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Pneumologia

Value of Neutrophil to Lymphocyte ratio as a new biomarker in Tuberculosis inflammation

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Abstract

English:

Neutrophil counts and, especially, neutrophil/lymphocyte ratio (NLR) seem to be a reliable biomarker to distinguish an active tuberculosis (TB) from a latent one or a pulmonary tuberculosis from a bacterial community-acquired pneumonia. In conditions of systemic inflammation, the rise in neutrophil count occurs due to reduced apoptosis of these cells. Consequently, the neutrophil-to-lymphocyte ratio increases, which correlates with elevated mortality rates. We conducted a retrospective study and we included 105 patients with a diagnosis of pulmonary tuberculosis who have been continuously admitted to the Pneumology/TB Department. The NLR average value was 6,92 and we observed increased values in patients with cachexia as comorbidities associated. Smoking status was another item that elevated NLR levels. Ratio value at discharge was lower than the NLR value at admission. The age group over 65 had the highest values. NLR has proven to be a valuable prognostic tool, correlating independently with mortality in various diseases like tuberculosis, pneumonia, COVID-19, and cancer.

Keywords

pulmonary tuberculosis • neutrophil/lymphocyte ratio • inflammation

Valoarea raportului neutrofile/limfocite ca și biomarker utlizat în inflamația din Tuberculoza Pulmonară

Rezumat

Romanian:

Numărul de neutrofile și, în special, raportul neutrofile/limfocite (NLR) par a fi un biomarker fiabil pentru a distinge o tuberculoză activă de una latentă sau o tuberculoză pulmonară de o pneumonie bacteriană comunitară dobândită. În condiții de inflamație sistemică, creșterea numărului de neutrofile apare datorită apoptozei reduse a acestor celule. În consecință, raportul neutrofile-limfocite crește, ceea ce se corelează cu rate ridicate ale mortalității. Am realizat un studiu retrospectiv și am inclus 105 pacienți cu diagnostic de tuberculoză pulmonară care au fost spitalizați în Secția Pneumologie-compartiment TBC a Spialului Clinic Județean Mureș. Valoarea medie NLR a fost de 6,92 și am observat valori crescute la pacienții cu caşexie ca și comorbiditate asociată. Statutul de fumător a fost un alt element care a ridicat nivelurile NLR. Valoarea raportului la externare a fost mai mică decât valoarea NLR la admitere. Grupa de vârstă de peste 65 de ani a avut cele mai mari valori ale raportului. NLR s-a dovedit a fi un instrument valoros de prognostic, corelându-se independent cu mortalitatea în diferite boli precum tuberculoza, pneumonia, COVID-19 și cancerul.

Cuvinte-cheie

tuberculoză pulmonară • raport neutrofile/limfocite • inflamație

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Introduction

Tuberculosis (TB) is the leading killer among all infectious diseases worldwide, despite extensive use of the Mycobacterium bovis bacillus Calmette-Guerin (BCG) vaccine. Approximately a quarter of the worldwide population is estimated to have a latent infection. When the host's immune system weakens, the previously asymptomatic dormant bacteria transforms into a transmissible, active state [1].

Besides inflammatory factors, cytokines and chemokines, such as C-reactive protein (CRP), interferon-γ (IFN-γ), interleukin-6 (IL-6) or tumor necrosis factor—α (TNF-α), other hematological inflammatory markers are evaluated in TB patients. Neutrophil counts and, especially, neutrophil/lymphocyte ratio (NLR) seem to be a reliable biomarker to distinguish an active TB from a latent one, or pulmonary tuberculosis from bacterial community-acquired pneumonia (B-CAP) [2, 3].

In conditions of systemic inflammation, the rise in neutrophil count occurs due to reduced apoptosis of these cells. Consequently, the neutrophil-to-lymphocyte ratio increases, which correlates with elevated mortality rates. Its swift escalation during acute conditions establishes its role as an early acute inflammatory marker, manifesting before other specific laboratory indicators like C-reactive protein (CRP) or leukocytosis.

However, several factors can yield false positive outcomes regarding the elevation of the neutrophil-to-lymphocyte ratio. These factors encompass aging, steroid therapy, active hematological disorders affecting cell counts, HIV infection, or endogenous sex hormone levels. Despite being an established significant mortality factor across various pathologies, its precise normal reference value remains under investigation [3, 4].

Notably, a low body mass index correlates with decreased lymphocyte counts, consequently contributing to an increased ratio value [4].

This ratio served as an indicator for differentiating pyogenic spinal infection (PSI) from spinal tuberculosis (STB). STB patients demonstrated decreased NLR values (median NLR: 3.85 (2.70–5.71)) compared to PSI cases: (median NLR: 10.82 (6.79–17.62)), with a p-value below 0.001. The optimal cut-off of the NLR level ≤6.742 is important to distinguish between PSI and STB [5].

In a retrospective study, scholars evaluated the relationship between immuno nutritional status and the occurrence of cavitation in the lung. Statistically significant association for developping pulmonary cavitation in tuberculosis patients was found for NLR ≥ 5 and serum albumin levels < 3 g/dl [6].

Material and Methods

In order to conduct this retrospective study, we gathered the required information from the observation sheets of patients who were treated for pulmonary tuberculosis in the Mures County Clinical Hospital's Pneumology Department between February 10, 2022, and February 10, 2023. The head of department and hospital management agreed and granted access to the hospital archive for the purpose of reviewing the observation sheets. This access was made possible by the consent of the ethical committee number 16722, dated September 30, 2023.

This study's primary goal was to evaluate the neutrophil/lymphocyte ratio's potential as an inflammatory biomarker that can predict how patients with pulmonary tuberculosis will respond in the future. Secondary goals included examining the variation in the neutrophil/lymphocyte ratio with smoking status, different types of associated comorbidities, or COVID infection, as well as the variability of this ratio's value in the group of patients analyzed between the time of hospitalization and the time of discharge (after treatment).

Inclusion criteria

Patients with a diagnosis of pulmonary tuberculosis who have been continuously admitted to the Pneumology/TB Department.

Exclusion criteria

Patients who were regularly admitted to the TB Department and Pneumology ward, but whose biohumoral results were not accessible for analysis.

After analyzing a database containing 140 hospitalized patients, 105 patients were included in the analyzed group after the criteria for inclusion and exclusion were applied.

The current study was approved by the ethics committee of the University of Medicine, Pharmacy, Sciences and Technology "G.E. Palade" from Targu Mures and was conducted in compliance with the Declaration of Helsinki.

Results

The analyzed group consisted of 105 patients, in which the neutrophil/lymphocyte ratio was calculated. The recorded average value of the ratio was 6.92. Additionally, elevated values (in descending order) were recorded in the group with associated comorbidities such as cachexia, anemia, and smoking (see Table 1).

The NLR value in patients who associated SarsCov2 infection with the diagnosis of pulmonary tuberculosis was 4.34. Within the study group, positive tests for SarsCov2 were recorded in

Table 1. The average N/L ratio value for each comorbidity and its percentage within the study group.

	Proportion of the entire study lot	N/L ratio's average value
All cases	-	**6.92**
Anemia	68.57%	8.51
Cachexia	24.76%	13.01
Cardiovascular comorbidities	18.09%	4.31
Smoker	63.8%	7.95
RT-PCR SARS-COV-2 positive	15.23%	4.34

16 patients (15.23%). The ratio was calculated based on the admission value, which might justify the NLR value (below the average case) (see Figure 1).

The association of smoking status with the diagnosis of pulmonary tuberculosis constitutes an additional risk factor for increasing the amplitude of the inflammatory profile. Among the 105 patients analyzed, 67 were smokers (63.8%). The association of smoking determined an increased value (7.95) above the average NLR cases.

From the initial cohort of this study (105 patients), a subgroup consisting of 52 patients was selected, in which the NLR value

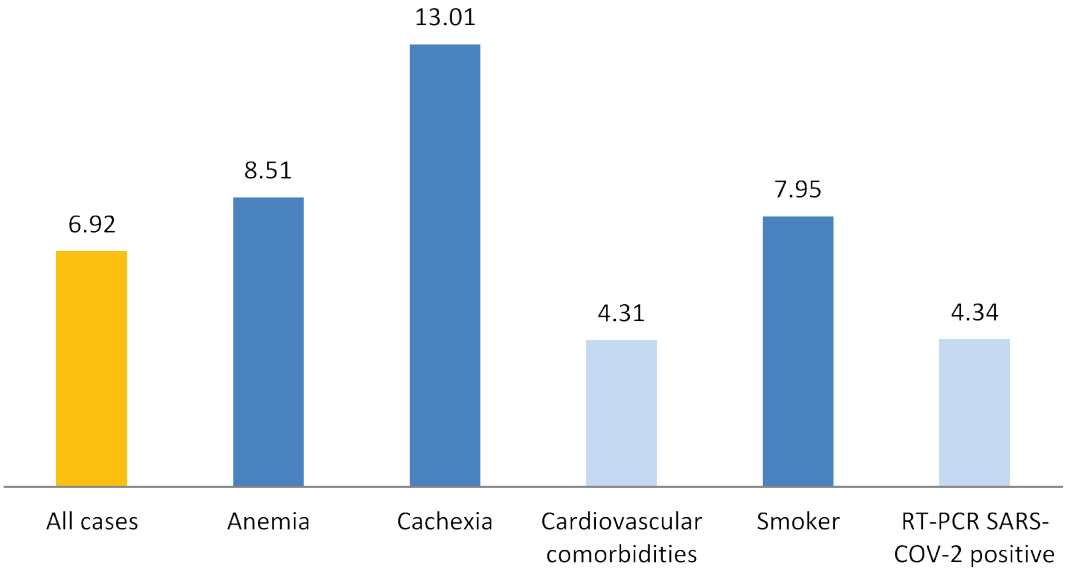

Figure 1. The N/L ratio's average value based on comorbidities.

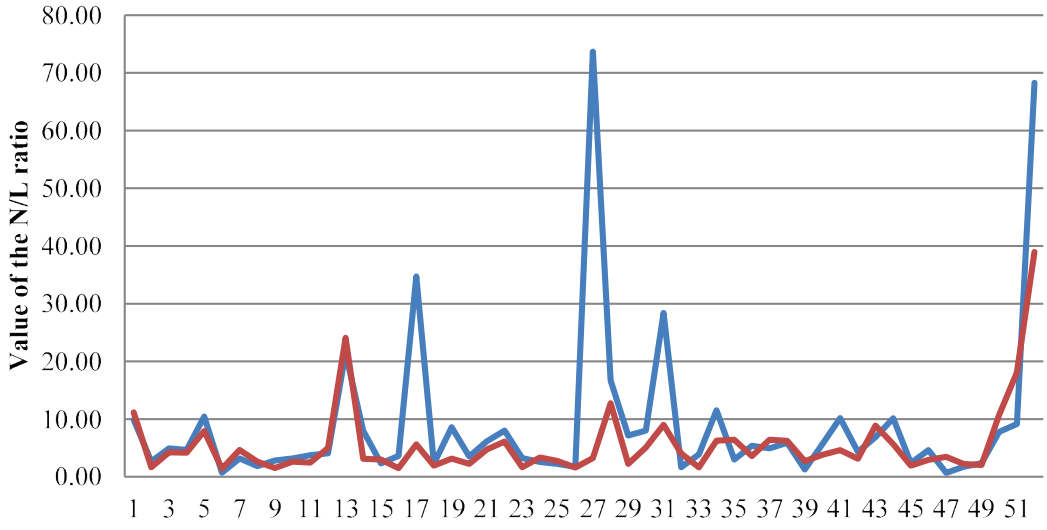

Figure 2. Changes in the N/L ratio's value upon admission (blue) and discharge (red).

was available both at admission and at discharge. For the mentioned subgroup, the calculated value of the NLR ratio at discharge was lower than the value at admission, a result explained by the decrease in inflammation after the treatment instituted during hospitalization (8.97 versus 5.59) (see Figure 2). The mean NLR at admission stood at 8,97, while the mean calculated ratio at discharge was 5.59. The downward trend in NLR values is also observed in smokers (10.03 at admission versus 6.10 at discharge), while in patients with concurrent TB and Sars Cov2 infection, the trend is upward (3.77 at hospitalization; 4.28 at discharge), a pattern rationalized by the combined inflammatory impact of both pathologies (see Table 2 and Figure 3).

The higher value of NLR in this subgroup (52 patients) compared to the initial group (105 patients) can be interpreted due to the fact that this group included a higher percentage of smokers (N=36; 69,23%) and cases with concomitant infection with SarsCov2 (N=10; 19,23%).

The downward trend in NLR between the value at admission and value at discharge is evident across intervals of 5-10, 10-20, and over 20. Conversely, within the intervals of 0.6-3 and 3-5, the average ratio value at discharge was higher

Table 2. Comparison of the average N/L ratio value at admission and discharge.

Patient group	NLR average at admission	NLR average at discharge
Subgroup (52 patients)	8.97	5.59
Smokers	10.03	6.10
TB and Sars-Cov-2 Patients	3.77	4.28

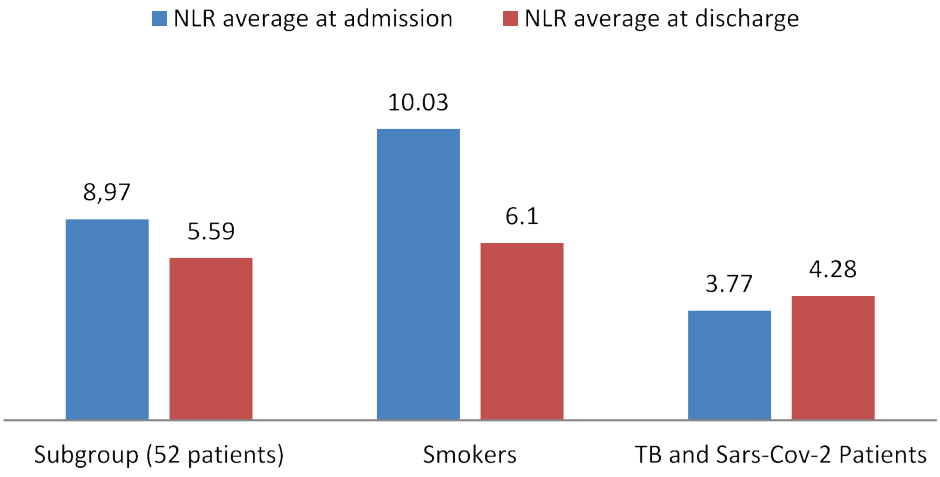

Figure 3. Comparison of the average N/L ratio value at admission and discharge.

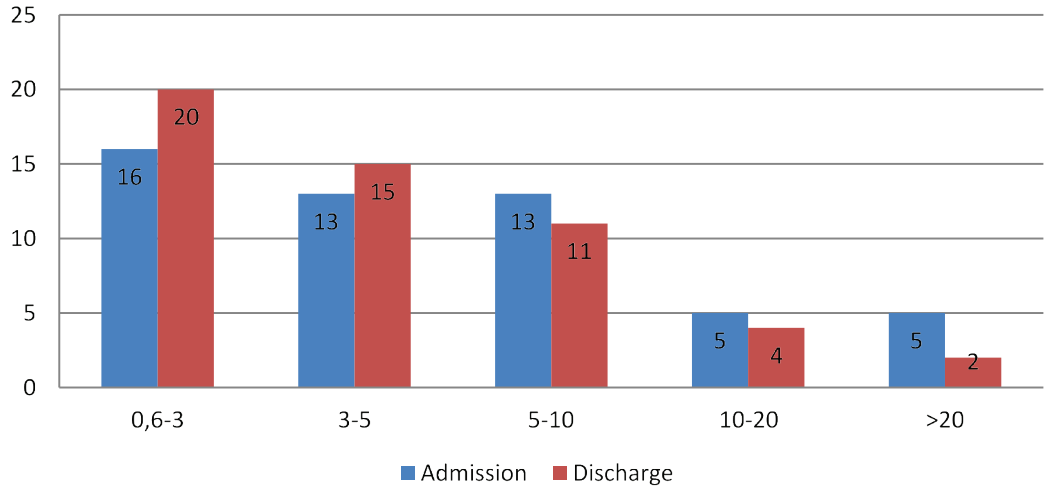

Figure 4. The change in the N/L ratio's value at admission (blue) and discharge (red), represented as intervals.

Table 3. The N/L ratio's value by age group

All cases	**6.92**
19-34 years	4.06
35-64 years	7.24
Over 65 years	7.82

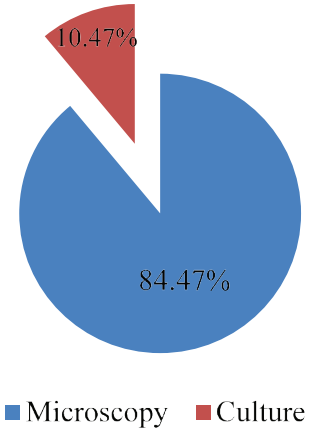

Figure 5. The percentage of cases confirmed by microscopy, respectively by culture.

than that at admission. This outcome may be elucidated by the association of inflammation in both comorbidities (see Figure 4).

The age group over 65 years registered higher values of NLR (7.82) compared to the average ratio value in the studied group (N=105). Age showed a direct, proportional correlation with increasing NLR values (see Table 3).

Confirmation of the diagnosis of pulmonary tuberculosis in the patients included in the study was obtained in most cases by microscopic examination (84.47%) (Fig. 5).

Discussions

The neutrophil-to-lymphocyte ratio (NLR) has emerged as a significant marker in biomedical research over the last decade. NLR serves as an indicator of immune system balance and subclinical inflammation. It has proven to be a valuable prognostic tool, correlating independently with mortality in various diseases like tuberculosis, pneumonia, COVID-19, and cancer [4, 7]. Various factors can give false-positive results in terms of increasing the neutrophil/lymphocyte ratio, among which are steroid-based treatment and active hematological diseases that change the number of these cells, HIV infection or endogenous sex hormones [4].

Smoking has been proven to increase systemic inflammation. This occurs through a reduction in the expression of toll-like receptors and the production of cytokines and chemokines in lung epithelial cells, and macrophages. Additionally, the sustained increase in lymphocytes, neutrophils, and monocytes is a prolonged consequence linked to the ongoing systemic inflammation caused by smoking [8, 9]. Also, cigarette smoking is a well-known risk factor for latent tuberculosis (TB) infection and active TB disease. Nicotine found in tobacco has been identified to attenuate the innate immune responses against TB [7, 9].

Gumus et al. showed in a prospective study that smoking contributes to the onset and progression of many physiological-pathological processes in healthy or clinically asymptomatic smokers, NLR ($p = 0,031$) values were found to be significantly higher for the smoker group. Similarly, in our study, NLR was found to be higher in smokers, because 63.8% of the patients included in the study are smokers and present an average NLR value of 7.95 compared with non-smokers patients [7]. Nonetheless, despite the well-documented significance of NLR as an inflammatory biomarker, Abakay et al. emphasized that smoking seemingly does not affect this measure. Their research indicated no discernible variance between smokers and non-smokers (1.95 vs. 1.63, $P > 0.05$) [10].

Moving forward, tuberculosis, in its pathological progression, like other chronic infections, induces a condition known as "inflammation-related anemia", which involves systemic inflammation and the release of cytokines including IL-6, IL-1, TNF-α, and IFN-γ [11,12,13]. Therefore, given the fact that NLR is an accessible biomarker of systemic inflammation, we pointed out in our study a directly proportional increase of this ratio among patients with anemia, 68.57% of patients had anemia and the average value of the NLR was 8.51, indicating that high values of the ratio are related to anemia. Consequently, the coexistence of anemia and high NLR results is a strong predictor of tuberculosis disease's progresion. Senait Ashenafi et colleagues conducted a post-hoc analysis utilizing available data from 2013 to 2015, obtaining that "anemia of inflammation" was detected in 43% of the patients with ongoing tuberculosis [11, 14].

In addition, activation of several cytokines, previously mentioned as a host response to M. tuberculosis, can directly influence muscle cells. This activation can stimulate protein loss, promoting weight loss and extreme fatigue [15]. Likewise, in our research, the NLR is significantly elevated (the average value is 13.01) among patients with cachexia (24.76% of the cohort), suggesting an increased risk of developing waste syndrome (cachexia) related to an inflammatory response. Suzanne W. Chang et al., in their prospective cohort study, pointed out that leptin binds to hypothalamic receptors. This binding results in reduced appetite and higher energy consumption. They also highlighted the correlation between leptin and inflammatory mediators, suggesting its pivotal role in the process of weight loss triggered by infections, notably tuberculosis [16].

Skupien et al. have also shown that the more severe the inflammation, the lower the leptin levels, the greater the weight loss, consequently resulting in significant weight loss among TB patients experiencing nutritional issues [17, 18].

Furthermore, the results of Quan-Xian et al.'s retrospective study involving 93 tuberculosis patients admitted to the West China Hospital's tuberculosis ward revealed that tuberculosis patients aged over 65 had reduced total lymphocyte counts compared to those under 65, while their NLR levels were higher, indicating that older tuberculosis patients were also prone to impaired immune function [17]. Comparable outcomes were observed in our study with patients over the age of 65. Specifically, the ratio was higher in this group (7.82), in comparison to values observed in age groups younger than 65 years.

As mentioned above, the neutrophil-to-lymphocyte ratio serves as a significant prognostic biomarker in various conditions, notably COVID-19. Several studies have mainly proven its predictive usefulness, particularly in indicating severe disease progression and mortality risk [4, 19, 20]. For instance, Cai J. et al.'s extensive cohort analysis of 12,862 COVID-19 cases revealed that an initial NLR level greater than 6.11 were associated with more severe illness [21]. Consequently, individuals presenting with a coinfection of COVID-19 and tuberculosis, compounded with specific risk factors such as smoking—known to sustain inflammation—face an elevated likelihood of experiencing severe illness and mortality [22, 23]. Therefore, in our investigation, 11 of 16 individuals with both COVID-19 and active TB infection were classified as active smokers. As a result, among these patients, the average value of NLR after discharge did not show a significant reduction, strengthening the previously stated concepts.

Esteves et al. analyzed hematological changes, particularly observing increased neutrophil counts and decreased lymphocyte levels, as well as the neutrophil-to-lymphocyte ratio (NLR), among patients categorized into three groups: those not infected with TB, individuals with latent TB infection, and those with active TB infection. Their study revealed a notably higher NLR value in patients with active TB compared to the control group ($P<0.0001$) [24]. In our study, anemia was analyzed as a hematological change, and patients with associated anemia in the context of chronic inflammation had an increased NLR (8.52).

Subsequently, another study corroborated these findings, examining pretreatment NLR alterations in patients with active pulmonary TB and those without. The study reported an average NLR value of 5.06 in patients with active pulmonary TB, in contrast to 1.89 in those without pulmonary TB, demonstrating a specificity of 78% and a sensitivity of 79% [25].

Furthermore, in a case-control study involving 62 newly diagnosed Pulmonary Tuberculosis (PTB) patients, Suryana et al. explored the association between pretreatment NLR levels and sputum conversion. Their findings indicated that an NLR value of ≥ 5.065 was linked to an elevated risk of delayed sputum conversion [26].

Besides the clinical implications of this ratio highlighted earlier, NLR proved to be an effective prognostic indicator in miliary TB as well. Although our study did not include patients with miliary TB in the cohort, it is essential to emphasize this aspect. Thus, Hu et al. demonstrated a relationship between NLR before treatment and overall outcomes in miliary TB patients. A notable finding was that nonsurvivors, in comparison to survivors during their hospitalization, exhibited notably higher NLR levels (13.6 ± 13.8 vs. 7.8 ± 5.9, $P = 0.010$). Moreover, an elevated NLR level was significantly associated with adverse clinical outcomes, including the onset of acute respiratory distress syndrome (ARDS), in-hospital mortality, and one-year mortality [27].

Another significant consideration is the global recognition of TB disease as a leading cause of mortality among individuals with HIV. For instance, Sulastri et al. demonstrated a notable increase in the neutrophil-to-lymphocyte ratio in cases of TB/HIV coinfection compared to pulmonary TB alone [28]. Moreover, NLR was investigated as a screening tool for TB in individuals with HIV in a prospective study by Miyahara et al., establishing NLR as a prognostic indicator for assessing the probability of tuberculosis in HIV-infected individuals. Elevated NLR levels (>2) were statistically associated with a heightened risk of developing tuberculosis among diagnosed HIV patients ($P = 0.007$) [29]. Although the limitation of our study involved the absence of patients with HIV/TB coinfection, the findings presented above are particularly important. They underscore the importance of identifying pulmonary TB patients who have very high NLR with low lymphocyte counts, because such patients should be targeted for HIV screening examination and follow-up.

Study limitations

The incomplete investigation of the inflammatory profile among the subjects in the study is a limitation of this research. Also, in the studied group, the evolution between admission and discharge could only be assessed in a subgroup of 52 patients due to the lack of data. Another limitation of the study was the lack of data on mortality and the subsequent course of the patients. HIV coinfection was not included in the analyzed parameters of the study.

Conclusions

The quantification of neutrophil/lymphocyte ratio (NLR) as a biomarker with prognostic utility in chronic inflammatory diseases has proven its utility for assessing disease severity.

The association of comorbidities such as cachexia or smoking in patients with pulmonary tuberculosis has led to much higher values of NLR since admission, which could represent a useful topic in terms of prevention of these risk factors. Although inflammation in pulmonary tuberculosis has been extensively studied, the introduction of new biomarkers in the investigation panel, although it requires additional studies, increases the clinical and prognostic assessment of these patients.

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Institutional Review Board Statement

Not applicable.

Ethical

The current study was approved by the ethics committee of the University of Medicine, Pharmacy, Sciences and Technology "G.E. Palade" from Targu Mures and was conducted in compliance with the Declaration of Helsinki.

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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