Original Article

Neutrophil-to-lymphocyte ratio in community-acquired pneumonia: Diagnostic potential and its limitations in the COVID era

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Abstract

Objective: To determine the diagnostic potential of neutrophil-to-lymphocyte ratio (NLR) as a POC marker to discriminate tuberculous from non-tuberculous CAP and identify limitations if any at a tertiary care centre in Uttarakhand, India. **Methods:** 225 patients presenting with respiratory complaints were recruited from the General Medicine clinics and investigated. NLR was noted at onset and correlated with final diagnosis. **Results:** NLR from both groups did not exhibit a statistically significant difference. The area under curve (AUC) exhibited an accuracy of 49.1% in differentiating tuberculous from non-tubercular CAP, and an anomalous effect of prior steroid exposure on NLR was noted as a limitation. **Conclusion:** The disparity of our results from previous studies warranted a review of literature which rendered a significant limitation of NLR. The NLR is affected by catecholamines, which makes the marker unreliable in patients with exogenous steroid exposure. This was not noted in the previous studies. We presume indiscriminate steroid usage in the pandemic confounded our findings. We propose that this limitation be accounted for in future studies so that NLR's true utility may be identified.

Keywords: CAP, NLR, point-of-care marker, steroids, tuberculosis

Introduction

Pneumonia is the leading cause of mortality and morbidity in India with nearly 4.3 cases reported annually, many of which are seen in primary are settings at the start.[1] Most guidelines such as American Thoracic Society (ATS) and National Institute for Health and Care Excellence (NICE) recommend empirical treatment in mild to moderate cases of community-acquired pneumonia (CAP). Empiric therapy provides broad spectrum coverage for common organisms, namely, Streptococcus pneumoniae, Hemophilus influenzae, and the atypical organisms.[2,3] Investigations are to be carried out in those with persistent infection or deterioration despite treatment. Though judicious, this approach has several pitfalls.

Often, viral and bacterial pneumonias are indistinguishable and may even coexist. Absence of dense consolidation, multi-focal patchy or bilateral ground-glass opacities are classic but not specific for viral pneumonias. In a primary care setting, differentiation is often difficult.[4]

Tuberculosis is endemic in India and contributes significantly to the burden of CAP. It is often confronted by primary care physicians at onset and can often be confounded by varying presentations. It is often indistinguishable clinically and

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Received: 11-12-2023 **Revised:** 18-03-2024
Accepted: 20-03-2024 **Published:** 26-07-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1940_23

How to cite this article: Abrol R, Ahmed S, Khanduri R. Neutrophil-to-lymphocyte ratio in community-acquired pneumonia: Diagnostic potential and its limitations in the COVID era. J Family Med Prim Care 2024;13:3179-83.

radiographically from non-tubercular causes, especially in the initial stages and in the smear negative.[1,5,6] For such cases, specific cultures such as BACTEC need to be undertaken, which can be very time-consuming and are often not readily available.[7,8]

The problem is further compounded by the loss to follow-up due to various socio-economic issues, worsening of the disease, unnecessary use of antibiotics, and delayed therapy besides the potential to transmit the infection by the sputum positives.[9] Therefore, the need of the hour is to develop and validate a point-of-care, inexpensive, easy-to-perform, and interpretable diagnostic modality for distinguishing tubercular from non-tubercular causes for CAP. Such markers are indispensable in the primary care setting as they can help the physician delineate the direction for the treatment before time-consuming investigations produce results.

Neutrophil-to-lymphocyte ratio (NLR) is a readily calculable parameter and has been successfully evaluated as a marker of systemic inflammation in coronary artery disease (CAD), autoimmune diseases, malignancies, and most relevantly sepsis.[10-12] Lymphocytopenia occurs due to margination, redistribution of lymphocytes within the lymphoid system, and accelerated apoptosis; neutrophilia apparently reactionary to the foreign surface markers is commonly observed in bacterial infections.[13-15]

Individually, these leucocytes exhibit a positive linear correlation with severity of bacteraemia.[16] The extent of lymphocytopenia correlated with the severity of sepsis and shock following major surgery.[12] Wyllie and colleagues described the quantitative association between lymphopenia and the risk of bacteraemia.[14] While lymphocytopenia is considered more accurate than the neutrophilia, their ratio has a greater discriminatory value over their individual status.

The mean values of NLR have been observed to be significantly lower in patients with pulmonary tuberculosis than in those with community-acquired pneumonia.[17,18] The NLR is an inexpensive and reproducible parameter with potential diagnostic value, and we intend to evaluate its potential to distinguish between tuberculous and non-tuberculous pneumonia.

Materials and Methods

We recruited 225 out- and in-patients with community-acquired pneumonia over 1 year (January 2020 to January 2021). Those with fever (>100.4 F) for more than a week, respiratory symptoms of cough, expectoration, chest pain, and/or dyspnoea along with radiologic evidence of consolidation were included. Unconscious patients, those requiring ventilatory support, those with associated acute coronary event, stroke, malignancy, autoimmune illnesses, and/or those with healthcare-associated pneumonias were excluded. A diagnosis of viral pneumonia (COVID RTPCR/rapid antigen positive), presumptive bacterial (sputum positive for Gram's stain and/or culture plus response to empirical antibiotics), or tubercular pneumonia (sputum positive for ZN stain) was made, and treatment was started accordingly.

All patients in the presumptive bacterial group were given empirical treatment with antibiotics for CAP derived from standard guidelines and were followed up after 2 weeks.

For those who did not respond clinically and radiologically to the empirical antibiotics, anti-tuberculous treatment (ATT) was initiated. They were followed for symptomatic and clinical improvement after 2 weeks (positive response to ATT) and 4 weeks (if suboptimal or no response to ATT after 2 weeks) and categorized as tubercular (if they responded to ATT) or excluded from the study if unresponsive.

Data pertaining to age; gender; duration; clinical features; co-morbidities; haematological parameters such as haemoglobin, red cell indices, platelet counts, and differential leucocyte count; blood and sputum cultures; Gram staining; and sputum for Ziehl–Neelson staining/CBNAAT were compiled. The NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count from the haemogram performed at the time of first contact with the patient.

The data were analysed statistically by using SPSS software version 22. Qualitative variables were represented in the form of frequency and percentage, while quantitative variables were expressed as mean ± SD. Student's *t*-test (for normally distributed) and Mann–Whitney-U test (for skewed distribution) and ANOVA were used for comparing the continuous variables. The association of categorical variables was assessed using Chi-square or Fisher's exact tests as applicable. In order to determine the cut-off value of NLR, ROC (receiver operating characteristics) curve analysis was used. Statistical significance was considered at $P < 0.05$.

Ethical Statement:

The study received ethical approval from the research ethics committee of Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun on 8-April-2022, Ref no: SRHU/HIMS/RC/2022/109.

Results

Of the 225 patients, 66.2% (n = 149) were males. 28.8% (n = 65) patients had tubercular pneumonia; 160 (71.1%) patients were categorised as non-tubercular pneumonia, 90 (56.2%) were bacterial pneumonias, and 69 (43.1%) COVID pneumonias. Duration of fever was greater in the tubercular group than in the non-tubercular group (9.8 ± 8 days vs 7.51 + 1.89 days; $P < 0.001$). Likewise, productive cough (7.68 + 5 days vs 1.0 + 0.89 days; $P < 0.0001$), weight loss (35 vs. 2; $P < 0.0001$), and haemoptysis (2 vs. 0; $P < 0.0263$) were significantly different between the two groups.

A comparison of the demographic, clinical, and laboratory parameters is shown in Table 1. The tubercular group exhibited an upper and middle zone preponderance of radiological

findings, while the non-tubercular group exhibited no such specification. While consolidation and/or pleural effusion were the common findings in bacterial pneumonia, ground glass opacities and interstitial pneumonias dominated the viral group on chest radiograph and computed tomograms. Consolidation with or without effusions dominated the radiological findings of the non-tubercular group. Radiograms in the tubercular group exhibited single lung consolidation (64.3%), fibrocystic changes (16%), pleural effusions (16.9%), and/or cavitation (8%); hydropneumothorax, collapse, and traction bronchiectasis were also observed in one patient each in addition to the consolidation [Figure 1].

The mean haemoglobin, MCV, MCH, platelets, and PCV differed significantly ($P < 0.05$) between the tubercular and non-tubercular groups. Higher mean monocyte ($P = 0.0033$) and eosinophil ($P = 0.0315$) counts were associated with tubercular CAPs compared to the non-tubercular CAP; however, the mean neutrophil and lymphocyte counts and the NLR were comparable in the two groups. Likewise, the NLR was comparable in the tubercular and non-tubercular groups as well as in the bacterial and the viral subgroups [Figure 2].

Discussion

NLR is thought to reflect a balance between innate and adaptive immune responses with the ratio exhibiting a greater sensitivity over absolute values of neutrophils and lymphocytes. Its utility has been observed in various inflammatory and non-inflammatory conditions.[19,20]

A high NLR has the ability to predict all-cause mortality at 28 days in patients with sepsis.[12,21] A composite of age, NLR, and delta neutrophil index was utilised as a reliable indicator to segregate septic patients in emergency settings.[22] Though the ratio has limited utility in determining the focus of sepsis, its effectiveness in identifying sepsis as an aetiology has been remarkable.

Table 1: Demographic and haematological parameters between non-tubercular and tubercular CAP

Name	Non-Tubercular (*n*=160)	Tubercular (*n*=65)	*P*
Age (years)	53.10±17.22	46.78±18.62	0.0156
Duration of fever (days)	7.51	19.75	<0.0001
Duration of cough (days)	6.11	18.08	<0.0001
Gender- Male/Female	105/55	44/21	0.0765
Hemoglobin (gm/dl)	11.85±2.3	11.15±2.2	0.039
Platelet count (×10^3/cumm)	290.79±169.2	368.94±185.9	0.002
MCV (femtolitres)	85.00±9.49	82.15±11.15	0.053
MCH (picograms/cell)	27.69±4.00	26.35±4.81	0.033
PCV (%)	35.97±6.48	33.86±6.32	0.026
Neutrophils (%)	79.5±10.7	77.60±9.90	0.022
Lymphocytes (%)	12.73±8.27	12.14±6.89	0.061
Monocyte count (%)	6.38±3.19	7.74±2.91	0.003
Eosinophil count (%)	0.92±1.75	1.50±1.98	0.031
Basophils (%)	0.32±0.34	0.25±0.30	

Its utility in the primary care setting is most pronounced in cases of community-acquired pneumonia where it can predict cases requiring hospitalisation.[23] Additionally, NLR has been studied for its diagnostic potential as well in CAP. Mean NLR has been significantly lower in those with tubercular as compared to non-tubercular CAPs.[17,24,25] Moreover, mean NLR has been found to be significantly lower in tuberculosis-related pleural effusion compared to malignant, para-pneumonic, and para-malignant effusions ($P = 0.001$, $P = 0.001$, $P = 0.012$, respectively).[26] A positive association between NLR and TB was observed in a study on NLR and granulomatous diseases, sarcoidosis and TB.[27,28] Hence, overwhelming evidence exists in favour of NLR and TB.

In contrast, we failed to find a significant difference between the tubercular patients and non-tubercular patients in terms of the mean neutrophil ($P = 0.221$) and lymphocyte counts ($P = 0.612$) as suggested by above-mentioned studies. The most appropriate cut-off of NLR of 7.01 had a low sensitivity (55.4%) and specificity (45.6%).

This disparity appears to be the result of the unprecedented situation of the COVID pandemic and the rampant use of steroids in almost all patients with respiratory symptoms and/or fever during the course of this study. However, serendipitously, this revealed a limitation of the marker. Glucocorticoids exert pleiotropic effects on leucocyte subsets that include depleting lymphocyte populations. This occurs due to the exhaustion of lymph node reserves by pro-apoptotic effects through gene modulation and by direct cytotoxicity in high doses. Additionally, cell adhesion and margination may be affected, and impaired migration to the site of inflammation may under-estimate lymphocytes in the bloodstream as well. This effect is most pronounced 4–6 hours post administration, but prolonged suppression occurs for at least 2 weeks.[29,30]

Neutrophils are generally resistant to glucocorticoid-induced apoptosis due to complex transcription regulation mechanisms. Additionally, glucocorticoids promote maturation and mobilisation of neutrophils from the bone marrow into circulation.[31-33]

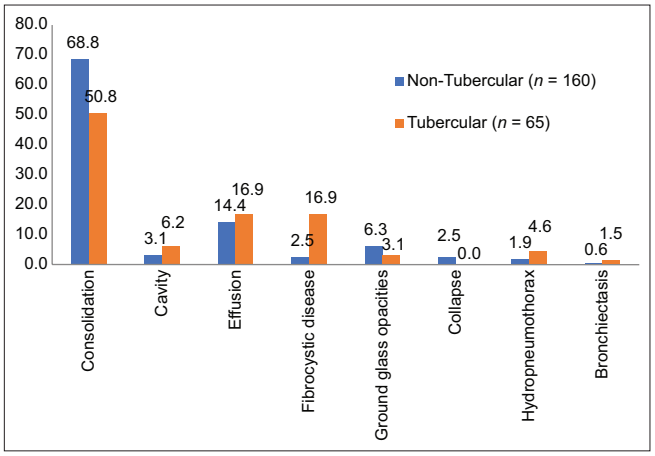

Figure 1: Radiographic findings in CAP

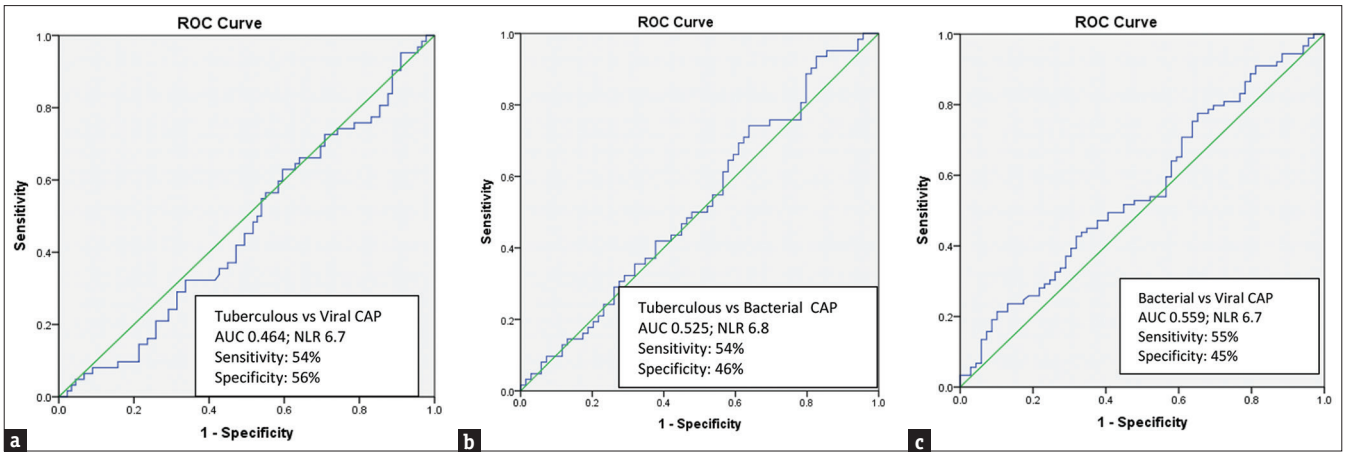

Figure 2: AUC, NLR, sensitivity, and specificity of NLR in (a) tubercular versus bacterial, (b) tubercular versus viral, and (c) bacterial versus viral CAPs

Glucocorticoids further modulate the expression and inhibition of pro- and anti-inflammatory genes in neutrophils, causing a net outcome of a pro-inflammatory state most pronounced in pulmonary diseases as observed by Langereis *et al.*[34]

These effects may be further influenced by micro-environment and pronounced in cases of hypoxia. As the study was conducted during the pandemic when corticosteroids were used indiscriminately, the same could have influenced the outcome seen by our study. Moreover, NLR was promoted as a reliable marker of severity and prognosis during the COVID-19 pandemic; however, the reliability was questionable post treatment initiation in most patients.[35]

The impact of steroid use across the board in CAPs during the pandemic, combined with the immune dysregulation observed in COVID-19 pneumonias, explains why our results were discordant. Significantly higher mean monocyte counts observed in those with tubercular CAP compared to the non-tubercular patients may be related to their involvement in anti-mycobacterial defence. A low mean eosinophil count in the non-tubercular group may be secondary to the association of eosinopenia with bacterial sepsis.[36]

Ayuningtyas *et al.*[37] have recently published similar findings in a comparative analysis between groups which had and had not been exposed to corticosteroids and have concurred that corticosteroid exposure can confound NLR, CRP, and LCR in patients starting from the 2nd up to the 14th day of exposure, thus limiting the originally touted usefulness of the marker.

The major limitations of our study were the pandemic, rampant steroid use, and overwhelmed health services. All these factors contributed to a low sensitivity and specificity of NLR in differentiating tubercular and non-tubercular pneumonias. Nevertheless, the contradictory results flagged the impact of steroids on NLR.

It also brought forth pertinent questions like the minimum duration and/or dose of steroid use affecting NLR, the duration after steroid use when NLR may be assessed again with credibility, and the safe corticosteroid in this context.

To summarise, NLR has been portrayed to be of particular usefulness to the primary care physician as it can be the ideal point-of-care marker. However, the pandemic has revealed certain limitations, which cautions us to use it judiciously. Its usefulness in determining deteriorating patients has been well studied; however, in certain exceptional cases such as prior steroid exposure, the primary care physician must be aware of its limitations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Organization WHO. Guidelines for Treatment of Tuberculosis. WHO; 2010.
2. NICE. Overview | Pneumonia (Community-Acquired): Antimicrobial Prescribing | Guidance | Nice.org.uk. 2019.
3. ATS/IDSA. Publishes Clinical Guideline on Community Acquired Pneumonia; 2019. Available from: www.thoracic.org.
4. van Vugt SF, Verheij TJM, de Jong PA, Butler CC, Hood K, Coenen S, *et al.* Diagnosing pneumonia in patients with acute cough: Clinical judgment compared to chest radiography. Eur Respir J 2013;42:1076–82.
5. Swai HF, Mugusi FM, Mbwambo JK. Sputum smear negative pulmonary tuberculosis: Sensitivity and specificity of diagnostic algorithm. BMC Res Notes 2011;4:475.
6. Nyamande K, Lalloo UG, John M. TB presenting as community-acquired pneumonia in a setting of high TB incidence and high HIV prevalence. Int J Tuberc Lung Dis 2007;11:1308–13.
7. Lawn SD, Mwaba P, Bates M, Piatek A, Alexander H, Marais BJ, *et al.* Advances in tuberculosis diagnostics: The XpertMTB/RIF assay and future prospects for a point-of-caretest.

Lancet Infect Dis 2013;13:349–61.

8. Lawn SD, Zumla AI. Tuberculosis. Lancet 2011;378:57–72.
9. Ferreira-Coimbra J, Sarda C, Rello J. Burden of community-acquired pneumonia and unmet clinical needs. Adv Ther 2020;37:1302–18.
10. Wang L, Wang C, Jia X, Yang M, Yu J. Relationship between neutrophil-to-lymphocyte ratio and systemic lupus erythematosus: A meta-analysis. Clinics (Sao Paulo) 2020;75:e1450.
11. Yin X, Wu L, Yang H, Yang H. Prognostic significance of neutrophil-lymphocyte ratio (NLR) in patients with ovarian cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e17475.
12. Martins EC, Silveira LDF, Viegas K, Beck AD, Fioravantti Júnior G, Cremonese RV, *et al.* Neutrophil-lymphocyte ratio in the early diagnosis of sepsis in an intensive care unit: A case-control study. Rev Bras Ter Intensiva 2019;31:64-70.
13. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, *et al.* Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA 2015;313:264-74.
14. Wyllie DH, Bowler ICJW, Peto TEA. Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. J Clin Pathol 2004;57:950–5.
15. Goodman DA, Goodman CB, Monk JS. Use of the neutrophil: Lymphocyte ratio in the diagnosis of appendicitis. Am Surg 1995;61:257-9.
16. Curbelo J, Bueno SL, Galván-Román JM, Ortega-Gómez M, Rajas O, Fernández-Jiménez G, *et al.* Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: Importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. PLoS One 2017;12:e0173947.
17. Yoon NB, Son C, Um SJ. Yoon NB, Son C, Um SJ. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Ann Lab Med 2013;33:105-10.
18. Taboubi A, Hedhli A, Toujani S, Ben Khaled S, Slim A, Cheikh Rouhou S, *et al.* Is neutrophil-lymphocyte ratio useful for differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Eur Respir J 2018;52(Suppl 62):PA2621.
19. Kim S, Eliot M, Koestler DC, Wu WC, Kelsey KT. Association of neutrophil-to-lymphocyte ratio with mortality and cardiovascular disease in the Jackson heart study and modification by the Duffy antigen variant. JAMA Cardiol 2018;3:455–62.
20. Shah N, Parikh V, Patel N, Patel N, Badheka A, Deshmukh A, *et al.* Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: Insights from the National Health and Nutrition Examination Survey-III. Int J Cardiol 2014;171:390–7.
21. Liu S, Wang X, She F, Zhang W, Liu H, Zhao X. Effects of neutrophil-to-lymphocyte ratio combined with interleukin-6 in predicting 28-day mortality in patients with sepsis. Front Immunol 2021;12:639735.
22. Jhun BW, Sim YS, Shin TR, Kim D-G. The utility of delta neutrophil index in differentiation of pulmonary tuberculosis from community acquired pneumonia. Sci Rep 2018;8:12343.
23. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, *et al.* Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373:415–27.
24. Kumar P, Reddy S, Prasad R, Maharaj, Ram S. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. JMSCR 2020;8:345-9.
25. Berhane M, Melku M, Amsalu A, Enawgaw B, Getaneh Z, Asrie F. The role of neutrophil to lymphocyte count ratio in the differential diagnosis of pulmonary tuberculosis and bacterial community-acquired pneumonia: A cross-sectional study at Ayder and Mekelle 2019;65. doi: 10.7754/Clin.Lab. 2018.180833.
26. Akturk UA, Ernam D, Akbay MO, Koçak ND, Ogur E, Irmak I. Role of the neutrophil-lymphocyte ratio in the differential diagnosis of exudative pleural effusion. Clinics (Sao Paulo) 2016;71:611-6.
27. Iliaz S, Iliaz R, Ortakoylu G, Bahadir A, Bagci BA, Caglar E. Value of neutrophil/lymphocyte ratio in the differential diagnosis of sarcoidosis and tuberculosis. Ann Thorac Med 2014;9:232–5.
28. Shojaan H, Kalami N, Ghasempour Alamdari M, Emami Alorizy SM, Ghaedi A, Bazrgar A, *et al.* Diagnostic value of the neutrophil lymphocyte ratio in discrimination between tuberculosis and bacterial community acquired pneumonia: A meta-analysis. J Clin Tuberc Other Mycobact Dis 2023;33:100395.
29. Marté JL, Toney NJ, Cordes L, Schlom J, Donahue RN, Gulley JL. Early changes in immune cell subsets with corticosteroids in patients with solid tumors: Implications for COVID-19 management. J Immunother Cancer 2020;8:e001019.
30. Gelzo M, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, Scialò F, *et al.* Prognostic role of neutrophil to lymphocyte ratio in COVID-19 patients: Still valid in patients that had started therapy? Front Public Health 2021;9:664108.
31. Wittermans E, van de Garde EM, Voorn GP, Aldenkamp AF, Janssen R, Grutters JC, *et al.* Neutrophil count, lymphocyte count and neutrophil-to-lymphocyte ratio in relation to response to adjunctive dexamethasone treatment in community-acquired pneumonia. Eur J Int Med 2022;96:102–8.
32. Saffar AS, Dragon S, Ezzati P, Shan L, Gounni AS. Phosphatidylinositol 3-kinase and p38 mitogen-activated protein kinase regulate induction of Mcl-1 and survival in glucocorticoid-treated human neutrophils. J Allergy Clin Immunol 2008;121:492-8.e10.
33. Ronchetti S, Ricci E, Migliorati G, Gentili M, Riccardi C. How glucocorticoids affect the neutrophil life. Int J Mol Sci 2018;19:4090.
34. Langereis JD, Oudijk E-JD, Schweizer RC, Lammers J-WJ, Koenderman L, Ulfman LH. Steroids induce a disequilibrium of secreted interleukin-1 receptor antagonist and interleukin-1β synthesis by human neutrophils. Eur Respir J 2011;37:406–15.
35. Qun S, Wang Y, Chen J, Huang X, Guo H, Lu Z, *et al.* Neutrophil-to-lymphocyte ratios are closely associated with the severity and course of non-mild COVID-19. Front Immunol 2020;11:2160.
36. Lavalett L, Ortega H, Barrera LF. Infection of Monocytes From Tuberculosis Patients With Two Virulent Clinical Isolates of Mycobacterium tuberculosis Induces Alterations in Myeloid Effector Functions. Frontiers in Cellular and Infection Microbiology 2020 Apr 23;10.
37. Ayuningtyas LV, Hermosaningtyas AA, Airlangga PS, Kusuma E, Utariani A, Waloejo CS, *et al.* Comparison of changes in inflammation markers NLR, CRP, and LCR after corticosteroid therapy in severe and critical COVID-19 patients. Trends Sci 2023;21:7242.