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

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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-Ismail 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 -80ºC 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-Ismail 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.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in this study.

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