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Research Article

THE CORRELATION BETWEEN NEUTROPHIL-TO-LYMPHOCYTE AND CLINICAL SEVERITY INPATIENTS WITH COVID-19 IN DAMMAM CITY, KINGDOM OF SAUDI ARABIA

Marai Alshakhs¹, Ahmed Als Salman, Abdullah Almuslam, Mohammed Almomtan,
Mohammed Almulaify, Ayat Boholigah, Mujtba Aljobran²

¹ Internal Medicine Consultant, Internal Medicine Department at Dammam Medical Complex

² Internal Medicine Resident, Internal Medicine Department at Dammam Medical complex

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Abstract:

Background: COVID-19 is a global pandemic. spreading via respiratory droplets. Patient condition who is infected with COVID-19 can deteriorate to acute respiratory distress syndrome and lead to death. Some laboratory parameters have to be obtained in order to assess the severity of that inflammation such as NLR.

Objective: To determine the relationship between NLR and mortality in COVID-19 patients, and to predict the outcome of high NLR in COVID-19 patients.

Design: Retrospective observational study.

Sitting: Dammam Medical Complex, Dammam city, kingdom of Saudi Arabia.

Methods: 162 patients aged above 15 years positively diagnosed with COVID-19 were reviewed.

Results: mean age of the patients was 46.5, with more than a half were in the older age. Males dominated than females with more than two-thirds were non-Saudis. prevalence of patients with chronic diseases was 43.2% while those with pneumonia was 58.6%. The outcome shows 92% recovered and (8%) death. NLR was higher in males compared to females ($T=1.523$; $p=0.004$) and in non-Saudi's versus Saudis ($T=-3.054$; $p<0.001$). Patients with pneumonia had higher NLR mean value ($T=4.295$; $p<0.001$). NLR mean value of non-survival patients was significantly higher compared to those who recovered ($T=5.663$; $p=0.001$).

Conclusion: high NLR was associated with an increased rate of morbidity and mortality in patients with COVID-19 infection. NLR remain extremely useful prognostic factors in categorizing illness severity due to COVID-19

Corresponding author:

Abdullah Almuslam,

E-mail: openheart77@hotmail.com

Mobile : +966565635025

QR code



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INTRODUCTION:

An outbreak of pneumonia of unidentified cause emerged in Wuhan city in December of 2019. In January of 2020, the novel Corona virus was identified from a throat sample in Wuhan city, and in March of 2020 the WHO declared the novel corona virus as a global pandemic. The virus was named COVID-19, as one of Corona viruses group members (1).

COVID-19 transmits from person to person by droplets, with an incubation period of 14 days. Patients usually present with fever, cough, malaise, shortness of breath, diarrhea and pneumonia which can deteriorate to acute respiratory distress syndrome (ARDS) (2).

COVID-19 leads to an inflammatory response in the body, and some laboratory parameters have to be obtained in order to assess the severity of that inflammation such as C-reactive protein, lymphocytes count, D-dimer and neutrophil to lymphocyte ratio (NLR) (3,4).

Several studies showed that an increased level of NLR was associated with a worse disease outcome, and thus NLR level can guide the clinicians to categorize the patient's severity accordingly and predict the disease outcome (1,3,4).

Our study aims to select one of the most useful prognostic factors, the NLR, to categorize illness severity due to COVID-19 in Dammam city, Kingdom of Saudi Arabia (KSA).

Literature review:

COVID-19, formally known as SARS-COV-2, is a member of Coronaviridae family, which are RNA viruses in nature (5). It emerged from Wuhan city, China, in December 2019 and was declared to be a pandemic by WHO in March of 2020 (1). It is thought to have been transmitted to humans from infected bats.

COVID-19 can be transmitted via respiratory droplets and direct contact of contaminated surfaces (5).

The clinical symptoms of patients with COVID-19 can be numerous and may include respiratory and gastrointestinal symptoms. Clinically, patients may

present with fever, malaise, fatigue, sore throat, and diarrhea. Their condition may worsen and patients may develop pneumonia or ARDS (2).

The population who is at most risk are the elderly and those with comorbidities, such as cardiovascular disease, diabetes mellitus and respiratory disease. These patients' condition can quickly deteriorate to ARDS and even death (4,6).

No effective treatment has been well established yet, and supportive measurement is the current mainstay of treatment (2).

COVID-19 pneumonia leads to an inflammatory response and raises inflammatory markers such as lymphocyte to c-reactive protein and NLR (3). Several studies have shown a correlation between a raised NLR, more severe COVID-19 illness and higher mortality rate.

Objective of our study:

To determine the relationship between NLR and mortality in COVID-19 patients, and to predict the outcome of high NLR in COVID-19 patients.

METHODOLOGY:

Retrospective observational study.

Inclusion criteria: males and females aged above 15 years positively diagnosed with COVID-19.

Exclusion criteria: younger than 15 years of age, pregnant females, patients with existing malignancy and any other infection other than COVID-19.

Statistical Analysis and result:

Descriptive statistics were summarized using numbers, percentages, median, minimum, maximum, mean and standard deviation, whenever appropriate. Neutrophil-to-lymphocyte ratio were compared with baseline characteristics and outcome of the patients by using Mann Whitney U test. Normality tests were conducted using Kolmogorov-Smirnov test as well as Shapiro Wilk test. The follows abnormal distribution. Thus, non-parametric tests were applied. A P-value <0.05 was considered statistically significant. All data analyses were performed using Statistical Packages for Social Sciences (SPSS) version 21 Armonk, NY: IBM Corporation.

RESULTS:**Table 1: Baseline characteristics and outcome of the patients (n=162)**

Study variables	N (%)
Age group (mean \pm SD)	46.5 \pm 12.2
•24 – 45 years	78 (48.1%)
•>45 years	84 (51.9%)
Gender	
•Male	120 (74.1%)
•Female	42 (25.9%)
Nationality	
•Saudi	51 (31.5%)
•Non-Saudi	111 (68.5%)
Associated chronic diseases	
•Yes	70 (43.2%)
•No	92 (56.8%)
Pneumonia	
•Yes	95 (58.6%)
•No	67 (41.4%)
Outcome	
•Death	13 (08.0%)
•Recovered	149 (92.0%)

The present study analyzed 162 patients who were diagnosed with COVID-19. As seen in table 1, the mean age of the patients was 46.5 (SD 12.2) with more than a half (51.9%) were in the older age group (>45 years). Males dominated the females (74.1% vs 25.9%) with more than two-thirds (68.5%) were non-Saudis. The prevalence of patients with associated chronic diseases was 43.2% while the prevalence of patients with pneumonia was 58.6%. The outcome shows that 92% recovered and the rest did not (8%).

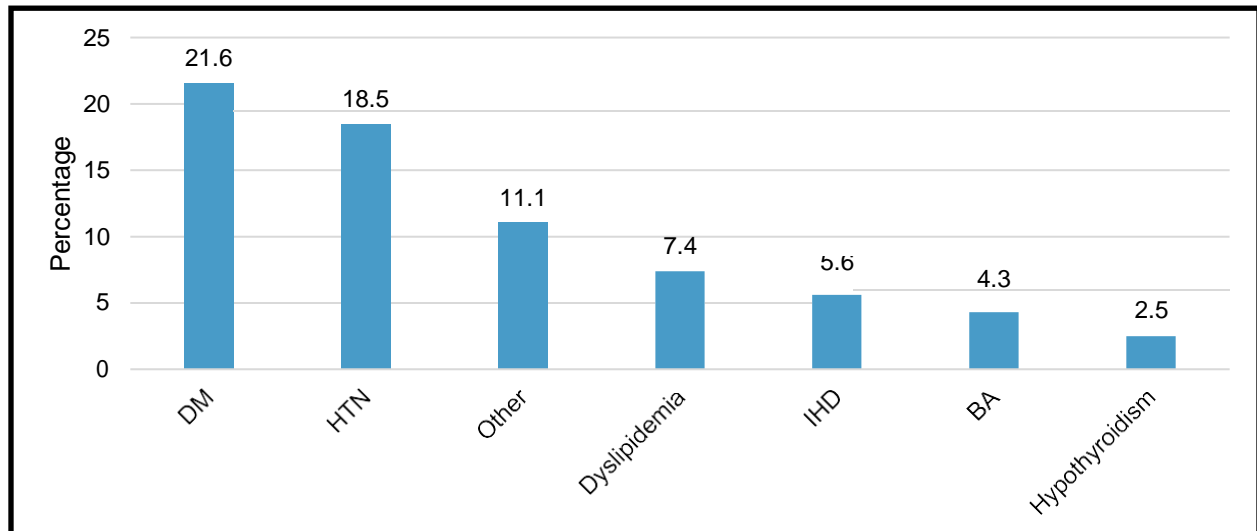
**Figure 1: Specific chronic diseases**

Figure 1 depicted the specific chronic diseases of the patients. It was revealed that the most commonly mentioned chronic diseases was DM (21.6%), followed by hypertension (18.5%) and dyslipidemia (7.4%) while hypothyroidism was the least mentioned (2.5%).

Table 2: Descriptive statistics of the Neutrophil-to-Lymphocyte ratio (NLR)

NLR	Results
Mean	3.97
SD	5.22
Median	2.59
Minimum	0.14
Maximum	56.1

The descriptive statistics of neutrophil-to-lymphocyte ratio is given in table 2. Based on the results, the mean value of NLR was 3.97 (SD 5.22; median 2.59; min 0.14; max 56.1).

Table 3: Statistical difference between NLR in relation to the baseline characteristics and outcome of the patients (n=162)

Factor	Mean ± SD	T-test	P-value §
Age group			
• 24 – 45 years	3.21 ± 2.69	-1.809	0.168
• >45 years	4.68 ± 6.72		
Gender			
• Male	4.34 ± 5.72	1.523	0.004 **
• Female	2.92 ± 3.29		
Nationality			
• Saudi	2.17 ± 1.87	-3.051	<0.001 **
• Non-Saudi	4.80 ± 6.01		
Associated chronic diseases			
• Yes	3.99 ± 3.91	0.036	0.680
• No	3.96 ± 6.06		
Pneumonia			
• Yes	5.38 ± 6.34	4.295	<0.001 **
• No	1.98 ± 1.55		
Outcome			
• Death	11.2 ± 14.5	5.663	0.002 **
• Recovered	3.34 ± 2.76		

§ P-value has been calculated using Mann Whitney U test.

** Significant at p<0.05 level.

When measuring the difference between NLR in relation to the baseline characteristics and outcome of the patients, our investigation revealed that the NLR mean value of males were statistically significantly higher when compared to females ($T=1.523$; $p=0.004$). We also observed that non-Saudis were significantly more associated with having higher NLR value ($T=-3.054$; $p<0.001$) compared to Saudis. Furthermore, patients with pneumonia showed statistically significantly higher NLR mean value ($T=4.295$; $p<0.001$). In addition, the NLR mean value of non-survival patients was statistically significantly higher compared to those who recovered ($T=5.663$; $p=0.001$) (Table 3).

DISCUSSION:

Novel corona virus (COVID-19) has caused a global pandemic, with the infection rapidly spreading from person to another via respiratory droplets. The main presenting symptoms of the virus include fever, cough, shortness of breath and occasionally GI symptoms (2).

Inflammation plays a significant role in the progression of viral pneumonia, including COVID-19 (6).

Several studies have researched the correlation of inflammatory response in the body, with laboratory values such as CRP, lymphocyte count, d-dimer and NLR and COVID-19 infection (1,3,7). Numerous studies have reported that severe cases of COVID-19 were likely to have higher neutrophil counts and lower lymphocyte counts compared with non-severe patients, thus the NLR tended to be higher in severely infected patients (7). NLR is proposed as a new biomarker for systemic inflammation. The inflammatory response stimulates the production of neutrophils and speeds up the death of lymphocytes. CD4+ T lymphocytes are destroyed in the process leading to the production of CD8+ T lymphocytes (7). This dysregulation of immune cells leads to excessive inflammation and may lead to a cytokine storm (3).

Our retrospective observational study was conducted on 162 COVID-19 positive patients and looked at the association of NLR and severity and mortality of the disease, with the mean age of 46.5 and higher percentage of male to female ratio. As expected, and similar to many previous studies conducted, our study found that a high NLR was associated with an increased rate of morbidity and mortality in patients with the COVID-19 infection (1,6,7,8,9). Furthermore, recent studies have investigated the relationship between age, gender, comorbidities and COVID-19 disease severity. The China report

illustrated that 50% of the COVID-19 patients hospitalized in the general ward and 66% admitted to the Intensive Care Unit had comorbidities (8). Similarly, our study found that those with chronic conditions had a higher NLR, with diabetes being the most common illness followed by hypertension and dyslipidemia. Our results also showed that males had a higher NLR and a more significant association with the risk of mortality compared to females. Further, non-Saudis compared to Saudis, and patients with pneumonia were found to have a higher NLR value. Finally, the NLR mean value of non-survival patients was statistically significantly higher compared to those who recovered, suggesting that an increased NLR was associated with a higher mortality rate.

The clinical implication of NLR is that it is a simple measure in routine blood investigation that can be calculated quickly to identify the severity of the infected patient to modify the treatment plan accordingly. Several reports indicate that the low lymphocyte count in COVID-19 patients stems from the increase of neutrophils and C-reactive protein in the body. However, some clinicians fail to consider the NLR as a prediction marker for the disease severity (3). Disregard for the prognosis prevents the medical sector from identifying and implementing effective interventions that will curb the mortality rates. The medical practitioners should focus on counting the serum levels of neutrophils, lymphocytes, D-dimers and IL-6 to analyze disease severity (9).

The limitations of our study is the sample size and the lack of long term follow up. Furthermore, the data was collected from one research center as compared to multiple research centers. A larger sample size, long term follows up, and data collection from multiple research centers are needed to strengthen the result of the NLR as a biomarker of COVID-19 disease severity.

CONCLUSION:

This retrospective cohort study identified NLR to be an extremely useful prognostic factor in categorizing illness severity due to COVID-19, with a higher NLR being associated with a worsened morbidity and mortality rate. To further confirm our findings and strengthen the predictive ability of NLR as a biomarker of COVID-19 disease severity, research studies need to be conducted with a larger sample size and a long term follow up.

Additionally, studies should be conducted to compare and identify the predictive nature of NLR during treatment, as compared to baseline NLR.

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