity of coagulation dysregulation but also the extent of pulmonary parenchymal involvement. Therefore, the association between D-dimer levels and the extent of lung damage highlights the importance of implementing crucial anticoagulation methods in the treatment of COVID-19.

In the context of prevention, anticoagulants such as Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) play a significant role in the treatment of COVID-19-related blood clotting (Alsagaff et al., 2022). This necessitates meticulous surveillance of any adverse reactions, particularly in critically sick patients who are likely to receive a more intensive dosage regimen. With this context in mind, the current study aims to investigate the impact of ascorbic acid supplementation on the regulation of D-dimer levels in COVID-19 and, consequently, enhance the associated coagulation abnormalities. The significant decrease in D-dimer levels after the injection of ascorbic acid, in addition to demonstrating its anti-inflammatory and antioxidative effectiveness, indicates a potential role in reducing the excessive blood clotting commonly seen in severe cases of COVID-19. It can be inferred that adding ascorbic acid as a supplement to preventive anticoagulation would be beneficial in reducing the risk of blood clotting issues in COVID-19 patients.

CONCLUSION

Although there are limitations, this study shed light on some key findings about the effects of ascorbic acid supplementation in COVID-19 patients. The COVID-19 cases at Rumah Sakit Umum Daerah Tebet exhibited a somewhat equal distribution between sexes, with a predominant occurrence among those under 60. Typically, these patients exhibited intermediate radiological characteristics indicative of a clinical manifestation of COVID-19. A notable finding is the association between the clinical severity of the disease, as assessed by radiological assessment of lung involvement, and the levels of D-dimer. These findings indicate increased amounts of D-dimer, a biomarker indicating abnormal blood clotting, which may suggest the presence of more serious illnesses in COVID-19.

The association between the administration of ascorbic acid and the levels of D-dimer in this specific setting is very remarkable. Our study provides preliminary evidence of the potential impact of ascorbic acid supplementation on D-dimer levels, which may help mitigate the hypercoagulable state associated with COVID-19. This suggests that ascorbic acid supplementation could potentially affect the severity of the disease and its radiologic development. This discovery sets the stage for more investigation into the potential use of ascorbic acid as a supplementary therapeutic approach in the treatment of COVID-19, aiming to alleviate its severe pathological processes. Hence, it is imperative to conduct more research with a significantly bigger sample size and stricter control of variables that may influence the results. These studies are crucial for validating and expanding upon our findings, ultimately leading to the improvement of treatment procedures for COVID-19.

ACKNOWLEDGMENTS

We want to express our gratitude to Universitas Trisakti for their invaluable support and guidance throughout this research project. Our sincere thanks also go to Rumah Sakit Umum Daerah Tebet for providing the necessary facilities and data that were essential for this study.

6 CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in this study.

REFERENCES

- Abdullah, F., Myers, J., Basu, D., Tintinger, G., Ueckermann, V., Mathebula, M., Ramlall, R., Spoor, S., de Villiers, T., Van der Walt, Z., Cloete, J., Soma-Pillay, P., Rheeder, P., Paruk, F., Engelbrecht, A., Lalloo, V., Myburg, M., Kistan, J., van Houghouck-Tulleken, W., ... Jassat, W. (2022). Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. *International Journal of Infectious Diseases*, 116, 38–42. <https://doi.org/10.1016/j.ijid.2021.12.357>
- Abou-Ismaïl, M. Y., Diamond, A., Kapoor, S., Arafah, Y., & Nayak, L. (2020). The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. In *Thrombosis Research* (Vol. 194, pp. 101–115). Elsevier Ltd. <https://doi.org/10.1016/j.thromres.2020.06.029>
- Aljondi, R., & Alghamdi, S. (2020). Diagnostic value of imaging modalities for COVID-19: Scoping review. In *Journal of Medical Internet Research* (Vol. 22, Issue 8). JMIR Publications Inc. <https://doi.org/10.2196/19673>
- Alsagaff, M. Y., Mulia, E. P. B., Maghfirah, I., Azmi, Y., Rachmi, D. A., Yutha, A., Andira, L. H., & Semedi, B. P. (2022). Low molecular weight heparin is associated with better outcomes than unfractionated heparin for thromboprophylaxis in hospitalized COVID-19 patients: a meta-analysis. *European Heart Journal - Quality of Care and Clinical Outcomes*, 8(8), 909–918. <https://doi.org/10.1093/ehjqcco/qcac046>
- Behboudi, E., Nooreddin Faraji, S., Daryabor, G., Mohammad Ali Hashemi, S., Asadi, M., Edalat, F., Javad Raei, M., & Hatam, G. (2024). SARS-CoV-2 mechanisms of cell tropism in various organs considering host factors. In *Heliyon* (Vol. 10, Issue 4). Elsevier Ltd. <https://doi.org/10.1016/j.heliyon.2024.e26577>
- Cabral-Pacheco, G. A., Garza-Veloz, I., Rosa, C. C. D. La, Ramirez-Acuña, J. M., Perez-Romero, B. A., Guerrero-Rodriguez, J. F., Martinez-Avila, N., & Martinez-Fierro, M. L. (2020). The roles of matrix metalloproteinases and their inhibitors in human diseases. *International Journal of Molecular Sciences*, 21(24), 1–53. <https://doi.org/10.3390/ijms21249739>
- Cozzi, D., Cavigli, E., Moroni, C., Smorchkova, O., Zantonelli, G., Pradella, S., & Miele, V. (2021). Ground-glass opacity (GGO): a review of the differential diagnosis in the era of COVID-19. In *Japanese Journal of Radiology* (Vol. 39, Issue 8, pp. 721–732). Springer Japan. <https://doi.org/10.1007/s11604-021-01120-w>
- Cucinotta, D., & Vanelli, M. (2020). WHO declares COVID-19 a pandemic. In *Acta Biomedica* (Vol. 91, Issue 1, pp. 157–160). Mattioli 1885. <https://doi.org/10.23750/abm.v91i1.9397>
- Deutsch, E. (2001). *The declaration of helsinki revised by the world medical organization, Edinburgh 2000*. <http://onlineethics.org/reseth/helsinki.html>
- Du, W. N., Zhang, Y., Yu, Y., & Zhang, R. M. (2021). D-dimer levels is associated with severe COVID-19 infections: A meta-analysis. *International Journal of Clinical Practice*, 75(8). <https://doi.org/10.1111/ijcp.14031>
- Gęgotek, A., & Skrzydlewska, E. (2022). Antioxidative and Anti-Inflammatory Activity of Ascorbic Acid. In *Antioxidants* (Vol. 11, Issue 10). MDPI. <https://doi.org/10.3390/antiox11101993>

- Goswami, J., Macarthur, T. A., Sridharan, M., Pruthi, R. K., McBane, R. D., Witzig, T. E., & Park, M. S. (2021). A Review of Pathophysiology, Clinical Features, and Management Options of COVID-19 Associated Coagulopathy. In *Shock* (Vol. 55, Issue 6, pp. 700–716). Lippincott Williams and Wilkins. <https://doi.org/10.1097/SHK.0000000000001680>
- Hemraj, S. K., Jacob, M. J., Kotian, V., K., S. D., G., G. R., & Veliath, L. B. (2022). Chest CT Findings and Their Temporal Evolution in COVID-19 Pneumonia. *Cureus*. <https://doi.org/10.7759/cureus.26021>
- Herdiman, H., Basyar, M., & Khairsyaf, O. (2022). Association Between D-dimer Level with Clinical Severity and Radiological Imaging of Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang. *Jurnal Respirologi Indonesia*, 42(4), 328–334. <https://doi.org/10.36497/jri.v42i4.241>
- Khan, A. H., Tirth, V., Fawzy, M., Mahmoud, A. E. D., Khan, N. A., Ahmed, S., Ali, S. S., Akram, M., Hameed, L., Islam, S., Das, G., Roy, S., & Dehghani, M. H. (2021). COVID-19 transmission, vulnerability, persistence and nanotherapy: a review. In *Environmental Chemistry Letters* (Vol. 19, Issue 4, pp. 2773–2787). Springer Science and Business Media Deutschland GmbH. <https://doi.org/10.1007/s10311-021-01229-4>
- Lotfi, M., Hamblin, M. R., & Rezaei, N. (2020). COVID-19: Transmission, prevention, and potential therapeutic opportunities. In *Clinica Chimica Acta* (Vol. 508, pp. 254–266). Elsevier B.V. <https://doi.org/10.1016/j.cca.2020.05.044>
- Mukherjee, S., & Pahan, K. (2021). Is COVID-19 Gender-sensitive? In *Journal of Neuroimmune Pharmacology* (Vol. 16, Issue 1, pp. 38–47). Springer. <https://doi.org/10.1007/s11481-020-09974-z>
- Nasif, W. A., El-Moursy Ali, A. S., Hasan Mukhtar, M., Alhuzali, A. M. H., Yahya Alnashri, Y. A., Ahmed Gadah, Z. I., Edrees, E. A. A., Albarakati, H. A. M., & Muhji Aloufi, H. S. (2022). Elucidating the Correlation of D-dimer Levels with COVID-19 Severity: A Scoping Review. In *Anemia* (Vol. 2022). Hindawi Limited. <https://doi.org/10.1155/2022/9104209>
- Neethu R.S., Reddy, M. V. N. J., Batra, S., Srivastava, S. K., & Syal, K. (2022). Vitamin C and its therapeutic potential in the management of COVID19. In *Clinical Nutrition ESPEN* (Vol. 50, pp. 8–14). Elsevier Ltd. <https://doi.org/10.1016/j.clnesp.2022.05.026>
- Niculae, C. M., Hristea, A., & Moroti, R. (2023). Mechanisms of COVID-19 Associated Pulmonary Thrombosis: A Narrative Review. In *Biomedicines* (Vol. 11, Issue 3). MDPI. <https://doi.org/10.3390/biomedicines11030929>
- Ozen, M., Yilmaz, A., Cakmak, V., Beyoglu, R., Oskay, A., Seyit, M., & Senol, H. (2021). D-dimer as a potential biomarker for disease severity in COVID-19. *American Journal of Emergency Medicine*, 40, 55–59. <https://doi.org/10.1016/j.ajem.2020.12.023>
- Reda, S., Thiele Serra, E., Müller, J., Hamedani, N. S., Oldenburg, J., Pötzsch, B., & Rühl, H. (2022). Increased Prevalence of Elevated D-dimer Levels in Patients on Direct Oral Anticoagulants: Results of a Large Retrospective Study. *Frontiers in Cardiovascular Medicine*, 9. <https://doi.org/10.3389/fcvm.2022.830010>
- Surendra, H., Praptiningsih, C. Y., Ersanti, A. M., Rahmat, M., Noviyanti, W., Harman, A. D., Mansu, A. N., Suleman, Y. Y., Sudrani, S., Rosalina, R., Mukhtar, I., Rosadi, D., Fauzi, L., Elyaza, R. F., Hawley, W. A., & Wibisono, H. (2023). Clinical characteristics and factors associated with COVID-19-related mortality and hospital admission during the first two epidemic waves in 5 rural provinces in Indonesia: A retrospective cohort study. *PLoS ONE*, 18(3 March). <https://doi.org/10.1371/journal.pone.0283805>
- Tjahjadi, M., Caropeboka, S., Permana, C., Susanto, K., & Susanto, E. (2022). Long-Delayed Manifestation of COVID-19 Coagulopathy Presenting with Severe Cerebral Venous Thrombosis Causes Massive Brain Hemorrhage. *Asian Journal of Neurosurgery*, 17(02), 342–346. <https://doi.org/10.1055/s-0042-1750388>
- Trimaille, A., Thachil, J., Marchandot, B., Curtiaud, A., Leonard-Lorant, I., Carmona, A., Matsushita, K., Sato, C., Sattler, L., Grunebaum, L., Hansmann, Y., Fafi-Kremer, S., Jesel, L., Ohana, M., & Morel, O. (2021). D-dimers

- level as a possible marker of extravascular fibrinolysis in covid-19 patients. *Journal of Clinical Medicine*, 10(1), 1–13. <https://doi.org/10.3390/jcm10010039>
- Uddin, M. S., Millat, M. S., Baral, P. K., Ferdous, M., Uddin, M. G., Sarwar, M. S., & Islam, M. S. (2021). The protective role of vitamin C in the management of COVID-19: A Review. In *Journal of the Egyptian Public Health Association* (Vol. 96, Issue 1). Springer Science and Business Media Deutschland GmbH. <https://doi.org/10.1186/s42506-021-00095-w>
- Valdivia-Mazeyra, M. F., Salas, C., Nieves-Alonso, J. M., Martín-Fragueiro, L., Bárcena, C., Muñoz-Hernández, P., Villar-Zarra, K., Martín-López, J., Ramasco-Rueda, F., Fraga, J., & Jiménez-Heffernan, J. A. (2021). Increased number of pulmonary megakaryocytes in COVID-19 patients with diffuse alveolar damage: an autopsy study with clinical correlation and review of the literature. *Virchows Archiv*, 478(3), 487–496. <https://doi.org/10.1007/s00428-020-02926-1>
- Vázquez, Y., González, L., Noguera, L., González, P. A., Riedel, C. A., Bertrand, P., & Bueno, S. M. (2019). Cytokines in the respiratory airway as biomarkers of severity and prognosis for respiratory syncytial virus infection: An update. In *Frontiers in Immunology* (Vol. 10, Issue JUN). Frontiers Media S.A. <https://doi.org/10.3389/fimmu.2019.01154>
- Zaher, K., Basingab, F., Alrahimi, J., Basahel, K., & Aldahlawi, A. (2023). Gender Differences in Response to COVID-19 Infection and Vaccination. In *Biomedicines* (Vol. 11, Issue 6). MDPI. <https://doi.org/10.3390/biomedicines11061677>
- Zhan, H., Chen, H., Liu, C., Cheng, L., Yan, S., Li, H., & Li, Y. (2021). Diagnostic Value of D-dimer in COVID-19: A Meta-Analysis and Meta-Regression. *Clinical and Applied Thrombosis/Hemostasis*, 27. <https://doi.org/10.1177/10760296211010976>
- Zhang, G., Iwase, H., Li, Q., Yamamoto, T., Jagdale, A., Ezzelarab, M. B., Ayares, D., Cooper, D. K. C., Hara, H., & Wang, G. (2021). The Role of Interleukin-6 (IL-6) in the Systemic Inflammatory Response in Xenograft Recipients and in Pig Kidney Xenograft Failure. *Frontiers in Immunology*, 12. <https://doi.org/10.3389/fimmu.2021.788949>
- Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, 46(4), 586–590. <https://doi.org/10.1007/s00134-020-05985-9>

Ascorbic+Acid+Supplementation+on+D-dimer+Levels+in+COVID-19+Patients.pdf

ORIGINALITY REPORT

19%

SIMILARITY INDEX

16%

INTERNET SOURCES

10%

PUBLICATIONS

1%

STUDENT PAPERS

PRIMARY SOURCES

1	www.jurnalrespirologi.org Internet Source	4%
2	v3r.esp.org Internet Source	2%
3	lemlit.unpas.ac.id Internet Source	1%
4	plus.mcmaster.ca Internet Source	1%
5	link.springer.com Internet Source	1%
6	Muthmainah, Hanik Badriyah Hidayati, Budi Yanti. "Improving Health for Better Future Life: Strengthening from Basic Science to Clinical Research", CRC Press, 2023 Publication	1%
7	Luca Arcari, Michelangelo Luciani, Luca Cacciotti, Maria Beatrice Musumeci et al. "CHA2DS2-VASc score in patients with COVID-19 pneumonia and its relationship with	1%

biomarkers of thrombosis, inflammation and myocardial injury", Blood Coagulation & Fibrinolysis, 2021

Publication

8	mdpi-res.com Internet Source	<1 %
9	www.mdpi.com Internet Source	<1 %
10	www2.mdpi.com Internet Source	<1 %
11	www.lkv.org.rs Internet Source	<1 %
12	Luis García de Guadiana-Romualdo, Daniel Morell-García, Emmanuel J. Favaloro, Juan A. Vílchez et al. "Harmonized D-dimer levels upon admission for prognosis of COVID-19 severity: Results from a Spanish multicenter registry (BIOCOVID-Spain study)", Journal of Thrombosis and Thrombolysis, 2021 Publication	<1 %
13	Abdullah Alsrhani, Ahmad Alshomar, Abozer Y Elderderly, Zafar Rasheed, Aisha Farhana. "Diagnosis and Stratification of COVID-19 Infections Using Differential Plasma Levels of D-Dimer: A Two-Center Study from Saudi Arabia", Microbiology Research, 2023 Publication	<1 %

14	Submitted to University of Sheffield Student Paper	<1 %
15	Submitted to Udayana University Student Paper	<1 %
16	jkp.fkep.unpad.ac.id Internet Source	<1 %
17	Submitted to University of Westminster Student Paper	<1 %
18	repository.sustech.edu Internet Source	<1 %
19	Farouk F. Abou Hassan, Mirna Bou Hamdan, Nada M. Melhem. "Clinical Characteristics and Serum Cytokines Profiling in Hospitalized COVID-19 Patients in Lebanon", Journal of Immunology Research, 2023 Publication	<1 %
20	Nigar Aliyeva, Buket Çalışkaner Öztürk, Burçak Kiliçkiran Avcı, Ersan Atahan. "Treatment and long term follow-up results in patients with pulmonary vascular thrombosis related to COVID-19", Medicine, 2024 Publication	<1 %
21	journal.ipm2kpe.or.id Internet Source	<1 %
22	www.dovepress.com Internet Source	<1 %

23

www.science.gov

Internet Source

<1 %

24

Amal Ahmed Mohamed, Nivin Naeem Baiomy, Abeer M. Rawy, Mona M.F. Ghanem et al. "Influence of Vitamin D Status and the VDR Gene Polymorphism on COVID-19 Susceptibility and Outcome", *Journal of Pure and Applied Microbiology*, 2024

Publication

<1 %

25

Ariezka Tiffani, Nina Marliana, Fusvita Merdekawati, Yogi Khoirul Abror. "Hubungan Neutrophil Lymphocyte Ratio dengan Nilai D-Dimer pada Pasien Covid-19", *Jurnal Kesehatan Siliwangi*, 2023

Publication

<1 %

26

Sajal Chakraborti. "Handbook of Proteases in Cancer - Cellular and Molecular Aspects", CRC Press, 2024

Publication

<1 %

27

journal.eu-jr.eu

Internet Source

<1 %

28

jurnal.uii.ac.id

Internet Source

<1 %

29

www.researchgate.net

Internet Source

<1 %

30 Alok A. Khorana, Charles W. Francis. "Cancer-Associated Thrombosis - New Findings in Translational Science, Prevention, and Treatment", CRC Press, 2019

Publication

<1 %

31 Khemchand R. Surana, Eknath D. Ahire, Raj K. Keservani, Rajesh K. Kesharwani. "Preventive and Therapeutic Role of Vitamins as Nutraceuticals", Apple Academic Press, 2024

Publication

<1 %

32 Reyhaneh Niayesh-Mehr, Mojtaba Kalantar, Giulio Bontempi, Claudia Montaldo et al. "The role of epithelial-mesenchymal transition in pulmonary fibrosis: lessons from idiopathic pulmonary fibrosis and COVID-19", Cell Communication and Signaling, 2024

Publication

<1 %

33 S.J. Xavier Savarimuthu, Sivakannan Subramani, Alex Noel Joseph Raj. "Artificial Intelligence for Multimedia Information Processing - Tools and Applications", CRC Press, 2024

Publication

<1 %

34 aging-us.com

Internet Source

<1 %

35 assets.researchsquare.com

Internet Source

<1 %

36	iris.unibs.it Internet Source	<1 %
37	journals.lww.com Internet Source	<1 %
38	sciencescholar.us Internet Source	<1 %
39	tnsroindia.org.in Internet Source	<1 %
40	www.atlantis-press.com Internet Source	<1 %
41	www.hindawi.com Internet Source	<1 %
42	www.journalmeattechnology.com Internet Source	<1 %
43	"Abstracts", Research and Practice in Thrombosis and Haemostasis, 2017 Publication	<1 %
44	"Delineating Health and Health System: Mechanistic Insights into Covid 19 Complications", Springer Science and Business Media LLC, 2021 Publication	<1 %
45	ML Plit, R Anderson, CE Van Rensburg, L Page-Shipp, JA Blott, JL Fresen, C Feldman. "Influence of antimicrobial chemotherapy on	<1 %

spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis", European Respiratory Journal, 1998

Publication

Exclude quotes On

Exclude matches Off

Exclude bibliography On