

# BMJ Open How to diagnose COVID-19 in family practice? Usability of complete blood count as a COVID-19 diagnostic tool: a cross-sectional study in Turkey

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## ABSTRACT

**Objective** COVID-19 is currently diagnosed in hospital settings. An easy and practical diagnosis of COVID-19 is needed in primary care. For this purpose, the usability of complete blood count in the diagnosis of COVID-19 was investigated.

**Design** Retrospective, cross-sectional study.

**Setting** Single-centre study in a tertiary university hospital in Erzurum, Turkey.

**Participants** Between March 2020 and February 2021, patients aged 18–70 years who applied to the hospital and underwent both complete blood count and reverse-transcription-PCR tests for COVID-19 were included and compared. Conditions affecting the test parameters (oncological–haematological conditions, chronic diseases, drug usage) were excluded.

**Outcome Measure** The complete blood count and COVID-19 results of eligible patients identified using diagnostic codes [U07.3 (COVID-19) or Z03.8 (observation for other suspected diseases and conditions)] were investigated.

**Results** Of the 978 patients included, 39.4% (n=385) were positive for COVID-19 and 60.6% (n=593) were negative. The mean age was 41.5±14.5 years, and 53.9% (n=527) were male. COVID-19-positive patients were found to have significantly lower leucocyte, neutrophil, lymphocyte, monocyte, basophil, platelet and immature granulocyte (IG) values (p<0.001). Neutrophil/lymphocyte, neutrophil/monocyte and IG/lymphocyte ratios were also found to be significantly decreased (p<0.001). With logistic regression analysis, low lymphocyte count (OR 0.695; 95% CI 0.597 to 0.809) and low red cell distribution width-coefficient of variation (RDW-CV) (OR 0.887; 95% CI 0.818 to 0.962) were significantly associated with COVID-19 positivity. In receiver operating characteristic analysis, the cut-off values of lymphocyte and RDW-CV were 0.745 and 12.35, respectively.

**Conclusion** Although our study was designed retrospectively and reflects regional data, it is important to determine that low lymphocyte count and RDW-CV can be used in the diagnosis of COVID-19 in primary care.

## INTRODUCTION

### Background

As it is known, the novel COVID-19 first seen in Wuhan in China was defined by the

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ In this study, the usability of 26 different complete blood count (CBC) parameters and 6 parameter ratios in the diagnosis of COVID-19 was investigated with a relatively large number of patients covering a period of 11 months (March 2020–February 2021).
- ⇒ Despite the relatively large number of participants, not all patients admitted to the hospital with COVID-19 were included, because not all patients had CBC tests at the same time as the reverse-transcription-PCR test.
- ⇒ As another limitation, variant changes of the virus, and the waves observed in the pandemic and their possible effects on the study results were not investigated.
- ⇒ Since this study was a single-centre study and the results were not validated externally from other countries or in three different continents, the obtained CBC results cannot be generalised to the whole world, which can be considered a regional response of COVID-19 disease.

WHO on 31 December 2019 and declared as a pandemic on 11 March 2020.<sup>1</sup> It continues to spread around the world, with more than 300 million positive cases and more than 5.5 million deaths as of January 2022.<sup>2</sup> This shows that 1 out of every 25 people all over the world is positive for COVID-19 and reveals that the struggle should be continued.

The diagnosis of COVID-19 is still performed worldwide by real-time reverse-transcription PCR (RT-PCR) test.<sup>3</sup> However, due to the cost of test kits and long result times, it would be very beneficial for physicians to use an inexpensive, practical and fast-resulting ancillary test that can be used in the diagnosis of COVID-19. The fact that the complete blood count test (CBC), which has been found to be the cheapest test in COVID-19 researches,<sup>4</sup> can be easily performed in all health institutions, including family medicine, reveals that

it should be investigated in terms of its usability as a diagnostic tool in COVID-19.

There are some studies in the literature on the use of CBC test parameters in COVID-19. In these studies, parameter ratios such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were investigated, and it was determined that especially increased NLR was associated with poor prognosis and mortality.<sup>5-7</sup> In addition, among these studies, a study reporting that the NLR is higher in COVID-19-positive patients at the time of first admission to the hospital is noteworthy in order to demonstrate its diagnostic usability.<sup>8</sup> There are also some studies developed for the usability of machine learning models in detecting COVID-19, confirming that CBC can be used diagnostically.<sup>9-11</sup> These studies express the potential of CBC as a diagnostic tool, and therefore, a comprehensive study is needed for the use of CBC parameters in the diagnosis of COVID-19 for use in family medicine.

### Objective

With the decrease in mortality rates in COVID-19 and the increasing tendency of COVID-19 cases to be accepted as colds like influenza, more practical and cheaper methods are needed, especially in family practice. For this purpose, the use of CBC test parameters in the diagnosis of COVID-19 was investigated by comparing the admission CBC test results of the patients who had a positive or negative RT-PCR.

## METHODS

### Study design

This study was designed as a retrospective, cross-sectional study.

### Setting

The study was carried out in a tertiary university hospital, which is one of the two large hospitals in one of the large cities in the Eastern part of Turkey, serving the surrounding provinces and serving approximately 4.5 million people.

### Informed consent

Patients admitted to the hospital and undergoing CBC and RT-PCR tests for COVID-19 were included in the study. During these procedures, necessary informed consents were obtained by the relevant health professionals. However, due to the retrospective design of the study in the form of scanning the hospital archive, it was not possible to obtain informed consent from the patients for participation in our study.

### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Participants

In our study, patients over the age of 18 who were diagnosed as U07.3 (COVID-19) or Z03.8 (observation for other suspected diseases and conditions) according to ICD-10 (International Classification of Diseases 10th Revision) codes during the study period were searched in the hospital archive. Those who had these diagnoses and had CBC test with RT-PCR test on the same day were included in the study. Patients over the age of 70 were excluded from the study because of the possibility of concomitant haematological problems in advanced age.

The eligible patients were investigated in terms of any disease or medication that could affect the CBC test result, by searching the other previous diagnoses and chronic medication reports of the patients. Oncological cases, patients with malignant neoplasm, haematological or chronic disease, medications, and pregnant women were excluded from the study.

The RT-PCR test results for COVID-19 of the patients included in the study were scanned from the database of the Ministry of Health. Missing test results or the patients who did not have a simultaneous CBC test were excluded. Patients with multiple hospital admissions and multiple RT-PCR test results, but not exceeding 3-months intervals, these subsequent tests were ignored due to the risk of possible effects of previous COVID-19 positivity on the CBC.

Although the RT-PCR test results of some patients were negative, it was observed that the test was repeated 48 hours later, and this second test result was found as positive. In these patients, the first negative test result was accepted as false negative and rejected, and the second positive result was evaluated. If simultaneous CBC test was not found with the second RT-PCR test in these patients, first CBC test result was included in the study.

## Instruments

RT-PCR tests were studied with the Bio-Speedy COVID-19 quantitative qPCR detection kit (Bioeksan Molecular Diagnostics, Istanbul, Turkey) in the reference laboratories of the Ministry of Health. CBC was performed in our laboratories on the automated haematology analyser Sysmex XN-10 (Sysmex, Kobe, Japan).

## Variables

Patients who met the inclusion criteria were divided into two as COVID-19-positive and COVID-19-negative according to RT-PCR test results, considering internationally accepted laboratory reference values. Among the CBC test parameters of both groups, white cell count (WCC), neutrophil, lymphocyte, monocyte, basophil, eosinophil, red cell count (RCC), haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), MCH concentration (MCHC), RCC distribution width (RDW), platelet, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet large cell ratio (PLCR) and immature granulocyte (IG) levels have been investigated. From

these parameters, NLR, neutrophil/monocyte ratio (NMR), lymphocyte/monocyte ratio (LMR), PLR, IG/neutrophil ratio and IG/lymphocyte ratio were calculated and compared between groups. The values of these test parameters are given in internationally accepted units.

### Sample size

The ethical approval was obtained in May 2020, but the study was conducted later, in February 2021. For the sample size, it was aimed to include all patients who applied to our hospital for COVID-19 and met the inclusion criteria. The hospital archive records were searched and filtered in a retrospective design, from February 2021 to the previous dates, to the onset of the pandemic (March 2020), and the eligible patients, who were diagnosed with U07.3 (COVID-19) or Z03.8 (observation for other suspected diseases and conditions) according to ICD-10 codes, were included.

### Statistical analysis

SPSS V.23.0 (IBM) program was used for statistical analysis. Missing values were excluded before the analyses. The data were investigated with the Kolmogorov-Smirnov test whether they were normally distributed or not. Categorical data were presented with frequency and percentage, numerical data were given with mean±SD, and with median and IQR. Student's t-test was used to compare two normally distributed independent groups, and Mann-Whitney U test was used for data that did not show normal distribution.  $\chi^2$  test was used in the analysis of categorical data. Binary logistic regression analysis was performed for the statistically significant parameters. The cut-off values were identified by the receiver operating characteristic (ROC) curve analysis. A  $p < 0.05$  was accepted for statistical significance in the whole study.

## RESULTS

### Participants

In the study, a total of 3267 patient records were retrieved between March 2020 and February 2021, who were diagnosed with U07.3 (COVID-19) or Z03.8 (observation for other suspected diseases and conditions) and their CBC tests were performed on the same date. According to the exclusion criteria of our study, patients under the age of 18 and over the age of 70 ( $n=636$ ), oncological cases ( $n=187$ ), organ and tissue transplant patients ( $n=75$ ), haematological disease ( $n=30$ ), pregnant women ( $n=7$ ), chronic diseases with reported drug use ( $n=149$ ), patients with missing information ( $n=61$ ), and therefore, a total of 1145 patients were excluded (figure 1).

RT-PCR test results and simultaneous CBC test results for COVID-19 of 2122 patients who were eligible to be included in the study were checked one by one. A total of 1144 individuals who were absent, missing RT-PCR test or not performed with CBC simultaneously were excluded from the study. Thus, a total of 978 people were included in the study.

### Descriptive data

The mean age of the included 978 patients was  $41.5 \pm 14.5$  years, with 53.9% ( $n=527$ ) male and 46.1% ( $n=451$ ) female. 39.4% ( $n=385$ ) of the participants were found to be COVID-19-positive and 60.6% ( $n=593$ ) COVID-19-negative. The mean age of COVID-19-positive patients was  $39.0 \pm 14.0$  years, younger than the COVID-19-negative group ( $43.0 \pm 14.7$ ), and this was found to be significantly different ( $p < 0.001$ ). While the percentage of women was higher in the COVID-19-positive group (51.7%), the proportion of men in the COVID-19-negative group was higher (57.5%), which was statistically significant ( $p=0.005$ ).

### Main results

The comparison of CBC test parameters of patients with positive and negative COVID-19 test results is presented in table 1. Accordingly, COVID-19-positive patients were found to have statistically significantly lower WCC, neutrophil, lymphocyte, monocyte, basophil, eosinophil, platelet, IG, MCH and MCHC, compared with negative patients ( $p \leq 0.001$ ).

The percentage of neutrophil was found to be significantly lower in COVID-19-positive patients ( $p < 0.001$ ), while the percentages of lymphocyte, basophil and monocyte were found to be significantly increased ( $p < 0.001$ ). Another significant result was that the PCT was lower in COVID-19-positive patients ( $p < 0.001$ ).

No significant difference was found in the eosinophil per cent, RCC, haemoglobin, haematocrit, MCV, MPV, PDW and PLCR values of the patients ( $p > 0.05$ ).

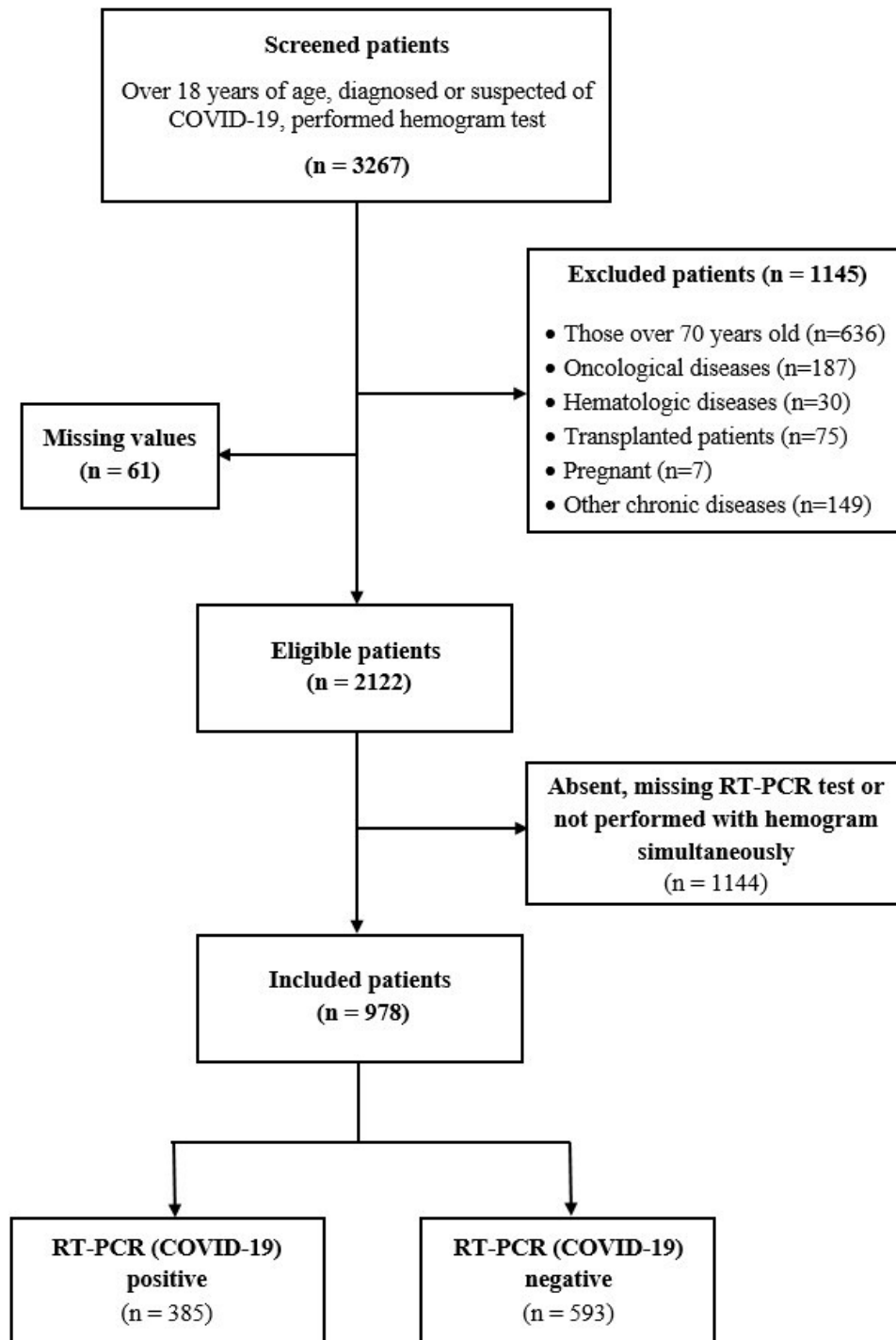
When the ratios of CBC parameters were examined, it was determined that the NLR, neutrophil/monocyte ratio and IG/lymphocyte ratios were significantly decreased in the COVID-19-positive group ( $p < 0.001$ ), while decrease in the platelet/lymphocyte and IG/neutrophil ratios was found at the level of  $p < 0.05$  (figure 2).

Binary logistic regression analysis was performed for statistically significant CBC test parameters. Accordingly, low lymphocyte count (OR 0.695; 95% CI 0.597 to 0.809) and low RDW-coefficient of variation (CV) level (OR 0.887; 95% CI 0.818 to 0.962) were significantly related with COVID-19 positivity (table 2).

When ROC analysis was conducted on the lymphocyte levels, the area under curve (AUC) was found as 0.566 (figure 3), and the cut-off value of lymphocyte was found as 0.745 in 96.1% sensitivity and 90.6% specificity. However, the AUC of RDW-CV was 0.526, and the cut-off value was 12.35 in 73.2% sensitivity and 72.7% specificity for the diagnosis of COVID-19.

## DISCUSSION

In our study, 26 different CBC test parameters and 6 different ratios of patients were compared. Accordingly, in COVID-19-positive patients, some parameters were found to be low (WCC, neutrophil, lymphocyte, monocyte, basophil, eosinophil, platelet and IG counts, neutrophil



**Figure 1** Flow chart of the study. RT-PCR, reverse-transcription PCR.

and IG percentages, RDW-CV and PCT), and some were higher (percentages of lymphocyte, monocyte and basophil). In addition, the calculated NLR, NMR, PLR, IG/neutrophil and IG/lymphocyte ratios were found to be significantly decreased. However, according to the logistic regression analysis, only the decrease in lymphocyte and lower RDW-CV values were found to be significantly associated with the COVID-19 positivity.

There have been some efforts to develop and improve laboratory test results for the diagnosis and the detection

of prognostic factors of COVID-19. In a systematic review, these models were collected and discussed to come up with a machine learning model using laboratory data, but the heterogeneity of the sample sizes, the populations, algorithms, analytical methods and the usage of different laboratory tests and clinical parameters were emphasised as the barriers to the development of machine learning.<sup>9</sup> CBC was found to be a frequent accompanying laboratory test in these studies.

**Table 1** Comparison of haemogram test parameters of COVID-19-positive and COVID-19-negative groups

	COVID-19-negative		COVID-19-positive		P value
	Mean, SD	Median, IQR	Mean, SD	Median, IQR	
WCC	9.43±4.23	8.78 (4.47)	6.02±2.10	5.91 (2.24)	<b>&lt;0.001</b>
Neutrophil #	6.56±3.94	5.62 (3.77)	3.55±1.89	3.28(2.07)	<b>&lt;0.001</b>
Neutrophil %	66.9±13.8	67.0 (18.9)	57.0±13.2	57.0 (17.8)	<b>&lt;0.001</b>
Lymphocyte #	2.00±1.11	1.93 (1.34)	1.72±0.70	1.65 (0.95)	<b>&lt;0.001</b>
Lymphocyte %	23.5±12.1	23.1 (16.8)	29.9±11.2	30.0 (16.9)	<b>&lt;0.001</b>
Monocyte #	0.69±0.37	0.64 (0.39)	0.58±0.27	0.55 (0.26)	<b>&lt;0.001</b>
Monocyte %	7.67±2.96	7.3 (3.1)	10.04±4.02	9.5 (5.0)	<b>&lt;0.001</b>
Basophil #	0.04±0.03	0.04 (0.04)	0.04±0.03	0.04 (0.04)	<b>0.001</b>
Basophil %	0.49±0.35	0.4 (0.4)	0.67±0.55	0.6 (0.8)	<b>&lt;0.001</b>
Eosinophil #	0.13±0.16	0.1 (0.15)	0.13±0.28	0.06 (0.11)	<b>&lt;0.001</b>
Eosinophil %	1.52±1.77	1.2 (1.8)	2.32±5.25	1.0 (1.7)	0.737
RCC	5.12±0.74	5.2 (0.8)	5.18±0.55	5.2 (0.7)	0.651
Haemoglobin	14.6±2.2	15.0 (2.5)	14.7±1.7	14.9 (2.2)	0.642
Haematocrit	43.7±6.0	44.5 (6.8)	44.0±4.3	44.5 (5.6)	0.986
MCV	85.6±5.6	86 (5.7)	85.3±5.3	86.2 (5.1)	0.430
MCH	28.7±2.5	29.1 (2.4)	28.4±2.3	28.8 (1.8)	<b>0.017</b>
MCHC	33.5±1.6	33.6 (2.0)	33.3±1.3	33.4 (1.6)	<b>0.024</b>
RDW-CV	13.3±2.0	12.8 (1.2)	13.1±1.3	12.7 (1.1)	<b>0.017</b>
RDW-SD	41.2±5.5	40.3 (4.2)	40.4±3.4	40.2 (3.6)	<b>0.009</b>
Platelet	263.6±95.9	260.0 (90)	234.4±64.0	231.0 (76.5)	<b>&lt;0.001</b>
MPV	9.91±1.4	9.9 (1.2)	9.92±1.32	10 (1.2)	0.967
PDW	11.2±2.2	11.1 (2.6)	11.2±2.1	11.1 (2.4)	0.985
PCT	0.26±0.09	0.26 (0.08)	0.23±0.06	0.23 (0.07)	<b>&lt;0.001</b>
P-LCR	24.9±7.5	24.4 (9.9)	24.9±7.2	24.5 (9.3)	0.971
IG#	0.06±0.14	0.03 (0.03)	0.03±0.04	0.02 (0.02)	<b>&lt;0.001</b>
IG%	0.6±1.02	0.4 (0.2)	0.41±0.63	0.3 (0.3)	<b>&lt;0.001</b>
Neutrophil/lymphocyte	4.86±5.48	2.92 (3.4)	2.52±2.39	1.89 (1.9)	<b>&lt;0.001</b>
Neutrophil/monocyte	11.96±18.56	8.77 (5.4)	7.01±5.01	6 (4.1)	<b>&lt;0.001</b>
Lymphocyte/monocyte	3.38±2.24	3.16 (2.4)	3.4±1.73	3.17 (2.5)	0.277
Platelet/lymphocyte	173.33±132.7	138.02 (92.2)	158.79±91.0	134.19 (78.4)	<b>0.042</b>
IG/neutrophil	0.01±0.02	0.006 (0.004)	0.01±0.01	0.005 (0.004)	<b>0.018</b>
IG/lymphocyte	0.04±0.1	0.017 (0.026)	0.02±0.05	0.012 (0.013)	<b>&lt;0.001</b>

Boldface values indicate that the value is statistically significant.

IG, immature granulocyte; MCH, mean corpuscular haemoglobin; MCHC, MCH concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; RCC, red cell count; RDW-CV, red cell distribution width-coefficient of variation; WCC, white cell count.

Since CBC is a practical, easy and cost-effective test, there are some promising studies in the literature within the scope of CBC results to be used in the diagnosis of COVID-19. A prediction analysis was conducted by Joshi *et al*, for the identification of PCR negative patients by CBC and patients' sex, and they concluded that, CBC results were better for allocating the COVID-19 test results.<sup>12</sup> In another study, Formica *et al* developed a criterion that included three CBC parameters with age, and found that CBC based scores have potential for

diagnosis of COVID-19.<sup>13</sup> Likewise, some studies have focused on machine learning models, including CBC, and these models have been found useful for diagnostic purposes.<sup>10 11 14 15</sup> However, these machine learning models may involve some complex calculations, and require adaptation and integration into diagnostic systems, and therefore, somehow difficult to use and adapt to every population.

To evaluate the utility of CBC in the diagnosis of COVID-19, our study investigated 26 different parameters and 6



**Figure 2** Haemogram parameter comparisons of COVID-19-negative and COVID-19-positive groups. ★ $p < 0.001$ , ✖ $p = 0.001$ , ✕ $p < 0.05$ . IG, immature granulocyte; MCH, mean corpuscular haemoglobin; MCHC, MCH concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; RCC, red cell count; PLCR, platelet large cell ratio; RDW-CV, red cell distribution width-coefficient of variation; WCC, white cell count.

different ratios of CBC, an in-depth, fully focused study of CBC parameters was conducted, and among these, lymphocyte and RDW-CV values were prominent.

In a study conducted by Sayed *et al*, hospitalisation CBC values of patients were investigated, and NLR was found to be higher in COVID-19 patients.<sup>8</sup> In that study, the authors focused on NLR values but also stated that

neutrophil values were at low-to-normal levels (3.8 in COVID-19-positive and 4.4 in control), which in turn shows that the main reason for high NLR is actually low lymphocyte levels (0.9 in COVID-19-positive and 2.1 in control), which is similar to our study. However, in our study, NLR was found to be lower in COVID-19-positive patients. Looking deeper, it is clear that neutrophil

**Table 2** Logistic regression analysis results of significant haemogram parameters

	B	Sig.	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Lymphocyte #	-0.364	0.000	0.695	0.597	0.809
RDW-CV	-0.120	0.004	0.887	0.818	0.962

RDW-CV, red cell distribution width-coefficient of variation.

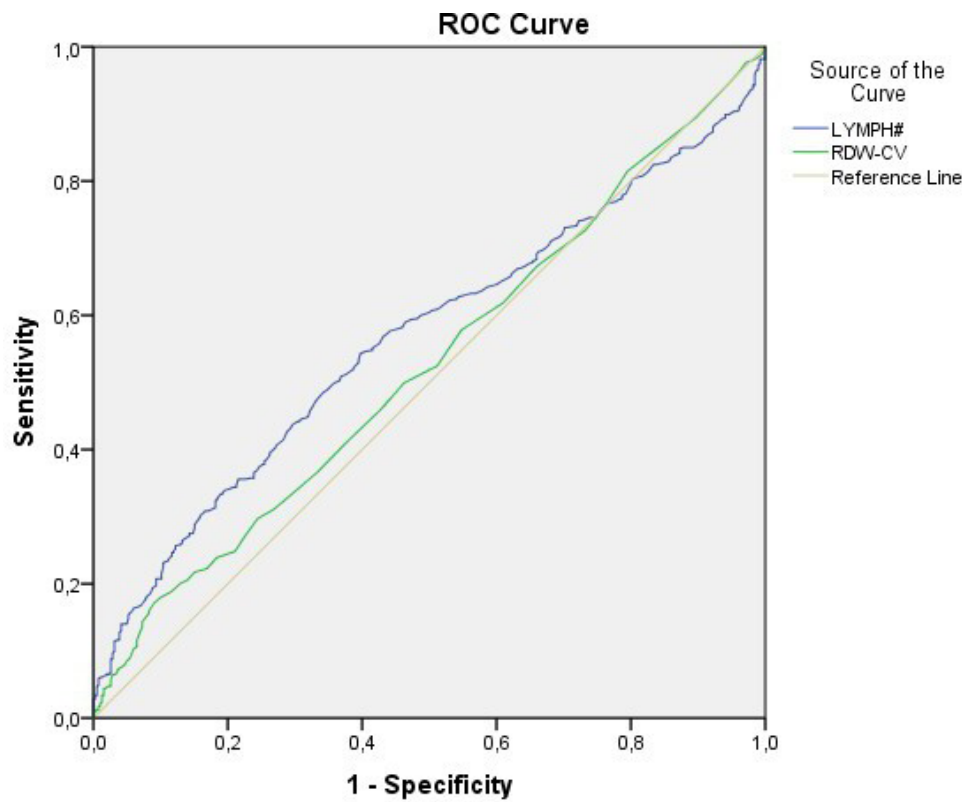
values were lower in COVID-19 patients in both our study and Sayed *et al's* study (3.55 vs 3.8, respectively), but the neutrophil values of the control groups were different (6.56 vs 4.4, respectively). The neutrophil values of the control group of our study were more normal as expected. The reason for this difference should be attributed to the study design of our study, as the RT-PCR test can be negative at the onset of the disease and turn positive when retested within 2 days, so we received these cases as COVID-19-positive. Therefore, negative and positive cases can be considered more accurate in our study.

Considering the studies investigating the CBC other than diagnostic purposes, a study conducted on a large group of patients in Spain investigated the NLR, PLR and NPR ratios of COVID-19-positive patients to determine the risk of admission to the intensive care unit. They determined that, especially high NPR was found to be significantly associated with the risk of patients being

admitted to the intensive care unit.<sup>16</sup> In another study, in which they investigated the relationship of these same ratios with hospital mortality, it was found that these values were significantly higher at the time of admission to the hospital in patients who died.<sup>17</sup>

In a study conducted in Turkey, the relationship between admission CBC parameters and the severity of COVID-19 and intensive care indication were investigated, and it was found that higher NLR, and MLR levels and lower PLR levels were significantly different.<sup>18</sup> In another study, it was determined that low haemoglobin, WCC and lymphocyte values were associated with poor prognosis in terms of intubation, intensive care and death.<sup>19</sup> In a cohort study with a smaller group of patients, WCC value, NLR and PLR ratios were found to be associated with mortality.<sup>20</sup>

In a study investigating the difference of CBC parameters compared with the healthy group, low lymphocyte and platelets, high WCC, neutrophil, NLR and PLR rates


**Figure 3** ROC curve analysis of lymphocyte count and RDW-CV levels. RDW-CV, red cell distribution width-coefficient of variation; ROC, receiver operating characteristic.



were found in COVID-19-positive patients.<sup>21</sup> This study investigated the differences in CBC parameters of COVID-19-positive patients compared with the healthy group, on a smaller number of subjects than our study. In our study, unlike that study, WCC, neutrophil, NLR and PLR rates were found to be low in COVID-19-positive patients, and lower lymphocyte value was found to be significantly associated with the COVID-19 positivity.

## CONCLUSION

In this study, which was carried out with a large patient group, the usability of CBC test parameters in the diagnosis of COVID-19 was investigated for a practical use in family medicine. It was determined that most of the CBC parameters and ratios were significantly differed in COVID-19-positive patients. Meaningfully, low lymphocyte count and low RDW-CV level can be used in the diagnosis of COVID-19.

**Contributors** MB and ET designed and conceptualised the research and collected data. MB processed the data, performed the analysis, drafted and wrote the paper. MB, ET and MNK discussed the results and commented on the manuscript. MB is the guarantor who accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The necessary approval was obtained from the Ministry of Health Scientific Research Board with the decision number 04.05.2020/T04.08.09; and then from the local ethics committee with the decision number 28.05.2020/06-32. Informed consent was not obtained from the patients due to the scanning of the hospital archive and the retrospective design of the study.

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**Data availability statement** Data are available on reasonable request.

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