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Lymphocyte count as a predictor of severity of COVID-19 infection

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Abstract
Background: Recent researches suggest that hematological profiles vary during SARS-CoV-2 infection. Patients with COVID-19 have a lower peripheral blood lymphocyte count in the early stages of the disease.
Aim of study: To evaluate if level of lymphocyte at admission can be used as a predictor for severity and mortality of COVID-19 infection.
Methods: A prospective observational study that was conducted at the COVID-19 ward in Al-Khidhir General Hospital during a period of one year. It included 350 patients who diagnosed with COVID-19 infection and admitted in the isolation wards. Complete blood count including WBC, hemoglobin, platelet count, lymphocyte count, neutrophil count, and monocyte count were assessed. Severity of disease was categorized into mild, moderate, severe, and critical.
Results: In this study, patients with severe infection had significant lower means of lymphocyte count (0.84 versus 1.73 $*10^9$/µl, P= 0.001). The cut point of N/L ratio was 1.0 $*10^9$/µl. Hence, lymphocyte count < 1.0 10^9/µl is predictive for severe or critical stage of COVID-19.
Conclusion: Hematological indices are easy and cheap way of assessing clinical progress in COVID-19 infection. One of the parameter is the lymphocyte count which show in our study significant correlation between the clinical stage. Lower count means progress to sever form of COVID-19.

Keywords: COVID-19, Hematological indices, severity, lymphocyte, Iraq

Introduction
Coronavirus disease, which causes severe acute respiratory infection, has emerged as a major public health concern in 2019. Since its discovery in December 2019 in Wuhan, China, it has rapidly spread across the globe [1]. The etiological agent is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the World Health Organisation (WHO) has dubbed the new epidemic disease Coronavirus Disease (COVID-19) [2]. The clinical manifestations of COVID-19 vary from person to person, ranging from asymptomatic to moderate infections to acute, life-threatening cases requiring admission to the intensive care unit (ICU) [3, 4]. COVID-19 manifests initially as shortness of breath, wheeze, fatigue, fever, dyspnea, myalgia, and muscle discomfort. Patients may develop acute respiratory distress syndrome (ARDS), multi-organ failure, shock, and metabolic acidosis [5] as the condition worsens. To date, COVID-19 has affected 212 countries/regions worldwide. As of April 16, 2021, the WHO had recorded 138,688,383 confirmed cases and 2, 9 million fatalities worldwide [6]. The patient's age, gender, and the existence of concomitant conditions like diabetes, hypertension, or pulmonary disease all affect how severe the COVID-19 infection is; however, it can be challenging to anticipate the severity of the infection at the time of hospital admission [7]. Because ARDS has a high mortality rate and a rapid onset, an early diagnosis is essential right away [8]. Currently, a variety of hematological markers are used to forecast outcomes and death in SARS CoV-2-infected individuals [9]. A complete blood count (CBC) is a simple and affordable procedure. Counts of leucocytes (neutrophils and lymphocytes) and thrombocytes, as well as indices of erythrocytes and certain ratios of these values, are all included in the CBC. The neutrophils are the most characteristic and important type of leucocyte in the immune system. The importance of lymphocytes in infections has been extensively established. Furthermore, thrombocytes play an important function in the control of numerous inflammatory processes [10, 11].

Hematological indices such as lymphocytes, white blood cells, platelets, neutrophils, etc. vary as a result of COVID-19 [12]. These modifications fluctuate from case to case and depending on the severity of the condition. Lymphopenia was the most prevalent blood count anomaly previously reported in roughly 35% - 85% of patients [13]. The aim of this study is to evaluate if level of lymphocyte at admission can be used as a predictor for severity and mortality of COVID-19 infection.

Patients and methods

Design, location, and time of the study: A prospective observational study was conducted at the medical ward of Al-Khidhir General Hospital, Al-Muthanna Province, Iraq, a hospital with a capacity of 200 patients, from June 1, 2019 to June 30, 2020. Study Population and quantity of the sample: The investigation included all patients diagnosed with COVID-19 infection using real-time PCR (qRT-PCR) on respiratory samples (oropharyngeal and nasopharyngeal swabs) and admitted to isolation facilities between June 2019 and June 2020. Patients under the age of 18, those who died within three days of hospitalisation, those who lacked essential data for analysis, and those who refused to participate were excluded from the study. Few clinicians are familiar with sample size calculations, and clinical researchers rarely disclose them for diagnostic studies. Frequently, researchers choose sample sizes arbitrarily, either for their own convenience or based on prior research (14). There were a total of 350 patients included in this study. According to (COVID-19) Outbreak in China (15), severity was determined based on four clinical stages: Mild Illness Patients with a mild illness may exhibit symptoms of a viral upper respiratory tract infection. Among the symptoms are dry cough, mild fever, nasal congestion, painful throat, headache, muscle aches, and malaise. Additionally, it is distinguished by the absence of significant symptoms such as dyspnea. Consequently, radiographic characteristics are also absent. Mildly ill patients can rapidly develop severe or hazardous conditions. Cough, shortness of breath, and tachypnea are common respiratory symptoms in patients with moderate disease. However, no signs or symptoms of a critical illness are present. Severe pneumonia is a symptom of patients suffering from severe illness. The clinical diagnosis is made, and radiographic examinations can be used to rule out complications. Clinical presentations include the occurrence of severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, SpO2 93%, PaO2/FiO2 300, and/or more than 50% lung infiltrates within 24 to 48 hours. Patients with cardiac injury, septic shock, respiratory failure, RNAaemia, respiratory failure, or multiple organ dysfunctions are afflicted with critical disease. The researcher distributed a questionnaire to all participants in order to collect the necessary data. It was based on prior material that was edited, evaluated, revised, and approved by a designated commission in accordance with national requirements. There were inquiries regarding age and gender, residence, chronic diseases, signs and symptoms, and the severity of COVID-19 infection. On the day of admission, a blood sample was obtained from all patients in order to conduct the following examination: CBC consisting of differential WBC. All haematological analyses were performed in the central laboratory of Al- Khidhir General Hospital using standard techniques. All patients were monitored to determine the severity of disease.

Ethical approval

As long as the patients' identity and the confidentiality of their medical records were respected, all of the patients signed informed consent forms allowing us to study their medical records for research reasons.

Statistical analysis

Version 26 of the Statistical Package for Social Sciences (SPSS) was used to analyze the data. The data were provided as mean, SD, and ranges. Expressed as frequencies and percentages for categorical data. Accordingly, the continuous variables were compared using an independent t-test (two tailed). Lymphocyte count was predicted using Receiver Operating Characteristic (ROC) curve analysis as a marker for severe or critical COVID-19. P values less than 0.05 were regarded as significant.

Result

In this study, mean age of patients was 52.3 ± 7.92 years; 64% of them were males; 60.6% were living in urban area; 20.9% were hypertensive; 63.1% showed mild to moderate COVID-19 infection severity; and 21.1% were died (Table 1).

Table 1: Distribution of study patients by certain characteristics

Variable	No. (n= 350)	Percentage (%)
Age (Year)		
< 40	154	44.0
40 - 59	137	39.1
≥ 60	59	16.9
Gender		
Male	224	64.0
Female	126	36.0
Residence		
Urban	212	60.6
Rural	138	39.4
Medical disease		
No	202	57.7
Hypertension	73	20.9
Diabetes mellitus	54	15.4
Hypertension and Diabetes	21	6.0
Stage of COVID-19		
Mild to moderate	221	63.1
Severe to critical	129	36.9
Mortality		
Yes	74	21.1
No	276	78.9

As shown in figure (1), the most common signs and symptoms were fever (73.4%) and fatigue (65.7%) followed by cough (59.1%).

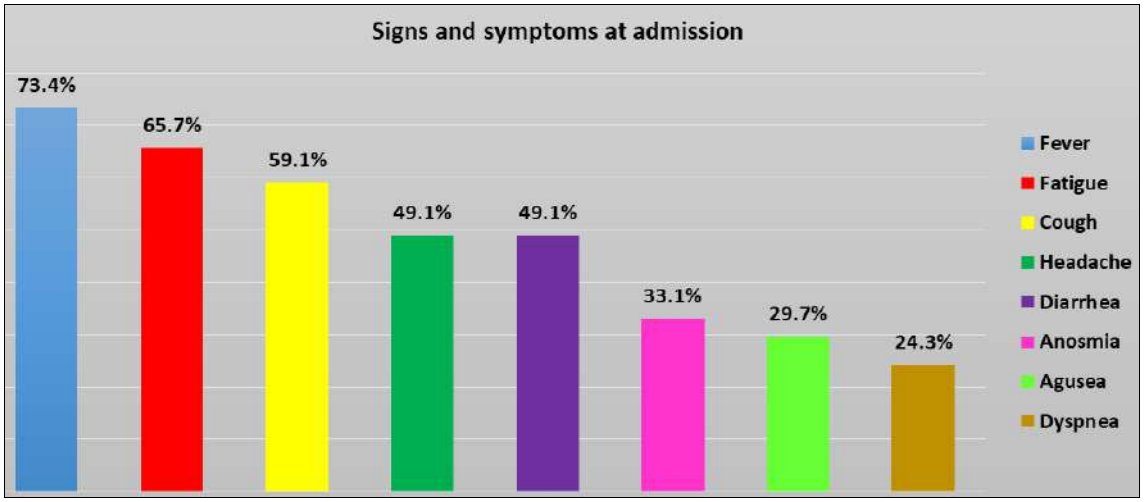

Fig 1: Distribution of study patients by signs and symptoms at admission

As shown in table (2), patients with severe infection had significant lower means of lymphocyte count (0.84 versus 1.73 $*10^9$/µl, P= 0.001) than that in those with non-severe disease.

Table 2: Comparison in mean lymphocyte count according severity and mortality

Severity of COVID-19 infection	Lymphocyte level ($*10^9$/µl) Mean ± SD	P - Value
Mild to moderate	1.73 ± 0.9	< 0.001
Severe to critical	0.84 ± 0.4	

Receiver operating characteristic (ROC) curve analysis was constructed for lymphocyte count as a predictor for severity of COVID- 19. The cut point of lymphocyte count was 1.0 $*10^9$/µl. Hence, lymphocyte count < 1.0 $*10^9$/µl is predictive for severe or critical stage of COVID-19, as a large significant area under the curve (AUC= 92.3%) indicating significant association between lower level of lymphocyte count and severity of COVID- 19. Lymphocyte count was 86% sensitive, 89.3% specific, and 87.7% accurate in predicting of severe or critical COVID-19. (Table 3) and (Figure 2).

Table 3: Diagnostic accuracy of lymphocyte count for prediction of severe or critical COVID-19

Lymphocyte ($*10^9$/µl)	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	1.0	86%	89.3%	87.8%	87.7%	87.7%

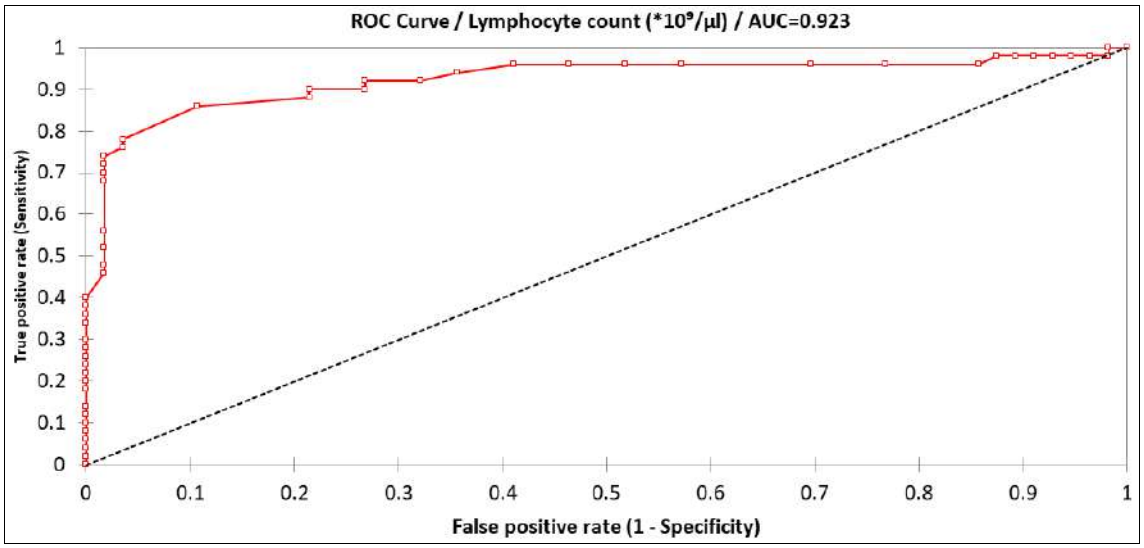

Fig 2: ROC curve for N/L ratio in diagnosis of severe or critical COVID- 19

Discussion

Infection with COVID-19 has become more prevalent in various countries around the world over the past few months. During the COVID-19 outbreak, several aberrant laboratory indicators, including haematological, inflammatory, and immunological markers, likely increased [16]. In deceased COVID-10 patients, lymphopenia, thrombocytopenia, and coagulation panel abnormalities are more severe. In order to improve outcomes, this demonstrated the importance of early detection and intervention in cases of anomalous hematologic findings [17]. Using a cutoff value of 1.0 *109/l, patients with severe infection had significantly lower mean lymphocyte counts than those with less severe disease. This result is consistent with findings from investigations conducted in 2021 by Zhang P *et al.* [18], Lee J *et al.* [19], and Li Y *et al.* [20]. According to studies, COVID-19 patients experience an early-onset decrease in peripheral blood lymphocyte count

that is lower than the normal reference range [21]. In addition, they discovered that patients who were critically and severely unwell had significantly lower lymphocyte counts than healthy and marginally ailing individuals [22]. However, additional research is required to determine whether there are differences in lymphocyte counts between patients who are severely and critically ill. By dynamically observing variations in lymphocyte count, we were able to confirm that lymphocyte count is a reliable predictor of COVID-19 severity and patient prognosis. In cellular immunological regulation, subsets of lymphocytes played a crucial role, with each cell constraining and regulating the others [18]. Lymphocytes, a crucial immune system component responsible for antigen recognition and memory, serve a crucial role in adaptive immunity. Other coronaviruses, such as SARS-CoV, MERS-CoV, and influenza viruses, induce varying degrees of lymphocyte depletion in infected individuals. This indicates that the number and subtypes of peripheral lymphocytes in critically ill patients are related to their prognosis [23]. We infer that COVID-19 lymphocytopenia is caused by lymphocyte sequestration in specific target organs, such as the lungs, gastrointestinal tract, and/or lymphoid tissues [24]. In conclusion, haematological indicators are a straightforward and economical method for tracking the progression of COVID-19 infection. In our analysis, lymphocyte count is one of the parameters that has a strong correlation with clinical stage. Lower counts indicate progression to the severe form of COVID-19; this can be used to stratify COVID-19 patient medical care and early referral to the intensive care unit.

Conflict of Interest
Not available

Financial Support
Not available

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