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Original Article

Chest-X-ray-Based Scoring, Total Leukocyte Count, and Neutrophil-to-Lymphocyte Ratio for Prediction of COVID-19 in Patients with Severe Acute Respiratory Illness

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Abstract

OBJECTIVE: This study aimed to use chest-X-ray (CXR)-based scores along with total leukocyte count (TLC) and neutrophil-to-lymphocyte ratio (NLR) in the prediction of coronavirus disease 2019 (COVID-19) in patients presenting with clinical features of severe acute respiratory illness (SARI).

MATERIAL AND METHODS: This is a retrospective study involving all patients who presented with clinical features of SARI and who had undergone bedside chest X-ray (CXR), hemograms with TLC, NLR, and reverse transcriptase-polymerase chain reaction (RT-PCR) at our institute from May 1 to June 30, 2020.

RESULTS: Of 204 patients, 115 tested RT-PCR-positive and 89 tested negative. The patients who presented with SARI, using CXR-based score of 4 or more, TLC of less than 8,700 cells/μL, and NLR of <7 had a statistically significant area under the curve ($p<0.001$) for diagnosing COVID-19. The sensitivity and specificity of the CXR score was 80.8% and 73.0%, of TLC was 70.1% and 74.7%, and of NLR was 70.1% and 59.0%, respectively, in diagnosing COVID-19 alone. The specificity further increased to 90.4% when we used the CXR score with NLR and to 92.8% when we used the CXR score with TLC. The post-test odds ("rule in" disease) of a positive test for having the disease were 3, 2.77, and 1.71 times with the use of either CXR score, TLC, or NLR criteria, respectively; whereas, combined use of CXR score and NLR increased the post-test odds by 5.53 times, and combination of CXR score with TLC increased the post-test odds by 7.5 times.

CONCLUSION: CXR score with TLC and NLR can predict COVID-19 infection among those who presented with features of SARI. This may help in the early isolation of the patient until the RT-PCR report becomes available.

KEYWORDS: Coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, chest X-ray, total leukocyte count, neutrophil-to-lymphocyte ratio

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INTRODUCTION

The first case of coronavirus was reported from Wuhan, China, in December 2019. Coronavirus disease 2019 (COVID-19) was the name given to the disease caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Since then, there was a continuous increase in the number of cases, and the World Health Organization (WHO) declared it a "public health emergency of international concern" on January 30, 2020, and a pandemic on March 11, 2020 [1]. In India, the first case was diagnosed in January 2020, and the cases started increasing since March 2020. As of September 15, 2020, the total number of COVID-19 cases reached 5 million in India [2].

In most of the cases, patients who are COVID-19 positive remain asymptomatic or have mild symptoms. The common symptoms of COVID-19 include fever, fatigue, myalgia, cough, sore throat, dyspnea, anosmia, and so on. Acute respiratory infection with a history of fever or documented fever of ≥38°C and cough with onset within the past 10 days, which requires overnight hospitalization, is called severe acute respiratory illness (SARI) [3]. SARI-like symptoms can be seen in many conditions other than COVID-19, such as viral or community-acquired pneumonia, pulmonary tuberculosis, acute exacerbation of chronic obstructive pulmonary disease, acute exacerbation of interstitial lung disease, cardiac diseases, and so on. Hence, it is difficult to differentiate SARI between COVID-19 and non-COVID-19 by clinical examination alone.

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The nucleic acid amplification tests, such as reverse transcriptase-polymerase chain reaction (RT-PCR) with viral RNA extraction, are used to detect coronavirus in various body secretions, predominantly nasopharyngeal and oropharyngeal secretions. The specificity of the RT-PCR test is high, but sensitivity ranges from 60% to 95%. The RT-PCR test result depends upon various factors, including sample collection, day of illness, type of testing kit, and so on [4-6]. A study by Kucirka et al. has found the minimum false negative result to be 20%-21% on days 8 and 9 of the disease [6]. The sensitivity of the bronchoalveolar lavage fluid is greater than nasal and pharyngeal swabs in terms of samples [5]. Therefore, all patients presenting to the hospital with symptoms of SARI undergo the RT-PCR test to diagnose or rule out COVID-19 infection. Under ideal circumstances, results from RT-PCR are obtained in 8 to 12 hours. It further depends upon the laboratory infrastructure and the number of patients to be tested. In addition, most of the laboratories approved for performing RT-PCR are in medical colleges and in district-level hospitals in India. The samples collected from peripheral or small healthcare facilities are sent to the nearest laboratories for evaluation, which further increases the turnaround time for test results.

Therefore, an investigation that is widely available and provides quicker result with better accuracy is required so that a patient with SARI can be triaged and isolated until the result of the RT-PCR test becomes available. The rapid antigen test is such a test that can be used; however, it also has variable sensitivity depending on the testing kit.

Coronavirus affects the lung, which leads to COVID-19 pneumonia, and the patients present with clinical features of SARI. COVID-19 pneumonia leads to various changes in the lung parenchyma, which can be detected by radiological imaging, which may be helpful in such situations. Most of the available literature is based on computed tomography (CT) changes in COVID-19 pneumonia. CT is a very sensitive and quick imaging modality for the detection of changes of COVID-19 pneumonia in the lungs. The disadvantages of CT include a lack of its availability at most of the small and peripheral hospitals, requirement for CT room decontamination after every patient is tested, chances of cross-infection to the healthcare workers, and other patients undergoing subsequent CT and radiation exposure [7, 8]. The American College of Radiology notes that post-CT scanning, decontamination of the CT scan room may disrupt the availability of radiological service [7-9].

Chest X-ray (CXR) is a radiological investigation that is available at most of the peripheral health centers and with the use of a portable machine, the risk of the cross-infection can also be reduced. The CXR can also detect the changes in the lung parenchyma in COVID-19 infections; although its sensitivity is lower than the CT scan, it can still be used for the diagnosis of COVID-19.

MAIN POINTS

- Chest X-ray based score is useful for prediction of Covid-19 in patients with SARI.
- Routine hemogram including NLR and TLC which is widely available at all the small health care facilities can also be used to predict the Covid-19.
- Combining the chest X-ray based score along with NLR and TLC further increases the sensitivity and specificity of prediction of Covid-19 and helpful in early isolation.

Another common detection method easily available at most of the healthcare facilities is a complete hemogram with total leukocyte count, absolute neutrophil count, absolute lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR). Neutrophils and lymphocytes are the components of the immune system that fight against various infections. Neutrophils are involved in the innate immune system, whereas lymphocytes are involved in adaptive immunity. The lymphocytes, predominantly CD4+ and CD8+ T-lymphocytes, are the main defense mechanism against COVID-19 infection. Similarly, coronavirus mainly acts on lymphocytes, CD4+ T cells, CD8+ T cells, B cells, and natural killer cells resulting in a decrease in their numbers [10].

CXR, TLC, and NLR are cheaper, quicker, and widely available tests at most peripheral hospitals. The CXR scoring, TLC, and NLR can be used together for the prediction of COVID-19 in patients with SARI. This may be helpful before the availability of RT-PCR test reports for decision making regarding the isolation of patients with SARI.

MATERIAL AND METHODS

After receiving the institutional ethical committee approval, a retrospective analysis was performed in all the patients who presented to our institute from May to June, 2020, with clinical features of SARI. The inclusion criteria included all the patients who presented with the clinical features of SARI and when CXR, hemogram, and RT-PCR tests were performed at the same admission. All the CXRs were performed using portable X-ray machines, Skanmobile (Skanray, India) in either posteroanterior or anteroposterior orientation. Only the baseline chest radiograph was used for scoring. All the patients with suspected/positive COVID-19 infection without SARI-like symptoms were excluded. All the CXRs were reviewed by 2 radiologists with an experience of 10 and 5 years who were blinded to the RT-PCR results, and consensus was reached about the score.

Similarly, a complete hemogram test was conducted using a venous blood sample in all patients. TLC and NLR reports were evaluated for each patient. RT-PCR test was performed using nasopharyngeal and oropharyngeal secretion samples in all patients.

For CXR scoring, each lung was divided into 3 zones using 2 horizontal lines similar to the method used by Borgeshi et al. [11]. The upper line passes through the inferior wall of the aortic arch and the lower line at the level of the right inferior pulmonary vein. The upper zone is located above the upper line, the mid-zone between both lines, and the lower zone below the lower line [11]. The imaging features on the CXRs, which were used for scoring, are described in Table 1 and Figure 1. The score for individual radiographs was calculated. TLC and NLR were also calculated for each patient.

Table 1. Imaging features on CXR for scoring

S. No	Features on chest radiograph	Score
1.	Right lower-zone consolidation and/or ground-glass and/or reticular opacity	1
2.	Left lower-zone consolidation and/or ground-glass and/or reticular opacity	1
3.	Right middle zone consolidation and/or ground-glass and/or reticular opacity	1
4.	Left middle zone consolidation and/or ground-glass and/or reticular opacity	1
5.	Right upper zone consolidation and/or ground-glass and/or reticular opacity along with mid or lower lobe involvement	1
6.	Left upper zone consolidation and/or ground-glass and/or reticular opacity along with mid or lower lobe involvement	1
7.	Isolated peripheral lung involvement	1
8.	Absence of cavitating lesion, clustered nodules, and mass	1
9.	Absence of unilateral severe lung involvement	1
10.	Absence of pleural effusion, pneumothorax, and cardiomegaly	1
	Total score	10

CXR: chest X-ray

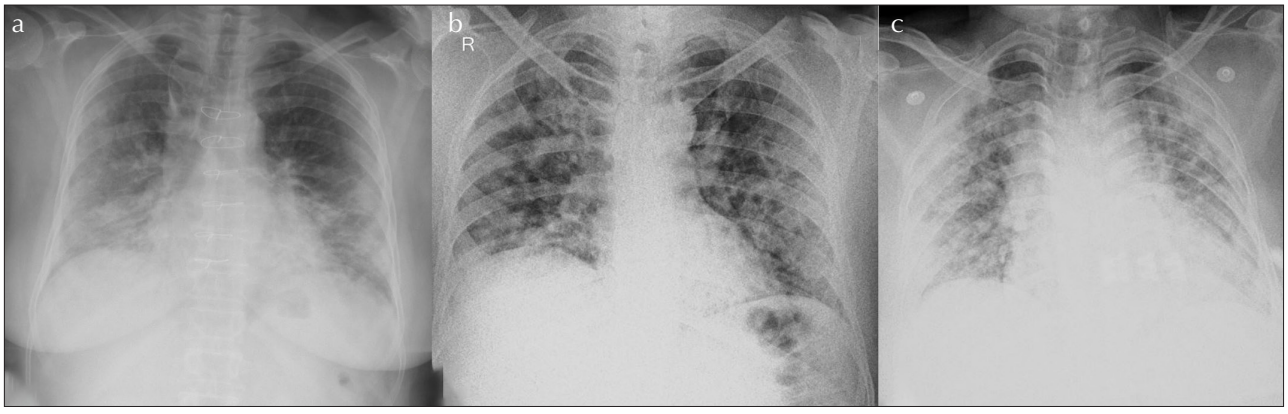

Figure 1. a-c. (a) Chest X-ray (CXR) showing consolidation with ground-glass opacity (GGO) involving bilateral middle and lower zones; total CXR score is 8. (b) CXR showing consolidation with reticulations involving peripheral as well as central lung field of bilateral lower, mid, and upper zones; total score is 9. (c) CXR showing consolidation with GGO of bilateral lower, mid, and upper zones involving peripheral lung field; the total score is 10

Statistical Analysis

Receiver operating characteristic (ROC) curves were used for the diagnostic evaluation of CXR scores, TLC, and NLR. Binary logistic regression was performed for all the mentioned parameters as they showed a significant correlation in univariate analysis. The analysis was performed using the Statistical Package for the Social Sciences, Version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). Sensitivity, specificity, and other diagnostic accuracy parameters were evaluated using the MedCalc easy to use statistical software (https://www.medcalc.org/calc/diagnostic_test.php).

RESULTS

A total of 235 patients with SARI were enrolled, of which 31 were excluded because of either non-availability or poor quality of CXR. Of the remaining 204 patients, 115 (56.4%) tested positive and 89 (43.6%) were reported negative for COVID-19 on the RT-PCR test. Of the 115 patients with COVID-19 infection, 78 (67.8%) were men and 37 (32.2%) were women. In the non-COVID-19 group, 56 (62.9%) were men and 33 (37.1%) were women. The patients who were positive for COVID-19 had an age range of 1-88 (mean, 51.8) years, and the non-COVID-19 group had an age range of 7-93 (mean, 51.3) years. The most common age group for both positive (43, 37.3%) and negative (28, 31.4%) patients was 41–60 years.

Among the COVID-19 group, the mean CXR score was increasing with increasing age with the highest mean of 6.5 in >80 years age group (Figure 2). In the non-COVID-19 group, the highest mean CXR score was 3.75, seen in 41–60 years age group, above which it started decreasing. It suggests that with age >60 years, it becomes easy to differentiate between patients with and without COVID-19 and infections using the CXR score.

The TLC and NLR reports were available for 190 patients; of them, 107 (56.3%) were positive for COVID-19 and 83 (43.7%) were negative. The average TLC count in the COVID-19 group was 9,190 cells/μL of blood and ranged from 330 to 92,590 cells/μL. The average TLC count in the non-COVID-19 group was 14,989 cells/μL of blood and ranged from 450 to 97,120 cells/μL.

Table 2. Chest X-ray and laboratory findings with probability of diagnosing COVID-19

X-ray and laboratory findings		COVID-19 Yes	COVID-19 No	p	Odds ratio (95% CI)
CXR score 4 or more	Yes	93 (80.9)	24 (27)	<0.001	OR=11.4 (5.92–22.14)
	No	22 (19.1)	65 (73)		
TLC less than 8,700	Yes	75(70.1)	21(25.3)	<0.001	OR=6.9 (3.63–13.19)
	No	32(29.9)	62(74.7)		
NLR less than 7	Yes	75 (70.1)	34 (41.0)	<0.001	OR=3.4 (1.85–6.16)
	No	32 (29.9)	49 (59.0)		
CXR score plus NLR present	Yes	57 (53.3)	8 (9.6)	<0.001	OR=10.6 (4.69–24.31)
	No	50 (46.7)	75 (90.4)		

COVID-19: coronavirus disease 2019; CXR: chest X-ray; TLC: total leukocyte count; NLR: neutrophil-to-lymphocyte ratio; CI: confidence interval; OR: odds ratio

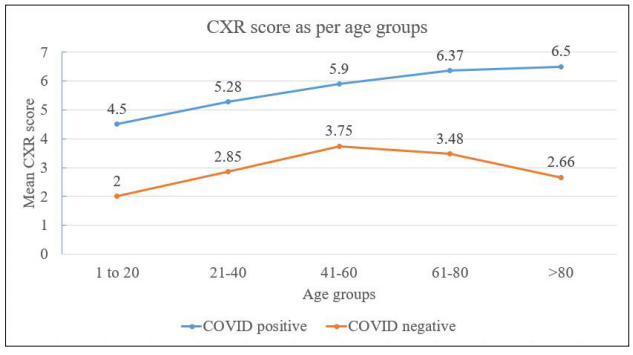

Figure 2. Chest X-ray score in relation to the various age groups of patients with coronavirus disease 2019 (COVID-19) and without COVID-19

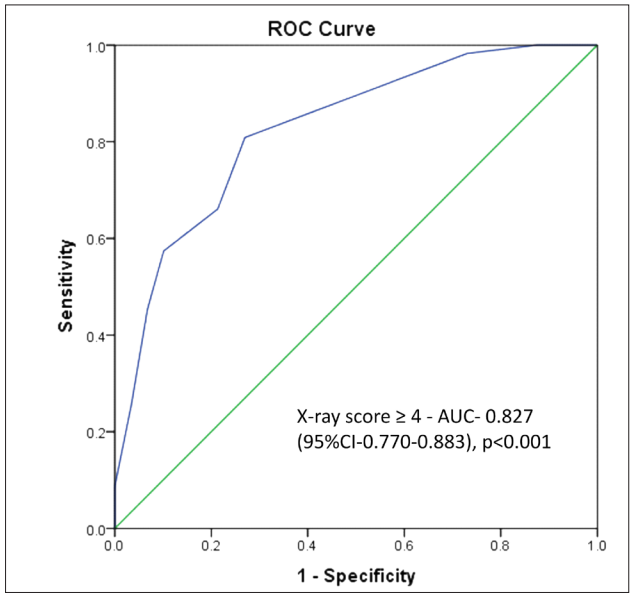

Figure 3. Receiver operating characteristic curves of chest X-ray score ≥4 showing an area under the curve of 0.827 (95% confidence interval, 0.770-0.883) and p<0.001 for diagnosing coronavirus disease 2019

The average NLR in the COVID-19 positive group was 5.89 (0.03-39.38) and in the non-COVID-19 group was 11.41 (0.23-40.74).

X-ray Features

In our study, the CXR was abnormal in 95 (82.6%) patients who were COVID-19 positive. The predominant pattern was

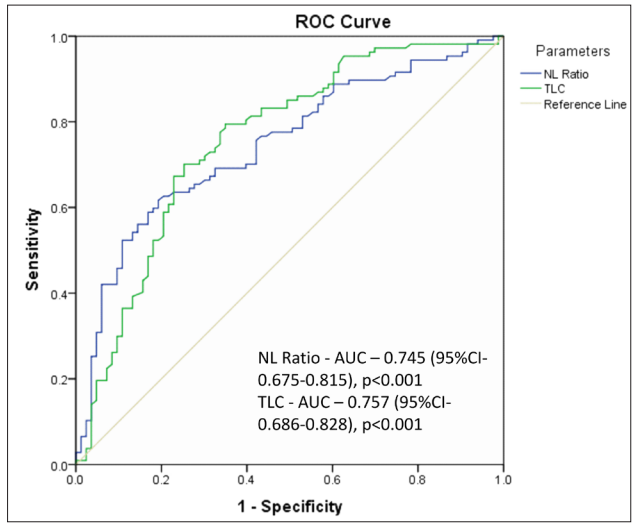

Figure 4. Receiver operating characteristic (ROC) curves of total leukocyte count showing an area under the curve (AUC) of 0.745 (95% confidence interval [CI], 0.675-0.815) with p<0.001 for diagnosing coronavirus disease 2019 (COVID-19). ROC of neutrophil-to-lymphocyte ratio showed an AUC of 0.757 (95% CI, 0.686–0.828) and p<0.001 for diagnosing COVID-19

consolidation with ground-glass opacity (GGO) (86, 78.9%), followed by reticular opacities (79, 72.5%). The abnormalities commonly involved bilateral lungs (71, 65.1%) with peripheral distribution and predominant lower-zone involvement. In a small number of patients who were COVID-19 positive, atypical features, such as cardiomegaly (7), pleural effusion (4), pneumothorax (1), clustered nodules (1), mass lesion (2), cavitation (1), old fibrotic changes (5), were also seen.

Among the patients negative with COVID-19 infection, an abnormal radiograph was seen in 64 (71.9%) patients with features, including reticular opacity, consolidation with GGO, cardiomegaly, pleural effusion, clustered nodules, mass lesion, old changes of fibrosis, and so on.

ROC curves of CXR, TLC, and NLR showed a significant area under the curve for diagnosing COVID-19. All 3 parameters had a statistically significant area under the curve (p<0.001) (Figure 3 and 4).

Table 3. Binary logistic regression (forward conditional) of chest X-ray and laboratory findings with probability of diagnostic accuracy

Parameters	Diagnostic odds ratio (95% CI)		p
Only X-ray findings present	10.7	5.42-21.02	<0.001
Only TLC <8,700	5.2	2.24-12.03	<0.001
Only NLR<7 present	2.5	1.05-5.87	0.038
CXR score, NLR, and TLC all present	13.1	5.84-29.58	<0.001

CXR: chest X-ray; TLC: total leukocyte count; NLR: neutrophil-to-lymphocyte ratio; CI: confidence interval

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive, and likelihood ratio negative for COVID-19 with chest x-ray and laboratory findings

Diagnostic criteria	(I) CXR score of ≥4 (N=204)	(II) TLC <8,700 (N=190)	(III) NLR <7 (N=190)	(IV) CXR score plus TLC (N=190)	(V) CXR score plus NLR (N=190)
Test positive/test negative in COVID-19	93/22	75/32	75/32	58/49	57/50
Test positive/test negative in non-COVID-19	24/65	21/62	34/49	6/77	8/75
Sensitivity	80.8% (72.48-87.61)	70.1% (60.48-78.56)	70.1% (60.48-78.56)	54.2% (44.30-63.88)	53.3% (43.38-62.98)
Specificity	73.0% (62.58-81.90)	74.7% (63.96-83.61)	59.0% (47.69-69.72)	92.8% (84.93-97.30)	90.4% (81.89-95.75)
PPV	10.79% (7.83-14.68)	9.30% (6.49-13.15)	3.7% (2.81-4.88)	44.5% (26.68-63.86)	29.8% (17.65-45.62)
NPV	98.9 % (98.45-99.29)	98.54% (98.01-98.93)	98.8% (98.42-99.20)	94.9% (93.86-95.92)	96.2% (95.32-96.90)
LR+	3 (2.11-4.27)	2.77 (1.88-4.09)	1.71 (1.28-2.28)	7.50 (3.40-16.52)	5.53 (2.79-10.93)
LR–	0.26 (0.18-0.39)	0.40 (0.29-0.55)	0.51 (0.36-0.71)	0.49 (0.40-0.61)	0.52 (0.42-0.64)
Diagnostic accuracy	73.3% (66.71-79.27)	74.5% (67.72-80.56)	59.3% (51.93-66.33)	89.1% (83.72-93.11)	87.7% (82.19-92.02)

COVID-19: coronavirus disease 2019; CXR: chest X-ray; TLC: total leukocyte count; NLR: neutrophil-to-lymphocyte ratio; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; LR+: likelihood ratio positive; LR-: likelihood ratio negative

In univariate analysis, the probability of accurately diagnosing COVID-19 infection is shown in Table 2. A CXR score of 4 or more, NLR of >7, and TLC of >8,700 had a significant association with COVID-19 infection.

During binary logistic regression, all the mentioned parameters showed significant relation with COVID-19 infection as in univariate analysis (Table 3). CXR score greater than 4 along with NLR less than 7 and TLC less than 8,700 had a significant association with diagnosing COVID-19, and combined use of all 3 increased the likelihood of a diagnosis of COVID-19 by 13 times.

Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive, and likelihood ratio negative for COVID-19 for individual as well combined parameters are shown in Table 4. The post-test odds ("rule in" disease) of the positive test for having the disease increased by 3, 2.77, and 1.71 times with the use of either criterion I (CXR) or II (TLC) or III (NLR), respectively, whereas the presence of criteria IV (CXR and TLC) and criteria V (CXR and NLR) increase the post-test odds by 7.5 and 5.53 times, respectively. Similarly, post-test odds of a negative test ("rule out" disease) for having the disease with criteria I, IV, and V decreased by 0.26, 0.49, and 0.52, respectively. The diagnostic accuracy with each criterion is shown in Table 4.

DISCUSSION

With the continuous increase in the number of COVID-19 cases, it becomes important for early isolation of the suspected patients to reduce cross-infection among healthcare workers as well as already admitted patients without COVID-19 infection. This combination of the CXR score along with TLC and NLR is useful in the prediction of COVID-19 before the availability of the RT-PCR test results.

In most of the published studies, the CXR sensitivity is variable with a range from 57% to 90% for the detection of COVID-19 [7, 12-14]. In our study, when we used the CXR score, the sensitivity was 80.8% (72.48%–87.61%) and specificity was 73.0% (62.58%–81.90%). The Italian Society of Radiology recommends CXR as the first imaging method for COVID-19 detection [13].

The various imaging features described on CXR according to the Fleischner Society's nomenclature are GGO, consolidation, and reticulation [7, 8, 15]. GGO alone is difficult to detect on CXR. GGO is usually seen in the presence of consolidation or reticulation. The most common pattern seen on the CXR is consolidation and GGO [7, 16]. In our study, the predominant pattern was consolidation with GGO (86, 78.9%) followed by reticular opacities (79, 72.5%) in patients with COVID-19 infection.

The abnormalities on CXR most commonly involve the lower lobes, peripherally and bilaterally [7, 13, 14, 16, 17]. Our study also showed bilateral lungs (71, 65.1%), peripheral distribution, and lower-zone involvement as the predominant distribution.

The various scoring systems according to chest radiographs have been proposed by various authors [8-11, 18-21]. The CXR score has been used to assess the outcome in patients admitted with COVID-19 and to predict the risk of in-hospital mortality in these patients [11, 19, 20]. The CXR score has also shown a significant positive correlation with C-reactive protein and lactate dehydrogenase levels and fever duration [21]. The score has also been used to assess the severity of lung involvement [8]. All these scoring systems were used to assess the clinical severity of patients infected with COVID-19 pneumonia. We propose a scoring system, which can be used to predict COVID-19 in patients admitted with clinical features of SARI.

In patients infected with COVID-19, usually the lymphocyte counts are decreased and NLR is elevated. Patients with severe disease have further lower levels of lymphocyte counts and elevated NLR [10]. In other causes of SARI-like bacterial community-acquired pneumonias, neutrophils are the main defense mechanism leading to neutrophilia and an increase in NLR. Owing to lymphopenia, the TLC count is low in patients with COVID-19 infection; whereas, neutrophilia leads to relatively high TLC in patients without COVID-19 infection.

Multiple studies have described the use of NLR in patients with COVID-19 [22-27]. Nalbant et al. [22] have concluded that patients with NLR ≥2.4 were 20.5 times more likely to have COVID-19 infection. Yang et al. [23] have found that NLR ≥3.3 correlated with the severity of the infection. Yan et al. [24] have found poor outcomes in critically ill patients with COVID-19 with an NLIR cutoff level of 11.75. Liu et al. [25, 26] have concluded that NLR is an independent risk factor for in-hospital mortality. An NLR of more than 11 can be used to identify high-risk patients with moderate to severe acute respiratory distress syndrome [27].

In our study, we concluded that the TLC <8,700 cells/μL is commonly seen in COVID-19 with a sensitivity and specificity of 70.1% and 74.7%, respectively. Similarly, an NLR <7 is commonly seen in COVID-19 with sensitivity and specificity of 70.1% and 59.0%, respectively. If we combine the CXR score with NLR, the specificity further increases to 90.4%, and if we combine CXR score with TLC, the specificity increases to 92.8%. The post-test odds ("rule in" disease) of the positive test for having the disease are increased by 5.53 and 7.5 times if we use a combination of CXR plus NLR and CXR plus TLC, respectively.

The limitation of our study was that it was a retrospective study with a small sample size. Moreover, the results of the RT-PCR test used for comparison were highly variable in sensitivity with a range of 30%-60%.

In conclusion, CXR, which can be performed at bedside using a portable X-ray machine, is a quick investigation to look for changes in the lung parenchyma although it is not as sensitive as a CT scan. The use of CXR-based scoring along with TLC and NLR in patients with clinical features of SARI can be useful in the prediction of COVID-19 quickly before the RT-PCR test results are available. Early prediction might help in better isolation of patients presenting with the clinical features of SARI.

Ethics Committee Approval: Ethics Committee approval for the study was obtained from the Institutional Ethical Committee of All India Institute of Medical Sciences, Jodhpur (AIIMS/IEC/2020/3135 dated 15/09/2020).

Informed Consent: Written informed consent was obtained from the all participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T. Ç., H.Ö., M. Y.; Design - T. Ç., H.Ö., M. Y.; Supervision - H.Ö., M. Y.; Resources - T. Ç., H.Ö., M.Y., A.C.İ., B.D., E.K., Ö.G., Ö.Ç., S.T., S.D.G., S.G.; Materials - T.Ç., H.Ö., M.Y., A.C.İ., B.D., E.K., Ö.G., Ö.Ç., S.T., S.D.G., S.G.; Data Collection and/or Processing - A.C.İ., B.D., E.K., Ö.G., Ö.Ç., S.T., S.D.G., S.G.; Analysis and/or Interpretation - T.Ç., H.Ö., M.Y., A.C.İ., B.D., E.K., Ö.G., Ö.Ç., S.T., S.D.G., S.G; Literature Review - T.Ç., H.Ö., M.Y., A.C.İ., B.D., E.K., Ö.G., Ö.Ç., S.T., S.D.G., S.G; Writing - T.Ç., H.Ö.; Critical Review - H.Ö., M.Y.

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