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Contribution of neutrophil/lymphocyte ratio to the diagnostic efficiency of computed tomography and polymerase chain reaction in COVID-19 patients

Serhat Örün and Mustafa Numan Erdem

Abstract

Background: 6.5% of the country's population was diagnosed with COVID-19 disease. Computed tomography scanning and polymerase chain reaction tests are considered reliable methods for the detection of COVID-19. However, the specificity and reliability of polymerase chain reaction tests and ground-glass opacity (GGO) on thorax computed tomography images in diagnosing COVID-19 are still being disputed. Our aim was to compare the neutrophil/lymphocyte ratio, whose efficiency in differentiating between viral and bacterial infections has previously been studied, with computed tomography and polymerase chain reaction for COVID-19 diagnosis.
Materials and methods: This was a retrospective study that included patients treated in a tertiary care hospital emergency service pandemic polyclinic between 14 March and 1 June 2020. The neutrophil/lymphocyte ratios of patients with polymerase chain reaction tests and ground-glass opacities on computed tomography were calculated. The neutrophil/lymphocyte ratios of polymerase chain reaction-negative patients with computed tomography images were compared with the neutrophil/lymphocyte ratios of polymerase chain reaction-positive patients with computed tomography images.
Results: A total of 631 patients were included in this study. Thorax computed tomography scans were obtained from all patients. The mean neutrophil/lymphocyte ratio of patients with ground-glass opacities was 3.50 ± 2.12, whereas that of patients without ground-glass opacities was 2.90 ± 2.01. This difference was also statistically significant. Polymerase chain reaction swab samples were obtained from 282 patients (44.7%). The mean neutrophil/lymphocyte ratio of polymerase chain reaction-positive patients was 2.38 ± 1.02, whereas that of polymerase chain reaction-negative patients was 3.97 ± 2.25. The difference was statistically significant.
Conclusion: Many studies are undoubtedly required to determine the efficiency of the neutrophil/lymphocyte ratio in COVID-19 diagnosis. However, we postulate that evaluating the neutrophil/lymphocyte ratio along with computed tomography and polymerase chain reaction can assist in the diagnosis of patients.

Keywords

COVID-19, neutrophil/lymphocyte ratio, ground-glass opacity, thorax computed tomography

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Introduction

Coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization on 11 March 2020, has placed heavy burdens on health systems. To contain the spread of the disease, whose mortality rate for critically ill patients has been estimated at 61.5%, early diagnosis of asymptomatic or mildly symptomatic cases and intensive care of severe cases are required.[1,2]

COVID-19 diagnosis is typically established using polymerase chain reaction (PCR) on nasal swab samples. However, because of the high false negative rates of SARS-CoV-2 PCR tests, clinical, laboratory, and radiological findings are also used for diagnosis.[3] Ground-glass opacity (GGO) seen on thorax computerized tomography (CT) is one such finding. However, the specificity and reliability of PCR tests and GGOs detected on thorax CT in diagnosing COVID-19 are still being disputed.

Faculty of Medicine, Namik Kemal University, Tekirdağ, Turkey

Corresponding author:
Serhat Örün, Faculty of Medicine, Namik Kemal University, Tekirdağ, Turkey.
Email: serhatorun@gmail.com

The neutrophil/lymphocyte ratio (NLR) has been widely reported to be an accurate and easily obtained laboratory marker of inflammation.[4–6] It is also used for the diagnosis, treatment, and prognosis of pneumonia.[5] Although conclusive proof is still lacking, evidence suggests significant relationships between bacterial infection and neutrophilia and between viral infection and lymphocytosis.[7] As the NLR is lower in viral than in bacterial infections, it can be used to differentiate between these kinds of infections.[7] Therefore, the aim of this study was to investigate the efficiency of the NLR in diagnosing COVID-19 by comparing it with patients' thorax CT findings and PCR test results.

Materials and methods

Study design and participants

This retrospective study included patients referring to a tertiary care hospital emergency service pandemic polyclinic between 14 March 2020, when the first suspicious case referred to the service, and 1 June 2020, when the government started to loosen lockdown restrictions across the country. All patients in this area were evaluated by an emergency room assistant. Later, these patients were consulted with the chest diseases and the infectious diseases department. Patients with cough, fever, expectoration, or shortness of breath were included the study. Patients with non-specific symptoms who had been exposure history were also included in the study. Patients under the age of 18 years, pregnant women, and patients evaluated directly in the resuscitation unit were excluded from the study. Thorax CT, hemograms, ferritin, D-dimer, and C-reactive protein (CRP) examinations were performed on all patients evaluated in this section. Moreover, oral-nasal swab samples were taken from all possible COVID-19 cases, and PCR tests were examined in 2 h after taken. For a person to be accepted as a possible case and to be evaluated for taking a swab sample; in addition to having at least one of the signs and symptoms of "fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell or diarrhea," this person must be in high-risk areas for COVID-19 disease or have had close contact with an individual with COVID-19 in the past 14 days. If at least two of the above-mentioned signs and symptoms are present, the person is considered a possible case. Even if the first PCR test was negative, a repeat PCR test was performed on the third day for the cases that continued to be possible case. Swab sample for PCR was not taken from the cases who are outside the possible cases but if they were contact with the COVID-19 patients they were asked to stay in self-quarantine to avoid risks and were discharged from the emergency room.

Real-time reverse transcription polymerase chain reaction (RT-PCR) Allplex™ 2019-nCoV Assay (Seegene, Korea) was used for SARS-CoV-2 RNA detection according to the manufacturer's instructions. The result was analyzed using Seegene Viewer (Seegene, Korea), in which a cycle threshold value <40 for all target genes was defined as a positive result.

All blood exams were performed in the emergency room laboratory and with the same device. CRP and D-dimer with immunoturbidimetric technique, and ferritin with electrochemiluminescence immunoassay were examined. All CT procedures were performed with a GE brand BrightSpeed model 16 detector device in the emergency department tomography unit. Thorax CT scans of all patients were examined by the same emergency physician for the study, and artificial intelligence was not used at any stage.

After the CT was examined, patients were divided into two groups with and without GGOs. PCR test studied cases were determined and divided into two groups as PCR positive and negative. Later, NLR of all created groups was calculated. NLR of cases with and without GGOs was compared. NLR of PCR-positive and PCR-negative cases was compared. The NLR of PCR-positive patients with GGOs and PCR-positive patients without GGOs was compared. The NLR of PCR-positive patients with GGOs and PCR-negative patients with GGOs was compared. All obtained data were entered into the patient records. NLR values of patients with ground-glass appearance on CT were determined. If the NLR was above 3.44, it was thought to be a false positive. If it was below 3.44, it was evaluated in favor of COVID-19. In patients with PCR test, when PCR test was positive, the patient was accepted as COVID-19, and when the PCR test was negative, the patients' NLR value was checked in. If the NLR value was below the determined cut-off value, it was thought that the test results can be false negative. If the NLR value is above the determined cut-off value, it was thought that the PCR result could be correct.

After collecting the data sample, size calculation was performed and the power of the study was defined. PCR test was performed on 126 of the patients with GGO. Twenty positive and 106 negative results were detected. The effect size calculated on the data of the specified patients was determined as 1.5588235. When α error was accepted 0.05, the power of the study was calculated as 99%.

Statistical analysis

Statistical analyses were performed using Statistical Program for the Social Sciences (SPSS) version 22.0 (SPSS Inc.) and Analyse-it Software Ltd. The Kolmogorov–Smirnov test was used to assess the normality of the distributions of the NLR-GGO and NLR-PCR parameters. Pearson's chi-square test was used to determine the relationship between categorical GGO and PCR variables. The Mann–Whitney U test was used to determine relationships between numerical variables. Continuous variables were expressed as mean values ± standard deviations. The numerical expressions of categorical values were expressed as absolute numbers and percentages. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 631 patients, 45.8% (n=289) of whom were female and 54.2% (n=342) were male, were included in the study. The average age of the patients was 43.74 ± 17.98 years. Among the patients, 55.7% presented with cough, 36.4% presented with fever, 23.3% presented with shortness of breath, and 11.4% presented with expectoration. The demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. The demographic and clinical characteristics of the patients.

Findings	*n* (%)
Age (mean ± SD)	43.74 ± 17.98
Gender	
Female	289 (45.8%)
Male	342 (54.2%)
Patient with CT	631 (100%)
Patient with GGO	150 (23.8%)
Patient with PCR test	282 (44.7%)
PCR-positive patient	27 (4.3%)
Patient presented with	
Cough	351 (55.7%)
Fever	229 (36.4%)
Shortness of breath	147 (23.3%)
Expectoration	72 (11.4%)
Vital sings	
MAP	98.51 ± 16.68
Pulse	98.15 ± 19.50
Saturation O_2	96.82 ± 3.20
Fever	37.16 ± 0.95
Respiratory examination findings	
Rales	73 (11.6%)
Ronkus	36 (5.7%)
Wheezing	3 (0.5%)

SD: standard deviation; CT: computerized tomography; GGO: ground-glass opacity; PCR: polymerase chain reaction; MAP: mean arterial pressure.

All included patients underwent thorax CT scanning. GGOs were observed in 150 (23.8%) patients (Figure 1). Twenty-nine of those patients had non-specific symptoms but were discharged from the hospital with the recommendation to self-quarantine at home because of having parenchymal involvement, 21 were discharged with the recommendation to self-quarantine at home because of having flu-like symptoms, 92 were hospitalized, and 8 were treated in the intensive care unit. A statistically significant difference was found between the disposition of patients with GGOs and those of patients without GGOs (Table 2).

Swab samples for PCR tests were taken from 282 patients (44.7%). Twenty-seven (9.6%) of them tested positive. The ratio of PCR-positive patients to the entire study population was 4.3%. A comparison of PCR results and patient outcomes revealed that 2 of 55 patients who were discharged tested positive. These discharged patients did not have specific symptoms. All 72 patients who were instructed to self-quarantine at home tested negative; these patients had flu-like symptoms. Twenty-five of 146 hospitalized patients tested positive. All nine patients treated in the intensive care unit tested negative. A statistically significant relationship was observed between patient disposition and PCR results (Table 3).

The mean NLR of PCR-positive patients was 2.70 ± 1.60, whereas that of PCR-negative patients was 3.42 ± 2.22. The difference was statistically significant (p=0.04; Table 4). The mean NLR of patients with GGOs was 3.50 ± 2.12, whereas that of patients without GGOs was 2.90 ± 2.01. This

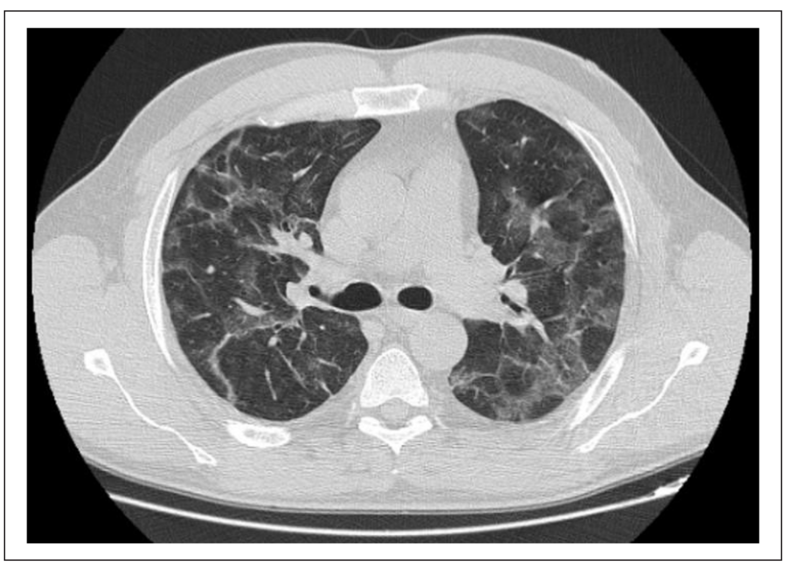

Figure 1. Thorax CT section with ground-glass opacity of the COVID-19 case.

Table 2. The comparison of GGO and patient disposition.

Patient outcomes	GGO (n=631)		p
	With	Without	
Self-quarantine (GGO)	29	233	<0.001
Self-quarantine (symptom)	21	171	<0.001
Non-ICU hospitalization	92	74	<0.001
ICU hospitalization	8	3	<0.001

GGO: ground-glass opacity; ICU: intensive care unit.

Table 3. The comparison PCR and patient disposition.

Patient outcomes	PCR (n=282)		p
	Positive	Negative	
Self-quarantine (PCR)	2	53	<0.001
Self-quarantine (symptom)	0	72	<0.001
Non-ICU hospitalization	25	121	<0.001
ICU hospitalization	0	9	<0.001

PCR: polymerase chain reaction; ICU: intensive care unit.

Table 4. The comparison of PCR with NLR and other blood tests.

Tests	PCR		p
	Positive	Positive	
Ferritin	201.55 ± 170.48	256.99 ± 391.30	0.5
D-dimer	0.53 ± 0.29	1.85 ± 4.94	0.000
CRP	16 ± 31	42 ± 68	0.001
NLR	2.70 ± 1.60	3.42 ± 2.22	0.04
Neutrophil	3.52 ± 1.91	7.51 ± 10.59	0.05
Lymphocyte	1.40 ± 0.43	3.26 ± 8.63	0.2
WBC	5.56 ± 2.18	9.02 ± 7.73	0.02

PCR: polymerase chain reaction; NLR: neutrophil/lymphocyte ratio; CRP: C-reactive protein; WBC: white blood cell.

difference was also statistically significant ($p < 0.01$). The comparison of the laboratory findings of patients with and without GGOs is shown in Table 5.

Of the 150 patients with GGOs, 126 (84%) underwent PCR tests. Of those, 20 tested positive and 106 tested negative. The mean NLR of PCR-positive patients was 2.38 ± 1.02, whereas that of PCR-negative patients was 3.97 ± 2.25. The difference was statistically significant ($p < 0.01$). However, the difference between the mean NLR of PCR-positive patients with GGOs and that of PCR-positive patients without GGOs was not statistically significant (p=0.2). The mean NLR of PCR-positive patients with GGOs was 2.38 ± 1.02, whereas that of PCR-positive patients without GGOs was 3.62 ± 2.56 (Table 6).

When the cut-off value for NLR was taken as 3.44, it was found to have 45% sensitivity and 74% specificity in

Table 5. The comparison of GGO with NLR and other blood tests.

Tests	GGO		p
	With	Without	
Ferritin	331.73 ± 427.54	169.77 ± 297.23	0.001
D-dimer	2.1 ± 5.41	1.84 ± 5.19	0.6
CRP	55 ± 77	19 ± 39	0.000
NLR	3.50 ± 2.12	2.90 ± 2.01	0.002
Neutrophil	7.71 ± 11.75	5.92 ± 6.11	0.015
Lymphocyte	3.63 ± 10.64	2.46 ± 3.24	0.1
WBC	9.16 ± 9.81	8.41 ± 3.21	0.1

GGO: ground-glass opacity; NLR: neutrophil/lymphocyte ratio; CRP: C-reactive protein; WBC: white blood cell.

Table 6. The comparison of GGO, PCR, and NLR.

	n	NLR (mean ± SD)	p
PCR+	27		
With GGO	20	2.38 ± 1.02	0.2
Without GGO	7	3.62 ± 2.56	
With GGO and PCR test	126		
PCR+	20	2.38 ± 1.02	<0.005
PCR−	106	3.97 ± 2.25	

SD: standard deviation; GGO: ground-glass opacity; PCR: polymerase chain reaction; NLR: neutrophil/lymphocyte ratio.

detecting patients with GGO on CT (odds ratio (OR)=2, area under the curve (AUC)=0.602, 95% confidence interval (CI)=(0.54–0.65)). At the same cut-off value, NLR was found to have 39% sensitivity and 75% specificity in detecting PCR-negative patients (OR=2, AUC=0.602, 95% CI=(0.54–0.65)).

Discussion

The COVID-19 pandemic has affected people in waves. While the intensity of each wave increased compared to the previous one, the fight against this disease became more effective with the experience gained from the data identified about the disease. The first wave of the pandemic was one of the most difficult parts of it. The lack of a known gold standard diagnosis method of the disease and the limited number of health centers where PCR tests were performed were among the reasons for this. Of course, it was tried to provide patient care as a standard by minimizing this problem with the current patient approach guides published by health authorities.

Recent evidence suggests that NLR is of critical importance in the diagnosis of viral infectious disease. In this study, the effectiveness of NLR in the diagnosis of COVID-19 was investigated by comparing with thorax CT and PCR. Zhang et al.[8] used NLR as an early diagnostic marker in AIV-H7N9 patients. Qin et al.[9] found that, as SARS-CoV-2 mainly affects lymphocytes, causing a cytokine storm and leading to a series of immune reactions that can damage organs, the NLR could be helpful for the diagnosis of COVID-19. Similarly, Usul et al.[7] suggested that the low NLR frequently detected in hemograms performed in emergency rooms could be used for the diagnosis of COVID-19. Consistent with these findings, in this study, the NLRs of patients with positive PCR results were significantly lower than those of patients with negative results. We also attribute this relationship to the interaction of SARS-CoV-2 with T-lymphocytes.

The symptoms of COVID-19 patients range from asymptomatic infection to severe respiratory insufficiency.[10,11] According to a review by Wiersinga et al.,[3] the most frequently observed symptoms in hospitalized patients are fever (up to 90% of the patients), dry cough (60%–86%), shortness of breath (53%–80%), fatigue (38%), nausea/vomiting or diarrhea (15%–39%), and myalgia (15%–44%). The median age of hospitalized patients is between 47 and 73 years, and most cohorts are dominated by males (around 60%).[3] Our results are consistent with these findings.

CT has an important role in the diagnosis of COVID-19. A review of Ye et al.[12] about CT manifestations of COVID-19 found that a bilateral distribution of consolidated and non-consolidated GGOs in the periphery and posterior of lungs is the most significant manifestation. Li et al.[13] suggested that there could be important clinical differences between mild and severe COVID-19 cases in terms of CT findings. Hani et al.[14] reported that CT undoubtedly plays an important role in the early diagnosis of COVID-19 pneumonia. However, in cases of uncertain CT findings, PCR is still required for confirmation, which could delay the diagnosis due to the necessity of repeating the test. In this study, we found a statistically significant relationship between thorax CT findings and PCR test results. We suggest that CT plays an important role in the diagnosis of patients with mild symptoms, although a PCR test is necessary for final diagnosis. In cases of inconclusive CT findings, the PCR test should be repeated to rule out the possibility of a false negative result.

Previous studies have shown that hospitalized patients with a COVID-19 diagnosis confirmed by PCR may have normal CT images, while other patients may have abnormal CT images consistent with COVID-19 days before the detection of SARS-CoV-2 RNA.[15,16] The total positivity rate of throat swab PCR has been estimated at 30%–60%; it has therefore been suggested that this test cannot be considered a gold standard for the diagnosis of this disease.[1,17] Our findings support the suggestion that PCR cannot be considered a gold standard for COVID-19 diagnosis.

The sensitivity and specificity of thorax CT and PCR in the diagnosis of COVID-19 differ. Ai et al.[17] found that the sensitivity of thorax CT in suggesting COVID-19 was 97% when compared to PCR results. Positive thorax CT findings were detected in 75% of PCR-negative patients. Moreover, CT findings were consistent with COVID-19 before the confirmation of a positive PCR test in 60%–93% of the patients. Furthermore, CT findings suggested recovery before a negative PCR result in 42% of the diagnosed cases.[15] Wang et al.[1] reported that the sensitivity and specificity of PCR tests for COVID-19 were 65% and 83%, respectively, when thorax CT was used as a diagnosis standard. The authors found that neither thorax CT nor PCR tests were sufficiently accurate for COVID-19 diagnosis when both specificity and sensitivity were taken into account.[1] Our results are consistent with the literature. This may be due to the fact that patients with mild or no symptoms may show no pulmonary involvement, while on the contrary, some cases may have suggestive CT findings days before the detection of SARS-CoV-2 RNA in oral-nasal swabs.

In this study, we found a statistically significant difference in NLR between patients with GGOs on CT and those without GGOs. Surprisingly, the mean NLR of COVID-19 patients with GGOs was higher than that of patients without GGOs. We attribute this finding to the fact that bacterial and viral infection coexistence could not be excluded and to the fact that although the sensitivity of CT findings for pulmonary involvement is high, their specificity is low. As the NLR correlated with CT findings and PCR results, we believe that low NLR value can be helpful for the diagnosis of patients with negative PCR tests but pulmonary involvement or for the decision to perform CT scanning. In addition, we think that by predicting the negative PCR result of patients with GGO above a certain cut-off value of NLR, it may be helpful to exclude COVID-19 in GGOs' patients.

Limitations

This study had several limitations. First, it was a retrospective, single center study of patients admitted to hospital; standardized data for a larger cohort would be better to assess. Second, the data of the all groups were not balanced, and the sample size of the PCR-positive group was relatively small. Third, COVID-19 patients with bacterial co-infection or superinfection could not be excluded from the study. This may affect NLR results. None of the patients had a lung biopsy so other potential causes of GGO, such as pulmonary edema and hemorrhage, could not be excluded. How many days after symptoms oral-nasal swab samples were taken could not detected.

Conclusion

To conclude, there is still no gold standard for the diagnosis of COVID-19. We think that NLR evaluation combined with CT and PCR may contribute to the diagnosis of COVID-19. However, many studies are needed to confirm this hypothesis.

Author contributions

The authors contributed to all the parts, proposal writing, data collection, data analysis, and writing the discussion. S.Ö. contributed to the study design, collecting data, conducted the data analysis, and contributed to the writing of manuscript. M.N.E. contributed to the study design and collecting data, and editing of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

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Informed consent

Since this study was retrospective, informed consent was waived with the approval of the ethics committee.

ORCID iD

Serhat Örün https://orcid.org/0000-0001-5879-7858

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