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Predictive Value Of The Neutrophil-To-Lymphocyte Ratio For Disease Severity And Hospital Mortality In Patients With COVID-19: A Retrospective Cohort Study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has an extended spectrum of disease severity, ranging from asymptomatic or mild infection to severe pneumonia, respiratory failure, multiorgan failure, and death. Early identification of patients at increased risk of clinical deterioration, severe or critical illness requiring intensive care unit (ICU) admission, and mechanical ventilation with prolonged hospital stay, as well as the potential increase of in-hospital mortality remains an integral part of Covid-19 patients' proper management. Neutrophil-to-lymphocyte ratio (NLR) reflects the balance between innate inflammatory response and adaptive immune suppression in Covid-19 patients. This study aimed to evaluate the predictive value of admission NLR for disease severity and mortality among hospitalized patients with COVID-19.

Methods: This retrospective cohort study included adult patients with laboratory-confirmed COVID-19 admitted to Zagazig University Hospitals from September 2021 till March 2022. Demographic characteristics, comorbidities, clinical findings, laboratory parameters, treatment characteristics, and outcomes were obtained from their medical records. NLR was calculated at hospital admission.

Results: A total of 389 patients were included. Severe/critical disease occurred in 48.1% of patients. The average age of severe cases was 52.3 ± 13.6 years, and 58% of them were male. At admission NLR was significantly higher in patients with severe/critical Covid-19. After adjustment for age, sex, relevant comorbidities, high NLR remained independently associated with severe disease (OR 2.2; 95% CI:1.7 - 2.9; $p < 0.001$), and in-hospital mortality (OR 2.2; 95% CI:1.5 – 3.1; $p < 0.001$). Admission NLR cutoff 5.7 could predict the Covid-19 severity (AUC: 0.86, 95% CI: 0.82 – 0.89), and admission NLR cutoff 9.4 could predict the Covid-19 mortality risk (AUC: 0.91, 95% CI: 0.88 – 0.93).

Conclusions: A higher neutrophil-to-lymphocyte ratio at hospital admission was independently associated with severe COVID-19 and in-hospital mortality. Because NLR is inexpensive, rapidly available, and derived from a routinely performed complete blood count, it may provide a practical tool for early risk stratification. NLR should nevertheless be interpreted as part of a broader clinical assessment rather than as a stand-alone predictor.

Keywords: COVID-19; SARS-CoV 2; Neutrophil-to-lymphocyte ratio; NLR; Disease severity, Hospital mortality.

Introduction

The Chinese Centre for Disease Control and Prevention announced the isolation of a novel corona virus from Wuhan city in January 2020. The virus was named severe acute respiratory syndrome coronavirus 2

(SARS-COV 2). The new virus was responsible for Corona Virus Disease 2019 (Covid-19) that was declared a global epidemic by the World Health Organization in March 2020.[1, 2]
SARS-CoV 2 is a single-stranded enveloped RNA virus that belongs to the Coronavirinae subfamily of the Coronaviridae family. SARS-CoV-2 is an RNA virus.[3]
The clinical spectrum COVID-19 is remarkably heterogeneous. While many infected individuals experience mild or self-limited disease, others develop extensive pulmonary involvement, hypoxemic respiratory failure, acute respiratory distress syndrome, multiorgan dysfunction, and death. This heterogeneity creates a persistent clinical challenge for early stratification and identifying patients who are at more risk for deterioration and/or mortality.[4]
With an increasing number of COVID-19 cases and the limited healthcare capacity, early prediction of COVID-19 severity and mortality is crucial in the patient triage process. Several demographic, clinical, radiological, and laboratory variables as well as scoring systems such as Acute Physiology and Chronic Health Evaluation (APACHE) II score and COVID-GRAM score have been investigated as potential predictors of adverse outcomes and in-hospital mortality.[5, 6]
However, many proposed biomarkers and scoring systems require specialized testing, are relatively expensive, cannot be implemented in resource-limited healthcare settings, or are not routinely available at the time of initial assessment. Therefore, the search for simple, noninvasive & relatively non-expensive laboratory tools that can be calculated from standard investigations obtained at hospital admission is still ongoing for early prediction of severity and mortality of Covid 19 patients.[7]
The neutrophil-to-lymphocyte ratio (NLR) is a hematocytometric index that is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. It represents a good predictor of the systemic inflammatory response. In Covid-19 infection, there is increased neutrophil activity secondary to an exaggerated innate immune response, whereas occurrence of lymphopenia may indicate impaired adaptive immunity.[8]
Early observations and subsequent systematic reviews and meta-analyses during the COVID-19 pandemic suggested that NLR was higher in patients with severe and critical Covid-19 disease. However, NLR prognostic performance varied significantly in literature secondary to the reported significant variability of NLR thresholds between populations, and differences in age, comorbidity burden, timing of blood sampling, treatment protocols, and healthcare setting.[9-11]
In the present study, we evaluated the prognostic performance of NLR measured at hospital admission to determine whether it could independently predict severe/critical COVID-19 and in-hospital mortality after adjusting for major demographic, clinical, and laboratory parameters.

Materials and Methods

Study design and setting

This retrospective observational study was conducted at Zagazig University Hospitals, Zagazig, Egypt. We reviewed the medical records of 389 adult patients with laboratory-confirmed COVID-19 who were admitted to Covid-19 isolation units of our tertiary centre between September 2021 and March 2022. The study was carried out in accordance with the principles of the Declaration of Helsinki in 1975. All participants gave written informed consents prior to enrollment.

Selection criteria

The inclusion criteria of our study included adult subjects ≥18 years old, both males and females, laboratory-confirmed SARS-CoV-2 infection, those who had a complete blood count obtained at or within 12 hours of hospital admission, and who had a documented clinical outcome. Patients were excluded from the study if they had incomplete clinical records, had autoimmune disorders, solid malignancy on chemotherapy, hematological malignancy or pre-admission corticosteroid therapy that substantially altered their leukocytic count.

Data collection

History taking with specific emphasis on demographic characteristics, smoking status, duration of symptoms, comorbidities such as diabetes mellitus, hypertension, chronic kidney disease (CKD), chronic liver disease, bronchial asthma, and chronic obstructive pulmonary disease (COPD). Thorough clinical

examination including body mass index, and oxygen saturation. At admission and follow up chest imaging and laboratory investigations including complete blood count (CBC), inflammatory markers, kidney and liver function tests, prothrombin time, and international normalized ratio (INR), as well as the clinical outcome including response to treatment, ICU admission, and the need for mechanical ventilation. The final clinical outcome including the length of hospital stay, and 30-day hospital mortality were extracted from the patients' medical records.

Diagnosis of Covid-19 infection

Reverse transcriptase-polymerase chain reaction (RT-PCR) was used as the standard diagnostic test to confirm Covid-19 infection. Bilateral ground-glass opacities (GGOs) with peripheral and posterior distribution in computed tomography (CT) scan of the chest were considered the hallmark of Covid-19 pneumonia in our study.[12, 13]

Calculation of NLR

The primary NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count in CBC that was first obtained at the time of hospital admission, or as close as possible to, initiation of major COVID-19-specific therapy.[14]

Definition of disease severity

Disease severity was classified according to the criteria reported in the Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition), issued by National Health Commission & National Administration of Traditional Chinese Medicine on August 18, 2020. [15]

Our patients were categorized as having non-severe (mild to moderate), or severe/critical disease:

Non-severe (mild to moderate) subjects: Mild cases show low-grade fever, mild fatigue, anosmia, ageusia, with no features of pneumonia in chest CT. Moderate cases show fever, respiratory symptoms, with CT evidence of pneumonia.

Severe/critical cases: Severe cases were characterized by one or more of the following: a respiratory rate ≥ 30 breaths/min, resting-state oxygen saturation ≤ 93% on room air, arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤ 300 mmHg, and/or progressive worsening of clinical symptoms and lung imaging shows significant lesion progression (>50%) within 24 to 48 hours. Critical cases were those who developed respiratory failure/acute respiratory distress syndrome (ARDS), septic shock or organ failure requiring admission and treatment in intensive care unit (ICU).

Study outcomes

The primary outcome was severe/critical COVID-19 infection included ICU admission, the need for mechanical ventilation, development of acute respiratory distress syndrome, and prolonged hospital stay. The secondary outcome was the 30-day in-hospital mortality.

Statistical analysis

Our data was analyzed using IBM SPSS Statistic Version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages and were compared using Fisher's exact test or Pearson's Chi-square test. Quantitative data was expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) according to normality of distribution, and were compared with unpaired Student's t-test or Mann–Whitney U-test. The significant differences between severe and non-severe cases were evaluated using univariate, and multivariable logistic regression analyses. The performance of NLR was evaluated by estimating the 95% confidence interval (95% CI) and the area under the receiver operating characteristic curve (AUROC). Significance was calculated as p-value < 0.05.

Results

A total of 389 patients with PCR-confirmed COVID-19 at or prior to hospital admission were included in our study. The median age of our cohort was 46.8 ± 11.8 years for mild to moderate cases, and 52.3 ± 13.6 years for severe/critical cases. Male subjects represented 46% of non-severe cases and 58% of severe cases. Severe/critical disease developed in 187 patients; 48.1%, while 54 patients; 28.9% of the severe/critical

subjects died within a period of 30 days of hospitalization. Baseline characteristics according to disease severity are presented in Table 1.

Table 2 revealed that at admission to hospital, in comparison to patients with mild to moderate Covid-19 infection, patients who developed severe/critical disease had a significantly more total leucocytic count, neutrophils count, serum total bilirubin, alanine transferase (ALT), aspartate transferase (AST), serum creatinine level and international normalized ratio. Additionally, NLR of 7.1 ± 4.6 compared with 2.2 ± 1.9 for patients with non-severe disease ($p<0.0001$). Moreover, patients with severe/critical disease had significantly less lymphocytic count, hemoglobin concentration (HB%), platelet count, and less serum albumin level at admission.

Multivariate regression analysis as shown in table 3 elucidated that advanced age, presence of diabetes mellitus, hypertension, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and at admission increased total leucocytic count, reduced platelet count and increased NLR are the main risk factors for increased severity and mortality of Covid-19 infection.

ROC analysis for NLR performance shown in table 4, figures 1 and 2 revealed that NLR cutoff (5.7) at admission could predict the Covid-19 disease severity with 90.7% sensitivity, and 81.4% specificity (AUC: 0.86, 95% CI: 0.82 – 0.89). Moreover, NLR cutoff (9.4) at hospital admission could predict the Covid-19 disease mortality risk with 86.2% sensitivity, and 96.5% specificity (AUC: 0.91, 95% CI: 0.88 – 0.93).

Discussion

The major finding of this study was that an increased NLR ratio at hospital admission was associated with a significantly increased risk of severe COVID-19 and in-hospital mortality. Furthermore, this association remained significant after adjustment for major demographic and clinical parameters, suggesting that NLR could serve as a predictor of Covid-19 disease prognosis beyond basic the patient characteristics.

The crucial clinical usefulness of NLR lies primarily in its simplicity. Unlike many proposed biomarkers, NLR requires no additional blood test. It can be calculated immediately from a standard complete blood count, is inexpensive, rapidly available, and can be incorporated into initial assessment of Covid-19 patients early at hospital admission.[16]

This finding is biologically valid. A major characteristic of severe/critical COVID-19 virus infection is the dysregulated inflammatory host response that could exaggerate to a proinflammatory cytokine surge and cytokine storm, as well as activation of the host innate and adaptive immune pathways with subsequent excess neutrophil recruitment, and variable degrees of reduced number and activity of B, T and natural killer lymphocytes.[17, 18]

The NLR is a hematocytometric index representing this distinct relationship between neutrophils and lymphocytes, the two essential components of the inflammatory response to Covid-19 virus infection.[19]

In univariate analysis, Covid-19 severity and mortality risk was associated with multiple demographic factors including advanced age, male sex, obesity, diabetes mellitus, hypertension, IHD, CKD, COPD/asthma, and prolonged hospital stay as well as laboratory parameters at hospital admission such as increased WBCs count, neutrophil count, serum total bilirubin, ALT, AST, serum creatinine level and INR, decreased lymphocytic count, HB%, PLT count, and serum albumin level. At admission NLR was significantly higher in patients with severe/critical disease compared to patients with non-severe disease ($p<0.0001$).

Gallo Marin et al. reported that older age was a major predictor of mortality in Covid-19 patients and that 62% of hospitalized Covid-19 patients were above age of 55.[20]

Zhou et al reported similar findings regarding increased mortality risk in patients with advanced age, diabetes mellitus, hypertension, IHD, acute kidney injury, increased WBCs count, increased serum creatinine and prothrombin time. However, they didn't find a correlation between current smoking, and COPD with Covid-19 mortality risk.[21]

In multivariate logistic regression, increased at admission NLR remained an independent predictor of, and was independently associated with disease severity (OR 2.2; 95% CI:1.7 - 2.9; $p < 0.001$), and disease in-hospital mortality (OR 2.2; 95% CI:1.5 – 3.1; $p < 0.001$) after adjustment for age, sex, and relevant comorbidities.

Comorbidities significantly associated with Covid-19 severity and mortality included advanced age (OR 1.5; 95% CI: 1.3 - 1.6; $p < 0.001$), and (OR1.64, 95% CI: 1.45 –1.85; $p < 0.001$), diabetes mellitus (OR 1.8, 95% CI: 1.4 - 2.2; $p < 0.001$) and (OR 1.85; 95% CI: 1.50 – 2.28, $p < 0.001$), hypertension (OR 1.5; 95% CI: 1.2 - 1.9; $p < 0.003$), and (OR 1.74; 95% CI: 1.16 – 2.61; $p <0.007$), CKD (OR 2.6; 95% CI: 1.8 - 3.8; $p < 0.001$), and (OR 3.02; 95% CI: 2.11 – 4.32; $p < 0.001$), COPD/asthma (OR 2.2; 95% CI: 1.6 - 3.1; $p < 0.001$), and (OR 2.44; 95% CI: 1.78 – 3.34; $p < 0.001$), increased WBCs count (OR 1.6; 95% CI: 1.02 – 2.4; $p <0.001$), and (OR 1.15; 95% CI: 1.06 – 1.25; $p <0.006$), and reduced platelet count (OR 1.6; 95% CI: 1.2 – 2.1; $p < 0.001$), and (OR 1.21; 95% CI: 1.09 – 1.34; $p < 0.001$) respectively.

Cecconi et al. found that clinical deterioration, ICU transfer and increased hospital mortality for Covid-19 patients were significantly associated with advanced age, ischemic heart disease, increased WBCs count, AST, serum creatinine and D-dimer levels. However, they reported no association with other comorbidities such as hypertension, diabetes mellitus, CKD, COPD. Moreover, they found no significant association with platelet count, ALT, serum bilirubin or serum albumin levels.[22]

Nevertheless, NLR should not be interpreted as isolation. An elevated NLR is not specific to COVID-19 and can be affected by bacterial infection, corticosteroid exposure, malignancy, chronic inflammatory disease, physiological stress, and other conditions.[23-26]

Potential strengths of our study include the use of a simple, inexpensive, and widely available laboratory index at hospital admission for early risk stratification, and evaluation of both severity and probable in-hospital mortality for Covid-19 patients. disease and mortality, and multivariable adjustment for clinically important confounders.

The main limitations of this study are the retrospective observational design, and the relatively small number of subjects with severe/critical Covid-19 infection.

Conclusions

NLR could serve as a reliable and inexpensive laboratory index for early risk stratification. Elevated NLR at hospital admission is suggested to be a reliable predictor for the severity and in-hospital mortality of Covid-19 patients.

Ethics approval and consent to participate: The study was approved by the institutional review board & ethical committee of Faculty of Medicine, Zagazig University, and was carried out in accordance with the principles of the Declaration of Helsinki in 1975. Written informed consents were obtained from the patients or their legal family guardian prior to enrollment.

Availability of data and material: The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Conflict of interests: None to be declared

Funding: None

Authors' Contributions: M.B. & M.H. conceived and planned the experiments. M.M. supervised data collection & laboratory investigations. All authors contributed to the interpretation of the results, writing and reviewing the manuscript.

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Tables

Table 1. Baseline characteristics of patients according to COVID-19 disease severity

Variable	Non-severe cases (No.=202)	Severe cases (No.=187)	p value
Age	46.8 ± 11.8	52.3 ± 13.6	<0.0001
Gender [Male]	93 (46%)	103 (58%)	0.02
Smoking	53 (26%)	62 (33.2%)	0.1
Presenting complaint			
Fever	53 (26%)	32 (17.1%)	0.03
Sore throat	67 (33.2 %)	17 (9.1%)	<0.0001
Cough	105 (52%)	102 (54.5%)	0.62
Shortness of breath	27 (13.4%)	123 (56.8)	<0.0001
Loss of taste and smell	28 (13.9)	29 (15.5%)	0.7
Decreased conscious level	0	16 (8.6%)	<0.0001
Body mass index (BMI)	23.1 ± 4.2	24.7 ± 3.5	0.0001
Diabetes	79 (39.1%)	94 (50.3%)	<0.0001
Hypertension	63 (31.2%)	67 (35.8%)	<0.0001
Ischemic heart disease	20 (9.9%)	31 (16.6%)	0.02
Chronic kidney disease	8 (4%)	19 (10.2%)	<0.0001
Chronic liver disease	18 (8.9%)	26 (13.9%)	0.12
COPD/bronchial asthma	24 (11.9%)	47 (25.1%)	0.0001
Duration of hospital stay (days)	3.8 ± 1.4	12.4 ± 3.1	<0.0001
30-day hospital mortality	7 (3.5%)	54 (28.9%)	<0.0001

Table 2. Comparison of laboratory parameters according to survival

Variable	Non-severe cases (n=202)	Severe cases (n=187)	p value
WBCs	8.4 ± 3.1	14.5 ± 4.3	<0.0001
Lymphocytes	24.2 ± 7.9	8.6 ± 4.3	<0.0001
Neutrophils	56.9 ± 17.2	84.2 ± 13.6	<0.0001
Neutrophil/lymphocyte ratio	2.2 ± 1.9	7.1 ± 4.6	<0.0001
HB%	13 ± 3.7	12 ± 2.9	0.003
PLT count	315 ± 51	272 ± 42	<0.0001
ALT	28.9 ± 4.2	37.3 ± 6.1	<0.0001
AST	31.5 ± 6.2	56.8 ± 7.6	<0.0001
Total bilirubin	1.2 ± 0.09	1.3 ± 0.2	<0.0001

Serum albumin	4.1 ± 0.4	3.6 ± 0.1	<0.0001
Serum creatinine	0.9 ± 0.2	1.3 ± 0.4	<0.0001
INR	0.9 ± 0.1	1.4 ± 0.6	<0.0001

Table 3. Multivariable logistic regression analysis of predictors of severe COVID-19 and mortality

Variable	Severe disease Adjusted OR (95% CI)	p value	Mortality Adjusted OR (95% CI)	p value
Age	1.5 (1.3 - 1.6)	< 0.001	1.64 (1.45 –1.85)	< 0.001
Diabetes mellitus	1.8 (1.4 - 2.2)	< 0.001	1.85 (1.50 – 2.28)	< 0.001
Hypertension	1.5 (1.2 - 1.9)	< 0.003	1.74 (1.16 – 2.61)	<0.007
Chronic kidney disease	2.6 (1.8 - 3.8)	< 0.001	3.02 (2.11 – 4.32)	< 0.001
COPD/asthma	2.2 (1.6 - 3.1)	< 0.001	2.44 (1.78 – 3.34)	< 0.001
WBCs	1.6 (1.02 – 2.4)	<0.001	1.15 (1.06 – 1.25)	<0.006
PLT count	1.6 (1.2 – 2.1)	< 0.001	1.21 (1.09 – 1.34)	< 0.001
NLR	2.2 (1.7 - 2.9)	< 0.001	2.2 (1.5 – 3.1)	< 0.001

Table 4. Diagnostic performance of admission NLR

Prediction of Covid-19	Cut-off	AUC	95% CI	Sensitivity	Specificity
Severity	5.7	0.86	0.82 – 0.89	90.7%	81.4%
Mortality	9.4	0.91	0.88 – 0.93	86.2%	96.5%

Figures

Figure 1: ROC curve of NLR performance in predicting the severity of Covid-19 infection (AUC: 0.86)
Figure 2: ROC curve of NLR performance in predicting the mortality of Covid-19 infection (AUC: 0.91)

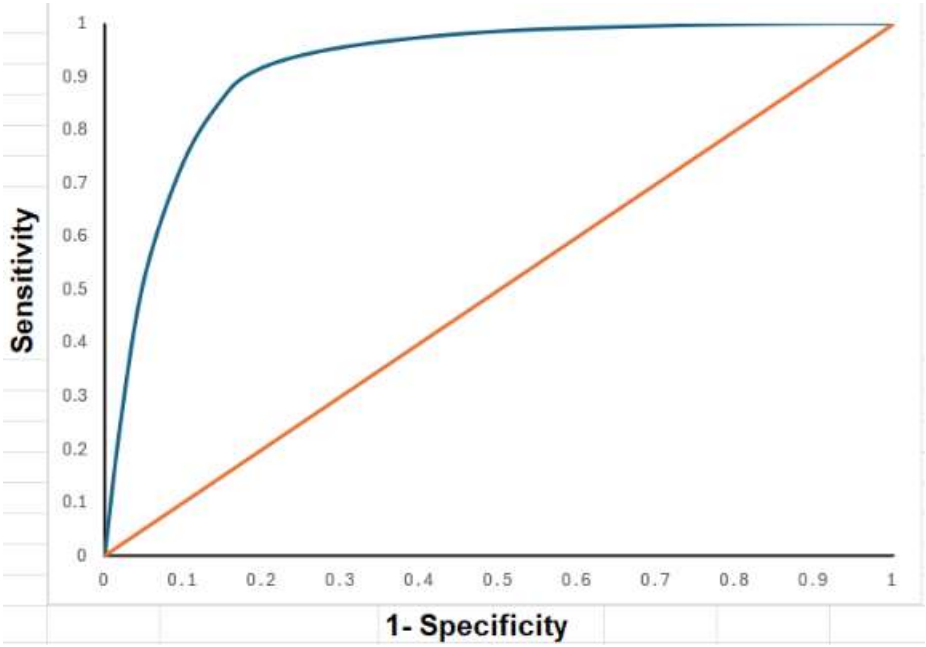


Figure 1: ROC curve of NLR performance in predicting the severity of Covid-19 infection (AUC: 0.86)

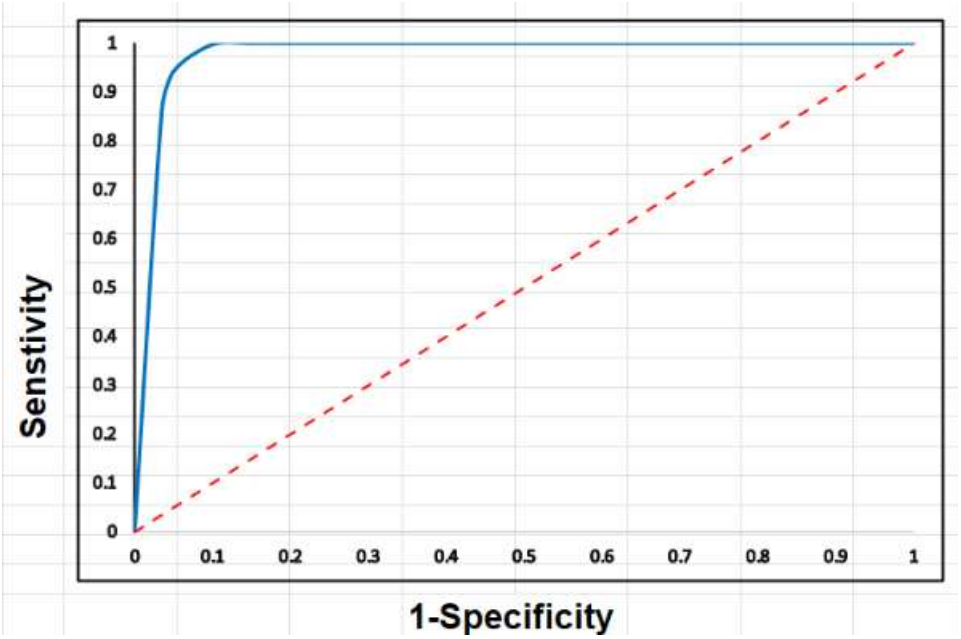


Figure 2: ROC curve of NLR performance in predicting the mortality of Covid-19 infection (AUC: 0.91)