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How to differentiate the B.1.1.7 variant from COVID-19 in hospitalized patients?

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ABSTRACT

Objectives: Little is known about COVID-19 and less about the B.1.1.7. There is a need for clinical information and tests to help doctors deal with the pandemic. This study aimed to investigate clinical and laboratory differences between hospitalized non-variant COVID-19 and the B.1.1.7 variant.

Methods: Data of 173 hospitalized non-variant COVID-19 and 176 B.1.1.7 variants were retrospectively investigated. D-dimer monocyte ratio (DMR) and ferritin monocyte ratio (FMR) values were calculated by dividing D-dimer and ferritin levels to monocyte count, respectively. Monocyte eosinophil ratio (MER) was obtained by dividing monocyte count by eosinophil levels.

Results: Clinical stay, intensive care unit (ICU) stay, and severe disease rates were found to be higher in the non-variant COVID-19. Eosinophil and basophil levels remained lower, whereas ferritin, FMR, and MER were more elevated in the same group. On ROC analysis, areas under the curve (AUC) of ferritin and FMR were found as 0.7 ($p = 0.001$) and 0.75 ($p = 0.001$), respectively.

Conclusions: The present study revealed that the B.1.1.7 variant had milder clinical manifestations, shorter clinic and ICU stay, and less severe disease rates than the non-variant COVID-19. Higher levels of ferritin, FMR, and MER may indicate the B.1.1.7 variant.

Keywords: The B.1.1.7, variant, COVID-19, monocyte eosinophil ratio, eosinophils

Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome−coronavirus 2 (SARS-CoV-2), is a reason for the illness and death of millions since it was identified. Later in the pandemic, genetic variants of SARS-CoV-2 have emerged and circulated the World. About a year later, on December 14, 2020, the United Kingdom (UK) Government was notified of the emergence of a SARS-CoV-2 variant under investigation, which was later defined as lineage B.1.1.7. [1]. In the following period, new concerns have emerged regarding the infectivity, pathogenicity, and mortality of the B.1.1.7 variant [2]. Undoubtedly, recognizing the disease has importance in both preventive medicine and treatment. Polymerized chain reaction (PCR) and genetic studies diagnose the illness and variant analysis. Yet genetic analysis is a time-consuming, expensive procedure and not available in every healthcare institution. There is a need for more clinical information and tests to help doctors during the diagnosis or give an idea about which patients should undergo a genetic study. Biomarkers of inflammation derived from the peripheral blood hemogram parameters have been investigated as independent predictors for the prognosis of systematic inflammatory diseases [3, 4]. In a previous study, high levels of PDW have been associated with

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COVID-19 mortality [5]. All parameters mentioned above are studied by routine complete blood count tests that clinicians might overlook. This study aimed to investigate clinical and laboratory differences between non-variant COVID-19 and the B.1.1.7 variant else-more to determine whether C-reactive protein (CRP) monocyte ratio (CMR), D-dimer CRP ratio (DCR), D-dimer monocyte ratio (DMR), ferritin monocyte ratio (FMR) and monocyte eosinophil ratio (MER) can help to differentiate non-variant COVID-19 from the B.1.1.7 variant. Also, to explore the most useful diagnostic biomarkers, optimal cut-off values, and correlations between these biomarkers.

METHODS

Data of randomly chosen unvaccinated hospitalized 173 Non-variant COVID-19 and 176 B.1.1.7 variants between January-April 2021 were retrospectively investigated. Patients who were found to be positive for SARS-CoV-2 polymerized chain reaction test (PCR) and who were found to have non-variant COVID-19 or B.1.1.7 as a result of genetic analysis between the specified dates were included in the study. Even if the clinical and tomographic findings were compatible, patients with negative SARS-CoV-2 PCR results and pregnant women were excluded from the study. In Turkey, vaccination against COVID-19 was started on14.01.2021 with healthcare providers and continued with citizens over the age 65 on 11.02.2021. Intensive vaccination was applied in march-april 2021.Vaccination rates were low during the data collection period and were not statistically sufficient for analysis, so individuals who were vaccinated at a very low rate were not included in the study. The demographic and clinical data of all patients are shown in table 1. The decision to hospitalize or home follow-up was given according to the general condition of the patients, blood analysis including a complete blood count, CRP, D-dimer, ferritin levels, the percent saturation of oxygen in the blood values (SpO2), and the severity of tomographic involvement. Patients with one of the following criteria; oxygen saturation below 93% in room air, C-reactive protein (CRP) value above 50 mg/L, D-dimer above one ug FEU/ml, ferritin above 500 ng/mL, lymphocyte values belove 500 103/µL, severe involvement on computed tomography were hospitalized. Severe disease is defined as suspected respiratory infection symptoms, plus any of the following; shortness of breath, respiratory rate above 30 breaths/min; at rest, oxygen saturation belove 93%; Pa02/Fi02 belove 300 mmHg (1 mmHg Z 0.133 kPa). The groups were compared by examining the hemogram parameters lymphocyte, monocyte, eosinophil, and SpO2 obtained on the same day of the diagnosis. The values of CMR, DMR, and FMR were calculated by dividing CRP, D-dimer, and ferritin levels by monocyte count. MER was obtained by dividing monocyte count by eosinophil, and DCR was obtained by dividing D-dimer by CRP. The ethical committee approval was obtained from Bursa City Hospital Clinical Research Ethical Committee (Date: 20.05.2021, No: 2021-9/2).

Statistical Analysis

All the statistical analyses were carried out using SPSS 25.0 software. A Kolmogorov-Smirnov test was performed for the normality of the sample data; continuous variables were defined by the mean ± standard deviation, median (interquartile range %25–%75), while the categorical variables were expressed as frequency and percent. A Student t-test for parametric assumptions and Mann Whitney U test for non-parametric hypotheses compared the independent groups. The Roc analysis was performed for optimal cut-off values to predict the B.1.1.7 variant.

RESULTS

The median age turned out to be 49 (range; 18-88) years in the non-variant COVID−19 group and 42 (range; 18-87) years in the B.1.1.7 variant group (Table 1). The mean age was significantly higher in the non-variant COVID-19 group ($p < 0.02$). Although the gender distribution in the non-variant COVID−19 group was 49.7% (n = 86) women and 50.3% (n = 87) men, it was 51.7% (n = 91) women and 48.3% (n = 85) men in the B.1.1.7 variant group. Hypertension (HT) was higher in the non-variant COVID-19 group ($p = 0.001$). No statistically significant difference was found between chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus (DM), coronary artery disease (CAD), and malignancy rates. Although no statistical differences were found, mortality rates

were higher in the non-variant COVID-19 group. Clinic stay and intensive care unit (ICU) stay were higher in the non-variant COVID-19 ($p = 0.001$ and $p = 0.046$, respectively). SpO_2 was lower in the non-variant COVID-19 ($p < 0.002$). Severe disease rates were higher in the non-variant COVID-19 group ($p = 0.04$). Lymphocyte, eosinophil, basophil levels and DCR remained lower in the non-variant COVID-19 ($p = 0.05$, $p = 0.001$, $p = 0.001$ and $p = 0.004$; respectively). D-dimer, CRP, ferritin, CMR, FMR, and MER were higher in the non-variant COVID-19. Optimal cut-off values calculated by the ROC analysis and the ROC curves are presented in Fig. 1. When non-variant COVID-19 patients were compared to the B.1.1.7 variants, the areas under the curve (AUC) of ferritin, CMR, FMR, and MER were found as 0.7 ($p = 0.001$),

Table 1. Demographic, clinical data, and laboratory findings of nonvariant COVID-19 and the B.1.1.7 variants

Variable	Non-variant COVID-19 (n = 173)	The B.1.1.7 variant (n = 176)	*p* value
Age (years)	49 (18-88)	42 (18-87)	**0.02***
Female	86 (49.7%)	91 (51.7%)	0.7
Male	87 (50.3 %)	85 (48.3%)	
Lymphocyte (10^3/µL)	1.58 ± 0.71	1.7 ± 1	**0.05***
Monocyte (10^3/µL)	0.51 (0.14-1.44)	0.63 (0.13-4.85)	0.07
Eosinophil (10^3/µL)	0.02 (0-1.45)	0.06 (0-3.2)	**0.001***
Basophil (10^3/µL)	0.01 (0-0.07)	0.03 (0-0.9)	**0.001***
D-dimer (ug FEU/ml)	0.45 (0.15-8.36)	0.42 (0.01-4.76)	0.3
CRP (mg/L)	18 (0.3-434)	12 (0.6-234)	**0.02***
Ferritin (ng/mL)	246 (8.2-1941)	101 (6-1438)	**0.001***
CMR	25 (0.43-1287)	17.4 (0.72-1021)	**0.001***
DCR	0.021 (0-2.6)	0.042 (0-4.2)	**0.004***
DMR	0.6 (0.14-519	0.56 (0.013-2.5)	0.06
FMR	530 (7.9-8695)	153 (12-6252)	**0.001***
MER	13 (0.14-82)	7.3 (0.18-98)	**0.003***
Death rate	24 (13.9%)	16 (9.1%)	0.16
Severe disease	32 (18.5%)	19 (10.8%)	**0.04***
Clinic stay	7.7 (0-40)	2.2 (0-35)	**0.001***
ICU stay	2.1 (0-61	1.3(0-13)	**0.046***
SpO2	94 (45-100)	98 (75-100)	**0.002***
COPD	1 (0.6%)	0 (0%)	0.3
Asthma	8 (4.6%)	14 (8%)	0.2
DM	15 (8.7%)	22 (12.5%)	0.24
HT	40 (23%)	15 (8.5%)	**0.001***
CAD	9 (5.2%)	9 (5.1%)	0.97
Malignancy	0 (0%)	2 (0.6%)	0.16

Data are shown as mean ± standard deviation or mean (ninimum-maximum or n (%). CRP = C-Reactive Protein, CMR = CRP monocyte ratio, DCR = D-dimer CRP ratio, DMR = D-dimer monocyte ratio, FMR = Ferritin monocyte ratio, MER = monocyte eosinophil ratio, ICU = Intensive Care Unit, SpO2 = median oxygen saturation, COPD = Chronic Obstructive Pulmonary Disease, DM = Diabetes Mellitus, CAD = Coronary Artery Disease.

*$p < 0.05$ statistically significant

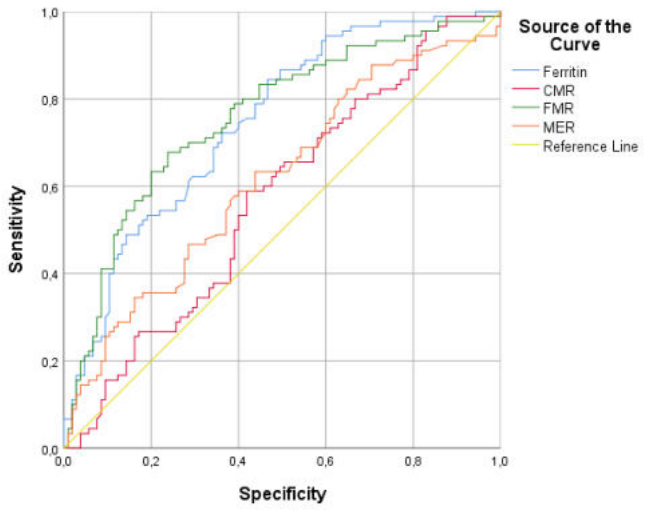

Fig. 1. ROC curves comparing the prediction of B.1.1.7 Variant, variables for ferritin, CMR = C-reactive protein monocyte ratio, FMR = ferritin monocyte ratio, MER = monocyte eosinophil ratio. Diagonal segments are produced by ties.

0.67 (p = 0.001), 0.75 (0.001), and 0.61 (p = 0.004), respectively (Table 2). The correlation analysis is shown in Table 3. Negative correlation detected between lymphocyte and CMR (r = 0.29, p = 0.001), DCR and CMR (r = 0.84, p = 0.001). Positive correlation detected between CRP and CMR (r = 0.59, p = 0.001), D-dimer and DMR (r = 0.51, p = 0.001), CMR and FMR (r = 0.36, p = 0.001). DMR and FMR (r = 0.28, p = 0.001).

DISCUSSION

When COVID-19 first appeared, little was known about the disease, making management difficult. Accumulation of knowledge has increased over time, but the emergence of new variants such as the B.1.1.7 variant has raised further questions about the disease.

The SARS-CoV-2 B.1.1.7 variant cases have increased rapidly worldwide and are reported to be more contagious than the non-variant COVID-19. To the best of our knowledge, no studies investigating CMR, DCR, DMR, FMR, and MER of COVID-19 cases infected with the B.1.1.7 variant have been published. This study examined clinical and blood parameter differences between the non-variant COVID-19 and the B.1.1.7 variants. According to a report from seven European countries, increased hospitalizations and ICU admission risk was associated with the SARS-CoV-2 variants, including the B.1.1.7. [6]. In the present study, the clinic stay and ICU hospitalization time were longer in non-variant COVID-19. More non-variant COVID-19 patients had more severe disease rates and lower median SpO2 levels. Lymphocytes are cells of immunity that play an essential role in the fight against pathogens. Following viral infections, different virus types may cause changes in total lymphocyte count. In a study, Wang *et al*. [7] reported decreased lymphocyte levels in patients with COVID-19. In the present study, lymphocyte levels were higher in the B.1.1.7 variant group. Current data suggest an essential role for monocyte activation in developing immunopathology of patients with COVID-19 [8]. According to the present study results, no difference was detected between groups regarding monocyte levels. Eosinophils are circulating cells with many functions. Some of them are; antiviral activity and immunoregulation. But there is limited information about their role in COVID-19. In a study, Xie *et al*. [9] reported a decrease in circulating eosinophil counts in COVID-19 patients more frequently than other types of pneumonia patients. Previously eosinopenia was reported in patients with acute respiratory deterioration during infection with SARS-CoV-2 [10]. In the present study, non-variant, COVID-19 patients had lower

Table 2. ROC analysis of non-variant COVID-19 patients versus B.1.1.7 variant

Variables	AUC (95% CI)	Cut-off	Sensitivity%	Specificity %	*p* value
Ferritin	0.7 (0.62-0.77)	172	63	63	**0.001***
CMR	0.67(0.6-0.75)	23.6	64	63	**0.001***
FMR	0.75 (0.68-0.81)	277	68	32	**0.001***
MER	0.61 (0.53-0.69)	9.7	59	58	**0.004***

AUC = Area Under ROC Curve, CMR = C-reactive protein monocyte ratio, FMR = ferritin monocyte ratio, MER = monocyte eosinophil ratio.

*p < 0.05 statistically significant

Table 3. Spearman correlations between laboratory findings of non-variant COVID-19 and the B.1.1.7 variants

		LYMPH	CRP	D-dimer	Ferritin	CMR	DCR	DMR	FMR	MER
LYMPH	r	1	-0.24	-0.09	-0.09	-0.29	0.18	-0.21	-0.12	-0.14
	p		**0.001***	0.16	0.09	**0.001***	**0.002***	**0.001***	**0.04***	**0.03***
CRP	r	-0.24	1	0.08	0.20	0.59	-0.55	0.04	0.12	0.16
	p	**0.001***		0.245	**0.001***	**0.001***	**0.001***	0.46	**0.04***	**0.02***
D-dimer	r	-0.09	0.08	1	0.10	0.08	0.20	0.51	0.12	0.04
	p	0.16	0.24		0.12	0.22	0.006*	0.001*	0.07	0.59
Ferritin	r	-0.09	0.2	0.1	1	0.08	-0.05	0.002	0.6	0.12
	p	0.09	**0.001***	0.12		0.17	0.39	0.97	**0.001***	0.07
CMR	r	-0.29	0.59	0.08	0.08	1	-0.84	0.24	0.36	0.12
	p	**0.001***	**0.001***	0.22	0.17		**0.001***	**0.001***	**0.001***	**0.05***
DCR	r	0.18	-0.55	0.20	-0.05	-0.84	1	0.26	-0.19	-0.20
	p	**0.002***	**0.001***	**0.006***	0.39	0.001*		**0.001***	**0.001***	**0.002***
DMR	r	-0.21	0.04	0.51	0.002	0.24	0.26	1	0.28	-0.15
	p	**0.001***	0.46	**0.001***	0.97	**0.001***	**0.001***		**0.001***	**0.02***
FMR	r	-0.12	0.12	0.12	0.60	0.36	-0.19	0.28	1	-0.04
	p	**0.04***	**0.04***	0.07	**0.001***	**0.001***	**0.001***	**0.001***		0.95
MER	r	-0.14	0.16	0.04	0.12	0.12	-0.20	-0.15	-0.04	1
	p	**0.03***	**0.02***	0.59	0.07	**0.05***	**0.002***	**0.02***	0.9	

LYMP = lymphocyte, CRP = C-reactive protein, CMR = CRP monocyte ratio, DCR = D-dimer CRP ratio, DMR = D-dimer monocyte ratio, FMR = ferritin monocyte ratio, MER = monocyte eosinophil ratio.

*$p < 0.05$ statistically significant

eosinophil levels than the B.1.1.7 variants. In a study Song *et al*. [11] reported higher levels of CRP and D-dimer in the B.1.1.7 variants compared to those non-variants. Unlike the study conducted by Song *et al*. [11] in the present research, non-variant, COVID-19 patients had higher levels of CRP, but no difference was detected between D-dimer levels. In some patient groups, especially in severe disease, COVID-19 is associated with inflammatory cytokine storm in which the inflammatory response may change the iron homeostasis. Zhou *et al*. [7] reported patients diagnosed with severe COVID-19 had higher serum ferritin levels than in other groups. In the present study, ferritin levels were lower in the B.1.1.7 variants. Different results might be due to heterogeneity of COVID-19 or the difference in the behavior of SARS-CoV-2 in geographical regions.

Increased risk of hospitalization, intensive care admission, and mortality rates were previously reported for B.1.1.7 [12, 13]. In the present study, severe disease rates were lower in the non-variant COVID-19 than in the B.1.1.7 variant. Even though no statistical difference was detected, death rates were also found to be higher in the non-variant COVID-19. In a study, Nyberg *et al*. [14] reported an increased risk of hospital admission for people infected with the B.1.1.7 variant. Different results between studies might be due to heterogenicity and other behavior of SARS-CoV-2.

Although similar case numbers are reported in different countries, mortality rates may differ.

Recently, ratios that are more accessible to researchers have been used in diagnosis and prognosis assessment. A high neutrophil-lymphocyte ratio (NLR) was reported in patients who tested positive for SARS-CoV-2 than controls [15]. A study from Wuhan/China by Yang *et al*. [16] reported elevated NLR was significantly associated with illness severity. Yang *et al*. [16] investigated 93 COVID-19 patients and found out that the lymphocyte to monocyte ratio (LMR) of severe patients was significantly higher than non-severe patients. This study thought that the proportions of essential parameters in terms of disease severity and prognosis in COVID-19 might help differentiate non-variant COVID-19 from the B.1.1.7 variant. CMR, DMR, FMR, and MER were higher in the non-variant COVID-19, whereas DCR was lower in the same group. CMR was moderately positively correlated with CRP, and ferritin was with FMR. CMR was strongly negatively correlated with DCR. To the best of our knowledge, this is the first study analyzing above mentioned ratios in patients with COVID-19.

Limitations

This study has limitations; besides being a retrospective study, even though all parameters belong to the first admission before undergoing an in-hospital treatment, they still might have been affected by age difference, comorbidities or medications used for these comorbidities. SpO2 measured at the first admission are instant measurements and can be affected by conditions such as the temperature and nail polish of the fingers and are not as objective as blood gas analysis. Since the study included unvaccinated patients, it does not provide information about vaccinated patients.

CONCLUSION

In conclusion, the present study revealed that the B.1.1.7 variant had less severe disease rates, and even though no statistical difference was found, fewer death rates were compared to non-variant COVID-19. Higher levels of ferritin, CMR, FMR, and MER might be indicating the B.1.1.7 variant.

Authors' Contribution

Study Conception: İK; Study Design: İK; Supervision: İK; Funding: İK, YTG; Materials: İK; Data Collection and/or Processing: İK; Statistical Analysis and/or Data Interpretation: İK, YTG; Literature Review: İK, YTG; Manuscript Preparation: İK, YTG and Critical Review: İK, YTG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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