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Research Paper

Neutrophil/Lymphocyte Ratio as a Predictor of Diagnosis and Severity of COVID-19 Infection in The Emergency Department of Baghdad Teaching Hospital

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ABSTRACT:

BACKGROUND:

Contracting the coronavirus results in the development of COVID-19, a condition characterized by swift human-to-human transmission and varying levels of mortality. Fatalities often stem from complications such as acute respiratory distress syndrome, multi-organ failure, and other severe health issues. The global application of the neutrophil-to-lymphocyte ratio serves as a widely utilized indicator to assess the prognosis of patients dealing with various infectious diseases, such as pneumonia, as well as non-infectious conditions like cancer.

OBJECTIVE:

The aim is to assess the diagnostic and severity predictive efficacy of the neutrophil-to-lymphocyte ratio in patients with Coronavirus disease.

METHODS:

A cross-sectional study done in the emergency department of Baghdad Teaching Hospital in Baghdad City-Iraq. Sample collected randomly and 528 patients who had symptoms of Corona virus disease were enrolled prospectively in the study.

RESULT:

Patients with a neutrophil-to-lymphocyte ratio ≥3.6 exhibited a 20.3 times higher likelihood of having Coronavirus disease compared to those with a neutrophil-to-lymphocyte ratio of ≤3.6. The neutrophil-to-lymphocyte ratio demonstrated a significant increase with the severity of the disease. While the age difference among patients did not show statistical significance in terms of diagnosis, it appeared to play a significant role in determining the severity of the disease. The optimal threshold at 4.3 for the neutrophil-to-lymphocyte ratio displayed superior predictive capabilities for identifying patients at risk of developing severe to critical disease, especially among those aged 51.5 years and older, showcasing the highest sensitivity and specificity.

CONCLUSION:

An increased neutrophil-to-lymphocyte ratio serves as an independent biomarker for both diagnosing and predicting the severity of Coronavirus disease. Additionally, age and the neutrophil-to-lymphocyte ratio emerge as independent risk factors influencing the severity of the infection.

KEYWORDS: Neutrophil, Lymphocyte, COVID-19, Coronavirus.

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INTRODUCTION:

In December 2019, a version of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS CoV2) was initially recognized in Wuhan, China[12]. Upon infection with this virus, individuals develop coronavirus disease (COVID-19). The transmission of COVID-19 has been observed to occur rapidly among humans, leading to various degrees of mortality. The severe outcomes are often associated with conditions such as acute respiratory distress syndrome, multi-organ failure, and other critical complications[34]. In 11 March 2020, more than 118000 Coronavirus disease 2019 (COVID-19) cases were confirmed world-wide, resulting in its announcement as a pandemic[5].

The world-wide spread of the pandemic has been swift since March 2020. By mid-April 2020, more than two million individuals had been

diagnosed with this disease, resulting in over one hundred fifty thousand deaths[6].

The majority of individuals with a coronavirus infection experienced mild symptoms. Moderate infections typically manifested with dyspnea occurring approximately one week after onset. In contrast, severely ill patients exhibited rapid progression to conditions such as acute respiratory failure, acute respiratory distress syndrome, coagulopathy, metabolic acidosis, and septic shock. Early identification of risk factors for severe infection facilitated the timely administration of appropriate supportive care and, if necessary, prompt admission to the intensive care unit (ICU). For those with mild illness, isolation and symptomatic treatment proved sufficient, and admission to the ICU was deemed unnecessary unless there was a rapid deterioration in the condition.[1]

Studies show that patients with COVID-19 had wide disease severities, and Elevated incidences of severe or critical illness and admission to the intensive care unit (ICU)[789].

Many studies have shown that high lymphocyte levels are signs of good prognosis. Lymphopenia pose a risk for severe illness and mortality in individuals with various diseases[1011].

It has been widely recognized in the early stage of this disease that the lymphocyte count is decreased. We suggest that a blood lymphocyte associated index could be a potential predictor of diagnosis and disease severity. The neutrophil to lymphocyte ratio is a world-wide used marker for estimating the prognosis of patients with other infectious diseases like pneumonia, tuberculosis and non-infectious like cancer[1213]. High NLR refers to poor clinical prognosis.

Many studies have demonstrate the clinical characteristics of patients with coronavirus (SARS CoV2) infected pneumonia (COVID-19), and shown that patients with severe illness tend to have higher neutrophil to lymphocyte ratio (NLR)[14]. Baseline NLR could be an independent marker of in-patient mortality.[14]

The neutrophil to lymphocyte ratio (NLR) serves as an excellent marker, easily calculable from a complete blood count, and demonstrates a close association with the inflammatory status of patients.[14]

Elevated NLR values indicate increased fatality risk, not only in infectious diseases but also in cancer cases[13]. Research has identified NLR as an independent risk factor for in-patient mortality associated with COVID-19. Recognizing a reliable and easily assessable indicator of disease progression can assist clinicians in optimizing treatment strategies and reducing COVID-19-related mortality without overburdening medical resources. Further investigations are needed to determine whether NLR can predict the progression from mild to critical illness in older patients with COVID-19[15].

Neutrophil releases high amounts of reactive oxygen species that can trigger cell DNA damage and free the virus out of the cells. Then, antibody dependent mediated cell (ADCC) can kill the virus in direct way, releasing virus antigen, and trigger cell-specific and humeral immunities[16]. also, Neutrophil stimulated by distinct cell populations and produces many cytokines and effectors molecules, like circulating vascular endothelial growth factor (VEGF). VEGF triggers tumor angiogenesis, growth, and metastasis[17]. VEGF-A and VEGF-C have significantly higher expressions in infection, and low expression of VEGF and VEGFR refer to markedly inhibited tissue and organ damage[17]. Moreover, Neutrophil can be stimulated by virus related inflammatory factors, like interleukin 8 and interleukin 6, granulocyte colony stimulating and tumor necrosis factor alpha factor, and interferon gamma factors, released by lymphocyte and endothelial cells[1819]. Furthermore, human immune response stimulated by viral infection mainly depend on lymphocyte, where systemic inflammation significantly reduces cellular immunity, which markedly decreases CD4+ T lymphocytes and increases CD8+ suppressor T lymphocyte[19]. so, virus-triggered inflammation expressed as high NLR.

Biomarkers provide valuable insights into the severity of COVID-19, offering a crucial tool to address the challenge of resource depletion during this pandemic. Early risk assessment for COVID-19 patients upon hospital admission is essential for delivering optimal care and efficiently managing both human and technical resources. This approach ensures that the available limited resources are allocated to the most deserving patients.

One such biomarker, the neutrophil-to-lymphocyte ratio (NLR), serves as an inflammatory marker derived by dividing the absolute counts of blood neutrophils and lymphocytes—two easily obtainable parameters in clinical settings. Recent studies have demonstrated significantly elevated NLR levels in more severe COVID-19 cases, indicating its prognostic value. The rationale behind utilizing this marker clinically lies in the observation that severe COVID-19 patients tend to exhibit higher levels of inflammation upon hospital admission. Consequently, assessing NLR levels at admission

enables early risk predictions, helping identify patients who should be prioritized for limited resources.[20]

In fact, NLR is a marker with a low cost compared to cytokines, as the use of the blood count in the emergency room is a routine. Therefore, NLR is a useful and helpful systemic inflammatory marker for diagnosis of COVID-19-infected patients and could be useful indicator of a poor prognosis at the initial moment of assessment. Added to that, it highlights the importance of further investigations to help the assessment of the patients' clinical status.[14]

MATERIALS AND METHODS:

Conducted as a cross-sectional study spanning from March 15, 2020, to December 31, 2020, this research involved the collection of samples using a randomized table. A total of 528 patients presenting symptoms of COVID-19 were prospectively enrolled in the study, with symptoms encompassing fever, fatigue, sore throat, cough, frequent bowel movements, eye redness, headache, taste or smell loss, skin rash, discoloration of fingers or toes, difficulty breathing or shortness of breath, chest pain, and loss of movement or speech.[14] Clinical examinations were performed, and the patients' clinical status and vital signs were recorded. All patients underwent COVID-19 testing using real-time transcription-polymerase chain reaction (RT-PCR), and those results were included in the study.

The patients were categorized into two groups: COVID-19 positive and COVID-19 negative. Neutrophil, lymphocyte, and the neutrophil-to-lymphocyte ratio (NLR) values were calculated. Complete blood count parameters were obtained using the NIHON KOHDEN MEK-6510K device. Reports from thoracic computed tomographies (CT scans of the chest) were obtained online by the on-call radiologist from April 2020 to mid-July. Subsequently, the CT interpretations were conducted by the researcher and the senior emergency medicine professional on call.

Patients were also grouped regarding their clinical situation into four groups, mild, moderate, severe and critical according to the National Guidance of COVID-19 Management published by the Iraqi Ministry of health**Error! Reference source not found.**. Ethical approvals were obtained from the Ministry of Health/Republic of Iraq and Baghdad Teaching Hospital.

Inclusion criteria:

Patients above 18 who had signs and symptoms of COVID-19.

Exclusion criteria:

- Patients under 18.
- Pregnant patients.
- Trauma patients.
- Patients on chronic Steroid therapy.
- Patients on chronic NSAIDs use.

The data were gathered and each questionnaire coded with an identifying serial number then recorded by the researcher using Statistical Package for Social Sciences (SPSS) version 24 with the help of a consultant statistician. The P value was assigned to be equal or less than 0.05 to consider Statistical significance.

RESULTS:

Out of the total 528 patients included in this study, 204 (38.6%) were females, and 324 (61.4%) were males (Fig 1). Among the 528 cases, 356 patients tested positive for COVID-19 (67.4%). The mean age for COVID-19 positive patients was 56 years, while it was 61 years for COVID-19 negative patients. (Fig 2). This age difference was statistically insignificant (P=0.073). Similarly, the gender distribution between the groups was also found to be insignificant (P=0.474).

Fever was present in 42% of COVID-19 positive patients, and the levels of fever were significantly higher when comparing COVID-19 positive cases to COVID-19 negative cases (P=0.008). The lymphocyte count was significantly lower (P=0.014) in COVID-19 positive cases compared to COVID-19 negative cases. Additionally, the neutrophil-to-lymphocyte ratio (NLR) value was significantly higher in COVID-19 positive patients compared to COVID-19 negative patients (P=0.023).

There were no significant differences between COVID-19 positive and negative patients regarding total white blood cell (WBC) count, neutrophil count, platelet count, heart rate, respiratory rate, and oxygen saturation. A strong correlation was observed between COVID-19 positive cases and chest computerized scans showing typical viral pneumonia signs in 328 cases (P <0.001). The laboratory and clinical characteristics of COVID-19 positive and negative patients are detailed in Table - 1.

Table 1: Laboratory and Clinical characteristic of patients' rT-PCR Positive and Negative COVİD-19 (n=528).

Various factors		COVID + n=356	COVID - n=172	P. value
Mean age (year)		56(±18)	61(±14)	0.073
Gender	Male	219	105	0.474
	Female	137	67	
WBC K/µL		6.5(±3.9)	5.5(±4.4)	0.676
Neutrophil K/µL		3.4(±1.6)	2.9(±1.3)	0.134
Lymphocyte K/µL		1.4(±0.6)	2.1(±0.9)	0.014
NLR		5.1(±2.8)	3.1(±1.7)	0.023
Platelet K/µL		188(±22)	231(±41)	0.631
Temp		37.7(±1.1)	36.9(±0.7)	0.008
RR		19(±6.5)	17(±5.5)	0.094
BP (MAP)		94(±17.7)	95(±16.3)	1.132
HR		95(±21)	80(±18)	0.083
SPO_2 %		93(±6.5)	95(±4.5)	0.069
CT chest (typical viral pneumoni		284	44	< 0.001

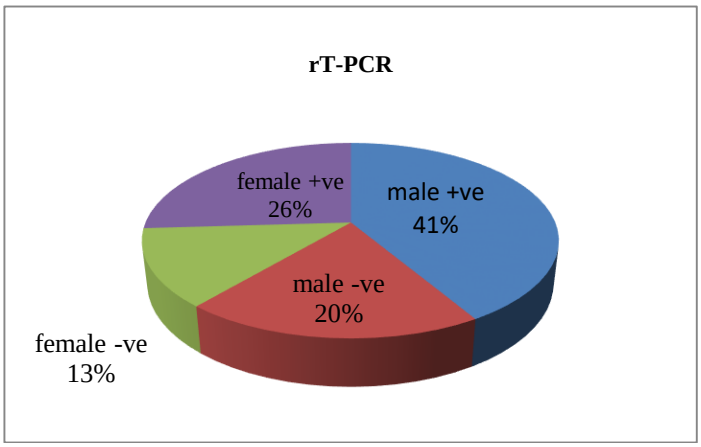


Fig 1: Pie chart showing the percentage of male and female with the rT-PCR result.

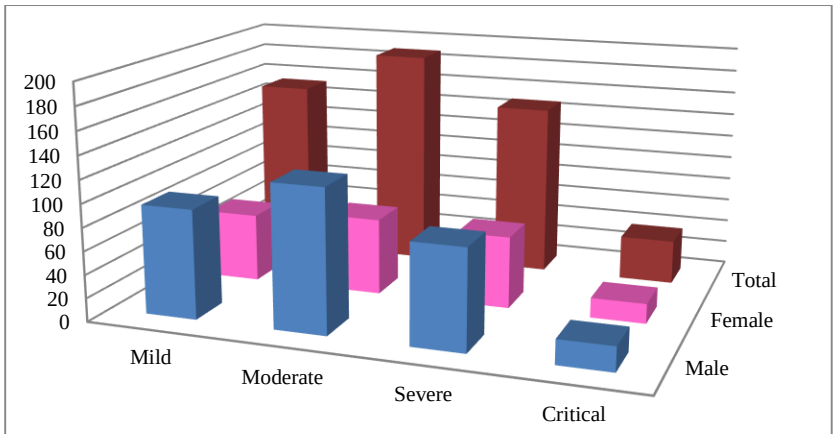
The impact of the neutrophil-to-lymphocyte ratio (NLR) on the diagnosis of COVID-19 was analyzed using ROC curve and AUC, revealing significance when NLR was ≥ 3.6 (AUC: 0.712; P=0.023, 95% CI 0.546 to 0.647) (Fig.3). The corresponding sensitivity and specificity were 69.02% and 64.40%, respectively, with a positive predictive value of 81%, negative predictive value of 52%, and a disease prevalence of 63.5%.

The impact of Fever on the COVİD-19 diagnosis was also analyzed via ROC curve and AUC, with significant results observed when temperature was ≥ 37.8 (AUC: 0.692; P=0.008, 95% CI 0.589 to 0.742). The associated sensitivity and specificity were 63.22% and 79.24%, respectively, along with a positive predictive value of 82%, negative predictive value of 41%, and a disease prevalence of 66.1%.

A logistic regression model was constructed, incorporating NLR ≥ 3.6 and fever ≥ 37.8. According to this model, the odds ratio for a positive COVID-19 result was 20.3 for NLR >3.6 and 10.5 for fever >37.8 (Standard Error = 1.324, Odds ratio = 20.3, P = 0.023) for NLR, and (Standard Error = 1.079, Odds ratio = 10.5, P = 0.029) for fever.

Patients were grouped regarding the severity of the clinical situation into four sub-groups, according to the National Guidance of COVID-

19 Management published by the Iraqi Ministry of health**Error! Reference source not found.**. Mild was (28.9%), moderate (35.8%), severe (28%) and critical was (7.19%) of the total included cases, Fig (4), There was no significant difference in disease severity between the groups regarding gender (P =0.352). Mean age for each group were (48.7y) for Mild, (55.5y) for Moderate, (59.3y) for Severe and (60.5y) for Critical patients. Results shows significant correlation between age and mild to moderate severity of the disease (p=0.031) and moderate to Severe (p=0.029), but when comparing the severe with the critical subgroups there were not any significantly correlation to age (p= 0.108). However, overall there was correlation and found to be significant between age and severity (p=<0.001). The Age distribution in relation to disease severity is shown in Fig. (5).



	Mild	Moderate	Severe	Critical
Male	94	123	86	21
Female	59	66	62	17
Total	153	189	148	38

Fig.4: Column chart showing the disease severity in relation to the Gender.

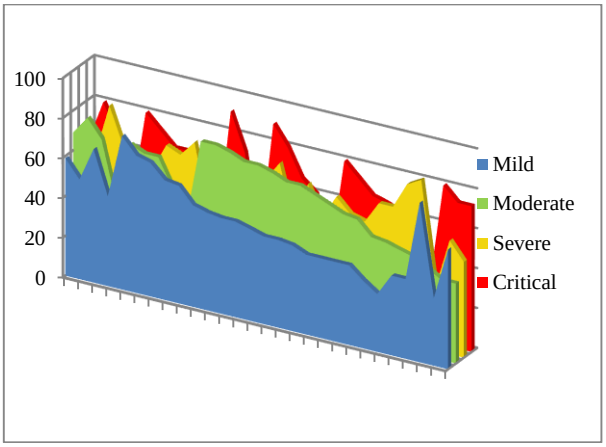


Fig 5: Age distribution in relation to disease severity.

WBC count was significantly correlated when comparing mild to critical severity (p= 0.044), overall severity has no significant correlation to WBC count.

Neutrophil count had a significant correlation to overall severity (p=0.002), and moderate to severe groups (p=0.023), but the significance decreases when comparing mild to moderate and severe to critical sub-groups.

Lymphocytes count was significantly lower (P=0.014) in COVID-19 (+) patient in comparison to COVID-19 (-) patients, but no significance noticed when comparing mild to moderate severity (p=0.110). However,

Lymphocytes noticed to be significantly low when comparing moderate to severe cases (p=0.041) and severe to critical cases (p=0.045). Overall there was significant correlation to severity (p=0.042).

NLR was significantly high as the severity increase (p=0.009). Mild to critical (p=0.002), moderate to severe (p= 0.022), severe to critical (p=0.050). But when comparing mild to moderate severity the NLR was not significantly correlated (p=0.110).

To identify patients with mild, moderate, severe and critical cases of COVID-19, we utilized optimal cut-off values determined through areas under the curve (AUC) and ROC analysis for Age and NLR, resulting in AUC values of 0.701 for age and 0.814 for NLR. The optimal cut-off value for NLR was determined to be 4.3, while the optimum cut-off value for age was 51.5 years.

The ROC curve (Shown in Fig (6)) illustrates the assigned thresholds for NLR and age. The optimal threshold at 4.3 for NLR indicates a prognostic potential for patients with severe to critical disease, exhibiting the highest sensitivity, specificity, and the largest AUC when age is ≥ 51.5 years old. Conversely, for patients with age < 51.5 years old and NLR < 4.3, there is a higher likelihood of having a mild to moderate disease.

Clinically, body temperatures and MAP had no significant correlation with the overall disease severity. However, when comparing mild to critical cases MAP was significantly lower (p=0.045).

Heart rate, Respiratory rate and SPO_2 were noticed to be significantly correlated to disease severity (P=<0.001). There was still a high significant relation when comparing sub-groups. Associations of various parameters with Severity of COVİD-19 are manifested in Table **(2)** Receiver Operating Characteristic Curve (ROC curve) for NLR and Age in relation to disease Severity.

Table 2: Association of various factors with Severity of COVİD-19 (n=528).

Various factors	Mild n=153	Moderate n=189	Severe n=148	Critical n=38	p-value
Mean age (SD), year	48.7(±17.4)	55.5(±16.9)	59.3(±15)	60.5(±20.3)	<0.001
Men	94	123	86	21	0.352
Women	59	66	62	17	
WBC K/µL	9.9(±5.5)	8.7(±3.2)	11.4(±3.8)	12.5(±4.4)	0.062
Neutrophil K/µL	6.1(±4.9)	6.7(±3.2)	8.5(±3.8)	9.4(±4.2)	0.002
Lymphocyte K/µL	2.4(±1.1)	2.1(±0.9)	1.6(±0.7)	1.2(±0.4)	0.042
NLR	2.1(±1.6)	2.3(±1.4)	8.7(±2.1)	16.2(±3.4)	0.009
Temp	37.3(±0.8)	37.7(±0.8)	37.6(±0.8)	37.7(±0.8)	0.543
RR	20(±4.4)	24(±4)	27(±4.2)	38(±5.5)	<0.001
BP (MAP)	95.6(±13.2)	90(±13.4)	93.3(±15.3)	83.9(±13.2)	0.139
HR	88(±17.1)	90(±17.4)	100(±14.2)	112(±24)	<0.001
SPO_2	95.5(±1.8)	94.6(±2.2)	83.5(±4.9)	72(±9.1)	<0.001
rT-PCR +	45	158	121	32	<0.001
rT-PCR -	108	31	27	6	<0.001
CT chest (typical viral pneumonia sign) n	0	189	103	36	<0.001

DISCUSSION:

In this investigation, a total of 528 patients were enrolled, with 356 testing positive for COVID-19 and 172 testing negative, as confirmed by laboratory results. Notably, the neutrophil-to-lymphocyte ratio (NLR) coupled with fever was significantly higher in COVID-19 positive patients. However, there was no significant difference observed between COVID-19 positive and negative cases regarding age and gender. Despite this, age emerged as a significant factor influencing the severity of the disease. Fever was identified as one of the key clinical symptoms of COVID-19, aligning with findings from a study published in The Lancet by Chen N, Zhou M et al., where fever was reported in 51% of COVID-19 patients[21],the rate was found to be 43.8% in a study done by Yang AP et al[22]. The levels of fever were found to be 42% in this study. In this study there was significant correlation between age and mild to moderate severity of the disease and moderate to Severe, but when comparing the severe with the critical subgroups there were not significantly correlate to age and that because the severe and critical patient were both tend to be older. However, overall there was a significant correlation between age and severity. Regarding

WBC count, in this study there was an insignificant correlation between COVID-19 (+) and (-) patients regarding WBC, in a study done by Olga Pozdnyakova et al**Error! Reference source not found.**, they also found no deference in WBC count between COVID (+) and (–) patients , however in other study done by Rajab Mardani et al**Error! Reference source not found.**, on a group of COVID19 patients in one month, they found that COVID-19 patient tend to have low WBC count, on the other hand in the same study WBC count was significantly high in severe cases, in this study the WBC is significantly high when comparing critical to mild cases (p= 0.044), but no significant difference found when comparing moderate and severe cases or severe and critical cases. In a study done by Zhou Y et al[25], difference was found to be insignificant between moderate and severe patients regarding the WBC count , and that is similar to what we found in this study. In this study, the difference was insignificant between COVID-19 (+) and (-) patients regarding Neutrophil count, but Neutrophil count had a significant correlation to overall severity (p=0.002), Neutrophilia was obvious in severe/critical cases when comparing to mild/moderate cases. In a study done by Yang AP et al[22], Lymphocytes count was significantly lower in COVID-19 (+) cases compared to COVID-19 (-) cases (P=0.014). However, Lymphocytes count noticed to be significantly low when comparing moderate to severe cases (p=0.041) and severe to critical cases (p=0.045). Overall there was significant correlation to severity (p=0.042). But no significance noticed when comparing mild to moderate severity cases (p=0.110). In a study done by Kim ES et al[26], a reduction in the peripheral blood lymphocyte count was identified in COVID-19 patients who were critically ill. A systematic review and meta-analysis done by Raymond Pranata and Ian Huang on 24 studies, the meta-analysis showed that Lymphopenia on admission was associated with poor outcome in patients with COVID-19.[27]The previous meta-analysis shows that Lymphopenia may be explained by the body immune response which is started by lymphocytes stimulated by viral infections. In this study, the NLR value was significantly higher in COVID-19 (+) cases compared to COVID-19 (-) cases (P=0.023).ROC curve and AUC were used to analyze the impact of NLR on the diagnosis of COVİD-19 and the result was found to be significant when NLR ≥ 3.6. in a study done by Ahmet Nalbant et al[28], they found NLR was significantly elevated in COVID-19 patients. NLR was significantly high as the severity
increase (p=0.009, In a study done by Ai-Ping Yang et al[22] , they found that elevated age and NLR can be considered independent biomarkers for indicating poor clinical outcomes. In a study done by Elnaz Vafadar Moradi et al, reported by the American journal of emergency medicine, they found that NLR was significantly high in severe and critical COVID-19 cases.[29] . In a study done by Danielle Tatum and Jacob Stoveret et al**Error! Reference source not found.**, they found that NLR is significantly high in critically ill COVID-19 patient, and found that NLR is a prognostic parameter for ICU admission and intubation during hospitalization. An elevated neutrophil-to-lymphocyte ratio (NLR) provides valuable insights into the progression of COVID-19. The clinical symptoms exhibited a pronounced increase in severity, and the transition from mild/moderate to severe/critical conditions occurred rapidly. Therefore, inflammation-related Neutrophilia and Lymphopenia increase NLR.

However, NLR is inexpensive, rapid, and helpful factor that would be easily determined by complete blood count.

CONCLUSION:

In conclusion, our study reveals that a high neutrophil-to-lymphocyte ratio (NLR) serves as an independent diagnostic marker for COVID-19 cases. The NLR was significantly elevated in COVID-19 positive patients, and a determined cut-off value showed that individuals with NLR ≥3.6 were 20.3 times more likely to have COVID-19 compared to those with NLR ≤3.6. Similarly, the likelihood of COVID-19 increased by 10.5 times when the body temperature was ≥37.8 °C. This study underscores the independent significance of elevated fever and NLR as markers for COVID-19 cases, aiding in early diagnosis.

Furthermore, our findings suggest a potential correlation between age and NLR with the severity of the disease, offering insights into the prognosis of clinical status. The identified optimal threshold at 4.3 for NLR demonstrated a heightened prognostic potential for predicting severe to critical disease, particularly with the highest sensitivity and specificity observed in individuals aged ≥51.5 years old.

RECOMMENDATIONS:

This finding can help the Emergency Department in the early triaging of COVID-19 patient, so we designed an Algorithmic protocol (Fig.7) to guide the Triage System in classifying each

COVID-19 patient according to Age and Lab result.

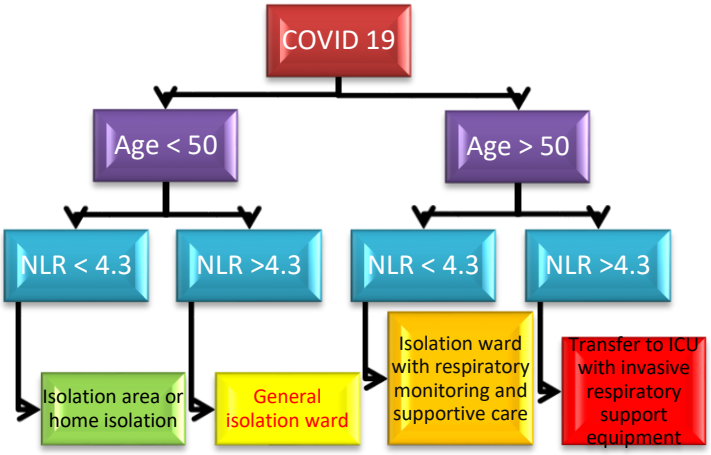


Fig.7: Algorithmic diagram to Guide early Triaging COVID-19 patients.

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