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Comparison of Serum and Pleural Fluid Neutrophil-to-Lymphocyte Ratios in Tuberculous, Parapneumonic, and Lung Cancer–Associated Exudative Pleural Effusions

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ABSTRACT: Neutrophil-to-lymphocyte ratio (NLR) is an inflammatory biomarker, but evidence comparing serum and pleural fluid NLR in pleural effusion is limited. This study compared NLR in 210 patients with exudative pleural effusion (70 tuberculous, 70 parapneumonic, and 70 lung cancer–associated pleural effusions) treated between January and December 2025. Serum NLR was calculated from blood neutrophil and lymphocyte counts and pleural fluid NLR from the polymorphonuclear-to-mononuclear cell ratio. Comparisons, regression, and receiver operating characteristic (ROC) analyses were performed. Serum NLR exceeded pleural fluid NLR (7.40 vs. 0.67, $p<0.001$). Serum NLR did not differ among etiologies (all $p>0.05$), but pleural fluid NLR was highest in parapneumonic pleural effusion, intermediate in lung cancer–associated effusion, and lowest in tuberculous effusion (all $p<0.001$). Serum and pleural fluid NLR were uncorrelated. Parapneumonic pleural effusion independently predicted higher pleural fluid NLR ($\beta=14.93$, $p=0.001$). Pleural fluid NLR showed performance for tuberculous pleural effusion (AUC=0.947; cut-off ≤0.43) and parapneumonic effusion (AUC=0.991; cut-off ≥1.04); serum NLR showed poor discrimination. Pleural fluid NLR outperformed serum NLR in differentiating exudative pleural effusion etiologies, particularly tuberculous versus parapneumonic effusions.

1. INTRODUCTION

pleural diseases to systemic disorders, and affects approximately 1.5 million individuals annually in the United States [1,2]. The initial diagnostic approach requires differentiation between transudative and exudative pleural effusions because subsequent investigations and management depend largely on this classification [3].

The Light's criteria remain the standard method for distinguishing exudative from transudative pleural effusions using pleural fluid and serum protein and lactate dehydrogenase concentrations [4]. However, these criteria may misclassify up to one-quarter of transudative effusions, particularly among patients receiving diuretic therapy, highlighting the need for complementary biomarkers that improve diagnostic accuracy [3,5].

Beyond biochemical analysis, differential leukocyte counts in pleural fluid provide important diagnostic information because the predominant inflammatory cell population reflects the underlying pathological process [6]. Lymphocyte-predominant

pleural effusions are typically associated with chronic inflammatory conditions such as tuberculosis and malignancy, whereas neutrophil predominance is more frequently observed in acute inflammatory disorders, including parapneumonic pleural effusions [7]. Nevertheless, considerable overlap in cellular profiles between different etiologies limits the diagnostic value of conventional cell counts alone [8].

The neutrophil-to-lymphocyte ratio (NLR) has emerged as an inexpensive and readily available biomarker that reflects the balance between innate inflammatory activation and adaptive immune responses [9]. Elevated neutrophil counts indicate systemic inflammation, whereas reduced lymphocyte counts may reflect immune dysregulation mediated by physiological stress, inflammatory cytokines, and endogenous corticosteroid responses [9,10]. Consequently, NLR has demonstrated prognostic and diagnostic value across various infectious, inflammatory, and malignant diseases, including pneumonia, sepsis, coronavirus disease, and lung cancer [10,11].

Although serum NLR has been extensively investigated, studies evaluating NLR in pleural fluid remain limited [8]. Existing evidence suggests that pleural fluid NLR differs among tuberculous, parapneumonic, and malignant pleural effusions, yet the diagnostic performance of comparing serum and pleural fluid NLR within the same patient has not been adequately established [8,12]. Furthermore, few studies have examined whether the magnitude of the serum–pleural fluid NLR difference varies according to the underlying etiology of exudative pleural effusion [12].

Therefore, this study aimed to compare serum and pleural fluid neutrophil-to-lymphocyte ratios in patients with tuberculous, parapneumonic, and lung cancer–associated exudative pleural effusions. We further evaluated whether the difference between serum and pleural fluid NLR could distinguish these major etiological groups and provide additional diagnostic information beyond conventional pleural fluid analysis.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This retrospective cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, a tertiary referral center. Medical records of patients diagnosed with exudative pleural effusion between January and December 2025 were reviewed. Data extraction and analysis were performed from March to May 2026.

2.2 Study Population

Adult patients (≥18 years) with exudative pleural effusion diagnosed according to Light's criteria were eligible for inclusion. Patients were required to have complete blood count results, including absolute neutrophil and lymphocyte counts, obtained within 24 hours of thoracentesis, as well as pleural fluid analysis including differential cell counts. Only patients with a confirmed diagnosis of tuberculous pleural effusion, parapneumonic pleural effusion, or lung cancer–associated pleural effusion were included.

Patients with transudative pleural effusion, human immunodeficiency virus infection, severe immunocompromised conditions, hematological malignancies, systemic sepsis unrelated to pneumonia, recent immunomodulatory corticosteroid or immunosuppressive therapy (within 30 days), chemotherapy within the preceding three months, or incomplete clinical and laboratory data were excluded.

2.3 Data Collection

Clinical and laboratory data were extracted from electronic medical records using a standardized data collection form. Demographic variables included age and sex, while clinical variables included pleural effusion etiology and relevant comorbidities. Laboratory variables comprised complete blood count, serum biochemical parameters, and pleural fluid biochemical and cytological analyses.

Serum NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count obtained from peripheral blood examination. Pleural fluid NLR was calculated as the ratio of polymorphonuclear (PMN) cells to mononuclear (MN) cells based on the differential leukocyte count of pleural fluid.

The etiological diagnosis of pleural effusion was established from the final diagnosis documented in the medical record. Tuberculous pleural effusion was defined by microbiological confirmation and/or compatible clinical and radiological findings.

Parapneumonic pleural effusion was diagnosed in patients with pneumonia accompanied by exudative pleural effusion and supportive pleural fluid findings. Lung cancer–associated pleural effusion was defined by a confirmed diagnosis of primary lung cancer with malignant pleural cytology or compatible clinicoradiological evidence.

2.4 Study Variables

The primary outcome was the difference between serum and pleural fluid NLR. Secondary outcomes included comparisons of serum NLR, pleural fluid NLR, and the magnitude of serum–pleural fluid NLR differences among patients with tuberculous, parapneumonic, and lung cancer–associated pleural effusions. Potential confounding variables included age, sex, diabetes mellitus, and timing of blood sampling relative to thoracentesis.

2.5 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk test and are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are presented as frequencies and percentages.

Comparisons between serum and pleural fluid NLR within the same patient were performed using the paired t-test or Wilcoxon signed-rank test according to data distribution. Differences among the three etiological groups were analyzed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, followed by appropriate post hoc analyses. Correlations between serum and pleural fluid NLR were evaluated using Pearson or Spearman correlation coefficients. Multivariable linear regression analysis was performed to determine the independent association between pleural effusion etiology and NLR after adjustment for clinically relevant covariates. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics

A total of 210 patients with exudative pleural effusion were included in the analysis after applying the predefined inclusion and exclusion criteria. The median age was 53.0 years (IQR 42.3–62.0), with a mean age of 51.2 ± 14.7 years. Most patients were aged 40–59 years (45.7%), followed by those aged ≥60 years (32.4%) and <40 years (21.9%). Male patients accounted for 53.3% (n=112) of the study population, while females comprised 46.7% (n=98). The study included an equal number of patients in each etiological group, consisting of tuberculous pleural effusion (n=70), parapneumonic pleural effusion (n=70), and lung cancer-associated pleural effusion (n=70) (Table 1).

3.2 Baseline Characteristics According to Etiology

The baseline characteristics according to the etiology of exudative pleural effusion are presented in Table 2. Age differed significantly among the three groups (p<0.001). Patients with tuberculous pleural effusion were the youngest (median, 45.0 years [IQR 31.5–55.8]), followed by those with parapneumonic pleural effusion (53.0 years [IQR 45.0–62.0]), whereas patients with lung cancer–associated pleural effusion were the oldest (59.0 years [IQR 50.0–64.8]). Likewise, the distribution of age categories differed significantly across etiologies (p<0.001), with patients aged <40 years predominating in the tuberculosis group (40.0%) and those aged ≥60 years being most frequent in the lung cancer group (45.7%).

Sex distribution was comparable among the three etiological groups (p=0.124). Male patients were more frequent in the tuberculosis (61.4%) and parapneumonic (54.3%) groups, whereas females predominated in the lung cancer–associated pleural effusion group (55.7%) (Table 2).

Table 1. General Characteristics of the Study Participants

Characteristic	Value
Total participants, n	210
Age, median (IQR), years	53.00 (42.25–62.00)
Age, mean ± SD, years	51.24 ± 14.68
Age group, n (%)	
<40 years	46 (21.9)
40–59 years	96 (45.7)

≥60 years	68 (32.4)
Sex, n (%)	
Male	112 (53.3)
Female	98 (46.7)
Etiology of exudative pleural effusion, n (%)	
Tuberculous pleural effusion	70 (33.3)
Parapneumonic pleural effusion	70 (33.3)
Lung cancer–associated pleural effusion	70 (33.3)

Table 2. Baseline Characteristics According to the Etiology of Exudative Pleural Effusion

Characteristic	Tuberculous Pleural Effusion (n = 70)	Parapneumonic Pleural Effusion (n = 70)	Lung Cancer–Associated Pleural Effusion (n = 70)	p-value
Age, median (IQR), years	45.00 (31.50–55.75)	53.00 (45.00–62.00)	59.00 (50.00–64.75)	<0.001†
Age, mean ± SD, years	45.63 ± 16.79	52.21 ± 13.87	55.87 ± 11.12	
Age group, n (%)				<0.001*
<40 years	28 (40.0)	13 (18.6)	5 (7.1)	
40–59 years	28 (40.0)	35 (50.0)	33 (47.1)	
≥60 years	14 (20.0)	22 (31.4)	32 (45.7)	
Sex, n (%)				0.124*
Male	43 (61.4)	38 (54.3)	31 (44.3)	
Female	27 (38.6)	32 (45.7)	39 (55.7)	

Abbreviations: IQR, interquartile range; SD, standard deviation. *Chi-square test. †Kruskal–Wallis test.

3.3 Comparison of Serum and Pleural Fluid NLR

The comparison of serum and pleural fluid NLR is presented in **Table 3**. Overall, serum NLR was significantly higher than pleural fluid NLR (median 7.40 [IQR 4.95–13.03] vs. 0.67 [IQR 0.27–1.78], p<0.001). The median serum–pleural fluid NLR difference was 6.07 (IQR 3.30–11.05).

Within each etiological group, serum NLR remained significantly higher than pleural fluid NLR. In tuberculous pleural effusion, the median serum and pleural fluid NLRs were 6.88 (IQR 4.08–13.03) and 0.20 (IQR 0.12–0.33), respectively (p<0.001). In parapneumonic pleural effusion, the corresponding values were 7.40 (IQR 5.75–12.62) and 2.33 (IQR 1.78–8.09) (p=0.008), whereas in lung cancer–associated pleural effusion they were 7.74 (IQR 5.09–12.62) and 0.67 (IQR 0.45–0.79), respectively (p<0.001). The median serum–pleural fluid NLR difference was lowest in the parapneumonic group and highest in the lung cancer–associated pleural effusion group (Table 3).

Pairwise comparisons demonstrated no significant differences in serum NLR among the three etiological groups (all p>0.05). In contrast, pleural fluid NLR differed significantly between all pairwise comparisons (all p<0.001). The serum–pleural fluid NLR difference was significantly smaller in parapneumonic pleural effusion than in tuberculous (p=0.025) and lung cancer–associated pleural effusions (p=0.021), whereas no significant difference was observed between tuberculous and lung cancer–associated pleural effusions (p=1.000).

Table 3. Comparison of Serum and Pleural Fluid NLR According to the Etiology of Exudative Pleural Effusion

Group	n	Serum NLR, Median (IQR)	Pleural Fluid NLR, Median (IQR)	Serum–Pleural Fluid NLR Difference, Median (IQR)	p-value*
Overall	210	7.40 (4.95–13.03)	0.67 (0.27–1.78)	6.07 (3.30–11.05)	<0.001
Tuberculous pleural effusion	70	6.88 (4.08–13.03)	0.20 (0.12–0.33)	6.70 (3.85–12.82)	<0.001
Parapneumonic pleural effusion	70	7.40 (5.75–12.62)	2.33 (1.78–8.09)	5.04 (−0.37–9.09)	0.008
Lung cancer–associated pleural effusion	70	7.74 (5.09–12.62)	0.67 (0.45–0.79)	7.12 (4.26–11.56)	<0.001

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range. *Wilcoxon signed-rank test comparing serum NLR and pleural fluid NLR within each group.

3.4 Comparison of NLR Between Etiologies of Exudative Pleural Effusion

A post-hoc analysis using the Mann–Whitney test with Bonferroni correction was conducted to evaluate differences in NLR between etiologies of exudative pleural effusion after the Kruskal–Wallis test showed a significant difference. The results of the analysis are presented in Table 4. Serum NLR did not show significant differences between the tuberculosis, parapneumonic, and lung cancer groups in all pairwise comparisons (all $p>0.05$). In contrast, pleural fluid NLR differed significantly between groups. Pleural fluid NLR values in the parapneumonic group were significantly higher than in the tuberculosis and lung cancer groups (both $p<0.001$), while the lung cancer group also showed higher values compared to the tuberculosis group ($p<0.001$). Analysis of the difference between serum and pleural fluid NLR also showed significant differences between etiologies. The NLR difference in the parapneumonic group was lower than that in the tuberculosis group ($p=0.021$) and the lung cancer group ($p=0.017$), whereas no significant difference was found between the tuberculosis and lung cancer groups ($p>0.05$). Overall, the results of the analysis indicate that differences between etiologies are mainly found in pleural fluid NLR and serum–pleural fluid NLR difference, while serum NLR does not show significant differences.

Table 4. Pairwise Comparison of Serum and Pleural Fluid NLR According to the Etiology of Exudative Pleural Effusion

Variable	Group Comparison	p-value
Serum NLR	Tuberculous pleural effusion vs. Parapneumonic pleural effusion	0.237
	Tuberculous pleural effusion vs. Lung cancer–associated pleural effusion	1.000
	Parapneumonic pleural effusion vs. Lung cancer–associated pleural effusion	0.657
Pleural fluid NLR	Tuberculous pleural effusion vs. Parapneumonic pleural effusion	<0.001
	Tuberculous pleural effusion vs. Lung cancer–associated pleural effusion	<0.001

	Parapneumonic pleural effusion vs. Lung cancer–associated pleural effusion	<0.001
Serum–Pleural Fluid NLR Difference	Tuberculous pleural effusion vs. Parapneumonic pleural effusion	0.025
	Tuberculous pleural effusion vs. Lung cancer–associated pleural effusion	1.000
	Parapneumonic pleural effusion vs. Lung cancer–associated pleural effusion	0.021

Abbreviations: NLR, neutrophil-to-lymphocyte ratio. *Pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni correction for multiple comparisons.

3.5 Factors Associated with Pleural Fluid NLR and the Serum–Pleural Fluid NLR Difference

Multivariable linear regression analyses were performed to identify factors independently associated with pleural fluid NLR and the serum–pleural fluid NLR difference (serum NLR − pleural fluid NLR). In both models, pleural effusion etiology, age, and sex were included as independent variables, with tuberculous pleural effusion as the reference category (Table 5).

In the first model, parapneumonic pleural effusion was independently associated with higher pleural fluid NLR compared with tuberculous pleural effusion (β = 14.93, 95% CI: 5.96–23.89, p = 0.001). Lung cancer–associated pleural effusion was not significantly associated with pleural fluid NLR (β = −0.48, 95% CI: −9.79 to 8.84, p = 0.919). Likewise, age (β = 0.17, 95% CI: −0.09 to 0.43, p = 0.195) and male sex (β = 3.94, 95% CI: −3.31 to 11.19, p = 0.285) were not significantly associated with pleural fluid NLR.

Table 5. Multivariable Linear Regression Analyses of Factors Associated with Pleural Fluid NLR and the Serum–Pleural Fluid NLR Difference

Variable	Pleural Fluid NLR			Serum–Pleural Fluid NLR Difference		
	β	95% CI	p-value	β	95% CI	p-value
Parapneumonic pleural effusion†	14.93	5.96 - 23.89	0.001	−12.26	−23.27 - 1.26	0.029
Lung cancer–associated pleural effusion†	−0.48	−9.70 - 8.75	0.919	−1.63	−12.96 - 9.70	0.777
Age	0.17	−0.09 - 0.43	0.195	−0.27	−0.58 - 0.05	0.096
Male sex	3.94	−3.31 - 11.20	0.285	−1.66	−10.57 - 7.24	0.713

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; CI, confidence interval. †Reference category: **tuberculous pleural effusion**.

In the second model, parapneumonic pleural effusion was independently associated with a smaller serum–pleural fluid NLR difference than tuberculous pleural effusion (β = −12.26, 95% CI: −23.27 to −1.26, p = 0.029). No significant associations were observed for lung cancer–associated pleural effusion (β = −1.63, 95% CI: −12.99 to 9.73, p = 0.777), age (β = −0.27, 95% CI: −0.58 to 0.05, p = 0.096), or male sex (β = −1.66, 95% CI: −10.58 to 7.25, p = 0.713).

3.6 Diagnostic Performance of Serum and Pleural Fluid NLR for Differentiating Exudative Pleural Effusion Etiologies

Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of serum and pleural fluid NLR for differentiating the etiologies of exudative pleural effusion. The area under the curve (AUC), optimal cut-off value, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are summarized in Table 6.

Serum NLR demonstrated poor discriminatory performance for all etiological comparisons. The AUC was 0.559 (95% CI: 0.475–0.642, p=0.166) for tuberculous versus non-tuberculous pleural effusion, 0.573 (95% CI: 0.490–0.656, p=0.085) for parapneumonic versus non-parapneumonic pleural effusion, and 0.514 (95% CI: 0.431–0.598, p=0.736) for lung cancer–associated versus non-lung cancer pleural effusion.

In contrast, pleural fluid NLR demonstrated excellent diagnostic performance for tuberculous and parapneumonic pleural effusions. For tuberculous pleural effusion, the AUC was 0.947 (95% CI: 0.909–0.984, p<0.001), with an optimal cut-off value of ≤0.43, yielding 97.1% sensitivity, 89.2% specificity, 81.9% PPV, and 98.4% NPV. For parapneumonic pleural effusion, the AUC was 0.991 (95% CI: 0.975–1.000, p<0.001), with a cut-off value of ≥1.04, corresponding to 100.0% sensitivity, 97.9% specificity, 95.8% PPV, and 100.0% NPV.

For lung cancer–associated pleural effusion, pleural fluid NLR showed limited discriminatory ability, with an AUC of 0.541 (95% CI: 0.457–0.624, p=0.340). The optimal cut-off value was ≤1.00, providing a sensitivity of 95.7% and specificity of 49.6%. Overall, pleural fluid NLR demonstrated substantially better diagnostic performance than serum NLR for differentiating tuberculous and parapneumonic pleural effusions, whereas neither marker showed satisfactory discrimination for lung cancer–associated pleural effusion in the one-versus-rest analysis.

Table 6. Receiver Operating Characteristic (ROC) Analysis of Serum and Pleural Fluid NLR for Differentiating the Etiology of Exudative Pleural Effusion

Target Etiology	Variable	AUC (95% CI)	Optimal Cut-off	Sensitivity (%)	Specificity (%)	p-value
Tuberculous pleural effusion vs. non-tuberculous pleural effusion	Serum NLR	0.559 (0.475 – 0.642)	≤4.92	38.6	82.9	0.166
Parapneumonic pleural effusion vs. non-parapneumonic pleural effusion	Serum NLR	0.573 (0.490 – 0.656)	≥4.97	87.1	31.4	0.085
Lung cancer–associated pleural effusion vs. non-lung cancer pleural effusion	Serum NLR	0.514 (0.431 – 0.598)	≤24.92	97.1	12.1	0.736

Tuberculous pleural effusion vs. non-tuberculous pleural effusion	Pleural fluid NLR	0.947 (0.909 – 0.984)	≤0.43	97.1	89.2	<0.001
Parapneumonic pleural effusion vs. non-parapneumonic pleural effusion	Pleural fluid NLR	0.991 (0.975 – 1.000)	≥1.04	100.0	97.9	<0.001
Lung cancer–associated pleural effusion vs. non-lung cancer pleural effusion	Pleural fluid NLR	0.541 (0.457 – 0.624)	≤1.00	95.7	49.6	0.340

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

3.7 Discussion

This study demonstrates that pleural fluid NLR has greater diagnostic value than serum NLR for differentiating tuberculous, parapneumonic, and lung cancer–associated exudative pleural effusions. Although serum NLR did not differ significantly among the three etiologies, pleural fluid NLR showed significant differences and superior diagnostic performance, suggesting that local inflammatory responses are more disease-specific than systemic inflammatory markers.

The demographic characteristics were consistent with the known epidemiology of pleural effusion. Patients with tuberculous pleural effusion were younger than those with malignant pleural effusion, whereas parapneumonic pleural effusion predominantly affected middle-aged adults. These findings are consistent with Jany and Welte (2019), who reported tuberculosis as a common cause of pleural effusion in younger individuals in endemic regions and malignancy as the predominant cause in older patients [13].

A key finding was the significant difference between serum and pleural fluid NLR across all etiologies, with serum NLR consistently higher than pleural fluid NLR. This finding suggests that serum NLR reflects systemic inflammation, whereas pleural fluid NLR better represents the local immune response within the pleural space. Similar observations have been reported by Barata et al. (2020) and Ferreiro et al. (2024), who emphasized that pleural fluid cellular composition is primarily determined by local inflammatory processes rather than systemic immune activation [1,14].

Consistent with this concept, no significant correlation was observed between serum and pleural fluid NLR. This finding supports previous evidence that peripheral inflammatory biomarkers cannot reliably predict the immune profile within the pleural cavity because leukocyte recruitment is regulated independently at the site of inflammation [10].

Pleural fluid NLR differed significantly among the three etiologies. The highest values were observed in parapneumonic pleural effusion, reflecting the intense neutrophilic response characteristic of acute bacterial infection. This finding is in line with Ewida et al. (2022) and Priel et al. (2025), who reported neutrophil predominance as the hallmark of parapneumonic pleural effusion [3,15].

Conversely, tuberculous pleural effusion demonstrated the lowest pleural fluid NLR because the inflammatory response is predominantly mediated by activated T lymphocytes and macrophages following delayed hypersensitivity to *Mycobacterium tuberculosis*. These findings agree with Li et al. (2022) and Akturk et al. (2016), who consistently reported lymphocyte-predominant pleural effusions with low pleural fluid NLR in tuberculosis [7,16].

Lung cancer–associated pleural effusion showed intermediate pleural fluid NLR values, likely reflecting the heterogeneous inflammatory tumor microenvironment involving lymphocytes, neutrophils, macrophages, and malignant cells. Similar findings have been described by Chan and Chan (2024), highlighting the complex interaction between tumor biology and host immune responses in malignant pleural effusion [17].

Unlike pleural fluid NLR, serum NLR showed poor discriminatory ability among the three etiologies. This contrasts with the findings of Yoon et al. (2013), who reported higher serum NLR in bacterial pneumonia than pulmonary tuberculosis [11]. The discrepancy is likely attributable to differences in study populations, as our study focused exclusively on patients with established pleural effusion rather than pulmonary infection alone.

ROC analysis further demonstrated the superior diagnostic performance of pleural fluid NLR over serum NLR. Pleural fluid NLR showed excellent discrimination between parapneumonic and tuberculous pleural effusions, consistent with previous studies by Ewida et al. (2022), Akturk et al. (2016), and Barata et al. (2020) [3,14,16]. These findings suggest that pleural fluid NLR may serve as a simple, inexpensive adjunctive biomarker for the diagnostic evaluation of exudative pleural effusion.

This study has several limitations. Its retrospective single-center design may limit generalizability, and the equal distribution of etiological groups does not reflect real-world disease prevalence. Furthermore, pleural fluid NLR was derived from polymorphonuclear-to-mononuclear cell ratios rather than absolute leukocyte counts. Therefore, prospective multicenter studies are needed to validate the proposed diagnostic thresholds.

In conclusion, pleural fluid NLR outperformed serum NLR in differentiating the major causes of exudative pleural effusion. While serum NLR reflects systemic inflammation, pleural fluid NLR more accurately represents local immune responses and may provide valuable complementary information alongside conventional biochemical, microbiological, and cytological investigations.

This study has several limitations. First, its retrospective single-center design relied on the completeness and accuracy of medical records, which may have introduced information bias and limited the generalizability of the findings. Second, only three major etiologies of exudative pleural effusion—tuberculous, parapneumonic, and lung cancer–associated pleural effusions—were included; therefore, the findings cannot be extrapolated to other causes of exudative pleural effusion, particularly malignant pleural effusions arising from non-pulmonary malignancies.

Third, the diagnosis of tuberculous pleural effusion was established using different microbiological sources, including pleural fluid and sputum, and the potential influence of these diagnostic approaches on NLR was not specifically evaluated. Finally, several potentially relevant clinical variables, such as the duration and volume of pleural effusion, disease severity, inflammatory burden, and the possibility of pseudo-exudates, were not assessed. Future prospective multicenter studies incorporating these variables are needed to validate the present findings and further define the clinical utility of pleural fluid NLR.

4. CONCLUSION

This study demonstrates that pleural fluid neutrophil-to-lymphocyte ratio (NLR) is superior to serum NLR in differentiating the major etiologies of exudative pleural effusion. While serum NLR did not significantly differ among tuberculous, parapneumonic, and lung cancer–associated pleural effusions, pleural fluid NLR showed distinct patterns according to etiology, with the highest values observed in parapneumonic pleural effusion, the lowest in tuberculous pleural effusion, and intermediate values in lung cancer–associated pleural effusion. Furthermore, the absence of a significant correlation between serum and pleural fluid NLR suggests that these biomarkers reflect different inflammatory compartments, representing systemic and local immune responses, respectively.

Given its excellent diagnostic performance, pleural fluid NLR may serve as a simple, inexpensive, and readily available adjunctive biomarker for the evaluation of exudative pleural effusion, particularly in distinguishing tuberculous from parapneumonic pleural effusions. However, pleural fluid NLR should be interpreted alongside clinical, radiological, microbiological, cytological,

and biochemical findings rather than as a standalone diagnostic test. Prospective multicenter studies are warranted to validate the proposed cut-off values and establish its role in routine clinical practice.

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AUTHOR CONTRIBUTIONS

AY: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing – Original Draft.

EA: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

NT: Methodology, Validation, Supervision, Writing – Review & Editing.

ID: Methodology, Validation, Resources, Supervision, Writing – Review & Editing.

MI: Formal Analysis, Validation, Resources, Writing – Review & Editing.

HAP: Investigation, Data Curation, Validation, Project Administration, Writing – Review & Editing.

All authors contributed to the interpretation of the data, critically revised the manuscript for important intellectual content, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin and Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia (Approval No. 451/UN4.6.4.5.31/PP36/2026; Protocol No. UH26020252), prior to data collection. As this was a retrospective study using anonymized medical records, the requirement for informed consent was waived by the Ethics Committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki**.**

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available because they contain confidential patient information but are available from the corresponding author on reasonable request and with permission from Dr. Wahidin Sudirohusodo Central General Hospital.

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