

ORIGINAL PAPER
INFECTIOUS DISEASES

The association between micronutrient and hemogram values and prognostic factors in COVID-19 patients: A single-center experience from Turkey

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Abstract

Aim: The contribution of micronutrients to the immune system has been known for a long time. This study aimed to investigate the association between the micronutrient levels and hemogram values and prognostic factors of the disease in COVID-19 patients in Ankara City Hospital.

Materials and methods: Our study is a descriptive observational study based on a retrospective review of patient files. COVID-19 patients over 18 years of age who were admitted to our hospital between 14 March and 1 June 2020, and with a complete micronutrient profile were included in the study. Age, gender, chronic diseases, micronutrient concentrations in the last 6 months, hemogram data on the day of hospitalization, total length of stay in hospital, and hospitalization to Intensive Care Unit (ICU)-intubation-death status of the patients were obtained from the patient files.

Results: A total of 310 patients whose parameters were thoroughly examined were included in our study; 51.9% of them were men and the mean age of all patients was 57.02 ± 18.28 years, and the most common comorbid disease was hypertension. The percentage of patients who were followed in the ICU, were intubated, and died was 34.5%, 13.9%, and 9.4%, respectively. The mean length of hospital stay was 15.87 ± 12.79 days. Low folate, iron, vitamin D, and hemoglobin levels of the patients and high vitamin B12 concentration were more related to poor prognostic factors. The number of white blood cells was significantly higher in patients with a worse prognosis, and the number of lymphocytes was lower in patients with ICU admission but higher in intubated and dead patients.

Conclusion: Micronutrient and hemogram values, advanced age, being male, and having comorbid diseases were correlated with the poor prognosis of COVID-19 infection. Deficiency of Iron, Folate, and vitamin D should be well-considered in COVID-19. Excessive vitamin B12 and multivitamin supplementation should be avoided by choosing supplement wisely. In addition, attention should be paid to leukocytosis, lymphocyte counts, and anemia during COVID-19 patient follow-up.

1 | INTRODUCTION

COVID-19, which emerged in Wuhan, China, at the end of 2019, rapidly spread to other countries and was declared a pandemic by the World Health Organization in March 2020, has caused many cases and deaths. The disease has a wide clinical course ranging from mild upper respiratory tract disease symptoms to pneumonia, thromboembolism, and ARDS. Research and vaccination studies for the treatment of the disease are still ongoing.¹ It has been stated that some micronutrients have an immunomodulatory and anti-inflammatory effect with antioxidant effects and thus play a protective role in respiratory tract infections.² It is discussed in the relevant literature that this effect occurs both by regulating the host's immune system and contributing to the change of the genome of the viruses causing infections.²

Looking at the studies on this subject and considering that a study to compile micronutrients is needed, and that it would be beneficial to see the effect of these micronutrients on the clinical course of the disease, we aimed to conduct a study examining vitamin B12, vitamin D, folate, iron, and hemogram levels in COVID-19 patients in the first quarter of the pandemic in Turkey. This study was conducted by reviewing the files of COVID-19 patients hospitalized in Ankara City Hospital, which is an important health center with 3810 beds in Ankara and has operated as a pandemic hospital during the pandemic period. We aimed to reveal the association between these micronutrients and hemogram values and prognostic factors in COVID-19. Thus, we aimed to provide ideas for further studies on whether these values may be predisposing factors or biomarkers that may affect the prognosis for COVID-19 infection.

2 | MATERIALS AND METHODS

Our research is a retrospective, descriptive observational study. Records of all patients who were admitted to our hospital between 14 March 2020, and 1 June 2020, and hospitalized with a diagnosis of COVID-19 (N: 1619) and whose serum 25(OH) vitamin D, vitamin B12, serum iron, and folate levels were tested in our hospital laboratories were examined. Our laboratory methods for these values: The Advia Centaur Folate and vitB12 assays are based on competitive immunoassay using direct chemiluminescent technology; The Advia chemistry xpt system for determining iron level is an assay that uses the ferrozinc method; The Advia Centaur vitD assay is used as an 18-minute antibody competitive immunoassay method and for hemograms, The Advia 2120i hematology system is used. Patients who had not been examined for any of the relevant micronutrient values in the last 6 months and individuals less than 18 years of age were not included in the study. No samples were taken within the scope of the study, and all patients who met the relevant criteria were evaluated within the scope of the study (n: 310). Data including COVID-19 PCR results, age, gender, presence of chronic disease, latest micronutrient values recorded in the hospital system in the last 6 months, hemogram levels measured on the day of hospitalization,

What's known

- Some micronutrients have an immunomodulatory and anti-inflammatory effect with antioxidant effects and thus play a protective role in respiratory tract infections as COVID-19.
- Vitamin D deficiency is found to be associated with poor prognostic factors in COVID-19.
- Lymphopenia is found to be associated with poor prognostic factors in COVID-19.

What's new

- According to the results obtained from our study, low iron and folate levels should be controlled first in patients diagnosed with COVID-19, low vitamin D levels should also be well-considered, and supplementation should be provided in the case of deficiencies. On the other hand excessive use of vitamin B12 should be avoided.
- The fact that all micronutrients should be evaluated and managed by choosing wisely rather than a complete multivitamin supplement approach was demonstrated by the differences in the poor prognosis levels of vitamin B12 versus the other micronutrients.
- In addition, it was found in our study that leukocytosis, lymphocyte counts, and anemia should be taken into consideration together when evaluating hemogram parameters in the follow-up of COVID-19 patients.

and the following prognostic factors were also examined to evaluate the clinical course of the patients:

- Number of days he/she was hospitalized
- Hospitalization in the ICU
- Number of days spent in the ICU
- Whether he/she was intubated or not
- How the patient left the hospital (discharge/exitus)

Patients were not supplemented with any micronutrients except routine treatments as per the national COVID-19 guidelines during their stay in our hospital. The national treatment protocols do not have any additional micronutrient supplements to be applied routinely.³

This information examined within the scope of the research was compiled anonymously by the hospital administration through the patient follow-up information system of our hospital in a way that did not include personal data. This study was conducted by the COVID-19 Scientific Research Evaluation Commission of the Ministry of Health of the Republic of Turkey, with approval of the study on 31 May 2020 and the approval of the Ethics Committee of Ankara City Hospital Clinical Research Ethics Committee No. 1 (date: 16/07/2020, No. 869).

In evaluating the statistics of the study, numerical data were given as means and standard deviations for descriptive statistics, and categorical data were given as numbers and percentages. The distribution of numerical data was examined with histogram graphs. The Student t-test, Mann-Whitney U test, and Kruskal-Wallis test were used in the analyses. Pearson correlation analysis was used for correlation. The significance value was accepted as $P < .05$. The SPSS 23.0 package program was used in the analyses.

3 | RESULTS

The data of 310 patients were included in this study. The mean age of all patients was 57.02 ± 18.28 years. The most common comorbid disease in patients was hypertension at a rate of 32.9% (n: 102). The average number of comorbid diseases was calculated as 1.35 ± 1.34 and it was observed that there were similar rates between men and women in terms of the number of comorbid diseases. Other sociodemographic information and chronic disease status of the patients are given in detail in Table 1.

When the prognostic data of our patients were examined, 107 (34.5%) of 310 patients were monitored in the intensive care unit, 43 patients (13.9%) were intubated, and 29 patients (9.4%) died. The mean total length of hospital stay was 15.87 ± 12.79 days, while the mean length of stay in the intensive care unit was 16.95 ± 17.08 days.

TABLE 1 Some sociodemographic characteristics and chronic disease status of the patients

	Characteristics	n	%
Gender	Male	161	51.9
	Female	149	48.1
Month of admission	March	28	9.0
	April	165	53.2
	May	117	37.7
<i>Chronic diseases</i>			
Hypertension	No	208	67.1
	Yes	102	32.9
DM	No	235	75.8
	Yes	75	24.2
CAD or heart failure	No	245	79.0
	Yes	65	21.0
Chronic respiratory diseases	No	272	87.7
	Yes	38	12.3
Cancer	No	281	90.6
	Yes	29	9.4
Chronic renal failure	No	290	93.5
	Yes	20	6.5

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus.

Bold values denote the percentages of the positive comorbid diseases of the COVID-19 patients.

When gender and prognostic data were compared, the number of male patients hospitalized in the intensive care unit was higher than the number of female patients, and a statistically significant difference was observed (Table 2). The mean total length of hospital stay of male patients was longer than that of female patients ($P = .034$) (Table 2). The association between each of the comorbid/chronic diseases and prognostic factors in COVID-19 patients are detailed in Table 2.

The mean age of the patients included in the study who were hospitalized in the intensive care unit, who underwent intubation, and who died was significantly higher than the mean age of the others ($P < .001$) (Table 3).

The highest, lowest, and mean values of the micronutrient and hemogram data of the patients included in this study, as well as the normal reference values of our hospital laboratories, are shown in detail in Table 4.

One of the main objectives of our study was to reveal the association between micronutrients and hemogram levels of COVID-19 patients and prognostic factors of the disease. The statistical comparison performed for this purpose is given in detail in Table 5.

The correlations of micronutrient and hemogram values with age, number of comorbid diseases, and length of hospital stay are given together in Table 6. Although there were significant correlations among the parameters in this table, they were found to be weak correlation. Also, there was no significant correlation between age and the total length of ICU stay ($P = .450$; $r = 0.031$), while there was a positive and weak correlation between age and the total hospitalization time ($P < .001$; $r = 0.242$).

4 | DISCUSSION

Although many studies have been conducted in response to the COVID-19 pandemic caused by SARS-CoV-2, there are still unknown aspects. Since the onset of the pandemic, supplementary foods have become a popular topic in Turkey and throughout the world. In this study, we investigated whether the micronutrient levels most commonly examined in the clinic and evaluated in terms of supplementation were related to prognostic factors in COVID-19 patients.

In many studies, hypertension has been reported to be the most common comorbid disease associated with COVID-19. However, this may not be enough to establish a causal relationship between the two diseases because hypertension is the most common chronic disease in elderly people, and this result is not surprising.⁴ In our study, the most common comorbid disease in patients was hypertension, with a rate of 32.9%. As with many infections, in COVID-19, comorbid diseases worsen the prognosis and cause an increase in mortality. In a systematic review of 54 articles by Zaki et al, diabetes and hypertension were found to have a significant relationship with COVID-19 severity.⁵ A meta-analysis by Nandy et al compiled 16 studies, according to which hypertension, diabetes mellitus, cardiovascular disease, COPD, and chronic kidney disease were significantly associated with poor prognosis in COVID-19 patients.⁶ In

TABLE 2 The association between gender and comorbid diseases and prognostic factors of patients with COVID-19

		ICU admission		Intubation		Death		Total hospitalization time (days)		Total length of stay in ICU (days)	
		No	Yes	No	Yes	No	Yes	Mean	SD	Mean	SD
Gender	Male	94	67	135	26	146	15	16.94	13.37	16.55	17.53
	Female	109	40	132	17	135	14	14.72	12.07	17.63	16.49
<i>P</i>		.006		.228		.981		.034		.447	
<i>Chronic diseases</i>											
DM	No	166	69	206	29	217	18	14.86	11.98	16.26	16.87
	Yes	37	38	61	14	64	11	19.07	14.67	18.21	17.61
<i>P</i>		.001		.168		.070		.002		.488	
HT	No	151	57	185	23	195	13	14.77	12.99	18.32	20.83
	Yes	52	50	82	20	86	16	18.12	12.13	15.40	11.42
<i>P</i>		<.001		.041		.007		.007		.985	
CAD/Heart Failure	No	171	74	217	28	226	19	14.99	11.00	16.31	14.26
	Yes	32	33	50	15	55	10	19.20	17.73	18.39	22.34
<i>P</i>		.002		.016		.060		.079		.766	
Chronic respiratory diseases	No	183	89	240	32	250	22	15.79	12.22	17.06	16.36
	Yes	20	18	27	11	31	7	16.45	16.49	16.44	20.78
<i>P</i>		.075		.004		.040		.649		.638	
Chronic renal failure	No	195	95	252	38	265	25	15.46	12.66	17.08	17.73
	Yes	8	12	15	5	16	4	21.95	13.39	15.92	11.05
<i>P</i>		.013		.137		.091		.009		.682	
Cancer	No	191	90	247	34	259	22	15.65	12.97	17.06	18.20
	Yes	12	17	20	9	22	7	18.03	10.79	16.41	9.46
<i>P</i>		.004		.005		.004		.078		.226	

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; ICU, intensive care unit; SD, standard deviation.

Bold values denote statistical significance at the $P < 0.05$ level.

TABLE 3 The association of age with prognostic factors in COVID-19 patients

		Age	
		Mean	SD
Admission to intensive care unit	No	51.09	17.280
	Yes	68.27	14.525
<i>P</i>		<.001	
Intubation	No	55.14	18.336
	Yes	68.70	13.014
<i>P</i>		<.001	
Death	No	55.77	18.246
	Yes	69.17	13.903
<i>P</i>		<.001	

Abbreviation: SD, standard deviation.

Bold values denote statistical significance at the $P < 0.05$ level.

our study, the rate of admission to the ICU was found to be high in patients with a history of diabetes mellitus, hypertension, coronary artery disease, chronic renal failure, and solid cancer, while

hypertension, chronic respiratory disease, and cancer history were likewise found to be more related to death in the aforementioned studies. Similarly, in our study, the length of hospital stay was significantly longer in patients with diabetes mellitus, hypertension, and chronic renal failure. Perhaps the point, we need to emphasize here is that all 6 diseases that we identified as comorbid diseases in our study were effective in both hospitalization in the intensive care unit and the occurrence of death. It was mostly found that there was a significant relationship between them, while others had a borderline significance relationship. In other words, it has been observed that having comorbid disease may be an important risk factor for the poor prognosis of COVID-19 infection.

The mean number of comorbid diseases of male and female patients in this study was found to be similar. Despite this homogeneous distribution, when the prognosis of the disease was evaluated according to the gender of the patients, the rate of hospitalization in the intensive care unit was found to be significantly higher in males. The length of hospital stay of male patients was also longer than that of females. The difference in intubation and mortality rates was not significant. When the literature data related to these results are reviewed, although an equal number of cases were observed between

TABLE 4 Distribution of micronutrient values and hemogram parameters of patients

	n	Min.	Max.	Mean	Standard deviation	Reference range (normal)
<i>Micronutrients</i>						
Vitamin B12 (pg/mL)	310	80	5920	457.40	490.770	211-911
25(OH)D (ng/mL)	310	4	113	17.70	16.131	30-150
Iron (mg/dL)	310	1	239	40.59	30.688	50-175
Folate (ng/mL)	310	1	142	10.58	9.982	>5.38
<i>Hemogram</i>						
WBC ($\times 10^6/L$)	310	60	60 830	8605.00	7298.945	3600-10500
LYM ($\times 10^6/L$)	310	20	49 620	1723.48	4286.370	1100-4500
HGB (g/dL)	310	4.4	20.0	12.736	2.4009	11.8-17.2
PLT ($\times 10^9/L$)	310	30	710	248.25	111.277	150-400

Abbreviations: HGB, hemoglobin; LYM, lymphocytes; Max, maximum; Min, minimum; PLT, platelets; WBC, white blood cells.

TABLE 5 The association of some micronutrient and hemogram values with prognostic factors

	ICU admission		Intubation		Death	
	No	Yes	No	Yes	No	Yes
Vitamin B12 (pg/mL)	360.94 ± 269.31	640.40 ± 715.73	395.84 ± 315.25	839.60 ± 984.33	405.86 ± 327.26	956.72 ± 1141.10
<i>P</i>	<.001		<.001		<.001	
25(OH)D (ng/mL)	19.19 ± 17.84	14.87 ± 11.79	18.30 ± 16.92	14.00 ± 9.18	18.05 ± 16.66	14.28 ± 8.99
<i>P</i>	.008		.110		.345	
Iron (mg/dL)	45.50 ± 32.76	31.28 ± 23.78	42.78 ± 31.44	27.02 ± 21.14	42.10 ± 31.03	25.3 ± 22.67
<i>P</i>	<.001		<.001		.001	
Folate (ng/mL)	11.03 ± 6.27	9.73 ± 14.64	10.88 ± 10.45	8.70 ± 6.00	10.77 ± 10.25	8.76 ± 6.70
<i>P</i>	<.001		.036		.055	
WBC ($\times 10^6/L$)	7558 ± 6083	10 591 ± 8872	8116 ± 6188	11 640 ± 11 768	8219.04 ± 6386.39	12 345 ± 12 809
<i>P</i>	<.001		.023		.017	
LYM ($\times 10^6/L$)	1806 ± 4367	1567 ± 4145	1695 ± 3868	1899 ± 6372	1657 ± 3770	2366 ± 7756
<i>P</i>	<.001		<.001		.004	
HGB (g/dL)	13.18 ± 2.05	11.87 ± 2.75	12.88 ± 2.32	11.83 ± 2.67	12.88 ± 2.32	11.31 ± 2.68
<i>P</i>	<.001		.013		.001	
PLT ($\times 10^9/L$)	244 ± 105	254 ± 122	250 ± 113	232 ± 99	250 ± 111	228 ± 108
<i>P</i>	.568		.538		.431	

Abbreviations: HGB, hemoglobin; LYM, lymphocytes; PLT, platelets; WBC, white blood cells.

Bold values denote statistical significance at the $P < 0.05$ level.

the sexes, the mortality rates for men were higher than those for women. According to a report by the Italian National Institute of Health, approximately 70% of 23 188 deaths from COVID-19 infection were male patients,⁷ while 59% of the 37 308 deaths reported by the National Center for Health Statistics in the United States were male.⁷ Similarly, in a study conducted in Wuhan, China, the male gender was found to be more dominant in deceased patients than in recovered patients.⁸

According to the studies conducted, it was seen that the symptomatic course of the disease in COVID-19 infection, admission to

the ICU, and risk of death increased depending on age.^{9,10} When we evaluated the association between age and clinical course in our study, similar to previous studies, the mean age of the patients with ICU hospitalization, intubation, and death was significantly higher than that of other patients, and a weak but significant positive correlation was found between age and length of hospital stay.

The mean number of comorbid diseases of the participants in our study was 1.35 ± 1.34 , the rate of admission to the ICU was 34.5%, the intubation rate was 13.9%, and the mortality rate was 9.4%. The reason why these figures are quite higher than the data

from the WHO and the Ministry of Health of the Republic of Turkey is that more parameters are examined in order to find the etiology and correct the clinical course in patients with poorer prognosis and all of the micronutrients that we examined in our study are evaluated more frequently for such patients. This can also be mentioned among the limitations of our study because it does not fully reflect our study universe. When the overall rate of patients who died of COVID-19 in our hospital between the dates of our study was examined, it was seen that it was 4.32%. In Turkey, according to official figures, the mortality rate between those dates was 2.77% among all COVID-19 patients.¹¹ The higher hospital rates may be because of the hospitalization of those who were symptomatic or whose clinical course was relatively worse, and since our hospital is a reference hospital, it may be because of the hospitalization of those who had a worse clinical course than patients in different hospitals in other provinces. According to official research data obtained in Ankara province in the same period, a total of 26 128 contact follow-up efforts for 7231 positive patients confirmed with 348 filiation teams consisting of 2 health personnel and 1 doctor and family physicians in the field were performed at a rate of 99.4%, and these people's isolation was ensured by follow-up within the framework of telehealth services every day for 14 days. Apart from these, 45 909 people from abroad or traveling domestically were also followed and the transmission chain was kept under control. In all of these follow-ups, contacts and passengers describing symptoms were transferred to hospitals by ambulance.¹²

Our study found that the general mean vitamin D and serum iron values of the patients were low, while the mean vitamin B12 and folate values were within the normal reference ranges. Although ferritin is a more reliable marker in showing iron storage levels in the body under normal conditions, it can reach very high levels in COVID-19 infection because of its acute phase reactant. Therefore, in our study, serum iron and hemoglobin levels were examined instead of ferritin. There was no significant decrease in the average hemoglobin of all patients, and the mean values of white blood cells,

lymphocytes, and platelets were found to be within the reference ranges. However, there were some significant changes in patients with poor prognostic factors.

Considering the relationship between micronutrient levels and COVID-19 infection in the literature, it was observed that the highest numbers of studies were conducted on vitamin D. Vitamin D has been shown to have anti-inflammatory and immunosuppressant effects, and there are publications stating that it may be effective in the prevention of respiratory tract infections.¹³ A study conducted by Baktash et al with 105 patients found that vitamin D deficiency was higher in PCR-positive patients, non-invasive mechanical ventilator usage was needed more in patients with deficiency, and no difference was found in terms of mortality rates.¹⁴ Ilie et al examined the data of 20 European countries and reported a negative correlation between vitamin D levels and SARS-CoV-2 incidence and mortality.¹⁵ In a meta-analysis by Ghasemian et al, 25(OH)D levels were 18.2 ng/mL in patients with severe COVID-19 and 26 ng/mL in non-severe patients.¹⁶ In a study conducted by Kerget et al with 108 patients in Erzurum City Hospital, it was stated that vitamin D levels of patients who died because of COVID-19 were lower than those who were discharged.¹⁷ In another study conducted with 154 patients, the mortality rate because of COVID-19 was 21% in patients with vitamin D deficiency and 3.1% in patients with normal vitamin D levels. In addition, it has been reported that the intensity of the inflammatory response is higher in patients with vitamin D deficiency.¹⁸ In another study, it was found that patients in the ICU mostly had low vitamin D levels, but there was no relationship between vitamin D and mortality.¹⁹ In our study, vitamin D levels were significantly lower in patients followed in the ICU than those followed elsewhere. It was observed that low vitamin D levels in intubated and deceased patients did not cause a significant difference, supporting the findings of related studies.

It is noteworthy that the average iron levels of the patients diagnosed with COVID-19 included in this study was significantly low. In addition, the iron level was observed to decrease as the prognostic

TABLE 6 Correlation of micronutrient and hemogram values with age, number of comorbid diseases, length of hospital stay, and length of stay in intensive care unit

Parameters	Age (p/r)	Number of comorbidities (p/r)	Total length of hospital stay (p/r)	Total length of stay in intensive care unit (p/r)
<i>Micronutrients</i>				
Vitamin B12	0.011/0.145	<0.001/0.275	<0.001/0.198	0.710/0.036
25(OH)D	0.836/-0.012	0.247/-0.066	0.110/-0.091	0.493/-0.067
Iron	<0.001/-0.227	0.021/-0.131	0.002/-0.174	0.421/-0.079
Folate	0.020/-0.132	0.076/-0.101	0.905/-0.007	0.951/0.006
<i>Hemogram</i>				
WBC	<0.001/0.235	<0.001/0.203	0.026/0.126	0.920/0.010
LYM	0.411/0.047	0.618/0.028	0.697/0.022	0.867/-0.016
HGB	<0.001/-0.320	<0.001/-0.264	0.004/-0.161	0.462/-0.072
PLT	0.273/0.062	0.250/0.066	0.830/-0.012	0.653/-0.044

Abbreviations: HGB, hemoglobin; LYM, lymphocytes; PLT, platelets; WBC, white blood cells.

Bold values denote statistical significance at the $P < 0.05$ level.

factors of these patients worsened. For example, the patients who lost their lives were the patients with the lowest average iron levels. No study on COVID-19 and serum iron levels has been found in the literature. However, iron is an important trace element for pathogens as well as humans. For this reason, in inflammatory conditions, an increase in ferritin and a decrease in serum iron may be observed in order to deprive pathogens of iron and support immunity.^{20,21} In addition, inflammation leads to increased iron intake in macrophages with decreased intestinal iron absorption and decreased serum iron levels. Decreased iron levels in circulation cause hemoglobin synthesis and decreased erythropoiesis.²² Indeed, studies are showing that hemoglobin levels are lower in severe COVID-19 patients. According to a study conducted by Tao et al in Wuhan, the incidence of serious COVID-19 was found to be higher in patients with anemia than in patients without anemia.²³ In another study conducted with 117 patients, lower hemoglobin levels were found in patients with a severe and critical course of COVID-19.²⁴ In our study, hemoglobin levels were lower in patients who were hospitalized, were intubated, or died, in accordance with these previous publications. Hemoglobin and length of hospital stay were also negatively and weakly significantly correlated. Therefore, avoidance of anemia, correction of anemia, and correction of iron deficiency by supplementation in COVID-19 infection, which has a significant relationship with prognostic factors, may be beneficial in terms of prognosis or more attention may be needed for these markers in terms of showing deterioration in the clinical course.

When the patients were compared in terms of folate level, it was found that the patients who were hospitalized and intubated in the ICU had significantly lower folate levels than the patients who were not, and the patients who died had significantly lower folate levels than the patients who were discharged. However, these mean low levels of the relevant group remained within the normal reference range. According to a study by Itelman et al in Israel, low folic acid levels were more common among patients with severe COVID-19.²⁵ In this respect, it can be concluded that similar findings were obtained in our study. This is important in terms of supporting folate deficiency as a marker of poor prognosis or revealing the importance of evaluating patients in COVID-19 follow-up in terms of folate deficiency.

Our study observed that vitamin B12 levels increased as the clinical course of the patients worsened. The average vitamin B12 level was above 911 pg/mL, the upper limit of the reference range, especially in intubated and deceased patients. Publications suggest that high B12 concentrations may be indicators of liver diseases and tumors.²⁶ In addition, Itelman et al classified patients with COVID-19 according to their prognosis and associated increased B12 levels with poor prognosis.²⁵ In another study by Im et al, COVID-19 patients were evaluated in terms of deficiencies of some micronutrients, and B12 deficiency was not detected in any of the groups classified according to severity.²⁷ In our study, excess vitamin B12 was significantly correlated with negative factors such as admission to the intensive care unit, intubation, and death, which are among the poor prognostic factors. Therefore, in addition to monitoring

and restoring the deficiencies emphasized for many micronutrients, excessive micronutrient use should also be avoided. The association between the excess vitamin B12 that we found in this study and the poor prognosis of COVID-19 infection shows that attention should be paid to this situation. The positive and weak significant correlation between vitamin B12 level and total length of hospital stay in our study also supports this. From this point of view, it is important to adopt a more person-centered approach to protecting individuals from COVID-19 infection and/or the follow-up of its treatment based on the concept of "choosing wisely" rather than direct multivitamin supplementation.²⁸ On the other hand, we can also note that the vitamin B12 levels of patients in our study may have increased because of comorbid diseases, or use of vitamin B12 may have increased because of dementia with age or may have had a negative effect on the worsening prognosis. Therefore, since there are very few studies on COVID-19 and vitamin B12 in the literature, this matter needs to be investigated further.

When we looked at the other hemogram data on white blood cells, lymphocytes, and platelets at the time of the first admission of our patients to the hospital, it was seen that the mean white blood cell count increased as the prognosis worsened while no significant difference was found in platelet counts. Lymphocyte counts were observed to be significantly lower in patients hospitalized in the ICU, while they were higher in intubated and deceased patients than in others. Studies have shown that COVID-19 infection causes lymphopenia, and lymphopenia is correlated with the severity of the disease.²⁹ In our study, the lower lymphocyte rates in ICU inpatients are consistent with this situation, and the higher rates in intubated and deceased patients may be associated with super-infections that develop after hospitalization. In a study conducted with 138 patients in China, among COVID-19 patients, white blood cell counts were high, lymphocyte counts were low, and no significant difference was found in platelet counts in the ICU compared to those followed elsewhere.³⁰ In another study, the number of white blood cells in patients who died of COVID-19 was found to be higher and lymphocytes and platelets were found to be lower than in those who were discharged.³¹ Therefore, we think that every increase and decrease in lymphocyte count can be used as an important biomarker in the clinical course and follow-up of COVID-19 infection, as in all patients. On the other hand, as a result of our study, we concluded that platelet follow-up was not very significant for COVID-19 infection.

5 | LIMITATIONS

Our study does not allow causal inferences because it is a cross-sectional study, which is among its limitations. The fact that it was performed only with hospitalized patients and that patients in clinics who were asymptomatic or did not require hospitalization were not included in the study caused selection bias. Only patients who were admitted for COVID-19 and had a comprehensive micronutrient profile were included in the study. Because of that, there was an important study limitation of inclusion bias. In addition, it can be

stated that since many parameters of potentially aggravated patients were examined and the patients in the population constituting the study were patients for whom all parameters were examined, the findings cannot be generalized to all hospitalized COVID-19 patients. Similarly, patients whose micronutrient levels were examined in the last 6 months were enrolled in the study, and the examination of some patients before hospitalization because of COVID-19 may have caused some limitations.

6 | CONCLUSION

This study showed us that serum iron, folate, and vitamin D deficiency and excess vitamin B12 were correlated with poor prognostic factors such as hospitalization to ICU, intubation, and death. Therefore, monitoring of micronutrient levels may be beneficial during COVID-19 pandemic. The fact that all micronutrients should be managed individually, rather than a complete multivitamin supplement approach, was demonstrated by the difference in the poor prognostic correlation with vitamin B12.

We hope that our study will be insightful for new research and studies that will examine the cause-and-effect relationships.

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DISCLOSURE

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All article steps were carried out by two authors.

ETHICAL APPROVAL

This study was conducted by the COVID-19 Scientific Research Evaluation Commission of the Ministry of Health of the Republic of Turkey, with approval of the study on 31/05/2020 and the approval of the Ethics Committee of Ankara City Hospital Clinical Research Ethics Committee No. 1 (date: 16/07/2020, No. 869).

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REFERENCES

- Ahn DG, Shin HJ, Kim MH, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). *J Microbiol Biotechnol.* 2020;30:313-324.
- Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. *Nutrients.* 2020;12:236.
- Guidelines of COVID-19 (SARS - CoV - 2 Infection) Adult Patient Management of The Ministry of Health of the Republic of Turkey [Internet]. <https://covid19.saglik.gov.tr/TR-66926/eriskin-hastatedavisi.html>. Accessed January 1, 2021.
- Schiffirin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. *Am J Hypertens.* 2020;33:373-374.
- Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: a systematic review. *Diabetes Metab Syndr.* 2020;14:1133-1142.
- Nandy K, Salunke A, Pathak SK, et al. Coronavirus disease (COVID-19): a systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. *Diabetes Metab Syndr.* 2020;14:1017-1025.
- Spagnolo PA, Manson JAE, Joffe H. Sex, and gender differences in health: what the COVID-19 pandemic can teach us. *Ann Int Med.* 2020;173:385-386.
- Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020;368(m1091):1-12.
- Kang SJ, Jung SI. Age-related morbidity and mortality among patients with COVID-19. *Infect Chemother.* 2020;52:154-164.
- Starke KR, Petereit-Haack G, Schubert M, et al. The age-related risk of severe outcomes due to covid-19 infection: a rapid review, meta-analysis, and meta-regression. *Int J Environ Res Public Health.* 2020;17:1-24.
- Genel Koronavirüs Tablosu [Internet]. <https://covid19.saglik.gov.tr/TR-66935/genel-koronavirus-tablosu.html#>. Accessed January 1, 2021.
- Şimşek AÇ, Kara A, Nur Baran-Aksakal F, et al. Contact tracing management of the COVID-19 pandemic. *Turk Hij Den Biyol Derg.* 2020;77:269-280.
- Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017;356(i6583):1-14.
- Baktash V, Hosack T, Patel N, et al. Vitamin D status and outcomes for hospitalised older patients with COVID-19. *Postgrad Med J.* 2020;1-6.
- Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res.* 2020;32:1195-1198.
- Ghasemian R, Shamshirian A, Heydari K, et al. The role of vitamin D in the age of COVID-19: a systematic review and meta-analysis along with an ecological approach. *medRxiv.* 2020;1-20. <https://doi.org/10.1101/2020.06.05.20123554>.
- Kerget B, Kerget F, Kızıltunç A, et al. Evaluation of the relationship of serum vitamin D levels in COVID-19 patients with clinical course and prognosis. *Tuberkuloz ve toraks.* 2020;68:227-235.
- Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. *Sci Rep.* 2020;10:20191.
- Panagiotou G, Tee SA, Ihsan Y, et al. Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. *Clin Endocrinol.* 2020;93:508-511.
- Wessling-Resnick M. Crossing the iron gate: why and how transferrin receptors mediate viral entry. *Annu Rev Nutr.* 2018;38:431-458.
- Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol.* 2017;29:401-409.
- Bellmann-Weiler R, Lanser L, Barket R, et al. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 infection. *J Clin Med.* 2020;9:2429.
- Tao Z, Xu J, Chen W, et al. Anemia is associated with severe illness in COVID-19: a retrospective cohort study. *J Med Virol.* 2021;93:1478-1488.
- Yuan X, Huang W, Ye B, et al. Changes of hematological and immunological parameters in COVID-19 patients. *Int J Hematol.* 2020;112:553-559.
- Itelman E, Wasserstrum Y, Segev A, et al. Clinical characterization of 162 COVID-19 patients in Israel: Preliminary Report from a Large Tertiary Center. *Isr Med Assoc J.* 2020;22:271-274.

26. Jammal M, Deneuille T, Mario N, et al. Concentration plasmatique élevée de la vitamine B12: Un indicateur des maladies hépatiques ou tumorales. *Rev Med Interne*. 2013;34:337-341.
27. Im JH, Je YS, Baek J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. *Int J Infect Dis*. 2020;100:390-393.
28. Dağcıoğlu BF. Aile Hekimliğinde Akıllı Seçimler. *Bütüncül Tıp Birinci Basamakta ve Aile Hekimliğinde Güncel Tanı ve Tedavi*. 2020;1:153-156.
29. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther*. 2020;5:33.
30. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-1069.
31. Li Q, Cao Y, Chen L, et al. Hematological features of persons with COVID-19. *Leukemia*. 2020;34:2163-2172.

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