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SCREENING ROLE OF COMPLETE BLOOD CELL COUNT INDICES AND C REACTIVE PROTEIN IN PATIENTS WHO ARE SYMPTOMATIC FOR COVID-19

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ABSTRACT

INTRODUCTION: Diagnosis of COVID-19 is through polymerase chain reaction (PCR) or typical involvement of the lung by the virus in computed tomography (CT) scan. However, PCR is not always available, and also CT scan has a high dose of radiation. This study was performed to find the role of complete blood cell (CBC) indices and qualitative C-reactive protein (CRP) in screening of symptomatic patients.

MATERIAL AND METHODS: A diagnostic accuracy study was performed on symptomatic cases in Abadan. Four stepwise logistic regression models were designed that the outcomes were PCR positivity, CT scan positivity, PCR and CT scan positivity, and COVID-19 positivity (*i.e.*, PCR or CT scan positivity). Post-estimation receiver operating characteristics (ROC) curve analysis was performed to report the area under the curve (AUC).

RESULTS: A total of 104 patients were studied. The most accurate model was for the prediction of CT scan positivity (AUC = 0.874) in which the predictors were age [odds ratio (OR) =1.063] and CRP (OR = 2.661 for each plus of positivity). The second accurate model was for the prediction of COVID-19 positivity (AUC = 0.828) in which the predictors were white blood cell count (OR = 0.735 for every 1000 counts per μL) and neutrophil per lymphocyte ratio (OR = 1.248).

CONCLUSIONS: Higher levels of CRP are associated with and predictor of lung involvement in COVID-19 infection. CRP qualitative levels can be measured before a CT scan if there is no other indication for imaging.

KEY WORDS: COVID-19; C-reactive protein; CT scan; clinical reasoning; statistical modeling

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INTRODUCTION

In late December 2019, several cases of pneumonia with unknown symptoms were identified in Wuhan, China, which in February 12, 2020, the International Committee on Taxonomy of Viruses called it acute respiratory syndrome coronavirus 2 (SARS--CoV-2), and on the same date the disease was named as coronavirus disease 2019 (COVID-19) [1, 2].

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This virus is a new strain of β-coronaviruses associated with severe acute respiratory syndrome (SARS) in 2002–2003 and the Middle East respiratory syndrome (MERS) in 2012–2014 [3]. The virus has a longer incubation period and less pathogenicity than SARS and MERS, but its prevalence is much higher. The disease spread rapidly to other parts of China and other countries, so who announced a pandemic [3]. The virus is a common virus between humans and animals and has not been previously reported in humans [2] and is rapidly transmitted from human to human by respiration [2, 4].

Its clinical symptoms are very diverse and include fever, dry cough, shortness of breath, fatigue, and in some patients nasal congestion, runny nose, sore throat, diarrhea, loss of sense of smell and taste, and in some severe cases lead to acute renal failure, acute respiratory syndrome and eventually death [2]. In severe cases, patients have shortness of breath or hypoxia, which usually begins one week after the onset of the disease and progresses rapidly to acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunction, which is also very difficult to improve coagulation function [2, 5].

Infection with the virus has been observed at all ages, as has been observed in children and infants born to infected mothers, in whom children are usually prone to upper respiratory tract infections [4]. However, in the elderly and patients with underlying diseases, complications are also very severe. Also, due to the similarity of the early symptoms of this disease with the flu, its initial diagnosis is not easy, especially in spring and winter [5]. Certainly, cytokine storm and virus escape from the cellular immune system play a key role in the progression and severity of the disease [6].

The definitive treatment for severe cases is not available and different treatment models, as well as its diagnostic methods, are still in the research stages [7]. Therefore, early diagnosis and identification of patients can be of great help in improving and preventing the disease from entering the respiratory phase and reducing mortality, improving the speed of treatment, and also preventing the spread of the disease [1].

Among the diagnostic methods real-time reverse-transcriptase polymerase chain (rRT-PCR) is used as the gold standard to identify and diagnose the disease [8, 9]. However, due to the limitations of rRT-PCR method including sampling, sample transfer, being times-consuming, lack of viral materials in some samples, and lack of diagnostic kits in some centers, other paraclinical tests such as total white blood cell count (WBC), lymphocyte count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP) level, D-Dimer, Fibrinogen, lactate dehydrogenase (LDH), procalcitonin, erythrocyte sedimentation rate (ESR) and computed tomographic (CT) scan are used in the diagnosis and follow-up of the disease [3, 9, 10].

Practically, the diagnosis of COVID-19 is through rRT-PCR or typical involvement of lung by the virus in CT scan. However, rRT-PCR is not always available, and also CT scan has a high dose of radiation. This study was performed to find the role of complete blood cell (CBC) indices and qualitative C reactive protein (CRP) in screening of symptomatic patients to overcome the limitations of rRT-PCR and CT scan. Because of this limitation that our investigated laboratory indices were not specific for COVID-19, the symptomatic patients were selected in order to increase pretest probability to control this limitation.

MATERIAL AND METHODS

A diagnostic accuracy study was conducted on the symptomatic cases of those who were suspected for COVID-19. The samples were collected from 17th Shahrivar Hospital of Abadan, Khuzestan, Iran during the first half of 2021 through convenient sampling. The patients had symptoms such as fever, cough, shortness of breath, and so on. The patients were visited by a physician and then referred for CT scan and rRT-PCR. The inclusion criteria were being symptomatic, lack of underlying disease, and lack of a previous confirmation of COVID-19. This study was approved by the ethics committee of Lorestan University of Medical Sciences with registration number IR.LUMS.REC.1400.224. Informed consent was obtained from the participated patients.

The studied variables were age, gender, weight blood cell (WBC) count, platelet (PLT) count, neutrophil per lymphocyte ratio (NLR), CRP (qualitative from negative to 4+), CT scan positivity, PCR positivity, CT scan or PCR positivity (considered as COVID-19 positivity), and CT scan and PCR positivity. CT scan positivity was defined as a typical pattern of lung involvement by COVID-19 confirmed by a radiologist regardless of PCR positivity.

Stepwise logistic regression was used to predict each of the following outcomes at significance level

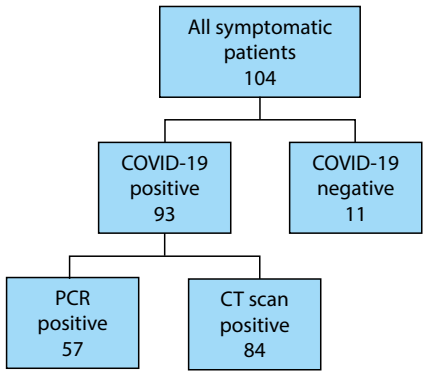

FIGURE 1. Flowchart of the patients based on PCR and CT scan positivity

of 0.1; 1) PCR positivity among the COVID-19 positive patient, 2) CT scan positivity among the COVID-19 positive patient, 3) PCR and CT scan positivity among the COVID-19 positive patient and 4) COVID-19 positivity among the suspected patients. Post-estimation receiver operating characteristics (ROC) curve analysis was performed to report the area under the curve (AUC) for each model. All the statistical analyses were performed in Stata 14 software (StataCrorp LLC, US).

RESULTS

A total of 104 patients were studied. Among them, 93 patients were COVID-19 positive that 57 patients were PCR positive, and 84 patients were CT scan positive (Fig. 1). Among the COVID-19 patients, in 48 patients, both PCR and CT scans were positive. The summary of the descriptive statistics of the variables is shown (Tab. 1).

The mentioned four models were designed with stepwise logistic regression. The most accurate model was for the prediction of CT scan

Table 1. Point estimation and dispersion of the variables

Variable	Frequency [%]/Mean [SD]	95% CI
Outcomes		
PCR positive	57 (54.81%)	45.08–64.53 (%)
CT scan positive	84 (80.77%)	73.07–88.4.7 (%)
Negative for COVID-19	11 (10.58%)	4.57–16.59 (%)
PCR or CT scan positive	93 (89.42%)	83.41–95.43 (%)
PCR and CT scan positive	48 (46.15%)	36.41–55.90 (%)
Total	104 (100%)	
Independent variables		
Gender [male]	58 (55.7%)	46.06–65.47 (%)
Age [year]	55.62 (19.34)	51.85–59.38
WBC [× 1000]	7.46 (3.35)	6.81–8.11
Lymphocyte ratio [%]	22.51 (12.05)	20.16–24.85
Neutrophil ratio [%]	68.31 (14.85)	65.43–71.20
NLR [ratio]	4.68 (4.19)	3.87–5.50
PLT [× 1000]	204.41 (88.55)	187.19–221.63
CRP [0 to 4+]	2.11 (1.19), Median: 3, IQR: 1–3	1.87–2.34
0	17 (16.35%)	
1+	13 (12.50%)	
2+	20 (19.23%)	
3+	50 (48.08%)	
4+	4 (3.85%)	
Total	104 (100%)	

COVID-19 — coronavirus disease 2019; CRP — C-reactive protein; CT — computed tomography; IQR — interquartile range; NLR — neutrophil to lymphocyte ratio; PCR — polymerase chain reaction; PLT — platelet; SD — standard deviation; WBC — white blood cell

Table 2. Stepwise logistic regression modeling for prediction of the outcomes at a significance level of 0.1 for covariate removal

Model		OR	p value	Pseudo *R* square	AIC	BIC	AUC
Outcome	Covariates						
PCR positive	Age [year]	0.977	0.070	0.055	123.369	130.967	0.643
	PLT [× 1000]	0.994	0.030				
	Constant	21.173[1]	0.006				
CT scan positive	Age [year]	1.063	0.026	0.287	48.155	55.753	0.874
	CRP [0 to 4+]	2.661	0.006				
	Constant	0.101	0.095				
PCR and CT scan positive	PLT [× 1000]	0.995	0.072	0.028	129.219	134.284	0.583
	Constant	2.806	0.071				
COVID-19 positive[2]	WBC [× 1000]	0.735	0.003	0.152	65.551	73.484	0.828
	NLR [ratio]	1.248	0.085				
	Constant	46.106	< 0.001				

1) All the constant amounts are in exponential form. 2) For this outcome, all the 104 patients were analyzed while for the other outcomes, only the 93 COVID-19 positive patients were selected; AIC — Akaike information criterion; AUC — area under the curve; BIC — Bayesian information criterion; COVID-19 — coronavirus disease 2019; CRP — C-reactive protein; CT — computed tomography; NLR — neutrophil to lymphocyte ratio; OR — odds ratio; PCR — polymerase chain reaction; PLT — platelet; WBC — white blood cell

positivity among the COVID-19 positive patient (AUC = 0.874) in which the predictors were age [odds ratio (OR) = 1.063] and CRP (OR = 2.661 for each plus of positivity). The second accurate model was for the prediction of COVID-19 positivity among all patients (AUC = 0.828) in which the predictors were white blood cell count (OR = 0.735 for every 1000 counts per μL) and neutrophil per lymphocyte ratio (OR = 1.248). The results of the two other models are also shown (Tab. 2).

As CRP seemed as an available and easy-to-use predictor according to the above findings, another modeling was performed for the prediction of CT scan positivity among the confirmed patients of COVID-19 for clinical use (this model was not multivariable). Briefly, CRP 3+ and 4+ were specific for lung involvement in CT scans while negative CRP was associated with a lack of lung involvement in CT scans. In addition, CRP 2+ was strongly suggestive of the involvement while CRP 1+ was not specific for the involvement. The details of this model are shown (Fig. 2).

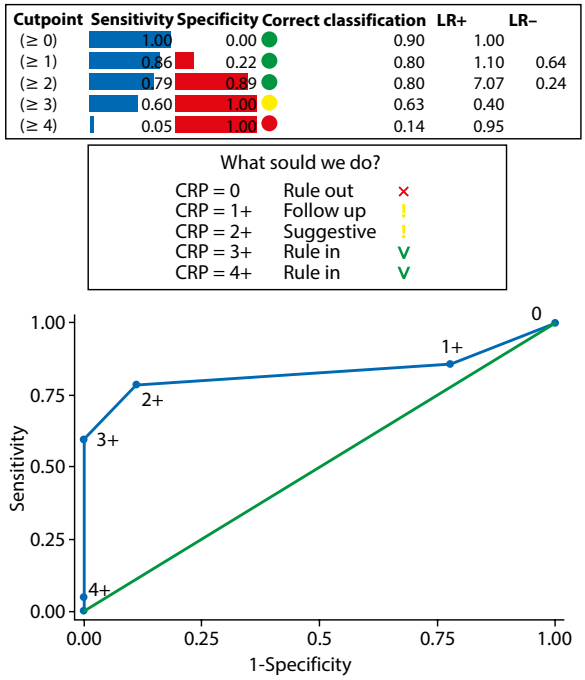

FIGURE 2. Diagnostic accuracy of CRP for CT scan positivity (lung involvement) in confirmed cases of COVID-19 by PCR or CT scan (n = 93). The results of this model should not be generalized to a general population without similar pretest probability; LR — likelihood ratio

DISCUSSION

The present study was designed to show how we can overcome the limitations rRT-PCR and CT scans using available blood tests in a small center. Briefly, lower PLT was associated with PCR positivity, higher ages and higher CRP were associated with CT scan positivity, and lower WBC count along with higher NLR was associated with COVID-19 positivity. The

most accurate model was for prediction of CT scan positivity based on age and CRP. In fact, increased CRP indicated higher inflammatory activity of lung which in turn might be seen as lung involvement in CT scan.

Wang et al. [7] examined CRP levels and CT scan in 27 patients with COVID-19 (including 11 mild, 12 moderate, 2 severe, and 2 critical) in Guizhou, China, and found an increase in CRP levels that was strongly associated with the severity of lung lesions.

Zhang et al. [1] in Hunan, China, by examining 177 patients (99 men and 78 women) with a definitive diagnosis of COVID-19 and dividing them into mild groups with 153 patients and severe patients with 24 patients, found that the laboratory parameters, albumin, total bilirubin, WBC, neutrophil count, neutrophil ratio, D-dimer, aspartate transaminase (AST), alanine transaminase (ALT), LDH, blood urea nitrogen (BUN), creatine kinase (CK), CRP, and CRP to albumin ratio (CAR), in the severe group had a significant increase. lymphocyte count and lymphocyte ratio tests have a significant decrease compared with the mild group, and they showed that high NLR could be a sign of disease progression to a serious condition and also NLR could be used as a very specific and sensitive indicator to predict the severity of the disease.

Wang et al. [11] examined the changes in lymphocyte subtypes in COVID-19 patients by examining 60 patients at Zhongnan Hospital in China and 245 healthy individuals. They showed that the total lymphocyte count in COVID-19 patients had decreased. In severe cases, the lymphocyte count had decreased more than in mild cases, and changes in peripheral lymphocyte subsets were associated with clinical features and treatment efficacy, and TCD8+ cells tend to independently predict the severity and effectiveness of COVID-19 treatment.

Tan et al. [5] with the aim of comparing laboratory markers between COVID-19 and influenza in 27 patients with COVID-19 including 6 severe and 21 mild and 75 patients with influenza A or B without a history of previous underlying disease and pregnancy showed that the increase in CRP, ESR, and neutrophil to lymphocyte ratio (NLR) was positively correlated with disease severity based on CT scan classification and the number of lymphocytes was negatively correlated with disease severity and CRP was increased in the early stages and was directly related to the prognosis of disease severity.

Wang et al. [12] in order to describe the clinical characteristics of patients and analyze related factors and find markers to predict the severity of the disease, studied 209 patients with a definitive diagnosis of COVID-19 and found that CRP could be a valuable marker for predicting the severity of disease and the possibility of needing to be admitted to the intensive care unit.

Mardani et al. [13] with the aim of increasing the accuracy of laboratory parameters in predicting positive PCR cases in Behpooyan Hospital in Tehran, examined 200 patients, 70 of whom had positive PCR, and found that increasing LDH, CRP, AST, and neutrophils could be used in the prognosis of PCR test results and help diagnose patients.

Poggiali et al. [6] in Italy examined 123 patients (91 men and 32 women) to confirm the use of routine laboratory tests, including a set of tissue damage and inflammatory tests for the prognosis of severe respiratory cases, especially in small emergencies where CT scan is not available. They found that LDH and CRP could play an important role in predicting respiratory disorders in COVID-19 patients and that these tests should be used in the initial identification of patients as well as the evaluation of acute respiratory cases and the improvement of treatment methods [6].

Liu et al. [14] with the aim of identifying specific serological methods for the diagnosis and assisting in the treatment of patients with coronavirus, studied 140 patients with COVID-19 (107 mild and 33 severe) and found that serum levels of interleukin (IL)-6 and CRP could be effective in diagnosing and predicting the severity of the disease.

Caruso et al. [10] to compare chest CT scan and rRT-PCR methods in the diagnosis of COVID-19 examined 158 patients with COVID-19 (83 men and 75 women) in Italy. Patients presented with fever, cough, shortness of breath, lymphopenia and increased CRP titers and LDH. They found that chest CT scan was more sensitive (97%) but less specific (56%) compared with rRT-PCR.

In order to find the relationship between hematological parameters and disease severity, Fu et al. [15] examined 75 patients for NLR, D-Dimer, and Fibrinogen in three groups of mild, moderate and severe diseases in China. They found that these parameters had different results in different groups and therefore NLR and D-Dimer could be used in the diagnosis and prognosis of moderate and mild cases conversion to severe cases.

Many of the previously published works supported our findings. The limitation of this study was

being a single center with a low sample size. However, we showed how we could validate our routine evaluations for clinical use in our own centers. In addition, the limitation of routine laboratory indices are their low diagnostic accuracies. Considering these indices within a diagnostic algorithm starting from the samples that have high pretest probability, helps clinician to overcome this limitation. Another limitation was that such indices could not show the causations or explanation of mechanisms. For instance, increased CRP level was supposed to be associated with increased inflammatory activity; but we observed CT scan positivity instead of direct observation of inflammation.

CONCLUSIONS

Higher levels of CRP are associated with and predictor of lung involvement in COVID-19 infection. In addition, leukopenia along with lymphopenia can show COVID-19 infection. CRP qualitative levels can be measured as a simple and widely available method before CT scan if there is no other indication for imaging. The approach of this study design may be suitable to be used in future pandemics of other diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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