LAMPIRAN

Lampiran 1

Cara Kerja Pemeriksaan NLR (*Neutrophil-Lymphocyte Ratio*)

A. Metode Manual

Alat:

1. Kamar Hitung *Improved Neubauer*
2. Pipet thoma leukosit
3. *Object glass*
4. *Cover glass*
5. Mikroskop
6. Rak pengecatan

Bahan:

1. Larutan Turk
2. Darah EDTA
3. Giemsa
4. Methanol absolute
5. Aquadest
6. Minyak emersi

Cara Kerja:

1. Hitung Jumlah Leukosit
   a. Hal pertama yang harus dilakukan adalah melakukan pengenceran darah menggunakan larutan Turk.
   b. Pengenceran dapat menggunakan pipet thoma leukosit maupun tabung, pada pemeriksaan ini darah diencerkan sebanyak 20 kali.
   c. Siapkan pipet thoma leukosit, lalu pasang karet pada salah satu ujung pipet yang berada di dekat bagian yang bulat.
   d. Sampel darah dicampurkan baik-baik hingga homogen kemudian hisap menggunakan pipet thoma leukosit sampai skala 0,5. Darah yang menempel di bagian luar ujung pipet dibersihkan dengan tissue.
   e. Selanjutnya hisap larutan pengencer sampai skala 11. Hindari terjadinya gelembung udara. Ujung pipet ditutup dengan ibu jari dan selanjutnya lepaskan selang karet. Kemudian tutup salah satu ujung pipet dengan ibu jari dan ujung pipet lainnya dengan jari tengah. Kocok tabung selama 2-3 menit supaya homogen.
   f. Letakkan pipet di tempat yang rata dan diamkan selama 3-5 menit.
   g. Selanjutnya mengisi bilik kamar hitung dengan sampel darah yang telah diencerkan, pastikan kebersihan permukaan area perhitungan dan kaca penutup (*cover glass*) dalam keadaan bersih.
   h. Letakkan kaca penutup sedemikian rupa sehingga kedua bidang yang dibagi pada bilik hitung tertutup. Agar kaca penutup dapat mudah melekat, kedua tanggul dibasahi sedikit dengan jari tangan yang basah.

i. Selanjutnya masukkan sampel yang telah diencerkan ke dalam bilik hitung.
j. Ambil pipet leukosit yang sebelumnya telah didiamkan tadi, buang 3-4 tetes pertama.
k. Posisikan ujung pipet pada tepi permukaan bilik hitung dengan menyentuh pinggiran kaca penutup.
l. Hitung jumlah sel leukosit pada empat bidang besar di tepi (N x 50).
m. Nilai normal 4.000-11.000 sel/µl sel darah.

2. Hitung Jenis Leukosit
   a. Siapkan alat dan bahan yang dibutuhkan.
   b. Teteskan sampel darah ke atas *object glass* yang bersih dan bebas lemak.
   c. Pegang bagian pinggir kaca objek dengan tangan kiri sementara tangan kanan memegang kaca penghapus yang diletakkan di sebelah kiri tetesan darah.
   d. Geser kaca penghapus ke kanan hingga menyentuh tetesan darah. Tunggu sampai darah menyebar pada sisi kaca penggeser.
   e. Kaca penghapus segera didorong/digeser ke kiri dengan sudut kemiringan 30^0-40^0 sampai ke ujung kaca objek. Tetesan darah harus sudah habis sebelum kaca penghapus mencapai ujung kaca objek.
   f. Sediaan dibiarkan mengering di udara, jangan lupa beri identitas pada kaca sediaan.
   g. Selanjutnya lakukan pengecatan menggunakan pewarnaan giemsa/wright.
   h. Lakukan fiksasi sediaan apus dengan methanol absolute. Genangi dengan methanol biarkan beberapa saat sampai mengering.
   i. Encerkan giemsa stock menggunakan aquadest dengan perbandingan 4 tetes giemsa : 1 mL aquadest.
   j. Letakkan sediaan yang telah difiksasi pada rak pengecatan, lalu teteskan giemsa yang telah diencerkan, biarkan selama 15-20 menit.
   k. Buang sisa cat giemsa yang ada pada sediaan, lalu siram dengan air mengalir secara perlahan.
   l. Letakkan sediaan pada posisi vertical atau miring agar segera mengering di udara.

m. Lakukan pembacaan dan penghitungan sediaan apusan darah pada mikroskop (perhitungan dilakukan dalam 100 sel leukosit dan hasilnya dilaporkan dalam %).

3. Pemeriksaan NLR (*Neutrophil-Lymphocyte Ratio*)

Pemeriksaan NLR (*Neutrophil-Lymphocyte Ratio*) dapat dilakukan dengan melakukan penghitungan dengan cara membagi jumlah neutrofil absolut dengan jumlah limfosit absolut.

Berikut rumus yang dapat digunakan untuk penrhitungan nilai NLR (*Neutrophil-Lymphocyte Ratio*):

a. $\text{ANC} = \frac{\text{Jumlah Neutrofil dalam SADT}}{100}$ x Jumlah Leukosit

b. $\text{ALC} = \frac{\text{Jumlah Limfosit dalam SADT}}{100}$ x Jumlah Leukosit

c. $\text{NLR} = \frac{\textit{Absolute Neutrophil Count}\ (\text{ANC})}{\textit{Absolute Lymphocyte Count}\ (\text{ALC})}$

Keterangan:

ANC = *Absolute Neutrophil Count*

ALC = *Absolute Lymphocyte Count*

NLR = *Neutrophil-Lymphocyte Ratio*

B. Metode Automatic Hematology Analyzer DIRUI BCC 300 B

Alat:

1. *Hematology Analyzer* DIRUI BCC 300 B

Bahan:

1. Sampel darah EDTA
2. *Diluent*
3. *Cleanser*
4. *Lise*
5. *Dirui Control*

Cara Kerja:

1. Pemeriksaan Darah Lengkap (Untuk melihat jumlah neutrofil dan limfosit pada darah)

a. Prosedur *Start-Up*

1. Nyalakan alat dengan menggunakan tombol On/Off yang berada pada bagia belakang alat.
2. Tunggu sekitar 3-5 menit agar alat stabil.
3. Alat melakukan *start-up* secara otomatis.
4. *Start-up* akan dinyatakan passed bila WBC < 0,3, RBC < 0,02, HGB < 0,3, PLT < 10.

5. Apabila *start-up failed* maka alat akan mengulang *start-up* sampai 3x.
6. Masukkan QC (*Quality Control*) menggunakan control hematologi.

b. Prosedur Sampel
    1. Tekan tombol "*Return*" masukkan sampel pasien dengan menekan tombol penghisap sampel.
    2. Biarkan alat melakukan perhitungan dan tunggu sampai hasilnya keluar dan dicetak.
    3. Hasil akan keluar dalam waktu 60 detik dalam bentuk *print out.*
    4. Kembali ke menu awal jika tidak ada sampel yang akan diperiksa kembali dengan menekan "Menu".

c. Prosedur *Shut Down* (Matikan Alat)
    1. Tekan tombol "*Shut Down*" dan biarkan alat melakukan pencucian.
    2. Matikan alat dengan menekan tombol ON/OFF yang berada dibagian belakang alat.

d. Prosedur Kalibrasi
    1. Tekan menu lalu pilih *calibration.*
    2. Akan muncul pilihan *calibration*, kemudian tekan "*Automatic Calibration*".
    3. Kemudian akan muncul "*Whole Blood Mode*".
    4. Lakukan calibration edit dengan masukkan nilai target dari *Calibration.*
    5. Homogenkan kalibrator dan pastikan tercampur sempurna untuk bisa dihisap oleh alat.
    6. Masukkan kalibrator dan tekan sampling untuk memulai kalibrasi, pada menu akan terlihat "*Testing*".
    7. Tunggu hasil akan keluar secara otomatis, lali tekan "*Enter*" untuk menyimpan kalibrasi yang baru.

       Catatan:

       Ketika dalam proses menghisap sampel kalibrator terdapat gelembung udara maka hasil tidak akan keluar atau invalid.

e. Prosedur Penggantian Reagen
    1. Tekan menu "*System Maintenance*".

2. Akan muncul menu: *Diluent prime, Cleanser prime, Lysenprime*. Pilih dan tekan sesuai reagen yang akan diganti secara otomatis akan mengganti.
3. Lalu kembali ke menu awal.
4. Prosedur pencucian:

   Pencucian dilakukan setiap hari sehabis melakukan pemeriksaan. Proses pencucian dilakukan sama seperti proses pergantian reagen.

f. Pemeriksaan NLR (*Neutrophil-Lymphocyte Ratio*)

1. Setelah *print out* hasil pemeriksaan keluar, tandai dan catat bagian pada lembar hasil pemeriksaan yang menunjukkan jumlah neutrofil dan limfosit pada sampel darah yang telah diperiksa.
2. Masukkan jumlah neutrofil dan limfosit ke dalam rumus untuk menghitung nilai NLR maka akan didapat nilai NLR dari sampel darah yang diperiksa.

$$\text{NLR} = \frac{\textit{Absolute Neutrophil Count}\ (\text{ANC})}{\textit{Absolute Lymphocyte Count}\ (\text{ALC})}$$

Keterangan:
ANC = *Absolute Neutrophil Count*
ALC = *Absolute Lymphocyte Count*
NLR = *Neutrophil-Lymphocyte Ratio*

Lampiran 2

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 2099–2102

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Differential white blood cell count in the COVID-19: A cross-sectional study of 148 patients

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ARTICLE INFO

Article history:
Received 13 October 2020
Received in revised form
28 October 2020
Accepted 30 October 2020

Keywords:
COVID-19
DLC
NLR
Diabetes
Hypertension

ABSTRACT

Background: SARS-CoV-2 infection alters various blood parameters, which may indicate disease severity and thus help in better clinical management.
Aim: To study the association between various hematological parameters and disease severity of COVID-19. To analyze the effects of hypertension and diabetes on neutrophil-lymphocyte ratio and neutrophil-monocyte ratio in patients suffering from COVID-19.
Materials and methods: The study was a cross-sectional study involving 148 laboratory-confirmed cases of SARS-CoV-2 infection. The patients were divided into three groups on the basis of disease severity. Various hematological parameters were analyzed. The effects of hypertension and diabetes on NLR and NMR in COVID-19 patients were evaluated.
Results: Of the 148 patients, 78.4%, 8.1% and 13.5% cases were in the mild, moderate and severe groups, respectively. Mean age was 42.63 ± 16.04 years (IQR: 29, 54.75; Range: 7–74). 58.8% patients were male while the rest (42.2%) were female. Mean TLC (cells/mm^3), neutrophil (%), lymphocyte (%), monocyte (%), eosinophil (%), neutrophil-lymphocyte ratio (NLR) and neutrophil-monocyte ratio (NMR) among mild, moderate and severe COVID-19 was statistically significant ($p < 0.05$). Basophil (%) and lymphocyte-monocyte ratio (LMR) was statistically insignificant among the three groups. Lymphocyte (%), monocyte (%) and eosinophil (%) were negatively correlated to disease severity. Among diabetics, both NLR and NMR were statistically significant ($p < 0.05$). However, among hypertensive cases, only the NLR was statistically significant.
Conclusion: Older age, higher TLC, neutrophilia, lymphopenia, eosinopenia, high NLR and high NMR are associated with severe COVID-19. High NLR and high NMR are indicative of severe disease among diabetic patients. High NLR also indicates severe disease among hypertensive patients.

1. Introduction

Ever since the emergence of COVID-19, the disease has affected 36,754,395 individuals worldwide and has resulted in deaths of 1,064,838 patients until the time of writing this report [1]. The agent responsible for this pandemic is a coronavirus, which was named SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2) by the W.H.O on 11 February 2020 [2].With a case fatality rate (CFR) of around 4% and no effective vaccine or treatment expected to come to the fore in near future, the problems posed by COVID-19 pandemic is unprecedented. The knowledge regarding the spectrum of effects that SARS-CoV-2 may have on its host and the modes of its transmission among humans is still evolving. The common clinical features of COVID-19 include fever, dry cough, dyspnea, fatigue, myalgia, headache, anosmia, ageusia and diarrhea [3,4]. Severe cases may develop life threatening complications like acute respiratory distress syndrome (ARDS), coagulopathy etc. Also, according to WHO, current evidences suggest that SARS-CoV-2 spreads among people via direct contact routes and by droplet, airborne and, fomite transmission [5].

COVID-19 may involve many organ systems in its host. Studies suggest that hematological profiles change during the course of SARS-CoV-2 illness. Neutrophils are involved in early anti-viral

Abbreviations: COVID-19, Coronavirus Disease-2019; SARS-CoV-2, Severe Acute Respiratory Syndrome-Coronavirus-2; NLR, Neutrophil-lymphocyte ratio; NMR, Neutrophil-monocyte ratio; LMR, Lymphocyte-monocyte ratio; TLC, Total Leukocyte Count; DLC, Differential Leukocyte Count; WHO, World Health Organization; BMI, Body mass index; IQR, Interquartile range.

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https://doi.org/10.1016/j.dsx.2020.10.029
1871-4021/

Lampiran 3

ISSN 1669-910631

ARTÍCULO ORIGINAL MEDICINA (Buenos Aires) 2020; Vol. 80 (Supl. III): 31-36

NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC MARKER IN COVID-19

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Abstract:

In December 2019, a new Coronavirus was identified as the cause of an outbreak of pneumonia and respiratory distress in Wuhan, China. It was declared pandemic in March 2020. It is important to know predictors of poor outcomes in order to optimize the strategies of care in newly diagnosed patients. The neutrophil to lymphocyte ratio (NLR) constitutes a novel prognostic marker for oncologic, cardiovascular and infectious diseases. We aimed to assess its prognostic value in COVID-19. We evaluated a retrospective cohort of 131 patients with COVID-19 from March to May 2020. We analyzed the association of an NLR ≥ 3 with severe COVID-19, baseline characteristics of the population and the mortality rate. The median age was 52 years, and 54% were men. 21 patients presented criteria of severe disease, 9 of them required mechanical ventilation. NLR ≥ 3 was found in 81% (18/21) of severe patients and in 33% (36/110) of mild patients (OR = 8.74. 95% CI 2.74-27.86; $p < 0.001$). Age and hypertension were associated with severe disease. A mortality rate of 7% (9) was obtained. Seven of the 9 patients who died presented NLR ≥ 3, with a significant association between mortality and NLR ≥ 3 ($p = 0.03$). NLR could be used in conjunction with other predictors, as an early prognostic marker in COVID-19 given its accessibility and low cost.

Keywords: COVID-19, neutrophil to lymphocyte ratio, prognostic factors

Lampiran 4

Thrombosis Research 192 (2020) 3–8

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: A retrospective study in Suzhou China

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ARTICLE INFO

Keywords:
Coronavirus disease 2019
Neutrophil to lymphocyte ratio
D-dimer

ABSTRACT

Objective: To investigate the clinical features of COVID-19 cases in Suzhou China. Biomarkers were screened out of hematological parameters for risk stratification.
Method: Confirmed COVID-19 adult patients in Suzhou were included. The patient data was collected, and the results of laboratory examinations were compared between the mild/moderate and severe COVID-19 groups. A ROC was calculated to compare the diagnostic performance of candidate indexes, and dynamic levels of hematological indexes were compared between the two groups.
Result: 75 patients were enrolled, with a mean age of 46.6 ± 14 years, and 45 patients were male. All patients were classified into two groups: the mild/moderate group and the severe group. WBC, neutrophil to lymphocyte ratio (NLR), D-dimer, and fibrinogen levels of the severe group were significantly higher ($P < 0.05$) than the mild/moderate, and the lymphocyte was lower. The ROC test showed that the hematological parameters had a larger AUC than that of inflammatory factors. There was a significant difference in lymphocyte and fibrinogen levels between the two groups on day 1 ($P < 0.05$). However, NLR of the severe group was higher than the mild/moderate on days 1, 4 and 14 ($P < 0.01$), and so was D-dimer on days 1, 7 and 14 ($P < 0.05$).
Conclusion: The common COVID-19 abnormal hematological indexes on admission included hyperfibrinogenemia, lymphopenia, the elevation of D-dimer, and leukopenia, which were significantly different between the mild/moderate and severe COVID-19 groups. Furthermore, the dynamic change of NLR and D-dimer level can distinguish severe COVID-19 cases from the mild/moderate.

1. Introduction

Since December 2019, an outbreak of cluster pneumonia of unknown cause happened in Wuhan, the capital city of Central China province, Hubei [1,2]. Subsequently, a novel coronavirus was isolated from patient groups in Wuhan and soon identified to be the causative pathogen of this highly contagious pneumonia [3,4]. In February 2020, the World Health Organization formally designated the disease COVID-19 (coronavirus disease 2019), and the novel coronavirus was designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In two months, the outbreak of COVID-19 spread from Wuhan to all other districts of China. SARS-CoV-2 also caused many hospital transmissions and more than three thousand Chinese health workers were infected until March 15, 2020 [5]. On January 26, Wuhan city was locked down in an unprecedented manner with the majority of public transport cancelled. The WHO recently announced the current situation of COVID-19 as a global pandemic. Up to now there are no available specific curative medicines and vaccines, and the treatment methods for COVID-19 are largely supportive.

Several abnormal hematological parameters were reported in COVID-19 patients [6–9], including lymphopenia, neutrophilia, elevated levels of D-dimer and fibrinogen, but the clinical implication of

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https://doi.org/10.1016/j.thromres.2020.05.006
Received 27 March 2020; Received in revised form 26 April 2020; Accepted 4 May 2020
Available online 06 May 2020

Lampiran 5

Significance of Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio for Predicting Clinical Outcomes in COVID-19

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Abstract:

Background: The epidemic of 2019 novel coronavirus (COVID-19) struck China in late December, 2019, resulting in about 200000 deaths all over the world. Numerous observational studies have suggested that the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte proportion and the platelet-to-lymphocyte ratio (PLR) are inflammatory markers. Our study aimed to detect the role of NLR, PLR in predicting the prognosis of COVID-19.

Methods: Four hundred and fifteen consecutive patients were enrolled in Shanghai Public Health Clinical Center affiliated to Fudan University, between 20 January and April 2020 with confirmed COVID-19. Epidemiology, symptoms, signs, and 21 laboratory examinations during the hospital stay were collected and compared 22 between non-severe and severe patients. Statistical analysis was performed by SPSS 23 25.0 software. **Results:** Four hundred and fifteen laboratory-confirmed COVID-19 patients were included in our study, among which 386 (93%) patients were not severe, and 27 (7%) were severe. The proportion of males in severe cases is higher than in non-severe cases (75.86% vs. 50.52%, P=0.008). The age between the two groups is different.

Lampiran 6

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Article type : Original Paper
Manuscript category : Original paper

Neutrophil/Lymphocyte Ratio – A Marker of COVID-19 Pneumonia Severity

Short running title:
NLR – Marker of COVID-19 Pneumonia Severity

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Abstract :

Aim: To determine the efficacy of neutrophil/lymphocyte ratio (NLR) as a marker of the severity of COVID19 pneumonia in the South-Asian population. Methods: This was a prospective, cross-sectional, analytic study conducted at HDU/ICU of District Headquarter Hospital, Faisalabad, Pakistan, from May through July 2020. Sixty-three eligible patients, admitted to the HDU/ICU, were prospectively enrolled in the study. Their NLR, C-reactive protein, serum albumin, and serum fibrinogen were measured. Patients' demographic characteristics, comorbidities, clinical manifestations of COVID-19 infection, medication use, and history of lung malignancy were retrieved from their medical history. Patients were categorized into either a general group (with mild COVID-19) or a heavy group (with moderate to severe COVID-19). Results: There were significant differences between the two groups in diabetes prevalence, NLR, Creactive protein, and serum albumin. NLR and C-reactive protein were positively correlated ($P < 0.001$, $P = 0.04$ respectively) whereas serum albumin was negatively correlated ($P = 0.009$) with severe COVID-19. NLR was found to be an independent risk factor for severe COVID-19 pneumonia in the heavy group (OR = 1.264, 95% CI: 1.046~1.526, $P = 0.015$). The calculated AUC using ROC for NLR was 0.831, with an optimal limit of 4.795, sensitivity of 0.83 and specificity of 0.75, which is highly suggestive of NLR being a marker for early detection of deteriorating severe COVID-19 infection. Conclusion: NLR can be used as an early warning signal for deteriorating severe COVID-19 infection and can provide an objective basis for early identification and management of severe COVID-19 pneumonia.

Keywords: COVID-19; Severity marker; Neutrophil/lymphocyte ratio; NLR; C-reactive protein; Albumin.

Lampiran 7

This is an Accepted Manuscript for Epidemiology & Infection as part of the Cambridge Coronavirus Collection.

Higher Level of Neutrophil-to-Lymphocyte is Associated with Severe COVID-19

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Abstract

In December 2019, cases of severe coronavirus 2019 (COVID-19) infection rapidly progressed to acute respiratory failure. This study aims to assess the association between the neutrophil-to-lymphocyte ratio (NLR) and the incidence of severe COVID-19 infection. A retrospective cohort study was conducted on 210 patients with

COVID-19 infection who were admitted to the Central Hospital of Wuhan from January 27, 2020 to March 9, 2020. Peripheral blood samples were collected and examined for lymphocyte subsets by flow cytometry. Associations between tertiles of NLR and the incidence of severe illness were analyzed by logistic regression.

Of the 210 patients with COVID-19, 87 were diagnosed as severe cases. The mean NLR of the severe group was higher than that of the mild group (6.6 vs. 3.3, P<0.001). The highest tertile of NLR (5.1–19.7) exhibited a 5.9-fold (95% CI 1.3, 28.5) increased incidence of severity relative to that of the lowest tertile (0.6–2.5) after adjustments for age, diabetes, hypertension, and other confounders. The number of T cells significantly decreased in the severe group (0.5 vs. 0.9， P <0.001). COVID-19 might mainly act on lymphocytes, particularly T lymphocytes. NLR was identified as an early risk factor for severe COVID-19 illness. Patients with increased NLR should be admitted to an isolation ward with respiratory monitoring and supportive care.

Keywords: COVID-19; Severe illness; NLR; Immune response

Lampiran 8

www.aging-us.com AGING 2020, Vol. 12, No. 14

Research Paper

High neutrophil-to-lymphocyte ratio associated with progression to critical illness in older patients with COVID-19: a multicenter retrospective study

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Keywords: SARS-CoV-2, COVID-19, older patients, neutrophil-to-lymphocyte ratio, risk factor
Received: May 2, 2020 **Accepted:** June 9, 2020 **Published:** July 30, 2020

ABSTRACT

This retrospective cohort study aimed to investigate the correlation of the neutrophil-to-lymphocyte ratio (NLR) with critical illness in older patients with COVID-19, and evaluate the prognostic power of the NLR at admission. We enrolled 232 patients with COVID-19, aged ≥60 y, in Zhejiang province from January 17 to March 3, 2020. Primary outcomes were evaluated until April 13. Cox regression was performed for prognostic factors. Twenty-nine (12.5%) patients progressed to critical illness. Age, shortness of breath, comorbidities including hypertension, heart disease, and chronic obstructive pulmonary disease, higher NLR, lower albumin levels, and multiple mottling and ground-glass opacity were associated with progression. In the multivariate analysis, older age (hazard ratio [HR] 1.121, confidence interval [CI] 1.070-1.174, P<0.001), heart disease (HR 2.587, CI 1.156-5.787, P=0.021), higher NLR (HR 1.136, CI 1.094-1.180, P < 0.001), and multiple mottling and ground-glass opacity (HR 4.518, CI 1.906-10.712, P<0.001) remained critical illness predictors. The NLR was independently associated with progression to critical illness; the relationship was significant and graded (HR: 1.16 per unit; 95% CI: 1.10-1.22; P for trend < 0.001). Therefore, NLR can be adopted as a prognostic tool to assist healthcare providers predict the clinical outcomes of older patients suffering from COVID-19.

INTRODUCTION

In December 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China [1–3]. Infection with the virus leads to coronavirus disease (COVID-19), which is characterized by rapid human-to-human transmission and varied degrees of fatality, due to acute respiratory distress syndrome, multi-organ failure, and other serious complications [4, 5]. The global spread of this pandemic has been rapid since March 2020. As of mid-April 2020, more than 2 million individuals had been diagnosed with the disease, leading to over 150,000 deaths.

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Received: 19 August 2020 | Revised: 13 September 2020 | Accepted: 8 October 2020

DOI: 10.1111/ijlh.13374

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

Neutrophil-to-lymphocyte ratio, a critical predictor for assessment of disease severity in patients with COVID-19

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Funding information This work was supported by the National Natural Science Foundation of China (81801984, 81830003); the National Key Research and Development Program of China (2019YFC130030); the China Postdoctoral Science Foundation (2019M664008); and the Military Medical Science and Technology Youth Cultivation Project (20QNPY092).

Abstract

Introduction: Monitoring of laboratory indicators is important for predicting changes in disease severity and clinical outcomes. We aimed to identify the critical predictors that can effectively assess the disease conditions of patients with COVID-19 by analyzing the clinical characteristics and laboratory findings of patients with SARS-CoV-2 infection.

Methods: All consecutive patients (n = 294) with confirmed SARS-CoV-2 infection admitted to the General Hospital of Central Theater Command of the PLA from February 6 to February 21, 2020, were enrolled. These patients were divided into the severe group and the nonsevere group according to disease severity during hospitalization.

Results: The median neutrophil-to-lymphocyte ratio (NLR) value of the severe patients was dramatically higher than that of the nonsevere patients (10.4 vs 2.6; $P < .001$). The NLR value equal to 5 was a boundary value worthy of reference, because more than 80% severe patients had an NLR value greater than 5 and over 80% nonsevere patients had an NLR value less than 5. The NLR value of these COVID-19 patients was positively and respectively correlated with the values of C-reactive protein ($R = .5921$, $P < .001$), lactate dehydrogenase ($R = .4509$, $P < .001$), procalcitonin ($R = .5504$, $P < .001$), fibrinogen ($R = .4710$, $P < .001$), and D-dimers ($R = .4425$, $P < .001$). However, the NLR value was merely and positively correlated with the interleukin-6 value ($R = .3594$, $P < .05$), but had no correlations with the values of interleukin-10, interleukin-4, interleukin-17, interferon-γ, and tumor necrosis factor-α ($P > .05$).

Discussion: Neutrophil-to-lymphocyte ratio is a critical predictor for assessment of disease severity in patients with COVID-19, and it has a close relation with the laboratory indicators related to disease conditions.

KEYWORDS

COVID-19, disease severity, neutrophil-to-lymphocyte ratio

Lei Liu and Yaqiong Zheng contributed equally to this work.

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Gastroenterology and Hepatology From Bed to Bench.

ORIGINAL ARTICLE

Neutrophil to lymphocyte ratio and C-reactive protein level as prognostic markers in mild versus severe COVID-19 patients

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ABSTRACT

Aim: This research aimed to investigate neutrophil□to□lymphocyte ratio (NLR) with C-reactive protein to identify potential clinical predictors and analyze differences among severe and non-severe COVID-19 patients.

Background: NLR and CRP are established markers that reflect systemic inflammatory, and these parameters alter in patients with novel coronavirus (SARS-CoV-2) pneumonia (COVID-19).

Methods: A population of patients with COVID-19 referred to Loghman Hospital in Tehran was analyzed. The baseline data of laboratory examinations, including NLR and CRP levels, was collected. Pearson analysis was used to assess the independent relationship between the NLR with disease severity and CRP levels.

Results: COVID-19 cases comprised 14 (20%) patients with severe disease and 56 (80%) with non-severe infection. The mean values of WBC, NEU, LYM, and NLR of the severe patients were significantly higher than those of the non-severe patients. Forty-six patients (65.7%) had NLR >1, and the remaining patients had NLR <1. Plasma CRP levels were higher in severe cases than in non-severe cases, and this difference was significant. The results showed that NLR was positively correlated with CRP levels (R=0.23) and negatively correlated with WBC (R=-0.38). CRP (AUC = 0.97, 95% CI: 0.95-0.99) and NLR (AUC = 0.87, 95% CI: 0.81-0.93) had very good accuracy in predicting the severity of COVID-19 disease.

Conclusion: The findings of this study indicated that the integration of NLR and CRP may lead to improved predictions and is recommended as a valuable early marker to assess prognosis and evaluate the severity of clinical symptoms in COVID-19 patients.

Keywords: SARS-CoV-2, neutrophil□to□lymphocyte ratio (NLR), CRP, COVID-19.

(Please cite as: Mousavi-Nasab SD, Mardani R, Nasr Azadani H, zali F, Ahmadi Vasmehjani A, Sabeti SH, et al. Neutrophil to lymphocyte ratio and C-reactive protein level as prognostic markers in mild versus severe COVID-19 patients. Gastroenterol Hepatol Bed Bench 2020;13(4):361-366).

Introduction

In December 2019, a novel betacoronavirus outbreak was identified in Wuhan, China (1). Compared with other betacoronaviruses, it was characterized as a highly contagious and deadly strain (2). The International Committee on Taxonomy of Viruses (ICTV) named the

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frontiers in Immunology

ORIGINAL RESEARCH
published: 02 September 2020
doi: 10.3389/fimmu.2020.02160

Neutrophil-to-Lymphocyte Ratios Are Closely Associated With the Severity and Course of Non-mild COVID-19

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OPEN ACCESS

Edited by:
Delmiro Fernandez-Reyes, University College London, United Kingdom

Reviewed by:
Yasser Mohamed El-Sherbiny, Nottingham Trent University, United Kingdom
Ana Maria Teixeira, University of Coimbra, Portugal

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Specialty section:
This article was submitted to Inflammation, a section of the journal Frontiers in Immunology

Received: 20 May 2020
Accepted: 07 August 2020
Published: 02 September 2020

Citation:
Qun S, Wang Y, Chen J, Huang X, Guo H, Lu Z, Wang J, Zheng C, Ma Y, Zhu Y, Xia D, Wang Y, He H, Wang Y, Fei M, Yin Y, Zheng M, Xu Y, Ge W, Hu F and Zhou J (2020) Neutrophil-to-Lymphocyte Ratios Are Closely Associated With the Severity and Course of Non-mild COVID-19. Front. Immunol. 11:2160. doi: 10.3389/fimmu.2020.02160

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is spreading worldwide. Measuring the prevention and control of the disease has become a matter requiring urgent focus.

Objective: Based on coronavirus disease 2019 (COVID-19) clinical data from Wuhan, we conducted an in-depth analysis to clarify some of the pathological mechanisms of the disease and identify simple measures to predict its severity early on.

Methods: A total of 230 patients with non-mild COVID-19 were recruited, and information on their clinical characteristics, inflammatory cytokines, and T lymphocyte subsets was collected. Risk factors for severity were analyzed by binary logistic regression, and the associations of neutrophil-to-lymphocyte ratios (N/LRs) with illness severity, disease course, CT grading, inflammatory cytokines, and T lymphocyte subsets were evaluated.

Results: Our results showed that the N/LRs were closely related to interleukin (IL)-6 and IL-10 ($P < 0.001$, $P = 0.024$) and to $CD3^+$ and $CD8^+$ T lymphocytes ($P < 0.001$, $P = 0.046$). In particular, the N/LRs were positively correlated with the severity and course of the disease ($P = 0.021$, $P < 0.001$). Compared to the values at the first test after admission, IL-6 and IL-10 were significantly decreased and increased, respectively, as of the last test before discharge ($P = 0.006$, $P < 0.001$). More importantly, through binary logistic regression, we found that male sex, underlying diseases (such as cardiovascular disease), pulse, and N/LRs were all closely related to the severity of the disease ($P = 0.004$, $P = 0.012$, $P = 0.013$, $P = 0.028$).

Conclusions: As a quick and convenient marker of inflammation, N/LRs may predict the disease course and severity level of non-mild COVID-19; male sex, cardiovascular disease, and pulse are also risk factors for the severity of non-mild COVID-19.

Keywords: Neutrophil-to-lymphocyte ratios, inflammation, cytokines, immune damage, severity and course of non-mild COVID-19

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The Value of Clinical Parameters in Predicting the Severity of COVID-19

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jmv.26031.

Abstract

Objective: To study the relationship between clinical indexes and the severity of coronavirus disease 2019 (COVID-19), and to explore its role in predicting the severity of COVID-19.

Methods: Clinical data of 443 patients with COVID-19 admitted to our hospital were retrospectively analyzed, which were divided into non-severe group (n=304) and severe group (n=139) according to their condition. Clinical indicators were compared between different groups. **Results:** The differences in gender, age, the proportion of patients with combined heart disease, leukocyte, neutrophil-to-lymphocyte ratio (NLR), neutrophil, lymphocyte, platelet, D-dimer, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase and albumin on admission between the two groups were statistically significant ($p<0.05$). Multivariate logistic regression analysis showed NLR and CRP were independent risk factors for severe COVID-19. Platelets were independent protective factors for severe COVID-19. Receiver Operating Characteristic (ROC) curve analysis demonstrated area under the curve (AUC) of NLR, platelet, CRP and combination was 0.737, 0.634, 0.734 and 0.774, respectively.

Conclusions: NLR, CRP and platelets can effectively assess the severity of COVID-19, among which NLR is the best predictor of severe COVID-19, and the combination of three clinical indicators can further predict severe COVID-19.

Key words: coronavirus disease 2019; novel coronavirus pneumonia; COVID-19; clinical characteristics

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J South Med Univ, 2020, 40(3): 333-336 doi 10.12122/j.issn.1673-4254.2020.03.06·333·

An Increased Neutrophil/Lymphocyte Ratio is an Early Warning Signal of Severe COVID-19

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Abstract:
Objective To identify the biomarkers as early warning signals for severe COVID-19. **Methods** We retrospectively analyzed the clinical data of 63 patients with COVID-19 from Hubei Provincial Hospital of Integrated Chinese and Western Medicine, including 32 moderate cases and 31 severe cases. The demographic data, underlying diseases, clinical manifestations and laboratory test results were compared between the two groups. Logistic regression analysis was performed to identify the factors that predicted the severity of COVID-19. The receiver-operating characteristic curve (ROC) of neutrophil/lymphocyte ratio (NLR) was calculated, and the area under the curve (AUC) was determined to estimate the optimal threshold of NLR for predicting severe cases of COVID-19. **Results** The patients with moderate and server COVID-19 showed significant differences in the rate of diabetes, NLR, serum amyloid A (SSA), C-reactive protein (CRP) and serum albumin (ALB) levels (P<0.05). The co- morbidity of diabetes, NLR, SSA and CRP were found to positively correlate and ALB to inversely correlate with the severity of COVID-19 (P<0.05). Multivariate logistic regression analysis showed that NLR was an independent risk factor for severe COVID-19 (OR=1.264, 95%*CI*: 1.046-1.526, P=0.015) with an AUC of 0.831 (95%*CI*: 0.730-0.932), an optimal diagnostic threshold of 4.795, a sensitivity of 0.839, and a specificity of 0.750. **Conclusion** An increased NLR can serve as an early warning signal of severe COVID-19.

Keywords: COVID-19; warning signal; neutrophil/lymphocyte ratio

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International Immunopharmacology 84 (2020) 106504

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients

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ARTICLE INFO

Keywords:
COVID-19
Neutrophil-to-lymphocyte ratio
Platelet-to-LYM ratio
Predictive
Age

ABSTRACT

Aim: To accumulate evidence that indicated the key role played by virus-triggered inflammation in the 2019-novel coronavirus disease (COVID-19) which emerged in Wuhan City and rapidly spread throughout China.
Methods: Age, neutrophil(NEU)-to-lymphocyte (LYM) ratio (NLR), lymphocyte-to-monocyte (MON) ratio, platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) of 93 patients with laboratory confirmed COVID-19 were investigated and compared. The receiver operating characteristic curve was applied to determine the thresholds for five bio-markers, and their prognostic values were assessed via the Kaplan–Meier curve and multivariate COX regression models.
Results: The median age was 46.4 years old, and 37cases were females. A total of 27.8% of patients had been to Wuhan, and 73.1% had contacted with people from Wuhan. Fever (83.8%) and cough (70.9%) were the two most common symptoms. Elevated NLR and age were significantly associated with illness severity. The binary logistic analysis identified elevated NLR (hazard risk [HR] 2.46, 95% confidence interval [CI] 1.98–4.57) and age (HR 2.52, 95% CI 1.65–4.83) as independent factors for poor clinical outcome of COVID-19. NLR exhibited the largest area under the curve at 0.841, with the highest specificity (63.6%) and sensitivity (88%).
Conclusions: Elevated age and NLR can be considered independent biomarkers for indicating poor clinical outcomes.

1. Introduction

In early December 2019, several cases of pneumonia of unknown etiology have been reported in Wuhan, Hubei province, China [1]. On January 7, 2020, the Chinese Center for Disease Control and Prevention (CDC) has revealed a novel beta-coronavirus from the throat swab sample of a patient through high-throughput sequencing [2]. The disease resembles severe acute respiratory syndrome coronavirus (SARS-CoV) [3] and has been subsequently named the 2019-novel coronavirus disease (COVID-19) by the World Health Organization (WHO). Evidence pointing to the person-to-person transmission has occurred among close contacts in hospital and family [4,5]. Considerable efforts for reducing transmission are required to control outbreaks. Coronaviruses, such as SARS-CoV [6] and MERS-CoV [7], can cause multiple system infections in various animals and mainly induce respiratory tract infections in humans [6]. Most patients exhibited mild symptoms and partial patients exhibited worse prognosis. To date, only a few COVID-19 patients have developed into severe pneumonia, pulmonary edema, acute respiratory distress syndrome [1,7], or multiple organ failure and eventually died. Given the rapid spread and serious harm of COVID-19, it is urgent to continuously improve and enrich its clinical diagnosis and treatment research. This updated analysis identified the defining laboratory results and clinical characteristics with improved precision and also elucidated the risk factors associated with mortality.

Inflammation is caused by infectious diseases, and growing evidence supports its significant role in the progression of various viral pneumonia, including COVID-19 [8]. Severe inflammatory responses contribute to weak adaptive immune response, thereby resulting in immune response imbalance. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients [9]. Peripheral white blood cell (WBC) count, neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), derived NLR ratio (d-NLR, neutrophil count divided by the result of WBC count minus neutrophil count), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are indicators of the systematic inflammatory response [10] that are widely investigated as useful

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https://doi.org/10.1016/j.intimp.2020.106504
Received 22 February 2020; Received in revised form 9 April 2020; Accepted 9 April 2020
Available online 13 April 2020

Lampiran 15

Received: 20 April 2020 | Revised: 8 July 2020 | Accepted: 21 July 2020

DOI: 10.1111/ijlh.13291

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

Clinical and hematological characteristics of 88 patients with COVID-19

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Abstract

Introduction: To retrospectively analyze epidemiological, clinical and hematological characteristics of COVID-19 patients.

Methods: The demographic, symptoms, and physiological parameters of 88 patients were collected and analyzed. The performance of complete blood count (CBC) indexes for monitoring and predicting the severity of COVID-19 in patients was evaluated by analyzing and comparing CBC results among different COVID-19 patient groups.

Results: White blood cells (WBCs), the neutrophil percentage (Neu%), absolute neutrophil count (Neu#), and neutrophil-to-lymphocyte ratio (NLR) were significantly higher in the critical group than in the other three groups ($P < .05$), while the lymphocyte percentage (Lym%), monocyte percentage (Mon%), lymphocyte count (Lym#), and lymphocyte-to-monocyte ratio (LMR) were significantly lower in the critical group than in the other three groups ($P < .05$). WBCs, the Neu%, Neu#, NLR, and neutrophil-to-monocyte ratio (NMR) were significantly higher in the severe group than in the mild and moderate groups ($P < .05$), while the Lym% was significantly lower in the severe group than in the mild and moderate groups ($P < .05$). The Mon%, Lym#, and LMR were significantly lower in the severe group than in the moderate group ($P < .05$). Using receiver operating characteristic (ROC) curve analysis to differentiate severe and nonsevere patients, the areas under the curve (AUCs) for the NLR, Neu%, and Lym% were 0.733, 0.732, and 0.730, respectively. When differentiating critical patients from noncritical patients, the AUCs for the NLR, Neu%, and Lym% were 0.832, 0.831, and 0.831.

Conclusions: The NLR is valuable for differentiating and predicting patients who will become critical within 4 weeks after the onset of COVID-19.

KEYWORDS

BC-6800plus, clinical characteristics, COVID-19, hematology, neutrophil-to-lymphocyte ratio, novel coronavirus (SARS-Cov-2)

Hongmei Zhang and Xiaocui Cao contributed equally to this work.

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An emerging marker predicting the severity of COVID-19: Neutrophil-Lymphocyte Count Ratio

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Research article:
Keywords : COVID-19, Coronavirus. SARS-CoV-2, Marker
DOI : https://doi.org/10.21203/rs-28850/v

Abstract :

Background: To analyze clinical features and laboratory indicators and identify the markers of exacerbation in COVID-19. Methods: We reviewed clinical histories of 177 patients with con rmed COVID19. The patients were categorized into mild group (153 patients) and severe group (24 patients). The baseline demographic and laboratory indicators of all patients were collected, including the neutrophillymphocyte count ratio (NLCR) and C-reactive protein to albumin ratio (CAR). Receiver operating characteristic curve (ROC) analysis was performed to search for indicators predicting exacerbation in COVID-19 patients, and acquiring the area under the curves (AUCs), sensitivity, speci city and cut-off value. Results: The age of the severe group were signi cantly older than those of the mild group (P <0.01). Fever was the typical symptom in all COVID-19 patients. Cough and fatigue were manifested in mild group, yet severe patients were more prominent in dyspnea. The laboratory indicators showing that the mild group mainly had an elevated C-reactive protein; the severe group had a decreased lymphocyte count and lymphocyte ratio. WBC, neutrophil count, neutrophil ratio, D-dimer, AST, ALT, LDH, BUN, CRP levels increased. Furthermore, compared to mild group, WBC, neutrophil count, neutrophil ratio (Neut%), Ddimer, total bilirubin, albumin, AST, ALT, LDH, BUN, creatine kinase, CRP, CAR, NLCR were signi cantly higher, the lymphocyte count, lymphocyte ratio, and APTT were signi cantly lower in severe group (P<0.05). The ROC indicating that NLCR, Neut%, CAR, CRP, and LDH were better at distinguishing mild and severe patients. The AUCs of NLCR was larger than others (NLCR>Neut%>CAR>CRP>LDH: 0.939>0.925>0.908>0.895>0.873), which suggested that NLCR was the optimal maker; a cut-off value for NLCR of 6.15 had 87.5% sensitivity and 97.6% speci city for predicting exacerbation in COVID-19 patients. Conclusions: The different types of COVID-19 had signi can't differences in age, clinical symptoms and laboratory indicators, and severe patients might be easier to suffer from the multiple organ damage. An elevated NLCR may indicate that the disease was progressing towards exacerbation. It was essential to dynamically monitor the serum NLCR levels which contributed to evaluate the patient's condition and e cacy. NLCR could be used as a novel, highly speci c and sensitive marker for predicting severity of COVID-19 patients.

Lampiran 17

Hubungan Tingkat Keparahan dengan Nilai NLR (*Neutrophil-Lymphocyte Ratio*) pada Pasien COVID-19 (Studi Pustaka)

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Abstrak

Coronavirus Disease 2019 (COVID-19) adalah penyakit menular yang disebabkan oleh virus SARS-CoV-2. Pada kasus yang berat, COVID-19 dapat menyebabkan pneumonia hingga menyebabkan kematian. Pemeriksaan NLR (*Neutrophil-Lymphocyte Ratio*) merupakan pemeriksaan laboratorium sederhana yang diketahui dapat digunakan sebagai faktor untuk menentukan prognosis dari pasien COVID-19. NLR diketahui berhubungan erat dengan tingkat keparahan dan perjalanan penyakit. Oleh karena itu, pada pasien dengan COVID-19, NLR akan mengalami peningkatan yang cukup signifikan pada berbagai kelompok keparahan penyakit. Penelitian ini bertujuan untuk mengetahui dan mengkaji tingkat keparahan pasien COVID-19, nilai rata-rata NLR, dan hubungan tingkat keparahan dengan nilai NLR, serta mengetahui profil NLR dari berbagai negara pada pasien COVID-19. Bidang penelitian ini adalah hematologi dan virologi. Jenis penelitian ini adalah studi pustaka. Berdasarkan hasil studi pustaka yang dilakukan pada 15 jurnal, tingkat keparahan pasien secara umum dikelompokkan menjadi empat kelompok keparahan penyakit, yakni ringan, sedang, berat, dan kritis, nilai rata-rata NLR pada keseluruhan artikel berkisar antara 0,89-26,39, keseluruhan artikel menyatakan bahwa terdapat hubungan antara tingkat keparahan dengan nilai NLR pada pasien COVID-19, nilai rata-rata NLR yang didapatkan di China berkisar antara 2,33-17,63, India berkisar antara 3,82-26,39, Pakistan berkisar antara 2,88-8,78, Iran berkisar antara 0,89-1,23 serta Argentina yang menunjukkan nilai rata-rata NLR dengan *cut off* ≥ 3.

Kata Kunci **:** Tingkat Keparahan, Nilai NLR, COVID-19

Correlation of Severity with NLR (*Neutrophil-Lymphocyte Ratio*) Values in COVID-19 Patients (Literature Review)

Abstract

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. In severe cases, COVID-19 can cause pneumonia to cause death. NLR (Neutrophil-Lymphocyte Ratio) examination is a simple laboratory test that is known to be used as a factor to determine the prognosis of COVID-19 patients. NLR is known to be closely related to the severity and course of the disease. Therefore, in patients with COVID-19, NLR will experience a significant increase in various disease severity groups. This study aims to determine and assess the severity of COVID-19 patients, the average NLR value, and the relationship between severity and NLR scores, as well as to determine the NLR profile from various countries in COVID-19 patients. The research fields are hematology and virology. This type of research is literature study. Based on the results of a literature study conducted in 15 journals, the severity of patients was generally grouped into four groups of disease severity, namely mild, moderate, severe, and critical, the average NLR value in all articles ranged from 0.89-26.39, the whole article states that there is a relationship between severity and NLR values in COVID-19 patients, the average NLR value obtained in China ranges from 2.33-17.63, India ranges from 3.82-26.39, Pakistan ranges between 2.88-8.78, Iran ranging from 0.89-1.23 and Argentina which shows the average value of NLR with a cut off ≥ 3.

Keywords **:** Severity, NLR Value, COVID-19

Pendahuluan

Coronavirus Disease 2019 (COVID-19) adalah penyakit menular yang disebabkan oleh *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2). SARS-CoV-2 merupakan coronavirus jenis baru yang belum pernah diidentifikasi sebelumnya pada manusia. Tanda dan gejala umum infeksi COVID-19 antara lain gejala gangguan pernapasan akut seperti demam, batuk dan sesak napas. Masa inkubasi rata-rata 5-6 hari dengan masa inkubasi terpanjang 14 hari. Pada kasus COVID-19 yang berat dapat menyebabkan pneumonia, sindrom pernapasan akut, gagal ginjal, dan bahkan kematian (Kemenkes RI, 2020).

Berdasarkan data WHO (2020), jumlah kasus terkonfirmasi positif COVID-19 secara global (sampai dengan 18 Desember 2020) mencapai angka 73.996.237 kasus dengan angka kematian sekitar 1.663.474 kasus kematian. Sedangkan di Indonesia sendiri angka kasus terkonfirmasi positif (sampai dengan 18 Desember 2020) telah mencapai angka 650.197 kasus dengan angka kematian sekitar 19.514 kasus kematian. Virus COVID-19 cukup menular dengan tingkat kematian yang relatif tinggi, tetapi informasi yang tersedia dalam laporan publik dan literatur yang diterbitkan angka ini terus meningkat pesat (Harapan, dkk., 2020). Sedangkan di Provinsi Lampung, kasus terkonfirmasi positif COVID-19 mencapai angka 5.125 kasus, dengan angka kematian mencapai angka 258 kasus kematian sampai dengan 17 Desember 2020 (Dinkes Provinsi Lampung, 2020).

Angka kematian yang terus meningkat ini menunjukkan bahwa COVID-19 tampak sebagai penyakit dengan tingkat penularan dan tingkat keparahan klinis yang tinggi sebagaimana terlihat dari angka kematian yang muncul di masa awal pandemi (Freitas dkk., 2020). Bahkan menurut data laporan WHO di China, 80% kasus yang dikonfirmasi laboratorium hingga 20 Februari 2020 memiliki penyakit tomoderate ringan - termasuk kasus non-pneumonia dan pneumonia, sekitar 13,8% berkembang menjadi penyakit parah dan 6,1% lainnya berkembang ke tahap kritis yang membutuhkan perawatan intensif (Verity dkk., 2020). Secara klinis, memprediksi keparahan sejak awal merupakan tahap yang sangat penting untuk mengurangi morbiditas klinis dan meningkatkan pengobatan untuk pneumonia COVID-19, oleh karena perlu dilakukan itu diagnosis banding dini dalam memprediksi tingkat keparahan infeksi SARS-CoV-2 pada pasien COVID-19. Beberapa penelitian lain juga menunjukkan identifikasi awal penyakit kritis dan manajemen stratifikasi resiko pada pasien COVID-19 dapat mengurangi kematian dan mengurangi beban sumber daya medis yang kurang (Mousavi-Nasab dkk., 2020).

Pada pasien COVID-19, tingkat keparahan klinis diklasifikasikan menjadi empat kelompok keparahan yang dikelompokkan berdasarkan gejala klinis dan keparahan dari pasien yang terinfeksi virus SARS-CoV-2, yakni kategori ringan, sedang/moderat, berat dan kritis (WHO, 2020). Beberapa penelitian menyebutkan bahwa pemeriksaan laboratorium yang ditemukan paling bermakna untuk memprediksi tingkat keparahan pada pasien COVID-19 adalah pemeriksaan NLR (*Neutrophil-Lymphocyte Ratio*). NLR merupakan salah satu parameter pemeriksaan hematologi yang sederhana, mudah dihitung dan selalu tersedia ini telah diteliti untuk digunakan dalam berbagai keadaan penyakit termasuk dalam kondisi peradangan dan dapat dihitung dengan cara membagi jumlah neutrofil absolut dengan jumlah limfosit absolut (Targher dkk., 2020), dan dengan aksebilitas dan biaya yang rendah inilah NLR banyak digunakan sebagai penanda prognostik awal pasien COVID-19 dengan berbagai tingkat keparahan (Basbus dkk., 2020).

Peningkatan jumlah neutrofil dan penurunan jumlah limfosit pada pasien COVID-19 dimulai saat virus masuk ke dalam tubuh manusia, dan kemudian tubuh akan membentuk sistem kekebalan bersamaan dengan proses dimana virus akan berusaha mengubah antigen

permukaannya (Subowo, 1993). Sistem kekebalan tubuh atau respon imun yang terbentuk terdiri dari sistem imun bawaan (alamiah) dan didapat (adaptif) (Olson & Nardin, 2017). Imunitas bawaan akan diaktivasi saat sel menggunakan serangkaian reseptor terspesialiasi untuk mengenali berbagai jenis mikroorganisme termasuk virus sedangkan imunitas adaptif terjadi atas sifat khusus limfosit yang dapat merespon secara selektif terhadap ribuan benda asing atau antigen yang berbeda. Melalui aktivasi mekanisme bawaan ini, respon adaptif seringkali menimbulkan inflamasi, baik akut maupun kronis (Playfair & Chain, 2009).

Pada proses replikasi *Coronavirus*, virus akan berikatan dengan reseptor *Angiotensin-Converting-Enzyme* II (AcE2) untuk selanjutnya dapat masuk ke dalam sel hospes, sehingga partikel virus dapat melepaskan amplop dan genomnya untuk masuk ke dalam sitoplasma sel hospes dan dalam keadaan infeksi inilah neutrofil akan aktif bergerak dan sejumlah besar dapat berkumpul di tempat jaringan cedera dalam waktu yang singkat. Sel-sel ini kemudian tertarik ke tempat cedera dan peradangan oleh suatu proses yang disebut kemotaksis (Sacher & McPherson, 2004).

Pada infeksi COVID-19, neutrofil akan bergerak secara aktif dan bermigrasi menuju sistem atau organ imunitas, dan mengeluarkan ROS (*Reactive Oxygen Species*) dalam jumlah besar yang kemudian menginduksi kerusakan dari DNA sel dan menyebabkan virus bebas keluar dari sel, sehingga AADC (*Antibody-Dependent Cell-Mediated Cell*) dapat langsung membunuh virus secara langsung dan memicu imunitas humoral (Yang dkk., 2020).

Oleh karena itu dalam keadaan infeksi COVID-19, jumlah neutrofil akan mengalami peningkatan. Demikian pula halnya dengan limfosit, pada pasien COVID-19 penurunan jumlah limfosit/limfositopenia menjadi ciri yang signifikan pada pasien dengan kategori parah/kritis. Penurunan jumlah limfosit ini diketahui sebagai hasil dari penghancuran limfosit yang disebabkan oleh penghancuran komponen sitoplasma setelah invasi yang ditargetkan oleh partikel virus (Hu dkk., 2020).

Tujuan penelitian kepustakaan ini adalah untuk mengetahui dan mengkaji hubungan tingkat keparahan dengan nilai NLR (*Neutrophil-Lymphocyte Ratio*) pada pasien COVID-19.

Metode

Jenis penelitian yang digunakan adalah Studi Kepustakaan (*Library Research*). Desain penelitian pada penelitian kepustakaan ini adalah desain penelitian kualitatif dengan pendekatan metode analisis isi. Penelitian ini didasarkan pada proses pengumpulan data-data yang dibutuhkan, dan kemudian dilakukan klasifikasi serta deskripsi, variabel independen yang digunakan adalah tingkat keparahan pasien COVID-19 sedangkan variabel dependen adalah nilai NLR (*Neutrophil-Lymphocyte Ratio*). Penelitian kepustakaan ini dilakukan dari Bulan Maret sampai dengan Bulan Juni 2021.

Informasi dalam penelitian ini dilakukan dengan cara menelusuri artikel yang sesuai dengan topik penelitian. Sumber data yang menjadi bahan penelitian pada penelitian kepustakaan ini adalah sumber data sekunder berupa jurnal, buku dan artikel yang sesuai dengan topik penelitian.

Pencarian literatur dilakukan menggunakan data terpilih dari *database Google Scholar*, *PubMED*, dan *ResearchGate* dengan kata kunci yang sesuai dengan topik penelitian. Pada proses pencarian data literatur pada penelitian kepustakaan ini diperoleh data sekitar 59 artikel yang menunjukkan keterkaitan yang sesuai dengan topik penelitian. Kata kunci yang digunakan pada proses pencarian data literatur penelitian ini adalah *severity of COVID-19*, *NLR in COVID-19*, tingkat keparahan pasien COVID-19, dan NLR pada pasien COVID-19.

Teknik analisis data yang digunakan dalam penelitian ini berupa metode analisis isi (*Content Analysis*), dan dari sekitar 59 artikel yang didapat setelah

dilakukan pencarian menggunakan kata kunci yang sesuai dengan topik penelitian, peneliti kemudian mengolah data-data berupa artikel jurnal, skripsi dan buku yang sudah dikumpulkan hingga ditemukan hasil berupa 15 artikel yang relevan dan sesuai dengan tujuan serta topik penelitian, yaitu hubungan tingkat keparahan dan nilai NLR (*Neutrophil-Lymphocyte Ratio*) pada pasien COVID-19.

Hasil dari analisa data akan dilakukan tahap pembahasan untuk dibahas lebih rinci, sehingga dihasilkan kesimpulan data yang akan membuktikan kebenaran variabel yang dianalisis.

Hasil

Berdasarkan hasil pengumpulan data tentang hubungan tingkat keparahan dengan nilai NLR (*Neutrophil-Lymphocyte Ratio*) pada pasien COVID-19, yang didapatkan melalui artikel, jurnal dan penelusuran internet dari database *Google Scholar, PubMED* dan *ResearchGate*, diperoleh 15 jurnal internasional yang dapat dikaji secara studi pustaka.

Tabel 1 Tabel Ringkasan 15 Artikel yang Menyatakan Terdapat Hubungan antara Tingkat Keparahan dengan Nilai NLR pada Pasien COVID-19.

No.	Nama Penulis dan Tahun	Tingkat Keparahan	Rata-Rata NLR	p-*value*	Negara
1	Fu dkk. (2020).	Ringan/ tidak parah	2,33	p < 0,001	China
		Berat/parah	6,29	p < 0,001	
2	Huang, Shaoping dkk. (2020).	Ringan/ tidak parah	> 3,5 (25,13%) ≤ 3,5 (74,87%)	p < 0,001	China
		Parah	> 3,5 (72,41%) ≤ 3,5 (27,59%)	p < 0,001	
3	Man Kong, dkk. (2020).	Tidak parah	3,3	p < 0,001	China
		Parah	6,6	p < 0,001	
4	Lian, Jiangshan dkk. (2020).	Sedang	2,45	p < 0,001	China
		Parah	4,08	p < 0,001	
		Kritis	9,67	p < 0,001	
5	Liu Lei dkk. (2020).	Ringan/ tidak parah	2,6	p < 0,001	China
		Parah	10,4	p < 0,001	
6	Qun, Sen dkk. (2020).	Umum	2,41	p < 0,001	China
		Parah	2,96	p < 0,001	
		Kritis	6,32	p < 0,001	
7	Shang Weifang dkk. (2020).	Tidak parah	2,38	p < 0,05	China
		Parah	4,75	p < 0,05	
8	Xintian, Xia dkk. (2020).	Sedang	2,889	p < 0,05	China
		Parah	8,780	p < 0,05	
9	Yang dkk. (2020).	Ringan/ tidak parah	4,8	p < 0,001	China
		Parah	20,7	p < 0,001	
10	Zhang, Hongmei dkk. (2020).	Ringan	2,33	p < 0,05	China
		Sedang/ moderat	5,98	p < 0,05	
		Parah	9,55	p < 0,05	
		Kritis	15,85	p < 0,05	
11	Zhang, Minping dkk. (2020).	Ringan	2,34	p < 0,05	China
		Berat	17,63	p < 0,05	
12	Anurag, Aditya dkk.	Ringan	3,82	p < 0,05	India

No.	Nama Penulis dan Tahun	Tingkat Keparahan	Rata-Rata NLR	p-*value*	Negara
	(2020).	Sedang/ moderat	15,18	p < 0,05	
		Berat	26,39	p < 0,05	
13	Imran dkk. (2020).	Ringan/ umum	2,88	p < 0,001	Pakistan
		Berat	8,78	p < 0,001	
14	Mousavi-Nasab SD dkk. (2020).	Ringan/ tidak parah	0,89	p < 0,001	Iran
		Berat/parah	1,65	p < 0,001	
15	Basbus, Luis dkk. (2020).	Ringan/ tidak parah	≥ 3 (33%) < 3 (67%)	p < 0,001	Argentina
		Berat/parah	≥ 3 (81%) < 3 (19%)	p < 0,001	

Peneliti telah melakukan meta analisis isi dari masing-masing artikel yang didapatkan, dan berdasarkan hasil pengkajian pada 15 artikel tersebut nampak bahwa dari keseluruhan 15 artikel ilmiah (100%) menyatakan terdapat hubungan antara tingkat keparahan dengan nilai NLR pada pasien COVID-19.

Tabel 2. Nilai Rata-Rata NLR pada Berbagai Tingkat Keparahan pada Pasien COVID-19

	Tingkat Keparahan			
	Ringan	**Sedang**	**Berat**	**Kritis**
Nilai Rata-Rata NLR	0,89-4,8	2,45-15,18	1,65-26,39	6,32-15,85

Tabel 2 menunjukkan perbedaan nilai rata-rata NLR pada pasien COVID-19 dengan berbagai tingkat keparahan.

Pembahasan

1. Tingkat Keparahan Pasien COVID-19

Berdasarkan hasil pengkajian pada 15 artikel penelitian yang dikaji pada penelitian kepustakaan ini 11 dari 15 artikel penelitian mengklasifikasikan tingkat keparahan menjadi dua kelompok keparahan penyakit yakni kelompok penyakit ringan/sedang dengan kelompok penyakit parah/berat dan 4 artikel lainnya mengklasifikasikan tingkat keparahan pasien COVID-19 menjadi tiga kelompok keparahan penyakit yaitu kelompok penyakit umum/ringan/sedang, kelompok penyakit parah/berat dan kelompok penyakit kritis. Pengelompokan ini pada dasarnya didasarkan pada gejala klinis yang dialami pasien selama masa perawatan. Pasien dengan gejala klinis tertentu akan dikelompokkan berdasarkan klasifikasi tingkat keparahan yang berbeda

Secara umum, tingkat keparahan penyakit akibat COVID-19 diklasifikasikan menjadi empat kelompok tingkat keparahan penyakit, yaitu kelompok penyakit ringan, sedang/moderat, berat/parah dan kelompok penyakit kritis yang sesuai dengan tingkat keparahan gejala klinisnya masing-masing. Namun, pada penelitian yang mengelompokkan tingkat keparahan penyakit akibat COVID-19 menjadi dua kelompok keparahan, pasien dikelompokkan menjadi dua kelompok penyakit saja yaitu kelompok penyakit parah/ringan dan kelompok penyakit tidak parah/ringan dan pada penelitian ini kelompok penyakit ringan terdiri dari kelompok penyakit ringan dan sedang sedangkan kelompok penyakit parah terdiri dari kelompok penyakit parah dan kritis (Shang dkk., 2020), dan penelitian yang mengelompokkan tingkat keparahan pasien COVID-19 menjadi tiga kelompok keparahan, pasien akan dikelompokkan

menjadi kelompok penyakit ringan/sedang, berat/parah dan kritis.

Pengelompokan pasien menjadi beberapa kelompok keparahan penyakit pada dasarnya digunakan untuk memantau perkembangan dan perjalanan klinis penderita COVID-19 yang dilakukan perawatan.

2. Nilai NLR (*Neutrophil-Lymphocyte Ratio*) pada Pasien COVID-19

Berdasarkan hasil analisis artikel yang telah dikaji, diperoleh hasil nilai rata-rata NLR (*Neutrophil-Lymphocyte Ratio*) pada penderita COVID-19 berkisar antara 0,89 sampai dengan 26,39. Kisaran nilai rata-rata ini tampak pada pasien dengan tingkat keparahan yang berbeda-beda.

Nilai rata-rata NLR pada kelompok penyakit ringan/tidak parah berkisar antara 0,89 sampai dengan 4,8; pada kelompok penyakit sedang/moderat berkisar antara 2,45-15,18; pada kelompok penyakit berat/parah berkisar antara 1,65 sampai dengan 26,39 serta pada kelompok penyakit kritis berkisar antara 6,32 sampai dengan 15,85.

Nilai NLR umumnya akan meningkat pada penderita COVID-19, dan peningkatan ini terjadi karena pada penderita COVID-19 neutrofil akan mengalami peningkatan sedangkan limfosit mengalami penurunan jumlah yang cukup signifikan. Peningkatan jumlah neutrofil dan penurunan jumlah limfosit ini berkaitan erat dengan sistem pertahanan tubuh manusia. Neutrofil merupakan komponen seluler penting dari pertahanan inang dalam sistem imun bawaan, sedangkan limfosit dianggap sebagai sel utama yang terlibat dalam sistem imun adaptif/didapat. Selanjutnya, limfosit akan memainkan peran kunci dalam regulasi respon inflamasi (Kong dkk., 2020).

Pada keseluruhan jurnal atau artikel penelitian yang dikaji, hasil penelitian menunjukkan perbedaan yang signifikan antara nilai rata-rata NLR pada pasien dengan tingkat keparahan yang berbeda, dan berdasarkan hasil penelitian tersebut, para peneliti menyatakan bahwa nilai NLR rata-rata pada kelompok penyakit parah/berat/kritis secara signifikan memiliki nilai yang lebih tinggi daripada kelompok penyakit keparahan lainnya.

Perbedaan yang cukup signifikan ini menunjukkan perbedaan nilai rata-rata yang berbeda pada tingkat keparahan yang berbeda-beda pula. NLR yang meningkat diketahui sebagai biomarker fungsional yang mempengaruhi perkembangan pneumonia pada pasien COVID-19 dan diketahui berhubungan dengan keparahan dari suatu penyakit dan dapat dipertimbangkan sebagai biomarker yang independent untuk mengindikasikan *outcome* yang buruk.

Berdasarkan analisis hasil dari keseluruhan artikel penelitian yang menunjukkan perbedaan nilai NLR pada tingkat keparahan yang berbeda-beda, maka dapat ditarik kesimpulan bahwa semakin parah kondisi klinis pasien yang mengalami perburukan, maka akan terjadi peningkatan nilai NLR yang signifikan.

3. Hubungan Tingkat Keparahan dengan Nilai NLR pada Pasien COVID-19

Berdasarkan hasil pengkajian kepustakaan pada penelitian ini terdapat 15 artikel yang menyatakan terdapat hubungan antara tingkat keparahan dengan nilai NLR pada pasien COVID-19. Hubungan ini tampak pada perbedaan nilai NLR pada pasien dengan COVID-19 pada tingkat keparahan yang berbeda-beda.

Hasil penelitian menunjukkan bahwa terdapat hubungan yang signifikan antara tingkat keparahan dengan nilai NLR pada pasien COVID-19, hal ini sesuai dengan teori yang menyatakan bahwa pasien dengan COVID-19 akan mengalami inflamasi yang menyebabkan peningkatan jumlah neutrofil dan penurunan jumlah limfosit. Kelainan laboratorium ini berkaitan dengan sistem imunitas tubuh manusia dalam melawan virus penyebab infeksi COVID-19. NLR merupakan salah satu parameter pemeriksaan hematologi yang diketahui dapat digunakan sebagai pemeriksaan diagnosis banding dini dalam mendeteksi keparahan COVID-19. Oleh

karena itu semakin tinggi nilai NLR, maka akan semakin serius pula penyakit tersebut.

Pada pasien COVID-19 identifikasi awal faktor resiko untuk pasien yang parah sangat penting untuk mendapatkan perawatan yang suportif, bahkan pada kasus yang parah akan terjadi penurunan jumlah limfosit dan peningkatan jumlah neutrofil yang signifikan (Kong dkk., 2020). Peningkatan jumlah neutrofil dan penurunan jumlah limfosit inilah yang menyebabkan tingginya nilai NLR pada pasien dengan COVID-19.

Penelitian yang dilakukan oleh Qun dkk (2020) menyatakan bahwa NLR berhubungan erat dengan tingkat keparahan dan perjalanan penyakit akibat COVID-19, hal ini tampak pada hasil penelitian yang menyatakan bahwa nilai NLR yang tinggi memiliki tingkat keparahan yang lebih tinggi dan perjalanan penyakit yang lebih lama. Sehingga dengan demikian terdapat hubungan yang signifikan dan NLR diketahui berkorelasi positif dengan keparahan penyakit ($p < 0,001$).

Berdasarkan hasil pengkajian pada 15 artikel yang telah dikaji, keseluruhan artikel menyatakan terdapat hubungan antara tingkat keparahan pasien dengan nilai NLR (Neutrophil-Lymphocyte Ratio) pada pasien COVID-19. Sehingga dengan demikian pada penelitian kepustakaan ini H_1 diterima/H_0 ditolak, yang artinya terdapat hubungan yang signifikan antara tingkat keparahan dengan nilai NLR (Neutrophil-Lymphocyte Ratio) pada pasien COVID-19.

Selanjutnya pada 15 artikel yang telah dikaji, 11 dari 15 artikel penelitian dilakukan di China yang menunjukkan nilai rata-rata NLR yang berkisar antara 2,33 sampai dengan 17,63 dari keseluruhan tingkat keparahan pasien COVID-19, dari ringan sampai kritis.

Pada penelitian lainnya, sebanyak 4 artikel penelitian dilakukan di India, Pakistan, Iran dan Argentina. Artikel penelitian yang berasal dari India memiliki kisaran nilai rata-rata NLR antara 3,82 sampai dengan 26,39, Pakistan 2,88 sampai dengan 8,78, Iran 0,89 sampai dengan 1,23, serta penelitian yang dilakukan di Argentina menunjukkan nilai rata-rata NLR pada pasien COVID-19 dengan batas cut off ≥ 3. Hasil penelitian tidak menunjukkan perbedaan yang begitu berarti dari rentang nilai rata-rata NLR dari setiap negara.

Simpulan dan Saran

Berdasarkan hasil studi pustaka yang dilakukan pada 15 artikel mengenai hubungan tingkat keparahan dengan nilai NLR pada pasien COVID-19 dapat ditarik kesimpulan sebagai berikut:

1. Tingkat keparahan pasien pada penderita COVID-19 dikelompokkan berdasarkan kriteria klinis tertentu yang menunjukkan perbedaan antara kelompok penyakit yang satu dengan yang lainnya. Pada artikel yang telah dianalisis, secara umum tingkat keparahan penyakit COVID-19 dibagi menjadi empat kategori yaitu kelompok penyakit ringan, sedang/moderat, berat/parah dan kritis.
2. Nilai NLR rata-rata keseluruhan pada keseluruan kelompok keparahan penyakit berkisar antara 0,89 sampai dengan 26,39, sedangkan pada kelompok penyakit ringan/tidak parah, kisaran nilai rata-rata NLR berkisar antara 0,89 sampai dengan 4,8; pada kelompok penyakit sedang berkisar antara 2,45 sampai dengan 15,18; pada kelompok penyakit berat/parah berkisar antara 1,65 sampai dengan 26,39 serta pada kelompok penyakit kritis berkisar antara 6,32 sampai dengan 15,85.
3. Terdapat hubungan yang signifikan antara tingkat keparahan penyakit dengan nilai NLR (*Neutrophil-Lymphocyte Ratio*) pada pasien COVID-19.
4. Nilai rata-rata NLR dari keseluruhan artikel penelitian yang dilakukan di China berkisar antara 2,33 sampai dengan 17,63, India berkisar antara 3,82 sampai dengan 26,39, Pakistan berkisar antara 2,88 sampai dengan 8,78, Iran berkisar antara 0,89 sampai dengan 1,23 serta penelitian yang

dilakukan di Argentina yang menunjukkan nilai rata-rata NLR dengan batas *cut off* ≥ 3.

Berdasarkan hasil studi pustaka mengenai hubungan tingkat keparahan dengan nilai NLR pada pasien COVID-19 disarankan untuk menjadikan pemeriksaan NLR sebagai pemeriksaan untuk penanda keparahan penyakit pada pasien COVID-19.

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Lampiran 18

KARTU BIMBINGAN PEMBIMBING UTAMA

Nama Mahasiswa : David Martua Sitinjak
Judul Skripsi : Hubungan Tingkat Keparahan dengan Nilai NLR (*Neutophil-Lymphocyte Ratio*) pada Pasien COVID-19 (Studi Pustaka)
Pembimbing Utama : Maria Tuntun Siregar, S. Pd., M. Biomed.

No.	Hari/Tanggal	Kegiatan	Keterangan	Paraf
1	Sabtu, 2 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
2	Senin, 4 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
3	Selasa, 12 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
4	Rabu, 13 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
5	Kamis, 14 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
6	Senin, 25 Januari 2021	Acc Seminar Proposal		
7	Senin, 3 Mei 2021	Perbaikan Proposal	Perbaikan	
8	Selasa, 25 Mei 2021	Konsultasi Bab I, II, III, IV dan V	Perbaikan	
9	Jumat, 4 Juni 2021	Konsultasi Bab I, II, III, IV dan V	Perbaikan	
10	Senin, 7 Juni 2021	Konsultasi Bab I, II, III, IV dan V	Perbaikan	
11	Selasa, 8 Juni 2021	Acc Seminar Hasil		
12	Jumat, 25 Juni 2021	Perbaikan Skripsi Seminar Hasil	Perbaikan	
13	Rabu, 30 Juni 2021	Acc Cetak		
14				
15				

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NIP. 19730103 199603 2 001

Lampiran 19

KARTU BIMBINGAN PEMBIMBING PENDAMPING

Nama Mahasiswa : David Martua Sitinjak
Judul Skripsi : Hubungan Tingkat Keparahan dengan Nilai NLR (*Neutophil-Lymphocyte Ratio*) pada Pasien COVID-19 (Studi Pustaka)
Pembimbing Pendamping : Sri Ujiani, S. Pd., M. Biomed.

No.	Hari/Tanggal	Kegiatan	Keterangan	Paraf
1	Jumat, 18 Desember 2020	Konsultasi Bab I, II dan III	Perbaikan	
2	Selasa, 22 Desember 2020	Konsultasi Bab I, II dan III	Perbaikan	
3	Senin, 28 Desember 2020	Konsultasi Bab I, II dan III	Perbaikan	
4	Senin, 4 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
5	Jumat, 8 Januari 2021	Konsultasi Bab I, II dan III	Perbaikan	
6	Rabu, 13 Januari 2021	Acc Seminar Proposal		
7	Senin, 3 Mei 2021	Perbaikan Proposal	Perbaikan	
8	Senin, 10 Mei 2021	Konsultasi Bab IV dan V	Perbaikan	
9	Jumat, 21 Mei 2021	Konsultasi Bab IV dan V	Perbaikan	
10	Senin, 31 Mei 2021	Konsultasi Bab IV dan V	Perbaikan	
11	Rabu, 2 Juni 2021	Acc Seminar Hasil		
12	Jumat, 25 Juni 2021	Perbaikan Skripsi Seminar Hasil	Perbaikan	
13	Senin, 28 Juni 2021	Acc Cetak		
14				
15				

Ketua Program Studi TLM
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