



# The Correlation between Lymphopenia and CT Findings in Suspected COVID-19 Cases: A Prospective Study

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## Abstract

**Objectives:** The predictive utility of lymphopenia in suspected COVID-19 cases is still poorly characterized. The primary objective of the present study was to correlate the presence of lymphopenia with CT chest at the initial triage diagnosis of COVID-19 in a sample of Egyptian patients. **Methods:** We conducted a single-center, observational, prospective study that recruited patients who presented with a cardiac complaint or routine cardiac follow-up and were suspected of COVID-19. Lymphopenia was defined as lymphocyte count  $\leq 1100$  cells/ $\mu\text{L}$ . **Results:** A total of 110 patients were included in this study. Lymphopenia was detected in 21.0% of the study cohort. Overall, 60.9% of the patients had positive CT findings. The diagnostic accuracy of lymphopenia based on CT chest diagnosis did not provide significantly accurate diagnosis of COVID-19 ( $p = 0.343$ ) with sensitivity of 20.90% (11.92% - 32.57%) and specificity of 85.71% (69.74% - 95.19%). Regarding the diagnostic accuracy of CT-chest compared with PCR results as a reference standard, sensitivity raised to 68.75% (53.75% - 81.34%) and specificity of 66.67% (9.43% to 99.16%). **Conclusion:** In patients presenting to the diagnostic triage center with symptoms suggestive of COVID-19 infection, lymphopenia is an unreliable predictor of infection. Only in predicting suspected patients with positive CT findings did lymphopenia have a sensitivity of 20%. As a result, the presence of lymphopenia in suspected patients presenting to diagnostic triage centers should not be considered a reliable diagnostic aid.

## Subject Areas

Cardiology

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## Keywords

COVID-19, SARS-CoV-2, Lymphopenia, CT Chest, Diagnosis

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## 1. Introduction

The COVID-19 pandemic, which has claimed nearly four and a half million lives so far [1], poses a significant challenge to healthcare services and societies around the world. SARS-CoV-2, the newest member of the coronavirus family, is the causative agent of COVID-19, which is transmitted by respiratory droplets [2]. While the majority of patients are asymptomatic, a subset of patients with COVID-19 is prone to a variety of severe complications, including acute respiratory distress, respiratory failure, microthrombi, septic shock, and, eventually, death [3] [4]. The virulence mechanism of SARS-CoV-2 is multifactorial and involves ACE2 expression within alveolar cells, pulmonary edema and proteinaceous exudates, and a “cytokine storm” [3] [4]. A significant contributor to the difficulty of adequately managing the outbreak is the sheer volume of cases, which threatens to overwhelm the available resources (such as ventilators and ICU beds) of healthcare facilities [5].

The confirmed diagnosis of COVID-19 is based mainly on the results of the polymerase chain reaction (PCR) test. Nonetheless, PCR-based diagnosis faces many challenges related to accuracy and inappropriate methods for sample collection and handling [6]. Chest computed tomographic (CT) is a rapid imaging modality for rapid assessment of suspected COVID-19 cases in triage, with acceptable sensitivity; on chest CT examination, COVID-19 cases usually exhibit ground-glass opacity; consolidation; or both [3]. Nonetheless, the use of chest CT is limited by low specificity, inaccuracy in mild and asymptomatic cases, and radiation-associated hazards [7] [8]. Recently, several laboratory tests were proposed to aid in the diagnosis of suspected COVID-19 cases at triage, in combination with chest CT findings. Of them, lymphopenia was proposed to play a predictive role in suspected COVID-19 cases when combined with clinical and imaging findings [9]. A previous report showed notable exhaustion of antiviral lymphocytes is reported in COVID-19 patients [10].

However, the predictive value of lymphopenia in suspected COVID-19 cases is still unknown. The primary goal of this study was to correlate the presence of lymphopenia with CT chest at the initial triage diagnosis of COVID-19 in an Egyptian patient population.

## 2. Methods

We followed the STROBE guidelines during the preparation of this report [11]. The present study runs in concordance with the principles of the declaration of Helsinki and applicable local regulatory laws. The local IRB committee of the National Heart Institute approved the study’s protocol. Written informed con-

sent was obtained from every eligible patient, or their relatives, before the study's enrollment.

## 2.1. Study Design and Setting

We conducted a single-center, observational, prospective study in which we recruited patients who presented to the National Heart Institute in Giza, Egypt, with cardiac complaints or routine cardiac follow-up and were suspected of having COVID-19 between July 1<sup>st</sup>, 2020, and September 30<sup>th</sup>, 2020.

Adults patients ( $\geq 18$  years old) of both sexes, who were admitted to the emergency department or clinics of the National Heart Institute with cardiac complaints or routine cardiac follow-up and were suspected of COVID-19 were included. Only patients with no history of recent PCR-confirmed COVID-19 were included. All subjects were suspected according to the principles of diagnosis provided by the World Health Organization (WHO) [1]. We excluded patients with chronic chest problems that interfere with definitive evaluation of CT scan; patients presenting with critical cardiac conditions that would not allow CT imaging; patients with hematologic disease; and patients with impaired kidney or liver functions. Pregnant or lactating women were excluded as well. Patients were recruited consecutively using a non-probability sampling technique.

## 2.2. Data Collection and Study Outcomes

A trained team of physicians collected the data from patients with suspected symptoms and was eligible for inclusion in our study. Eligible patients were assessed for age, smoking, and chronic illness (encompassing dyslipidemia, hypertension, diabetes, and chronic obstructive pulmonary disease). Data regarding symptomatology including fever, sore throat, cough, shortness of breath, malaise, bony aches, headache, loss of smell and taste, nausea and vomiting, running nose, diarrhea, and palpitations were collected. Then, all eligible patients were subjected to a complete blood count (CBC) examination, chest CT scan, and PCR test. Patients were followed-up until hospitalization or discharge.

The CBC examination was done using a fully automated cell counter (sysmix, Germany). The PCR was performed using the CE-IVD kit GeneFinder<sup>TM</sup> COVID-19 Plus RealAmp Kit (ELITE InGenius<sup>®</sup>). The chest CT scan was done using Canon Philips Brilliance 64 64 slices by a consultant radiologist. CT images were classified according to the CO-RADS classification, which was recently created by the Dutch Association of Radiologists (NVVR) [12]. A CO-RADS score of 1 - 3 was classified as non-COVID-19, whereas a CO-RADS score of 4 or 5 was classified as COVID-19 positive. A standardized reporting format was developed.

The primary outcome of the present study is the association between the presence of lymphopenia with CT chest at initial triage diagnosis of COVID-19 in a sample of Egyptian patients. Lymphopenia was defined as lymphocyte count  $\leq 1100$  cells/ $\mu\text{L}$ . The secondary outcomes were the association between the

presence of lymphopenia and the severity of chest CT findings; the relation between cardiovascular risk factors and COVID-19; and the diagnostic accuracy of lymphopenia and chest CT findings in the detection of PCR-confirmed COVID-19.

### 2.3. Statistical Methods

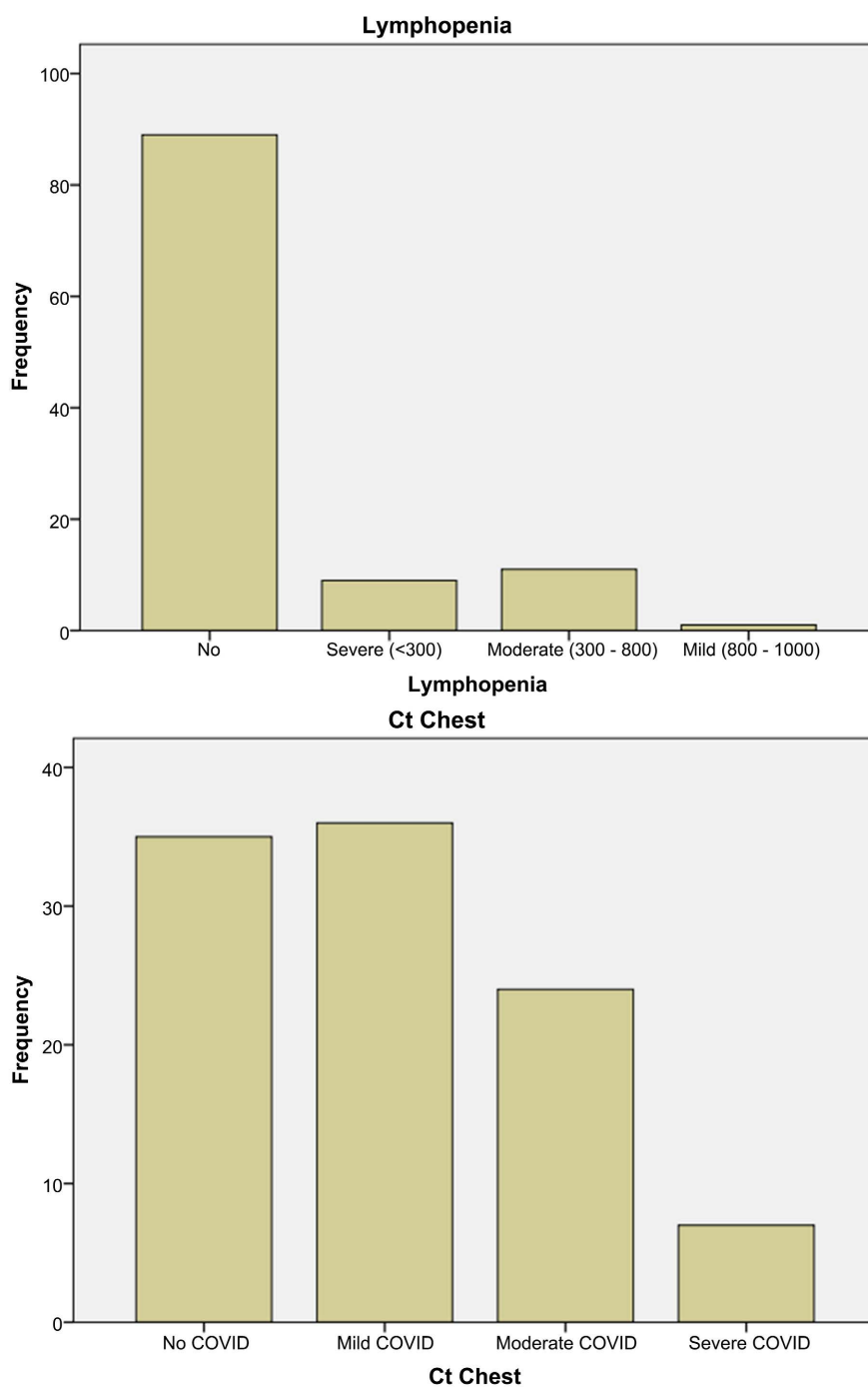
Values were presented as means + SD or as numbers and proportions, as appropriate. The association between lymphopenia, NLR, and COVID-19 cases diagnosed by chest CT was evaluated using the McNemar test. The difference between patients infected with COVID-19 and non-infected individuals was evaluated using the Chi-square test or Fisher's exact test for qualitative variables. Continuous variables were assessed using the Unpaired t-test. Variables with P values < 0.1 in univariate analysis were introduced in a logistic regression model to detect independent predictors of COVID-19 as indicated by chest CT. All tests were bilateral and a P value of 5% was the limit of statistical significance. Analysis was performed by statistical package software IBM-SPSS version 21.

### 3. Results

A total of 110 patients were included in this study. The average age was 50.7 years (Range, 21 - 83 years), and 59.5% were females. The most reported symptoms were fever (71.2%), cough (42.3%), malaise and bony pains (40.5%), shortness of breath (36.0%), and loss of smell and taste (29.7%). 25% of the patients had a history of cardiac disease, 18% were diabetic, 17.1% were hypertensive, 6.3% had dyslipidemia, and 5.4% were smokers. For the study cohort, the total leukocytic count was considered high in 14.4% of the patients, and low in 19.8% of the patients. However, the rest of the patients (64.9%) were within the normal range. Most of the patients were having lymphocytic count > 1. Also, neutrophils were more than 11 in 7.2% of the patients and 4 to 11 in 45.0% of the patients. Lymphopenia was detected in 21.0% of the study cohort. PCR was performed for only 53 patients and 50 patients were positive and the rest were negative (**Table 1**).

After doing the CT chest, the patients were categorized into no, mild, moderate, and severe COVID-19 infection. Only 6.6% were considered a severe infection, however, 32.7% of the patients were mild infections, and 21.6% were moderate infections (**Figure 1**). Overall, 60.9% of the patients had positive CT findings. Patients with positive CT findings were significantly older ( $p = 0.036$ ), had a higher incidence of dyspnea ( $p = 0.009$ ), and higher prevalence of cardiac risk factors ( $p < 0.001$ ) than patients with negative findings (**Table 1**). Further univariate logistic regression revealed that cardiac risk factor was a significant predictor (OR 18.977, 95% CI [2.44 - 147.46],  $p = 0.005$ ) of the positive CT-chest finding during COVID-19 diagnosis.

The diagnostic accuracy of lymphopenia based on CT chest diagnosis did not provide significantly accurate diagnosis of COVID-19 ( $p = 0.343$ ) with sensitivity



**Figure 1.** The distribution of lymphopenia and CT findings.

**Table 1.** Correlation between CT findings, symptomatology, and risk factors of the study cohort.

Parameters	All (n= 110)	CT Chest findings (n = 102)		P value
		Yes (n = 67)	No (n= 35)	
Age, mean (SD)	50.79 ( $\pm$ 13.38)	53.58 ( $\pm$ 13.6)	47.83 ( $\pm$ 11.61)	<b>0.036</b>
Male, n (%)	44 (39.6%)	28 (41.8%)	12 (34.3%)	0.461

## Continued

	Clinical Presentation			
Fever, <i>n</i> (%)	79 (71.2%)	50 (74.6%)	24 (68.6%)	0.515
Sore throat, <i>n</i> (%)	14 (12.6%)	8 (11.9%)	6 (17.1%)	0.469
Cough, <i>n</i> (%)	47 (42.3%)	31 (46.3%)	14 (40.0%)	0.545
Shortness of breath, <i>n</i> (%)	40 (36.0%)	31 (46.3%)	7 (20%)	<b>0.009</b>
Malaise and bony pains, <i>n</i> (%)	45 (40.5%)	29 (43.3%)	12 (34.3%)	0.379
Headache, <i>n</i> (%)	17 (15.3%)	10 (14.9%)	5 (14.3%)	0.931
Loss of smell and taste, <i>n</i> (%)	33 (29.7%)	19 (28.4%)	13 (37.1%)	0.364
Nausea and vomiting, <i>n</i> (%)	13 (11.7%)	11 (16.4%)	1 (2.9%)	0.054
Running nose, <i>n</i> (%)	8 (7.2%)	3 (4.5%)	4 (11.4%)	0.228
Diarrhea, <i>n</i> (%)	21 (18.9%)	14 (20.9%)	6 (17.1%)	0.650
Palpitation, <i>n</i> (%)	12 (10.8%)	8 (11.9%)	4 (11.4%)	0.999
	Comorbidities			
Obesity, <i>n</i> (%)	7 (6.3%)	5 (7.5%)	1 (2.9%)	0.661
Smoking, <i>n</i> (%)	6 (5.4%)	4 (6.0%)	2 (5.7%)	0.999
Hypertension, <i>n</i> (%)	19 (17.1%)	15 (22.4%)	3 (8.6%)	0.082
Diabetic, <i>n</i> (%)	20 (18.0%)	16 (23.9%)	3 (8.6%)	0.059
Cardiac risk factor, <i>n</i> (%)	28 (25.2%)	24 (35.8%)	1 (2.9%)	<b>&lt;0.001</b>
Dyslipidemia, <i>n</i> (%)	7 (6.3%)	5 (7.5%)	2 (5.7%)	0.999
COPD, <i>n</i> (%)	6 (5.4%)	6 (9.0%)	0 (0.0%)	0.091

of 20.90% (11.92% - 32.57%) and specificity of 85.71% (69.74% - 95.19%) (Figure 2). Regarding the diagnostic accuracy of CT-chest compared with PCR results as reference standard, sensitivity raised to 68.75% (53.75% - 81.34%) and specificity of 66.67% (9.43% to 99.16%) (Table 2).

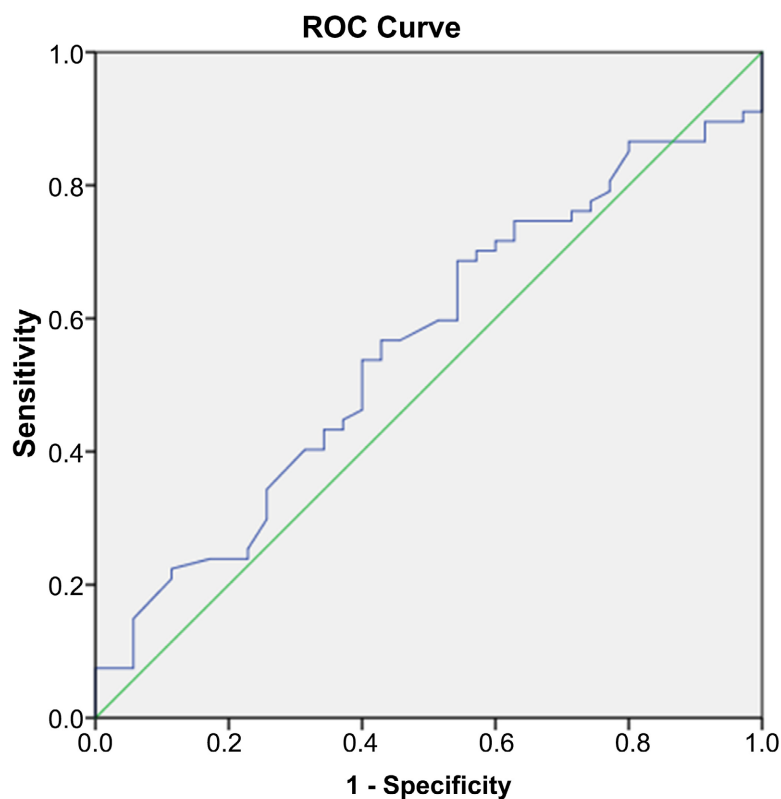
#### 4. Discussion

The current study aimed to correlate lymphopenia with CT chest at initial COVID-19 triage diagnosis in a group of Egyptian patients. We discovered no link between chest CT and lymphopenia in suspected COVID-19 cases. The ROC curve showed that the diagnostic yield of lymphopenia was too weak to detect COVID-19 infection in suspected patients. On the other hand, the multivariate analysis showed that age, COPD, diabetes, hypertension, and history of cardiac disease were tested as predictors for COVID-19. Only a history of cardiac disease was discovered to be a significant predictor. According to the findings, being a cardiac patient increases your chances of contracting the COVID-19 virus by 18.98 times.

A positive PCR test is the only way to confirm the presence of COVID-19 infection. However, PCR tests are not widely available at the initial diagnostic triage center. As a result, current Egyptian guidelines recommend that suspected

**Table 2.** Diagnostic accuracy data of lymphopenia and CT diagnosis for COVID-19 diagnosis.

Diagnostic procedure	Sensitivity (95% CI)	Specificity (95% CI)
Lymphopenia (Based on CT diagnosis as reference standard)	20.90% (11.92% - 32.57%)	85.71% (69.74% - 95.19%)
CT diagnosis (Based on PCR confirmation as a reference standard)	68.75% (53.75% - 81.34%)	66.67% (9.43% - 99.16%)

**Figure 2.** ROC curve for diagnostic accuracy of lymphopenia based on CT chest diagnosis.

patients be referred for a chest CT. Nonetheless, the use of chest CT is constrained by low specificity, inaccuracy in mild and asymptomatic cases, and radiation-related risks [7] [8]. As a result, several authors have attempted to identify biomarkers that could only aid in referring patients with high susceptibility, to lower the associated costs and radiation hazards of chest CT. When combined with clinical and imaging findings, lymphopenia has been proposed to play a predictive role in suspected COVID-19 cases [9]. Previous research has linked beta-CoV infections to a significant decrease in peripheral T lymphocytes, with subsequent lymphocyte sequestration [13]. The involvement of ACE2 receptors in the pathogenesis of COVID-19 may also induce interleukin-induced lymphocyte damage [14]. However, all of these mechanisms typically occur as COVID-19 progresses to a more severe stage, whereas patients in the early stage

do not experience a significant release of T lymphocytes and pro-inflammatory cytokines [15]. In the present study, we found no relation between chest CT and the presence of lymphopenia in suspected COVID-19 cases. The ROC curve showed that the diagnostic yield of lymphopenia was too weak to detect COVID-19 infection in suspected patients. Such findings run in parallel with recent reports demonstrating the poor performance of lymphopenia in the diagnosis of COVID-19 [16].

COVID-19 appears to spread differently depending on geographical area and patient characteristics. Most African countries reported fewer confirmed COVID-19 cases than the rest of the world, which is thought to be due to the high temperature and genetic characteristics of Africans [17]. In addition, severe forms of the disease affect the elderly population and patients with comorbidities or poor immunity [3] [18]. Males were reported to be at higher risk of COVID-19 as well [19]. In addition, the risk of symptomatic COVID-19 was reported to be higher in patients with comorbidities and immunocompromised conditions such as diabetes, hypertension, and cancer. Moreover, patients' characteristics are strong predictors of disease outcomes. Elderly, hypertensive, and/or diabetic patients, alongside patients with malignancy, were reported to have longer disease duration, higher symptoms severity, and higher risk of mechanical ventilation than the general population [20]. Cytokine storm and mortality are higher in this type of population as well [17].

There are several limitations to the current study. For starters, the sample size was small. The sample was drawn from a single-center, which may affect its representation of the entire Egyptian population who presented to the initial triage center during the acute phase of the Covid19 outbreak for clinical cardiac reasons. Second, all confirmed COVID-19 cases were transferred to designated hospitals per Egyptian Ministry of Health guidelines. As a result, we were unable to calculate the case-fatality ratio or predictors of mortality. The low number of patients who underwent PCR reduced confidence in the calculated diagnostic accuracy of CT image findings.

## 5. Conclusion

Lymphopenia is an unreliable predictor of COVID-19 infection in patients who present to the diagnostic triage center with symptoms suggestive of COVID-19 infection. We discovered that lymphopenia had a sensitivity of 20% only in predicting suspected patients with positive CT findings. As a result, the presence of lymphopenia in suspected patients presenting to diagnostic triage centers should not be considered a reliable diagnostic aid. Future multicenter studies should investigate the role of lymphopenia in predicting the outcomes of COVID-19 patients.

## Conflicts of Interest

The authors declare no conflicts of interest.



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