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Original article

# Association Between Low Serum Folic Acid and Vitamin $B_{12}$ Levels with Covid-19 Prognosis

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**Abstract.** *Background and aim:* It is important that the immune system is active and strong in protection from the COVID-19 pandemic. Folic acid and vitamin $B_{12}$ are involved in the initiation, maintenance and regulation of both innate and adaptive immune reactions of the host against infections. In this study, it was aimed to investigate the relationship between serum folic acid and vitamin $B_{12}$ levels of COVID-19 patients on the prognosis of the disease. *Methods:* The sample of the study consists of 529 individuals hospitalized in the Pandemic Chest Diseases Intensive Care Unit. General characteristics of the individuals, biochemical parameters checked routinely (white blood cell (WBC), platelet (PLT), lymphocyte, Neutrophil/Lymphocyte (N/L) rate, C-reactive protein (CRP), oxygen ($O_2$) saturation at the time of admission), serum vitamin $B_{12}$ and folic acid levels, length of stay in intensive care units (ICUs) and hospitalization, and mortality were recorded. *Results:* The mean age of individuals was 62.8±15.12 years, and 50.9% were men and 49.1% were women. The mean level of serum folic acid in the subjects was 9.1±4.91 (ng/mL), and 2.4% had folic acid deficiency and 28.4% had folic acid insufficiency. The mean serum vitamin $B_{12}$ was 295.6±229.98 (pg/mL), and vitamin $B_{12}$ deficiency was observed only in 14.4%. The increase in serum folic acid levels reduces the total length of hospitalization and the risk of mortality ($p<0.05$). On the other hand, no correlation was found between $B_{12}$ levels and the length of stay in ICU, hospitalization, and mortality. It was shown that WBC and N/L rates decreased as serum folic acid levels increased, and $O_2$ saturation at the first hospital admission was higher. *Conclusions:* Folate deficiency and insufficiency are common among hospitalized COVID-19 patients and cause progression to severe disease. Therefore, examining COVID-19 patients in terms of nutritional deficiencies is critical in monitoring the clinical outcomes of the disease.

**Key words:** COVID-19, folic acid, vitamin $B_{12}$

## Introduction

In late December 2019, a new type of coronavirus (COVID-19) from the Coronaviridae family was identified in Wuhan, China. The virus spread rapidly all over the world and was declared a pandemic by the World Health Organization (WHO) in March 2020 (1). More than 6 million deaths have occurred around the globe due to the COVID-19 disease, for which no cure has been found to date (2). The disease can be asymptomatic; however, it has a wide spectrum from a mild course such as upper respiratory tract infection to cases with a moderate/severe clinical course with complications due to pneumonia, acute respiratory distress syndrome, and other system (gastrointestinal system, cardiovascular system, central nervous system, etc.) involvement (3).

Individuals with weakened immune systems are at higher risk of developing complications associated with COVID-19. For this reason, it is important that the immune system is active, and strong in protection from

the COVID-19 pandemic, together with environmental measures (4). Optimal nutrition is essential for supporting the functions of immune cells, and for the formation of an effective immune response against pathogens. It has been reported that poor nutritional status increases the severity of COVID-19 disease (5, 6).

Micronutrients are involved in the initiation, maintenance, and regulation of both innate and adaptive immune reactions of the host against the virus. Since there is still no specific treatment for COVID-19 disease, it is important to keep the immune system active and strong (7). The most characteristic feature of COVID-19 infection is the increase in proinflammatory cytokines, chemokines, and reactive oxygen species, leading to pulmonary fibrosis and respiratory distress, which are risk factors for mortality (8). Folic acid and vitamin $B_{12}$ help support the host's resistance to infections due to their critical roles in the synthesis of nucleic acids, protein synthesis, and cell proliferation (7, 9). Folic acid has an important role in supporting the innate, and adaptive immune system by maintaining natural killer (NK) cell cytotoxic activity, T-helper 1 (Th1) mediated immune response, and antibody production (10). It is also stated that folic acid inhibits furin enzyme activity, preventing the binding of SARS-CoV-2 spike protein, and may help prevent or alleviate respiratory involvement associated with COVID-19 (11). Low serum $B_{12}$ levels increase methylmalonic acid and homocysteine levels, causing a rise in reactive oxygen species and oxidative stress. It is known that hyperhomocysteinemia not only causes endothelial dysfunction and megaloblastic anemia but also reduces the immune response. It is also reported that low $B_{12}$ levels may cause respiratory distress and serum $B_{12}$ levels in COVID-19 patients may be associated with the prognosis of the disease (12, 13). Based on these data, the relationship between serum folic acid and $B_{12}$ levels of COVID-19 patients and the prognosis of the disease was investigated in this study.

## Materials and Methods

This retrospective study included 529 individuals over the age of 18, who were diagnosed with COVID-19 by polymerase chain reaction test and hospitalized in the Pandemic Chest Diseases Service and Intensive Care Service of the University of Health Sciences Antalya Training and Research Hospital between April 2019 and October 2021, and whose serum $B_{12}$ or folic acid levels were examined for any reason in addition to the biochemical parameters associated with COVID-19. Subjects who had a history of vitamin-mineral use and were pregnant were excluded from the study. Required permissions were obtained in advance from the Ministry of Health Commission of COVID-19 Scientific Research Platform (Project no: 2021-08-26T15_01_47) and the University of Health Sciences Antalya Training and Research Hospital Ethics Committee (2021-14/11).

The patient examination information filled by the Chest Diseases Specialist during hospitalization was scanned retrospectively from the hospital information system. Patients' age, gender, comorbidities, tomography results, and biochemical parameters checked routinely (white blood cell (WBC), platelet (PLT), lymphocyte, Neutrophil/Lymphocyte (N/L) rate, C-reactive protein (CRP), oxygen ($O_2$) saturation at the time of admission), serum $B_{12}$ and folic acid levels, length of stay in intensive care unit (ICU) and hospitalization, and mortality were recorded. Serum folic acid and $B_{12}$ levels were classified based on the reference values of the kits used in the hospital. Accordingly, folic acid levels of <3.0 ng/mL were considered as deficiency, 3.0-5.9 ng/mL as insufficiency, and 6.0-20 ng/mL as normal; and $B_{12}$ levels of <126 pg/mL as low, 126-505 pg/mL as normal, and >505 pg/mL as high.

Statistical Package for Social Sciences (SPSS) Windows 22.0 package was used in all statistical analyzes. For statistical significance, $p<0.05$ was set. Continuous variables were indicated in mean±standard deviation (SD) and interquartile range (IQR)- median, depending on data distribution, and discrete variables in numbers and percentages. Kolomogorov-Smirnow test was used for normality test. Comparisons of the subjects' serum folic acid and $B_{12}$ levels based on serum $O_2$ at the time of admission, length of stay in ICU, total hospitalization day and mortality were evaluated with the Independent t-test in cases of normal distribution, and with Mann-Whitney U test in cases where there was no normal distribution. The independent effects of serum folic acid level on mortality and total

hospitalization day were assessed in a multivariate linear regression model. The study population was divided into quartiles according to serum folic acid and $B_{12}$ levels to see whether increased levels of serum folic acid and $B_{12}$ affected clinical results. Kruskal Wallis test was used for non-parametric comparison of numerical variables according to quartiles, and ANOVA test for comparisons according to quartiles when the assumption of normal distribution was met.

## Results

Table 1 shows the classification of the subjects by their general characteristics. The mean age of individuals was 62.8±15.12 years, and 50.9% were men and 49.1% were women. The most common comorbid diseases in the subjects were hypertension (35.5%) and diabetes (27.8%). The tomography results showed that the majority of them (78.5%) had unilateral or bilateral involvement in the lungs. It was determined that more than half of the subjects (61.6%) were provided with $O_2$ support at the time of admission, and $O_2$ support was most frequently provided through nasal (28.2%), a reservoir mask (25.5%), and a mask (22.4%). 43.1% needed ICU care, and the average length of stay in ICU was 10.5±8.85 days. Total hospitalization day was 10.8±8.31. The mortality rate was 38.9%. The mean level of serum folic acid in the subjects was 9.1±4.91 (ng/mL), and 2.4% had folic acid deficiency and 28.4% had folic acid insufficiency. The mean serum vitamin $B_{12}$ was 295.6±229.98 (pg/mL), and vitamin $B_{12}$ deficiency was observed only in 14.4%.

Table 2 shows the length of stay in ICU and total hospitalization of the subjects and their serum folic acid and $B_{12}$ levels based on their mortality. No significant difference was present between serum folic acid levels of those whose length of stay in ICU less or more than 7 days. Folic acid levels in subjects with a total hospitalization of fewer than 9 days (9.8±4.80 ng/mL) were significantly lower than those with a hospitalization of ≥9 days (8.4±4.92 ng/mL) and with existing mortality (10.4±5.19 ng/mL and 7.3±3.93 ng/mL, respectively) ($p<0.05$). No statistically significant difference was observed between the serum $B_{12}$ levels and the length of stay in ICU, hospitalization days and mortality ($p>0.05$).

**Table 1.** General characteristics of patients

| | n | % |
|---|---|---|
| **Gender** | | |
| Male | 269 | 50.9 |
| Female | 260 | 49.1 |
| **Comorbidity** | | |
| Coronary artery disease | 31 | 5.9 |
| Peripheral arterial disease | 7 | 1.3 |
| Cerebrovascular disease | 27 | 5.1 |
| Dementia | 19 | 3.6 |
| Chronic obstructive pulmonary disease | 25 | 4.7 |
| Rheumatological diseases | 9 | 1.7 |
| Diabetes mellitus | 147 | 27.8 |
| Chronic kidney disease | 31 | 5.9 |
| Cancer | 35 | 6.6 |
| Hypertension | 188 | 35.5 |
| Hyperlipidemia | 9 | 1.7 |
| **Thorax Computed Tomography** | | |
| No finding | 114 | 21.6 |
| Unilateral involvement | 57 | 10.8 |
| Bilateral involvement | 358 | 67.7 |
| **$O_2$ support at the time of admission** | 326 | 61.6 |
| Nasal mask | 92 | 17.4 |
| Mask | 73 | 13.8 |
| Reservoir mask | 83 | 15.7 |
| High-flow Nasal Cannula | 34 | 6.4 |
| Continuous positive airway pressure | 9 | 1.7 |
| Mecanic ventilation | 35 | 6.6 |
| **Mortality** | 206 | 38.9 |
| **Need ICU care** | 228 | 43.1 |
| **Length of ICU (days) (X ± SD)** | 10.5±8.85 | |
| **Hospitalization days (X ± SD)** | 10.8±8.31 | |
| **Serum Folic acid (ng/mL) (X ± SD)** | 9.1±4.91 | |
| Deficiency | 11 | 2.4 |
| Insufficiency | 129 | 28.4 |
| Normal | 314 | 69.2 |
| **Serum $B_{12}$ (pg/mL) (X ± SD)** | 295.6±229.98 | |
| Low | 52 | 14.4 |
| Normal | 264 | 72.9 |
| High | 46 | 12.7 |

**Table 2.** Serum folic acid and $B_{12}$ levels according to the length of stay in ICU, hospitalization days and mortality of individuals

| | **Folic acid (ng/mL)** | | **Vitamin $B_{12}$ (pg/mL)** | |
|---|---|---|---|---|
| **Length of stay in ICU** | (X±SD) | p | (X±SD) | p |
| <7 days | 8.1±4.07 | | 317.6±293.05 | |
| ≥7 days | 7.1±3.99 | 0.065 | 296.3±270.36 | 0.710 |
| **Hospitalization days** | | | | |
| <9 days | 9.8±4.80 | | 272.6±176.72 | |
| ≥9 days | 8.4±4.92 | 0.002* | 318.5±272.08 | 0.505 |
| **Mortality** | | | | |
| No | 10.4±5.19 | | 300.4±220.27 | |
| Yes | 7.3±3.93 | 0.032** | 279.5±259.04 | 0.460 |

*Independent t-test, p<0.05
**Mann-Whitney U test, p<0.05

**Table 3.** Multiple Linear Regression Analysis of the Relationship of Serum Folic Acid Levels of Individuals with Hospitalization Days and Mortality

| **Variables** | **B** | **SE** | **Beta** | **t** | **p** | **95% CI** |
|---|---|---|---|---|---|---|
| Constant | 10.947 | 0.387 | | 28.290 | 0.000 | 10.187 11.708 |
| Hospitalization days | -0.054 | 0.026 | -0.095 | -2.098 | **0.036** | -0.105 -0.003 |
| Mortality | -2.882 | 0.446 | -0.291 | -6.456 | **0.000** | -3.736 -1.968 |

$R^2$ = 0.322, (*p < 0.05), β: Coefficient of regression, SE: Standard error of mean

Table 3 presents a multiple linear regression analysis of the association of the subjects' serum folic acid levels with total hospitalization days and mortality. The increase in serum folic acid levels reduces the total length of hospitalization and the risk of mortality.

Table 4 shows the mean±SD and IQR values of some biochemical parameters related to COVID-19 according to the quartiles of serum folic acid and $B_{12}$ levels. Considering the folic acid levels, those in the first quartile (<5.39 ng/mL) had higher WBC, N/L rate, and hospitalization, and lower $O_2$ saturation at admission compared to those in the third (7.8-11.3 ng/mL) and fourth (>11.3 ng/mL) quartiles (p<0.05). In terms of serum $B_{12}$ levels, on the other hand, the first quartile (<157.5 pg/mL) had higher WBC and N/L rates than the third (231.0-355.0 pg/mL) quartile, and the second quartile (157.5-230.0 pg/mL) had lower WBC levels than the fourth quartile (>355.0 pg/mL) (p<0.05).

## Discussion

In this study, we found that the increase in serum folic acid levels reduced the total length of hospitalization and the risk of mortality. It was shown that WBC and N/L rates decreased as serum folic acid levels increased, and $O_2$ saturation at the first hospital admission was higher.

Decreased immunity is a critical risk factor for infections from respiratory viruses (14). In addition to adhering to adequate and balanced nutrition, good nutritional status is also a key factor in developing an optimal immune response for preventing infections. It is suggested that some micronutrients have a protective role in respiratory tract infections such as COVID-19 due to their anti-inflammatory and immunomodulatory effects. For this reason, it is becoming more and more clear that vitamin and mineral deficiencies affect the prognosis of COVID-19 (15).

**Table 4.** Patient baseline characteristics according to serum folic acid and $B_{12}$ levels quartiles.

| | **Folic Acid (ng/mL) (X±SD)** | | | | **Vitamin $B_{12}$ (pg/mL) (X±SD)** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Q1 (<5.39)** | **Q2 (5.39-7.79)** | **Q3 (7.80-11.30)** | **Q4 (>11.30)** | **Q1 (<157.5)** | **Q2 (157.5-230.0)** | **Q3 (231.0-355.0)** | **Q4 (>355.0)** |
| WBC ($mm^3x10^3$) | 11.2±6.8[a]<br>9.7 (8.1) | 9.8±6.85<br>7.3 (7.2) | 8.7±5.30[a]<br>6.8 (5.5) | 8.5±5.59[a]<br>6.5 (4.9) | 9.0±5.19[a]<br>7.3 (6.6) | 7.2±3.87[a,b]<br>5.6 (4.2) | 7.6±4.38<br>6.1 (3.6) | 8.9±6.27[b]<br>7.1 (5.6) |
| | p=0.040** | | | | p=0.041** | | | |
| Platelet ($mm^3x10^3$) | 225.8±130.81 | 216.3±105.67 | 219.9±102.30 | 219.2±107.91 | 214.7±107.26 | 229.7±116.74 | 215.0±98.92 | 214.3±9.55 |
| | p=0.985 | | | | p=0.721 | | | |
| Lymphocyte (%) | 12.4±11.3 | 15.7±13.23 | 16.7±12.30 | 17.1±20.42 | 16.2±13.91 | 28.2±84.94 | 19.8±12.03 | 16.6±11.29 |
| | p=0.071 | | | | p=0.236 | | | |
| N/L | 15.1±15.82[a]<br>10.4 (17.8) | 11.3±12.60<br>5.7 (9.1) | 9.3±10.67[a]<br>5.5 (9.4) | 8.9±8.56[a]<br>4.9 (8.0) | 16.8±11.63[a]<br>5.4 (10.2) | 8.1±9.59<br>4.1 (7.4) | 6.4±6.06[a]<br>3.8 (4.9) | 8.6±9.79<br>4.6 (7.0) |
| | p=0.002** | | | | p=0.029** | | | |
| CRP (mg/dL) | 145.8±102.60[a] | 127.0±106.85 | 94.0±82.87[a] | 103.7±94.45[a] | 112.4±89.61 | 80.5±80.86 | 95.8±86.92 | 86.4±78.48 |
| | p=0.000* | | | | p=0.096 | | | |
| $O_2$ Saturation | 91.7±7.99[a]<br>94.0 (7.0) | 92.6±5.93<br>95.0 (7.0) | 94.3±4.10[a]<br>95.5 (5.0) | 94.0±6.18<br>95.0 (4.0) | 94.6±3.99 | 93.7±4.70 | 94.7±4.40 | 93.9±4.73 |
| | p= 0.020** | | | | p=0.437 | | | |
| Hospitalization days | 14.1±10.17[a]<br>12.0 (10.0) | 11.3±7.90<br>9.5 (9.0) | 9.9±7.46[a]<br>8.0 (7.0) | 9.6±8.03[a]<br>8.0 (8.0) | 9.9±6.64 | 9.2±7.68 | 9.8±7.13 | 10.2±5.80 |
| | p= 0.000** | | | | p=0.762 | | | |

WBC: White Blood Cell; N/L: Neutrophil/ Lymphocyte; CRP: C- Reactive Protein

Folic Acid Quartile ranges are as follows: Quartile 1: <5.39 ng/mL, Quartile 2: 5.39-7.79 ng/mL, Quartile 3: 7.80-11.30 ng/mL, Quartile 4: >11.30 ng/mL.

B12 Quartile ranges are as follows: Quartile 1: <157.5 pg/mL, Quartile 2: 157.5-230.0 pg/mL, Quartile 3: 231.0-355.0 pg/mL, Quartile 4: >355.0 pg/mL. Variables are presented as mean±standard deviation, median and interquartile range

*p<0.05 ANOVA, ** p<0.05 Kruskal Wallis

Folic acid is an essential micronutrient involved in one-carbon metabolism, conversion of serine, glycine, and homocysteine to methionine, production of nucleic acids, deoxyribonucleic acid methylation, and gene expression. It is stated that folic acid has a strong immunomodulatory and anti-inflammatory effect by increasing lymphocyte and NK cell activity, regulating Treg cell metabolism and reducing the release of Nuclear Factor kappa B, and therefore it may play a protective role against SARS-CoV-2 virus (16). It is reported that in addition to its functions in the immune response, folic acid may also act on the SARS-CoV-2 virus through some inhibitory mechanisms. Since 3CL hydrolase, also known as the main protease, has a critical role in the life cycle of the SARS-CoV-2 virus, folic acid molecules form hydrogen bonds with this enzyme and can disrupt the life cycle of the virus by inhibiting its activity (17). Due to this inhibitory effect, it is thought that folic acid may be useful for the treatment of COVID-19 (18). Studies report that folic acid, and especially folic acid derivatives such as 5-methyl tetrahydrofolic acid and tetrahydrofolic, prevent the entry of SARS-CoV-2 virus into the cell (11, 19). Low folic acid levels are known to be associated with hyperhomocysteinemia. Hyperhomocysteinemia causes a decrease in nitric oxide bioavailability and oxidative stress, leading to vascular endothelial changes and may trigger pulmonary hypertension (20). It is suggested that high-dose folic acid (5-10 mg/day) activates endothelial nitric oxide synthase (eNOS) to induce vasodilation and may be a useful therapeutic option in patients with pulmonary hypertension and/or refractory severe hypoxemic COVID-19 (21). Acosta-Elias & Espinosa-Tanguma (22) reported that folic acid supplementation was a protective factor that resulted in a ten times lower rate of hospitalization for SARS-CoV-2 infection in pregnant women compared to data obtained during the 2009 $H_1N_1$ pandemic. A study conducted in Israel also suggested that low folic acid levels in COVID-19 patients were associated with the severity of the disease (23). Another similar study showed that folate deficiency was common (11.4%) in hospitalized COVID-19 patients; however, no association was found between serum folate levels and clinical outcomes (14). Ersöz and Yılmaz(15) determined the mean serum folate levels as 10.8±9.982 ng/mL and reported that the serum folate levels of those who were admitted to the ICU, intubated and mortality was lower ($p<0.05$). Our study also showed that approximately one out of every three people has folic acid deficiency and insufficiency, WBC and N/L rate decreased as serum folic acid levels increased, and $O_2$ saturation at the first hospital admission was higher. Similarly, those with longer hospitalization and mortality had lower serum folic acid levels. In this context, it is crucial to evaluate serum folic acid levels in terms of COVID-19 prognosis.

In addition to the presence of $B_{12}$ deficiency in 14.4% of the subjects in our study, no correlation was found between $B_{12}$ levels and the length of stay in ICU, hospitalization, and mortality. Although the WBC levels of the group with lower serum $B_{12}$ levels were higher than the one with higher $B_{12}$ levels, the subjects in the group with the highest $B_{12}$ levels had increased WBC levels. Similarly, although statistically insignificant, the N/L rate also decreased from the first to the third quartile and increased again in the fourth quartile. Furthermore, the fourth quartile had the highest number of total hospitalization days. Similar studies indicate that high $B_{12}$ levels are associated with poor COVID-19 poor prognostic factor (15, 23, 24). In these studies, it is thought that increased $B_{12}$ levels may have affected the poor prognosis due to comorbidities or supplement use. In addition, it was stated that high vitamin $B_{12}$ levels could be explained by high levels of carrier protein, decreased clearance of vitamin $B_{12}$ by the liver, and decreased uptake of vitamin $B_{12}$ by peripheral tissues (15, 24). It is also thought that high $B_{12}$ levels may adversely affect the prognosis in individuals with kidney disease and especially diabetic nephropathy (25). In addition to the mechanisms clarifying the relationship between high $B_{12}$ levels and poor prognosis, the fact that 5.9% of the subjects in our study had kidney disease and approximately one out of every 4 people had diabetes may account for such a relationship. Similar studies in the literature show that the mean $B_{12}$ levels of the patients with a poor prognosis is much higher than that of the subjects in our study, which can be mainly due to the exclusion of the participants, who took vitamin and mineral supplements, at the beginning of the study. As the serum $B_{12}$ levels of the subjects

in our study were not excessively high, the relationship between high $B_{12}$ levels and poor prognosis may have been found weaker, similar to the literature. The relationship between high serum vitamin $B_{12}$ levels and prognosis is unclear, due to the relatively small number of studies investigating the relationship between vitamin $B_{12}$ and COVID-19. However, it is known that $B_{12}$ deficiency may adversely affect the prognosis of COVID-19 as it causes immunological (natural and adaptive immunity, cellular and humoral responses, etc.) and hematological (coagulation) problems and increases inflammation and oxidative stress (26). Therefore, it should be noted that $B_{12}$ deficiency is a modifiable risk factor in the fight against COVID-19.

Since this is a retrospective study, food consumption records were not taken and the subjects' dietary total folate or vitamin $B_{12}$ could not be evaluated, some anthropometric measurements (body weight, body mass index) were not taken, and the homocysteine levels were not evaluated, which are among the limitations of the study. Nevertheless, the limited number of studies focusing on the relationship between serum folic acid, $B_{12}$ levels, and COVID-19, and the high sample size are the strengths of our study.

In conclusion, folic acid and vitamin $B_{12}$ are key micronutrients in increasing the immune response and reducing the rate of viral infections. Therefore, examining COVID-19 patients in terms of nutritional deficiencies is critical in monitoring the clinical outcomes of the disease. In addition, since the effects of high serum $B_{12}$ levels on the prognosis of the disease are not clear, unnecessary supplement use should be avoided, and in case of nutrient deficiency/insufficiency, a vitamin supplement is recommended by the clinician and/or dietitian should be used.

**Conflict of Interest:** All authors declare no conflict of interest related to this study.

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