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Original Article

The Prognostic Value of (NLR) Ratio in Patients with COVID-19

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Abstract *- Coronavirus disease 2019, COVID-19, has worried the world since the beginning of its spread and posed a threat to public health. An elevated NLR is an independent risk factor for death in covid-19. This study aims to highlight the importance of the high NLR in predicting the severity of the disease and severe clinical outcomes. A cohort study included 203 patients diagnosed with COVID-19 by CT chest and swab positivity PCR technique. The primary follow-up endpoint considered death, and the secondary was the need for intensive care or invasive or non-invasive mechanical ventilation. We performed a cut-off ROC curve for the NLR to predict poor prognosis in COVID-19 patients regarding death, need for mechanical ventilation or intensive care. The NLR was statistically significantly higher in patients who died or required intensive care and mechanical ventilation compared with patients who did not require intensive care or survived. We found that age, smoking, ischemic heart disease, chronic lung disease, NLR and CURB 65 are statistically significant and independent factors in predicting the need for mechanical ventilation and the prognosis of death in patients with COVID. The most sensitive inflammatory indicator for predicting death was the NLR. The best cut-off point for the NLR was also determined. It is the point with the highest sensitivity and specificity for predicting a lousy prognosis, NLR = 9.5, where the sensitivity is 70% and the specificity is 65%.*

Keywords *- Covid-19 disease, Neutrophils, Lymphocytes, Death, Mechanical ventilation, NLR.*

I. Introduction

Because of COVID-19, the world has lost many lives [1]. Coronaviruses are a large virus family that may lead to self-limited, mild, and joint infections like the common cold and more severe infections like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). These viruses may lead to clinical conditions with various degrees of respiratory, enteric, hepatic, nephritic, and neurological involvement. The ratio of neutrophils to lymphocytes NLR is a prognostic indicator of disease severity and has a vital role in predicting clinical outcomes [2-3].

Identifying and treating severe cases early may improve disease prognosis and reduce the resulting economic burden. Lab tests help determine the severity of the disease, but we need quick, inexpensive and valuable tests. One such marker is a complete blood count (CBC) profile, out of which neutrophils and lymphocytes are essential.

The neutrophils increase in bacterial infection, and lymphocytes are reduced during viremia. Examining these two parameters can greatly help assess the COVID-19 infection [4].

Neutrophil to Lymphocyte Ratio (NLR) is an independent risk factor for death in COVID-19 and gives us an idea of the balance between innate immunity, represented by neutrophils, and adaptive immunity, represented by lymphocytes [5]. NLR calculates by dividing the absolute number of neutrophils by the absolute number of lymphocytes or the percentage of neutrophils divided by the percentage of lymphocytes from the peripheral blood sample. Thus, the NLR value can be obtained immediately by carrying out routine blood tests upon admission to the hospital. The physician can identify the risks in the early stages of Covid-19 patients; thus, the treatment can be adjusted to reduce hospital deaths [6].

2. Aim of the Study

The study evaluates the elevated neutrophil-to-lymphocyte ratio (NLR) in its ability to warn of mortality in patients with Covid-19 disease and the severity of the disease and serious clinical outcomes.

3. Materials and Methods

A cohort study conducts on 203 patients diagnosed with COVID-19 by CT chest and swab positivity (PCR) technique.

Those admitted to the Isolation Division at Tishreen University Hospital in Latakia between December 2020 and December 2021. And the investigators for the inclusion criteria in the research.

Information related to the demographic variables of patients' age, gender, and patients divided into three age groups (less than 60 years old, 60-74 years old, and 75 years old and over).

Patients' antecedents and risk factors, such as smoking, ischemic heart disease, hypertension, chronic lung disease and diabetes mellitus, were analysed. The following laboratory tests record upon admission to the patients: WBC, LYM, NEU, CRP, D-DIMER, and LDH, with the NLR value calculated for all of them and the CURB65 index also calculated**.**

The primary follow-up endpoint was considered dead, and the secondary was the need for intensive care or invasive or non-invasive mechanical ventilation**.**

We performed a cut-off ROC curve for the NLR to predict poor prognosis in COVID-19 patients in terms of death, need for mechanical ventilation or intensive care**.**

Our study's statistical assessment performs using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 25, manufactured by IBM Corp, located in Armonk, NY, USA and summarised as frequencies and proportions. $P<0.05$ value was accepted to be statistically significant. The results indicate an average ±SD and percentage (%). One-way ANOVA uses to compare groups. The independent-sample t-test uses for comparing the two groups, and the t-test is used for variables.

3.1. Definitions

COVID-19 is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) and quickly spread worldwide [7]. It is characterised by the following clinical manifestations: high fever, muscle weakness and pain, dry cough, dyspnea, and diarrhea. Its clinical manifestations range from asymptomatic cases to upper respiratory infection, viral pneumonia, ARDS, multiorgan failure and death.

The severity of pathological conditions ranges from mild to moderate (80%), severe (15%) and critical (5%), and the pathological mechanisms are still not fully understood [8].

The neutrophil to lymphocyte ratio (NLR) is a key indicator of the severity of inflammation in the body. It is the quotient of the averages by the lymphocytes in the CBC test. It can be performed at any time during the day and does not require patient preparation, such as fasting. It reflects the balance between the innate immune response (neutrophils) and adaptive immunity (lymphocytes). It is also an independent marker of poor clinical outcomes and an early warning sign of severe infection in patients with COVID-19[9].

3.1.1. Neutrophil

Neutrophil are also known as polymorphonuclear neutrophils (PMNs), and they are the most abundant cell type in human blood; they are one of the most important active factors in the innate immune system. Moreover, it is vital in the immune system against germs and fungi. It is involved in host defense mechanisms through the production of ROS-reactive oxygen species, phagocytosis and formation of NETs- neutrophil extracellular traps. It also plays an essential role in the third type (III) of the hypersensitivity reaction.

Human neutrophils constitute about 55 to 70% of the circulating leukocytes in the circulation, that is, 2500 to 8000 neutrophils per cubic millimeter [10-11].

3.1.2. Lymphocytes

Lymphocytes are one of the most important cells in cellular immunity [12]. Ranging in size from 7 to 20 μm in diameter [13].

Lymphocytes play an essential role in the immune system and regulate inflammatory responses to pathogens [14]. Furthermore, they also contribute directly to the inhibition of inflammation and the maintenance of tissue homeostasis [15-16].

The different forms of lymphocytes arise from a lymphoid progenitor before differentiation into distinct lymphoid types, and after maturation, the lymphocytes enter the circulation and peripheral lymphoid organs [17].

Its normal number is from 1,000 to 4,000 cells per cubic millimeter, which is 20% to 40% of the white blood cell count [10].

4. Results

Our study included 203 patients admitted to the isolation department at Tishreen University Hospital and diagnosed with COVID-19 infection.

The number of males in the study sample was 124 patients or 61.1%, and the number of females was 79, or 38.9%.

The patients' ages ranged between 14 and 92 years, with a mean age of 62.3 ± 16.2 years.

The number of patients who required intensive care or mechanical ventilation was 86, or 42.4%.

The number of deaths reached 81 patients or 39.9%.

Table 1. Distribution of risk factors for COVID-19 patients in the study sample

Risk Factor	Number of Patients	%
Smoking	75	19.2%
Ischemic heart disease	39	19.2%
Arterial hypertension	96	47.3%
Diabetes	57	28.1%
COPD	45	22.2%

Table 2. Comparison of patients who required and did not require intensive care or mechanical ventilation

		Did not require ICU (N=117)	Required ICU (N=86)	P Value
Gender	Male	70 (59.8%)	54 (62.8%)	0.669
	Female	47 (40.2%)	32 (37.2%)	
Age		16.2 ± 59.4	15.4±66.4	0.002
Age categories	< 60 year	51 (43.6%)	26 (30.2%)	0.050
	60 -74year	45 (38.5%)	36 (41.9%)	
	≥75year	21 (17.9%)	24 (27.9%)	
Smoking		34 (29.3%)	41 (47.7%)	0.008
Ischemic heart disease		13 (11.1%)	26 (30.6%)	0.001
Arterial hypertension		50 (43.1%)	46 (54.1%)	0.060
Diabetes		30 (26.5%)	27 (33.8%)	0.092
COPD		19 (17%)	26 (33.3%)	0.009
WBC		5142± 9769	8512± 14087	<0.001
Neu		4600 ± 8084	6633 ± 11395	<0.001
Lym		762± 1111	1389 ± 1460	0.038
NLR		6 ± 8.8	6.3 ± 12.8	<0.001
LDH		335 ± 613.4	592.1 ± 870.5	0.014
D-Dimer		2181 ± 2987	3242 ± 2681	0.475
CRP		100.1 ± 75	111 ± 86	0.359
CURB 65		2.4 ± 0.53	3.9 ± 0.7	0.001

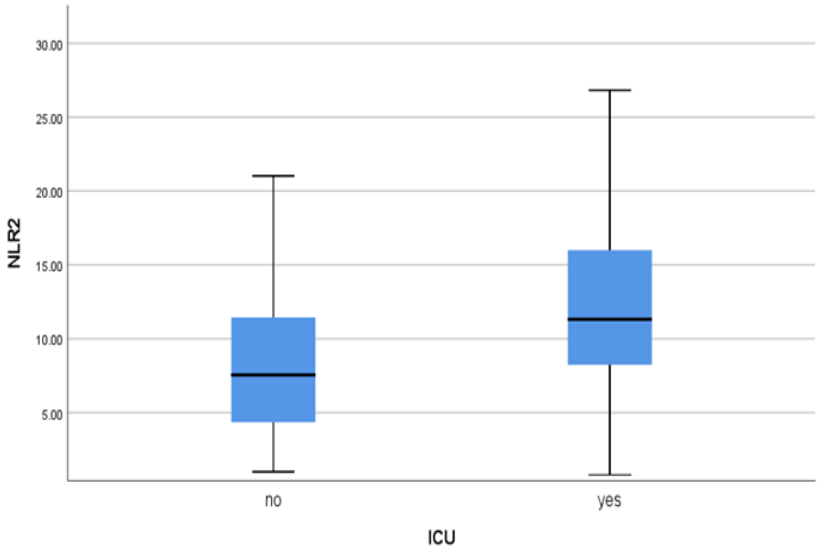

Fig. 1 Simple box plot comparing NLR values between the group of patients who required intensive care and the group that did not.

In addition, we included the items for the statistically significant variables within a binary logic regression model in order to isolate the statistically independent factors, and we got the following results:

Table 3. Multivariate analysis to isolate statistically independent factors to predict the prognostic need for care in patients with COVID-19

Variable	Odds Ratio (OR)	Confidence Interval (CI)		P Value
		Minimum	Maximum	
Age	19	1.4	4.1	0.023
Smoking	2.5	1.2	5.5	0.014
Ischemic heart disease	3.4	1.5	7.7	0.004
Arterial hypertension	1.1	0.6	2.3	0.776
Diabetes	2.1	0.93	4.5	0.073
COPD	1.6	1.1	3.7	0.045
WBC	1	0.9	1.01	0.480
Neu	1	0.9	1.01	0.632
Lym	1	0.9	1.01	0.770
NLR	1.1	1.01	1.2	0.008
LDH	1.01	1	1.06	0.022
CURB 65	1.4	0.6	3.1	0.404

Table 4. Comparison of patients who died and patients who survived

		Deaths (N=81)	Alive (N=122)	P Value
Gender	Male	51 (63%)	73 (59.8%)	0.665
	Female	30 (37%)	49 (40.2%)	
Age		66 ± 15.2	59.9± 16.5	0.008
age categories	< 60 year	24 (29.6%)	35 (43.4%)	0.050
	60 -74year	37 (45.7%)	44 (36.1%)	
	≥75year	20 (24.7%0	25 (20.5%)	
Smoking		39 (48.1%)	36 (29.8%)	0.008
Ischemic heart disease		24 (30%)	15 (12.3%)	0.002
Arterial hypertension		43 (53.8%)	53 (43.8%)	0.108
Diabetes		27 (36%)	30 (25.4%)	0.116
COPD		25 (34.2%)	20 (17.1%)	0.007
WBC		14079 ± 8691	9952 ± 5205	<0.001
Neu		11394 ± 663	8184 ± 4611	<0.001
Lym		1415 ± 1369	1111 ± 762	0.093
NLR		13.2 ± 6.3	8.8 ± 5.9	<0.001
LDH		886 ± 602	611.4 ± 329	0.011
D-Dimer		3416 ± 2859	2132 ± 2132	0.412
CRP		111 ± 88.4	100.8 ± 75	0.309
CURB 65		4.3 ± 0.7	2.1 ± 0.53	<0.001

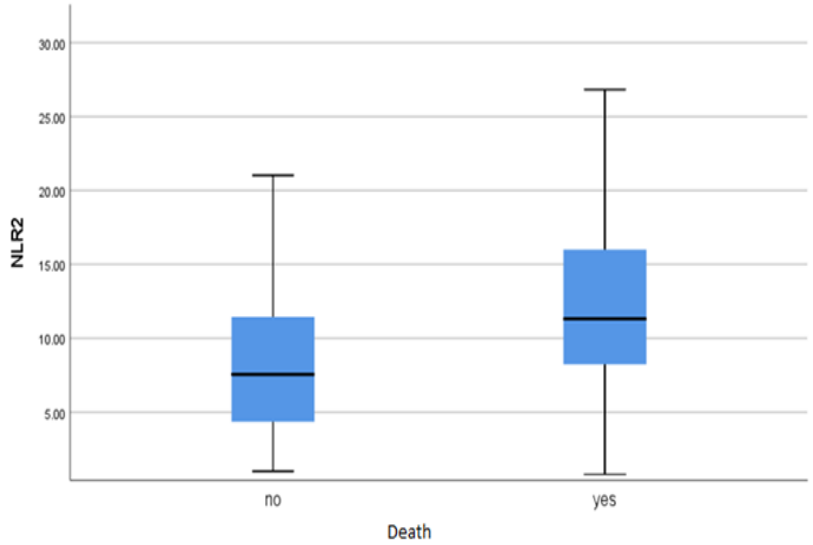

Fig. 2 Simple box plot comparing NLR values between the two groups of patients who died and those who survived

Table 5. Multivariate analysis to isolate statistically independent factors for prognosticating death prognosis in COVID-19 patients

Variable	Odds Ratio (OR)	Confidence Interval (CI)		P Value
		Minimum	Maximum	
Age	2	1.5	4	0.019
smoking	2.3	1.1	5.2	0.018
Ischemic heart disease	2.9	1.5	5.7	0.011
Arterial hypertension	0.9	0.5	2.8	0.799
Diabetes	2.2	1.01	3.3	0.060
COPD	1.7	1.2	3.2	0.035
WBC	1	0.9	1.01	0.681
Neu	1	0.9	1.01	0.832
Lym	1	0.9	1.01	0.791
NLR	1.3	1.1	2	0.004
LDH	1	0.8	1.06	0.122
CURB 65	1.4	1.2	2.1	0.044

We also performed a ROC curve to determine the cut-off point of the NLR in order to predict the poor prognosis in COVID-19 patients represented by death or the need for mechanical ventilation and intensive care. The result was as follows:

Table 6. ROC curve to determine the cut-off point of the NLR

The area under the curve	Confidence Interval (95% CI)		P Value
	Minimum	Maximum	
0.722	0.652	0.792	<0.001

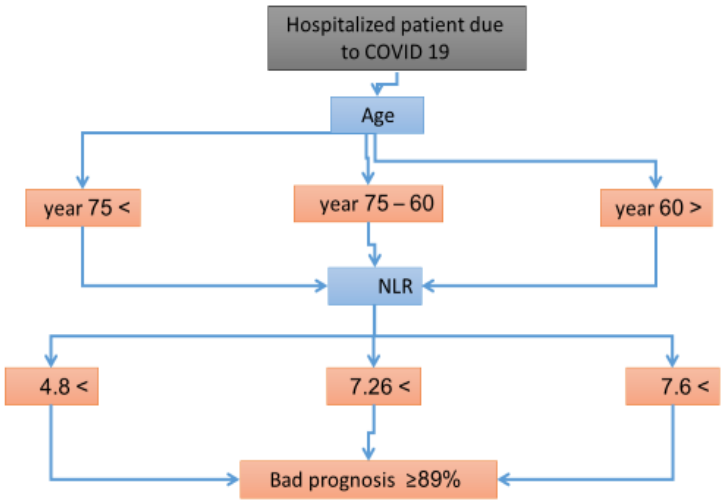

Fig. 3 NLR prediction of severe COVID-19

The highest point of sensitivity and specificity for predicting a bad prognosis was NLR = 9.5, with a sensitivity of 70% and a specificity of 65%.

Also, given the previous results that we obtained in our study regarding the importance of age as a risk factor in Covid19 patients, we determined the cut-off points for the NLR for each age group separately and obtained the following:

Age <60: the high specificity cut-off (NLR = 7.6) had a sensitivity of 53% and a specificity of 89%.

Age 60-75: high specific cut-off point (NLR = 7.26) sensitivity 42% and specificity 89%.

Age > 75: high cut-off specificity (NLR = 4.8), a sensitivity of 34% and a specificity of 88%.

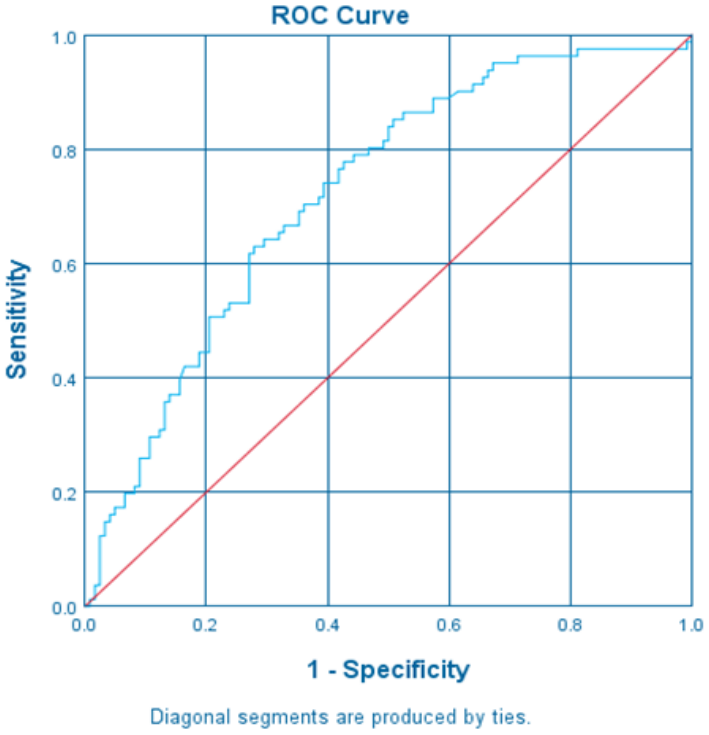

Fig. 4 The cut-off points for the NLR for each age group.

5. Discussion

COVID-19 disease mainly affects the lungs, and in severe cases, it leads to the infection of several organs and may lead to death. SARS-CoV-2 binds to the alveolar receptors 2 and releases several inflammatory factors, stimulating the immune system and resulting in a cytokine storm [18-19]. Therefore, it is crucial to identify severe cases of COVID-19 and treat them promptly, especially in patients with high-risk factors.

A study reported that patients with severe cases of COVID-19 had lower lymphocytes, lower T-helper cells, and slower lymphocyte recovery, which may lead to immune paralysis associated with infection with the virus [20].

In view of the poor economic conditions that Syria suffers from and its impact on malnutrition of patients and its consequences on immunity, in addition to the lack of studies on the ratio of NLR in Covid19 disease, so we aimed in this research to know the relationship between the ratio of neutrophils to lymphocytes NLR and the severity of Covid19 disease, and the prognostic value of this ratio as a predictor of death or the need for intensive care and mechanical ventilation in patients with COVID-19 in our patients. This test is better than white blood cell count because it is more sensitive [21].

In addition to the prominent role of neutrophils in the body's immune mechanism, recent studies on COVID-19 have found the following

1. The abundance, phenotype, and function of neutrophils change, and there is apparent heterogeneity between them, and immature neutrophils increase dramatically.
2. Moderates inhibit T-cell proliferation and INFg production.
3. The ability of neutrophils to form networks increases, and platelets-neutrophil clumps increase, which contributes to increasing the formation of networks and the occurrence of blood clots, especially in the lungs.
4. Hypoxia contributes to neutrophil activation, reinforcing the vicious cycle of neutrophil interaction in damaged lung tissue.
5. The programmed death (Apoptosis) of inflammatory moderates in severe Covid19 delays, so their lifespan is longer than that of circulating moderates, and it also contributes to causing a cytokine storm [22].

In addition to the prominent role of lymphocytes in the body's immune mechanism and the known reasons for their decline, recent studies on COVID-19 have focused on the following points:

1. In COVID-19, lymphocytes spread to all affected organs, and T cells depleted functionally, especially CD4 and CD8 cells. Its significant activation leads to a decrease in the production of type 1 interferon.
2. Neutrophils prevent lymphocytes from multiplying and producing INFg.
3. A negative correlation was observed between the number of T lymphocytes and the levels of (IL10, IL6, and TNF-α).
4. Compensation (T-helper 2) responses are enhanced and accompanied by overexpression of its derived cytokines (IL4, IL5, IL13).
5. Studies have found the absence of ACE2 from the surface of T cells, which suggests that its decrease is not due to direct infection, and on the contrary, other studies have found that the Covid-19 virus was able to infect two lines of T cells in vitro (A3.01 - MT-2), with the inability to reproduce within it.
6. Other causes of low lymphocytes include: cytokine storm, laryngitis, programmed cell death (Apoptosis), especially in (CD4 and CD8), and programmed cell death by inflammation (Pyroptosis) [23-24].

As a preliminary observation, we find that the percentage of patients who died or required intensive care is high compared to the global rates of Covid19 injuries, and this is logically justified because the patients included in our study are all hospitalised patients and need oxygen.

Comparing patients who required intensive care with patients who did not need it:

We did not obtain a statistically significant effect of the patient's gender on the need for intensive care, with males dominating females in the two groups. However, it found a statistically significant effect of advanced age on the need for care or mechanical ventilation (P value = 0.002).

We also found all the risk factors included in our study (smoking, ischemic heart disease, diabetes, arterial hypertension, and chronic obstructive pulmonary disease). It was higher in the group of patients who required intensive care, noting that this difference bears a statistically significant significance in Smoking status (P Value=0.008), ischemic heart disease (P Value=0.001), and chronic lung disease (P Value=0.009) only.

As for the laboratory indicators, our study showed that the neutrophils (NEU), leukocytes (WBC), and the level of neutrophils to lymphocytes (NLR) carried a statistically significant significance between the two previous groups with (P value <0.001), and lymphocytes (LYM) also carried a significant significance. Statistical significance with (P Value=0.038), in addition to (CURB65) with (P Value=0.001), and lactate dehydrogenase (LDH) with (P Value=0.014), all previous laboratory indicators as mentioned showed statistically significant differences between the group of patients. Those who needed intensive care and patients who did not need it. At the same time, the C-reactive protein (CRP) and the level of fibrinogen degradation (D-DIMER) did not have a statistically significant difference between the two groups.

Based on the findings of our study, ischemic heart disease is the most important statistically independent factor in predicting the need for intensive care and mechanical ventilation in patients with Covid19 (P value = 0.004), followed by NLR (P value = 0.008) and then smoking (P value = 0.014).

We also made a comparison between patients who died with patients who survived:

We found that there is no effect of the patient's gender on the death prognosis, while there is a statistically significant effect of advanced age on the prognosis. We also found that all risk factors were higher within the mortality group, noting that this difference carries a statistically significant significance only in the case of smoking (P Value=0.008), ischemic heart disease (P Value=0.002) and chronic lung disease (P Value=0.007).

In terms of laboratory parameters, the NEU showed a statistically significant significance between the group of patients who died and the patients who survived with (P value < 0.001), as well as for white blood cells (P value < 0.001) and lactate dehydrogenase LDH. (P Value=0.011), CURB65 marker (P Value<0.001), and neutrophil to lymphocyte ratio NLR with (P Value<0.001).

While lymphocytes LYM, C-reactive protein CRP, and the level of fibrinogen degradation D-DIMER all did not have a statistically significant difference between the two groups.

Here, it seems clear from our statistical study that NLR is the best statistically independent factor for predicting the death prognosis in Covid-19 patients among the other independent factors that we obtained (P Value= 0.004), which supports our theoretical study on the importance of its prognostic value. Next in importance is ischemic heart disease (P Value= 0.011) and then smoking (P Value= 0.018).

A recent systematic review and meta-analysis by Feng et al. to re-identify inflammatory immune factors in COVID-19 infection concluded that the NLR is associated with infection development and can be used by clinicians to identify high-risk or early deterioration. Several other studies have also reported their findings that the NLR can be used as an early warning signal for severe COVID-19 infection and is considered an independent marker of poor clinical outcome and mortality [25-26].

In their study, li et al. found that patients with COVID-19 pneumonia who were admitted to the intensive care unit had higher levels of (IL2, IL7, and IL10,) as well as higher levels of (IP10, MCP1, GSCF, MIP1A, TNFα). in plasma, reflecting a severe systemic inflammatory response [27].

Some studies have reported that malnutrition is a consistent risk factor for COVID-19, demonstrating an influential association with NLR [28-29].

We also performed a ROC curve to determine the cut-off point of the NLR in order to predict the bad prognosis in COVID-19 patients represented by death or the need for mechanical ventilation and intensive care. % and the quality is 65% with (P Value <0.001), this reflects a good relationship between NLR and poor prognosis in COVID-19 patients.

Given the high importance of both NLR and CURB 65 in predicting poor prognosis for COVID-19 patients, we made a comparison between these two indicators and observed the following:

1. The NLR was an easy-to-use predictor that was faster than CURB65.
2. NLR outperformed CURB65 as a statistically significant and independent factor with (P value = 0.004) for the first versus (P value = 0.044) for the second.
3. There is a positive correlation between the two; that is, the NLR values were statistically significantly lower when the CURB 65 values were less, with (P value < 0.001), and this confirms the expression NLR of the general condition of the patient and enhances the value of the prognostic significance It has a prognostic indicator in covid-19 disease.

We studied the relationship between the duration of hospitalisation and the NLR value of survivors and the deceased independently. The average duration of hospitalisation for survivors was (7.5 ± 3.1), and for the deceased was (7.8 ± 5.5) with the value of (P value) not achieving statistical significance. The statistically significant relationship between NLR and hospitalisation period was absent in our study in deceased patients and survivors. This explains by the fact that all patients included in our study were patients with moderate to severe conditions and in need of hospitalisation, unlike other studies that included patients with mild conditions who did not need hospitalisation. Our study did not include follow-up values for NLR during hospitalisation, discharge or death. Thus, we found no value for NLR upon acceptance in affecting the duration of hospitalisation, but its expected effect is investigated by studying its follow-up values until the patient's discharge or death and linking them to the results.

Thus, it appeared that we have an inverse relationship between the cut-off point for NLR and age; that is, the higher the patient's age, the lower the value of the NLR that is capable of a bad prognosis for the disease, and the contrary, the lower the patient's age, the higher the NLR needs to carry the same lousy prognosis. It confirms the importance of age in the prognosis of Covid19 disease. It is in line with the principle that younger ages of patients exhibit more excellent

immunity and resistance to the disease, as well as enjoy better prognosis, as physiological and immune functions gradually decline in the elderly.

6. Conclusion

There is a statistically significant relationship between the ratio NLR and the severity of Covid19 disease, as it was positively associated with it. Therefore NLR can be used as an early warning signal for the deterioration of severe Covid-19 infection, and it can also provide an objective basis for early detection of severe pneumonia in Covid-19 and dealing with it. This sign is significant in our environment where lack of resources often prevents expensive tests, especially in light of disease pandemics.

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