

The platelet-to-lymphocyte ratio versus neutrophil-to-lymphocyte ratio in prediction of COVID-19 outcome

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Резюме

Clinical presentation is an undependable prognostic indicator of COVID-19 (*CoronaVirus Disease 2019*). So, a more objective predictor is needed to precisely evaluate and classify the prognosis. Immune dysregulation to lymphocytes, mainly T-lymphocytes, have been noticed between COVID-19 patients. **The aim.** This study was planned to determine the role of platelet-to-lymphocyte count ratio and neutrophil-to-lymphocyte ratio in assessment of COVID-19 prognosis. **Methods.** 70 hospitalized patients with confirmed COVID-19 were included in this study. All included patients underwent a consistent clinical, radiological and blood examination. Laboratory analysis was made by means of a commercially accessible kit. Blood cells ratios were computed by dividing their absolute counts. **Results.** Non-significant association was found between laboratory data and COVID-19 clinical severity. A significant association between CT classification and platelet-to-lymphocyte count ratio (higher value in L type; $p = 0.001$) was detected. Platelet-to-lymphocyte count ratio was significantly higher among intubated cases. However, Non-significant association was found between neutrophil-to-lymphocyte ratio and need of endotracheal intubation. **Conclusion.** Routine blood values are abnormal in patients with COVID-19. Platelet-to-lymphocyte count ratios could be used as more meaningful biomarker than other values in predicting the prognosis of COVID-19. LMR helpful in COVID-19 severity.

Key words: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte count ratio, COVID-19.

Conflict of interests. Authors declare no conflict of interest.

Ethical expertise. This study was conducted within the essential ethics guidelines of Mansoura institutional research board (code number: R.20.07.935). Each patient gave a written informed consent to participate in the study.

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Сравнение показателей соотношений тромбоциты / лимфоциты и нейтрофилы / лимфоциты в качестве предикторов исхода COVID-19

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Abstract

Клиническая картина является ненадежным показателем прогноза исхода новой коронавирусной инфекции (НКИ), поэтому для точной оценки и классификации прогноза необходим более объективный прогнозирующий фактор. У пациентов, перенесших НКИ, отмечается нарушение регуляции иммунного ответа со стороны лимфоцитов, в основном Т-лимфоцитов. **Целью** исследования явилось определение роли показателей соотношений тромбоциты / лимфоциты и нейтрофилы / лимфоциты при оценке прогноза COVID-19. **Материалы и методы.** В исследование были включены госпитализированные пациенты ($n = 70$) с подтвержденным COVID-19 (*CoronaVirus Disease 2019*). У всех пациентов проводились последовательное клиническое и рентгенологическое обследование и анализ крови. Лабораторные анализы выполнялись с помощью коммерческого набора. Соотношения показателей клеток крови рассчитывались путем деления их абсолютного количества. **Результаты.** Обнаружена незначимая связь между лабораторными показателями и степенью тяжести COVID-19. Выявлена значимая связь между степенью поражения легких по данным компьютерной томографии и показателем соотношения тромбоциты / лимфоциты (более высокое значение для L-типа; $p = 0,001$). У интубированных пациентов соотношение показателя тромбоциты / лимфоциты было значимо выше. Однако обнаружена незначимая связь между показателем соотношения нейтрофилы / лимфоциты и необходимостью интубации трахеи. **Заключение.** У пациентов с COVID-19 наблюдаются отклонения показателей рутинных анализов крови. Показатель соотношения тромбоциты / лимфоциты может служить биомаркером при прогнозировании течения COVID-19, а показатель соотношения лимфоциты / моноциты полезен при прогнозировании степени тяжести COVID-19.

Ключевые слова: соотношение нейтрофилы / лимфоциты, соотношение тромбоциты / лимфоциты, COVID-19, новая коронавирусная инфекция.

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Although most patients infected with Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) are either asymptomatic or have a mild febrile course. A minority will develop a severe course which is characterized by respiratory failure [1]. Moreover, patients with quite normal clinical status may deteriorate rapidly within a few days, making clinical presentation an undependable prognostic indicator of CoronaVirus Disease 2019 (COVID-19). So, a more objective predictor is needed to precisely evaluate and classify the prognosis of COVID-19 patients [2].

Immune dysregulation and destruction of lymphocytes, mainly T-lymphocytes, have been noticed in COVID-19 patients. Elevated blood serum values of proinflammatory cytokines (TNF- α , IL-1, and IL-6) and chemokines (IL-8) were detected in severe COVID-19 cases, in comparison to patients with mild disease, which implies a probable role for hyperinflammatory response in the COVID-19 pathogenesis [3]. Patients' laboratory tests demonstrate normal or decreased leukocyte count, decreased lymphocyte count, decreased platelet count, raised transaminases, high lactate dehydrogenase, and elevated myoglobin. Decreased lymphocyte count was reported in a few severe cases [4].

The platelet-to-lymphocyte count ratio (PLR) was suggested as a possible test for risk classification of critically ill cases with sepsis [5]. Later, many researchers showed that PLR is a clear and independent prognostic element in cardiovascular disorders [6]. Neutrophil-to-lymphocyte ratio (NLR) is utilized to evaluate the inflammatory status of a patient. It can be simply calculated using a complete blood count, a frequently utilized blood test [7]. NLR was demonstrated to predict outcomes in a range of disorders including various types of cancers, as well as in cardiovascular and rheumatic disorders [8, 9].

The aim was to determine the role of PLR and NLR (as objective predictors) in assessment of COVID-19 prognosis.

Methods

70 hospitalized patients with confirmed COVID-19 admitted to Mansoura university quarantine hospital from August 2020 to December 2020 were included in this diagnostic study. This study was conducted within the essential ethics guidelines of Mansoura institutional research board (code number: R.20.07.935). Each patient gave a written informed consent to participate in the study. Patients with chronic pulmonary diseases, hematological disorders, chronic liver disease, history of radiotherapy and chemotherapy were excluded. All included patients underwent a consistent clinical, radiological and blood examination.

The diagnosis of COVID-19 was confirmed by RT-PCR. COVID-19 infection was clinically classified according to the Ministry of Health and Population in Egypt as

moderate or severe. A moderate case was defined as the occurrence of symptoms indicative of COVID-19 infection with radiological sign of pneumonia. A severe case was defined as a moderate case who meet any of the following criteria: oxygen saturation < 93%, respiratory rate \geq 30 breaths/min at rest and patients with > 50% pulmonary lesion progression within 24 to 48 h.

Pulmonary computerized tomography (CT) pattern of COVID-19 was divided into [10]:

- type L COVID-19 pneumonia; subpleural and beside the lung fissures ground-glass densities with moderately raised lung weight;
- type H COVID-19 pneumonia; the enlarged quantity of non-aerated tissue.

Venous blood samples were drawn soon after hospital admission. Blood samples were collected from each patient utilizing ethylenediaminetetraacetic acid tubes to avoid blood clotting. 2 ml of blood was used for a complete blood count (RBC, WBC, neutrophil, platelet, and lymphocyte counts) for each patient utilizing automatic blood counting system. Laboratory analysis was performed with a commercially available kit. PLR, NLR, lymphocyte monocyte ratio (LMR) was computed by dividing their absolute counts. The endpoint of the study included the need of endotracheal intubation.

Statistical Package for Social Science (SPSS) version 26 was utilized for statistical analysis. Shapiro – Wilk tests were used to test the normality. Continuous variables were presented as mean (SD) or median (min – max). The Independent-Samples Mann–Whitney U-test was used for non-parametric data, while Welch's t-test was used for parametric data. The significance level was chosen at $p = 0.05$.

Results

The study included 70 patients (the mean age was 50 years). About quarter of them were women. Hypertension was the most frequent comorbidity (30%). COVID-19 was classified clinically as moderate in 69% of the patients. Although non-significant association was found between laboratory data and COVID-19 clinical severity, lower platelet and lymphocyte counts were noticed in severe COVID-19 infection as compared to the moderate cases (platelet count mean 129,541.7 vs 145,066.7 and lymphocyte count median 155 vs. 1300). Also, LMR was higher in patients with the severe disease (Table 1).

Meanwhile a significant association was found between CT-classification and PLR (higher value in L type, $p = 0.001$), creatinine level ($p = 0.001$), LMR (higher in H type, $p = 0.01$), D-Dimer level (higher in H type, $p = 0.009$). No other parameters were found to be associated with CT-classification, see Table 2.

Table 1
The association of patients' laboratory parameters with COVID-19 severity

Таблица 1
Связь лабораторных показателей пациентов с тяжестью течения COVID-19

Parameter		Moderate	Severe	Significance	<i>p</i>
Lymphocytes, absolute count	Median (min – max)	1 300 (1 010 – 2 100)	155 (1 000 – 2 000)	Z = 0.404	0.686
WBCs	Mean (SD)	7 122.2 (1 675.8)	7 520.8 (1995.8)	<i>t</i> = –0.88	0.409
Platelets	Mean (SD)	14 5066.7 (125 555.9)	12 9541.7 (17 641.3)	<i>t</i> = 0.82	0.419
PLR	Mean (SD)	93.1 (21.7)	92.5 (24.8)	<i>t</i> = 0.11	0.911
Neutrophils	Mean (SD)	4 433.3 (762.2)	4 066 (1 006.3)	<i>t</i> = 1.6	0.127
Monocyte ratio	Mean (SD)	7.4 (1.5)	7.5 (1.8)	<i>t</i> = –0.13	0.898
Monocyte count	Mean (SD)	112.4 (42.9)	103.6 (42.4)	<i>t</i> = 0.82	0.42
NLR	Mean (SD)	3.3 (0.9)	2.9 (0.9)	<i>t</i> = 1.7	0.092
LMR	Median (min – max)	13.1 (4.9 – 33.3)	17.1 (6.0 – 44.6)	Z = 1.43	0.151

Note: PLR, Platelet lymphocyte ratio; NLR, Neutrophil lymphocyte ratio; LMR, Lymphocyte monocyte ratio.

Table 2
The association of patients' laboratory parameters with CT-classification

Таблица 2
Взаимосвязь лабораторных показателей пациентов и данных компьютерной томографии

Parameter		L-phenotype	H-phenotype	Significance	<i>p</i>
Lymphocytes, absolute count	Median (min – max)	1 300 (1 000 – 2 100)	1 500 (1 100 – 2 000)	Z = 1.7	0.083
WBCs	Mean (SD)	7 122.5 (1 849)	7 600 (1 635.8)	* <i>t</i> = –1.1	0.28
Platelet count	Mean (SD)	146 104.1 (121 196.7)	124 952.3 (19 566.5)	* <i>t</i> = 1.2	0.245
Neutrophil count	Mean (SD)	4 272.9 (741.1)	4 380 (1117.4)	* <i>t</i> = –0.41	0.688
Monocytes, %	Mean (SD)	7.5 (1.7)	7.3 (1.6)	* <i>t</i> = 0.27	0.782
Monocyte count	Median (min – max)	107.7 (50.0 – 264.7)	90.0 (44.8 – 222.2)	Z = –1.7	0.085
NLR	Mean (SD)	3.2 (0.9)	2.9 (1.2)	* <i>t</i> = 0.79	0.434
PLR	Mean (SD)	98.4 (25.2)	82 (14.7)	<i>t</i> = 3.3	0.001
LMR	Median (min – max)	12.9 (4.9 – 33.3)	17.4 (8.1 – 44.6)	Z = 2.34	0.019**
Creatinine	Median (min – max)	1.1 (0.6 – 1.5)	0.8 (0.5 – 1.4)	Z = –3.4	0.001

Note: NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LMR, Lymphocyte monocyte ratio.

Gender was significantly associated with absolute lymphocyte count (lower in females, $p = 0.005$), PLR (higher in females, $p = 0.003$), monocyte count (higher in females, $p = 0.02$), NLR (lower in females, $p = 0.004$), LMR (lower in females, $p = 0.002$), see Table 3. As regard the association between PLR, NLR, LMR and intubation, only PLR was significantly higher among intubated cases ($p = 0.02$), see Table 4.

Discussion

In severe COVID-19 cases, the disease progresses quickly. Septic shock and coagulation dysfunction might appear within a few days. Some patients develop a severe inflammatory storm leading to death [11]. Consequently, assessing the prognosis of the disease at an early stage, and getting efficient therapy for patients who could have severe disease can successfully decrease the mortality rate [12].

Platelets perform an important role in hemostasis, innate immunity, and inflammatory response. Variations in

its count and activity are directly associated with a variety of disorders [13]. The absolute count of lymphocytes and platelets can be utilized as sensitive predictors of infection and inflammation [12].

So, this study was planned to determine the role of PLR and NLR (as objective predictors) in assessment of COVID-19 prognosis. Our results showed lower platelet and lymphocyte counts in severe COVID-19 as compared to the moderate cases. No difference was observed in PLR and NLR between the moderate and severe cases. However, LMR was higher in the severe cases. PLR was significantly higher among intubated patients as compared to NLR and LMR.

According to *R. Qu et al.* [12], the older patients with decreased lymphocyte and platelet counts were diagnosed with more severe disease and stayed longer in hospital. NLR, LMR, PLR of severe patients were significantly higher than those of non-severe patients in *A. P. Yang et al.* [14]. However, NLR exhibited the largest area under the curve with the highest specificity (63.6%) and sensitivity (88%).

Table 3
The association of the patients' laboratory parameter with gender
Таблица 3
Взаимосвязь лабораторных показателей с полом пациентов

Parameter		Male	Female	Significance	p
Lymphocytes, absolute count	Median (min – max)	1 400 (1010 – 2 100)	1 200 (1 000 – 1 900)	Z = -2.8	0.005
WBCs	Mean (SD)	7 372.2 (1581.8)	6 860 (2420.1)	t = -0.775	0.449
PLR	Median (min – max)	85.7 (40.9-132)	108 (63-143)	Z = -2.9	0.003
Neutrophil count	Mean (SD)	4 396.3 (768.2)	3 980 (1074.5)	t = 1.4	0.178
Monocyte %	Mean (SD)	7 (5 – 12)	8 (5 – 10)	Z = 1.5	0.122
Monocyte count	Median (min – max)	96.7 (44.8 – 264.7)	114 (50.2 – 222.2)	Z = 2.2	0.029
NLR	Mean (SD)	16 (6.8)	11 (5.1)	t = 3.1	0.004
PLR	Mean (SD)	89 (22.3)	108 (22.3)	t = -3	0.006
MR	Median (min – max)	14 (4.9 – 44.6)	9 (6 – 23.5)	Z = -3.1	0.002
Creatinine	Median (min – max)	0.9 (0.5 – 1.5)	1.2 (0.5 – 1.4)	Z = 0.73	0.463
Albumin	Median (min – max)	3.4 (2.7 – 4.1)	3.2 (2.8 – 4.0)	Z = -0.5	0.613
Ferritin	Median (min – max)	810 (120 – 1 700)	800 (260 – 1 650)	Z = 1.1	0.278
D-dimer	Median (min – max)	1 000 (400 – 2 000)	700 (480 – 2 100)	Z = 0.226	0.821

Note: NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LMR, Lymphocyte monocyte ratio.

Table 4
The association of platelet lymphocyte ratio, neutrophil lymphocyte ratio and lymphocyte monocyte ratio (LMR) with intubation
Таблица 4
Взаимосвязь соотношения тромбоцитов к лимфоцитам, нейтрофилов к лимфоцитам и лимфоцитов к моноцитам с интубацией

Parameter		Non intubated	Intubated	Significance	p
PLR	Mean (SD)	86.3 (19.5)	97.5 (23.7)	*t = -2.06	0.03
NLR	Mean (SD)	2.9 (0.7)	3.2 (1)	*t = -1.4	0.1
LMR	Median (min – max)	13.5 (4.9 – 33.3)	13.8 (6.0 – 44.6)	Z = -0.2	0.8

Note: NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LMR, Lymphocyte monocyte ratio.

The results of *A.Erdogan et al.* [15] showed that there was no statistically significant difference between non severe and severe clinical outcomes (severe meaning that the patients were intubated, needed intensive care, or died) in terms of the LMR, but there was a statistically significant difference in terms of NLR and PLR. The median NLR and PLR values were lower in the non-severe clinical outcome group. Also, *A.Erdogan et al.* [15] found that lymphocyte and monocyte counts were lower in the severe group ($p < 0.001$), but neutrophil ($p = 0.416$) and platelet ($p = 0.998$) counts were not statistically different between the groups.

NLR is the best predictor of severe COVID-19, and the combination of NLR, CRP, and platelets helped predict severe COVID-19 in *W.Shang et al.* [16]. *Z.Xu et al.* found that lymphocytes are predominant in the lung interstitium [17]. This constitutes the cause for the considerable reduction in lymphocyte count. Similarly, in our study, the lymphocyte counts of the patients with severe COVID-19 were lower. As a result of thrombosis, platelet consumption rises and the platelets count decreases [18].

Conclusion

Routine blood values are abnormal in patients with COVID-19. PLR ratios could be a more meaningful biomarker than other parameters in predicting the prognosis of COVID-19.

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