EARLY IDENTIFICATION OF HIGH RISK COVID-19 PATIENTS USING HEMATOLOGICAL INDICES

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Abstract

Coronavirus disease 2019 (COVID-19) is a recent respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with serious complications, severe acute respiratory syndrome (ARDS), cytokine storm, and coagulopathies. Complete blood count (CBC) is a routine inexpensive and easy test that provides information regarding formed blood content such as white blood cells (WBC), platelet, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) to detect degree of inflammation. This study attempts to assess, at an early phase of the disease, the prognosis of COVID-19 patients and predict high risk patients who will most probably develop ARDS and cytokine storm by analyzing blood cells count. This study is a single-center case series on COVID-19 patients who were prospectively analyzed at Al-Furat General Hospital in Baghdad from March to August 2020. Up to 123 Covid-19 patients in two groups, 100 who survived versus 23 who did not survive were included. Patients with abnormal renal and hepatic tests were excluded. Results revealed that the median age of patients was 40 years, ranging from 2-84 years of age. Males (61.8%) were more affected by COVID-19 than females (38.2%). Survived patients exhibited far lowered WBC count (6.06±3.17) than non-survived patients (11.4±6.08; $p<0.0001$). Lymphocyte count in survived patients (1.6±1.1) were higher than non-survived patients (1.1±0.4; $p<0.004$). Neutrophils showed lower count (3.7±2.7) in survived patients than non-survived patients (8.9±4.5). Also, receiver operator characteristic (ROC) analysis for NLR, LMR and PLR revealed a cut off value for abnormally high or low NLR >5, LMR ≤1.8, and PLR >176 with area under curve (AUC) 0.9, 0.8, and 0.6, respectively. These cut off values represent landmarks above or below which poor prognosis and non-survival is highly predicted. NLR was found to be the most prognostic index to detect bad prognosis and non-survival of the disease at 90% sensitivity, followed by LMR and then PLR. The percentage of non-survived patients who had abnormally high NLR (82.6%), LMR (65.2%) and PLR (56.5%) were far higher than survived patients (NLR: 9%; LMR: 8%; PLR: 22%).

Keywords: Covid-19, Cytokine Storm, Platelet-to-lymphocyte Ratio, Neutrophil Lymphocyte Ratio, Lymphocyte-Monocyte Ratio

Introduction

Coronavirus disease 2019 (COVID-19) is a newly developed respiratory infection which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with serious complications such as severe acute respiratory syndrome (ARDS) (1, 2). The virus has a peculiar crown-like shape due to the existence of glycoprotein spikes on its surface (3). It is a single-stranded enveloped RNA virus with four viral glycoproteins, S (richly glycosylated), M (matrix transmembrane protein) located inside the envelope, small envelope or E protein, and nucleocapsid or N protein (4, 5).

The virus targets organs which express angiotensin converting enzyme 2 (ACE2), which includes pulmonary alveoli, cardiac tissue, renal system and digestive tract (6, 7). The commonest complains of patients with COVID-19 are elevated body temperature, fatigue, cough, and progressively growing dyspnea. Majority of cases had mild symptoms and did not experience elevated temperature. Less common symptoms were abdominal pain, headache, erythema and chest pain (8, 9).

Alterations of various hematological parameters have been observed with SARS-CoV-2 infection, and these parameters may be related to the severity and prognosis of COVID-19 outcome. Patients with serious illness and those who died had appreciable leukocytosis, lymphopenia, and thrombocytopenia in comparison to patients with non-severe illness and survived COVID-19 (10, 11). Liu *et al.,* (2020) reported that the commencement of inflammatory cytokine storm due to COVID-19 resulted in the development of severe pulmonary damage, pulmonary failure and multi-organ failure (12).

Lymphocytes are considered the major immune-active cells of the human body. In fact, white blood cell (WBC) and lymphocyte counts are rapid markers for physiological distress of systemic inflammation. Platelet factor 4 (PF4) can inhibit agglutinin-A from inhibiting lymphocyte generation (13). Also, activated platelets can enhance lymphocyte adhesion to the endothelium. The advantage of the platelet- lymphocyte ratio (PLR) is that it reflects both aggregation and inflammatory pathways, and may be more valuable in identifying different types of inflammation than platelet or lymphocyte counts alone (13, 14). Death rates tend to decline with the increment of platelet count, implying that the clotting process had subsided and platelets are no more depleted into clots.

Antibodies that accumulate on the surface of platelets, forming immune complexes, were identified via the reticuloendothelial system and these antibodies, through their FC portion would drive platelets to lysis and damage as target cells contributing to enormous platelet damage. Platelets with similar antigens may be covered by anti-platelet antibodies and immune complexes, contributing to immune-mediated destruction. Destruction of pulmonary tissue and endothelial cells may activate platelets in pulmonary tissues, resulting in aggregation and microthrombi formation leading to platelet destruction (8, 15).

Yaqing *et al.* (2016) mentioned that the neutrophil-lymphocyte ratio (NLR) has good discrimination and assessment for short-term mortality (16). Recently, Fu *et al.* (2020) revealed that NLR values appear to increase significantly in COVID-19 patients with serious illness (17). In addition, lymphocyte-to-monocyte ratio (LMR) has proven to be a more adequate prognostic biomarker than NLR in most chronic inflammatory diseases, including metastatic cancer and autoimmune pathologies as LMR measures macrophage activation syndrome, which occurs concomitantly with remarkable lymphocyte depletion, more precisely (18-22). However, its profile and prognostic significance in relations to COVID-19 have yet to be investigated and established. Hence, the current study is designed to assess the early clinical predictive potential of NLR, PLR, and LMR for the development and prognosis of COVID-19 disease.

Materials and Methods

The current study encompassed 123 confirmed COVID-19 patients who were admitted to the Al-Furat General Hospital, Iraq. All patients were diagnosed via a positive PCR test result from a nasopharyngeal swab. All patients were symptomatic with cough, fever, tiredness and dyspnea for a median duration of 5 days, ranging from 3-8 days. At day of admission, according to the World Health Organization (WHO) guidelines, all patients were classified as moderate to severe COVID-19 patients. Among them, 100 patients survived while 23 patients died. The patients were grouped into two groups: survived and non-survived patients. Patients were subjected to complete blood count (CBC) examination at day of admission and hematological findings were recorded. Informed written consent from all patients involved in this study was pursued; the current study was approved by the Ethical Committee in Al-Karkh Health General Directorate (Ethics No.: KE-78).

Up to 2 ml of venous blood was drawn into an ethylene diamine tetra acetic acid (EDTA) tube. The blood count was estimated using the QBC Autoread Plus Hematology System (Drucker Diagnostics, USA). NLR was estimated as neutrophil-lymphocyte ratio, PLR as platelet-lymphocyte ratio, and LMR as lymphocyte-monocyte ratio.

Statistical analysis

Data were analyzed using Statistical Analysis System (SAS) Release 9.1. Independent *t* test was performed to assess significant differences between means, and $p<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve was used to determine the effectiveness of parameters as an index. The parameters were correlated according to area under curve. The analysis was submitted via MedCalc Statistical Software version 2.1.4.

Results and Discussions

The ages of the 123 patients, comprising both sexes, ranged from 2 to 84 years, with a median age of 40 years. The

findings of this study revealed that 25% of survived patients and 78.2% of non-survived patients were ≥50 years. This may be due to the possibility that younger patients have better immunity and less comorbidity than the elderly. This finding is comparable with Wan *et al.* (2020) who proposed that older individuals and those with comorbidities (such as heart disease, pulmonary illness, and hyperglycemia) are at an increased risk of severe illness and fatality (23). The median duration of hospitalization was 7.5 days for survived patients versus 28 days for non-survived patients. Females and males in this study constituted 38.2% and 61.8%, respectively (Figure 1). Hence, males can be considered as a risk factor for COVID-19. This observation may be attributed to the hormone estrogen, which confers resistance to viruses in women. Di Stadio *et al.* (2020) stated that estrogen is responsible for the high resistance of cells to local and systemic inflammatory effects (24). Taneja (2018) also reported that estrogen stimulates the immune system by modulating the function of B-cells and improving T-helper 2 cell activity (25).

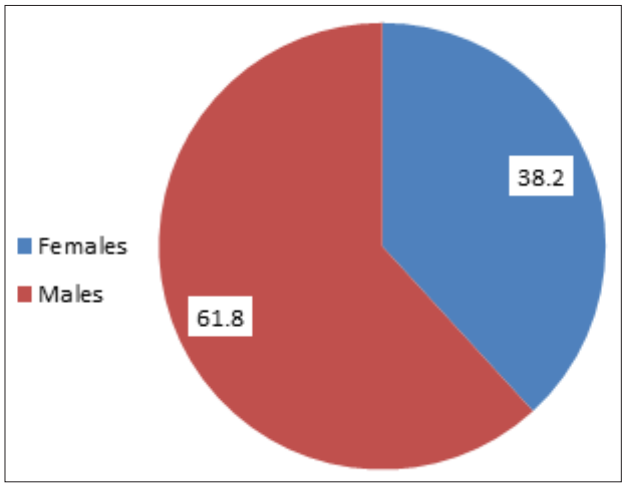

Figure 1: Distribution of COVID-19 patients according to sex

Mean WBC count in the survived group was found to be 6.065±3.17 x10^{3}cell/µl; 7% had leukocytosis. In contrast, the non-survived group, with no evident bacterial infection, had a mean WBC count of 11.46±6.08 x10^{3}cell/µl; 47.8% had leukocytosis. Henry *et al,* (2020) reported that COVID-19 patients with serious illness have remarkable increase in leukocytes and this may imply clinical deterioration with an increased risk of poor outcome (10).

The mean lymphocyte count in survived group was 1.6±0.7 x10^{3}cell/µl. Merely 5% of survived patients had lymphopenia and 60% had a hospitalization period of ≥10 days. On the other hand, the mean lymphocyte count in the non-survived group was 1.12±0.47 x10^{3}cell/µl, 30.4% had lymphopenia (Figure 2). Based on these data, COVID-19 may have a lowering effect on lymphocytes during the course of the disease. These results propose that SARS-CoV-2 can primarily act on lymphocytes, particularly T lymphocytes, similar to SARS-CoV-2 (26). This is comparable with Tan *et al.* (2020) who found in a two-time points study that COVID-19 patients had 20% lymphocytes 10-12 days from the onset of disease, but had 5% lymphocytes 17-19 days after the onset of disease, exhibiting worst prognosis (26).

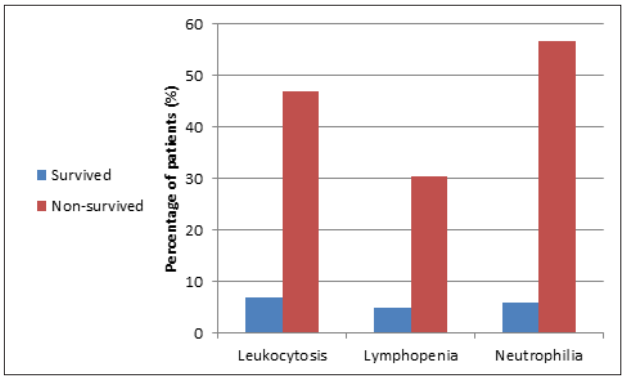

Figure 2: Distribution of COVID-19 patients according to leukocytosis, lymphopenia, neutrophilia

Dysregulation of peripheral immune cells (e.g. lymphocytes) can induce a cytokine storm in the body, generating a series of immune responses caused by virus particles, and this will spread across the respiratory mucosa and affect various cells. It was proposed that a considerable reduction of total lymphocyte count indicates that SARS-CoV-2 may hijack hosts' immune cells and prohibit the body's cellular immune function. De Wit *et al.* (2016) mentioned that the destruction of T lymphocytes could be an influential factor promoting patients worsening symptoms (27).

Our study found that the mean neutrophil count in the survived group was 3.79±2.7 x10^{3}cell/µl; 6% had neutrophilia and 66.6% has hospitalization ≥10 days. In contrast, the mean neutrophil count in the non-survived group was 8.9±4.56 x10^{3}cell/µl ($p<0.0001$), 56.7% had neutrophilia (Figure 2). High levels of cytokines have important effector function on WBC and induce stimulation of neutrophils, suggesting a protective immunity against the virus. Wu *et al.* (2020) mentioned that among cases with ARDS, higher neutrophil counts were noted in those who died (28). Moreover, it was shown that severe pneumonia and death were mainly associated with elevated neutrophils (29). The same observations were found in patients with SARS (30) and Middle East Respiratory Syndrome (MERS) (31).

There is developing interest in analysis designed towards superior understanding of disease status and/or to anticipate the prognosis of patients using simple blood tests that are associated with systemic inflammation, such as NLR, PLR and LMR (See Table 1 for associated criterion with sensitivity and specificity). Data from our study revealed that the mean NLR in survived patients (2.70±2.4) was much lower than the non-survived group (8.73±4.49; $p<0.0001$). NLR as an inflammatory marker was shown

to have an abnormally high cut-off value >5, with 90.4% sensitivity. Therefore, NLR can be used as a predicting index for the early prognosis of COVID-19 and facilitate timely detection (Table 1; Figure 3).

Table 1: Sensitivity and specificity for lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in COVID-19 patients

	LMR	NLR	PLR
Associated criterion	≤1.8	>5	<176
Sensitivity	71.43	90.48	54.55
Specificity	91.40	91.58	79.00

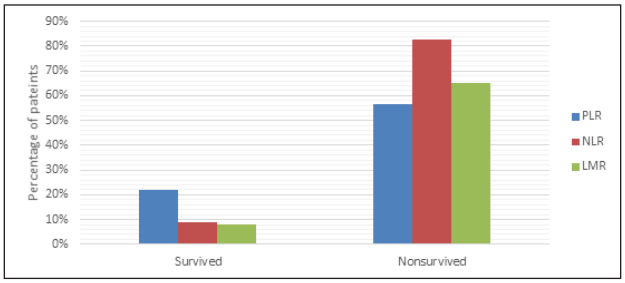

Figure 3: Percentage of COVID-19 patients with abnormally high PLR, LMR and NLR

Based on the ROC analysis (Figure 4), the area under curve (AUC) of NLR was shown to be 0.921 (95% CI: 0.855 - 0.964). This result shows that NLR is most effective in predicting the severity and prognosis of COVID-19 patients. Hence, NLR may be performed as a main alternate predictor for early risk in COVID 19 infection. Zahorec (2001) mentioned that NLR can be used as a marker for systemic inflammation (32).

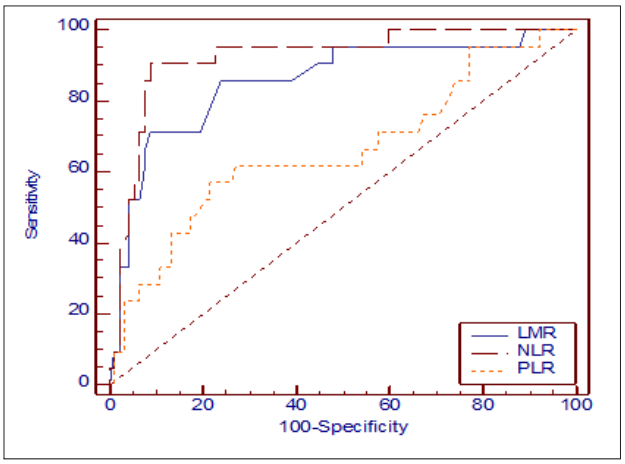

Figure 4: ROC analysis of NLR, PLR and LMR along with their cut-off values' sensitivity and specificity

Our study revealed that 9% of survived patients had high NLR in comparison to 82.6% of non-survived patients (Figure 4). In addition, 65.2% of non-survived patients were aged ≥50, with high NLR >5. This finding is in accordance with Liu *et al.* (2020) who found that patients of aged ≥50 with NLR ≥3.13 have a high risk of serious disease, and they should have rapid access to the intensive care unit (ICU), if necessary (33). Other studies demonstrated that higher levels of inflammatory cytokines, chemokines and NLR in infected patients were correlated with disease severity, proposing the involvement of a cytokine storm (34). Yanga *et al.* (2020) mentioned that 46.1% of COVID-19 patients with mild illness, who are ≥49.5 years old with an NLR ≥3.3, will develop serious disease with a mean time of only 6.3 days (35). Hence, those cases should be intently observed by clinicians. In contrast, COVID-19 patients with mild illness, who are <49.5 years old with an NLR <3.3, will most likely improve and sent home in ~13.5 days.

In addition, our study revealed that the mean LMR in the survived group was 3.80±1.96, while the non-survived was 1.70±1.31. ROC analysis revealed that the AUC for LMR was 0.8 (95% CI: 0.777 - 0.915; Figure 4). The cut-off value of LMR ≤1.8 was predictive for poor prognosis, with 71.43% sensitivity (Table 1). We found that 65.2% of non-survived patients had low LMR, while only 8% of survived patients had low LMR. Merely 50% of the latter were hospitalized for more than 10 days. Lissoni *et al*. (2020) showed that declining lymphocytes in patients with COVID-19- induced respiratory distress is associated with a concomitant increase in monocyte count, with a subsequent decrease in LMR values (36).

The mean PLR of the survived group in our study was 152±135 compared to 148.6±99.9 of the non-survived group ($p<0.0001$). 22% of the survived group and 56.5% of the non-survived group had increased PLR; ~68.1% of patients from the survived group stayed ≥10 days in the hospital (Figure 4). Qu *et al.* (2020) reported that PLR may serve as a recent index in monitoring COVID-19 cases. ROC analysis revealed that the AUC of PLR is 0.6 (95% CI: 0.566 - 0.748) (Figure 4) (13). Accordingly, these findings show that PLR is an additional reliable marker for poor prognosis of COVID-19, following NLR and LMR, with an associated criterion of >176, at 54.5% sensitivity (Table 1). The activation of platelets in this manner, even in the absence of vascular destruction, initiates diverse platelet functions, specifically inflammation and immune regulation. Moreover, the pro-inflammatory cytokine activity of platelets is thought to be mediated by interactions with other WBC in the blood stream, resulting in the release of cytokines and chemokines to stimulate inflammation (37).

Conclusion

Overall, the current study revealed that non-survived COVID-19 patients had significant increase in leukocytosis with neutrophilia, while lymphocytes and platelets were reduced in comparison to survived COVID-19 patients. As

biomarkers of inflammation, high NLR >5 may indicate a cytokine storm and predicts poor prognosis of the disease at 90% sensitivity. This is followed by LMR ≤1.8 at 71% sensitivity, then PLR < 176 at 54% sensitivity. Therefore, early application of these parameters is thought to affect management of the clinical course for COVID-19 patients. These parameters can be considered as reliable predictive indices for serious COVID-19 cases, permitting physicians to take early management steps and close observations to shorten the hospitalization period and reduce mortality rate.

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Competing interests

All authors declare that they have no competing interests.

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