EUR REV MED PHARMACOL SCI
2025; 29: 387-397

DIAGNOSTIC VALUE OF CRP/ALBUMIN-GLOBULIN RATIO AND MONOCYTE-TO-LYMPHOCYTE RATIO IN DIFFERENTIATING PARAPNEUMONIC EFFUSION TYPES

N.A. YETKIN, F.M. SIMSEK, B. BARAN, B. RABAHOGLU, N. TUTAR, İ. GULMEZ

• • •

Department of Pulmonology, Faculty of Medicine, Erciyes University, Kayseri, Turkiye

Corresponding Author
Nur Aleyna Yetkin, MD; e-mail: nuryetkin@erciyes.edu.tr; alleynakemik@gmail.com

ABSTRACT – ***Objective:*** Parapneumonic effusion (PPE), a pneumonia-related complication, can progress to complicated PPE (CPPE) and often requires invasive treatment. Although early differentiation is essential, the diagnostic role of hematological inflammatory markers remains unclear. This study evaluated hematological inflammatory markers to distinguish between pleural effusion types, particularly CPPE and uncomplicated PPE (uCPPE), in order to identify the most reliable biomarkers.

Materials and Methods: This retrospective study analyzed 94 cases of pleural effusion classified as transudative, malignant, tuberculous, or PPE. PPE was further divided into CPPE and uCPPE. C-reactive protein (CRP) and procalcitonin (PCT) levels, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), CRP/albumin-globulin ratio (CAGR), albumin-globulin ratio (AGR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) were analyzed. Receiver Operating Characteristic (ROC) curve analysis was used to determine the diagnostic accuracy via the area under the curve (AUC) and optimal cut-off values.

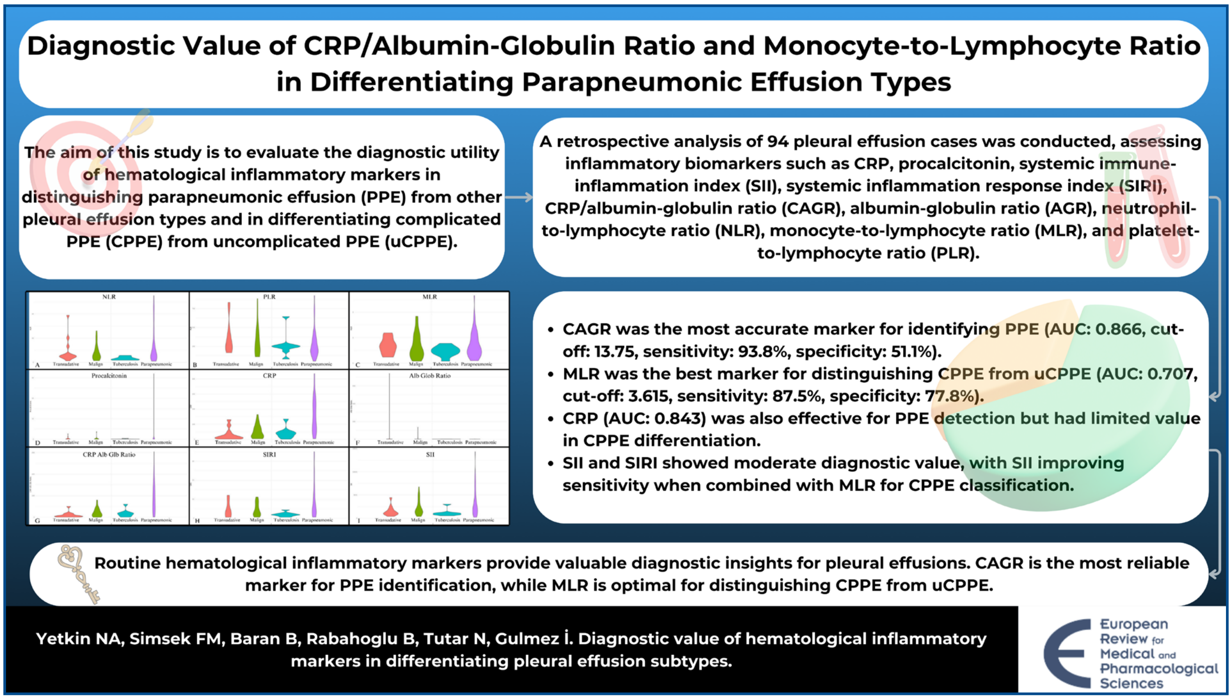
Results: Inflammatory markers effectively differentiated pleural effusion types, with CAGR showing the highest accuracy for PPE diagnosis (AUC, 0.866; cut-off: 13.75; sensitivity = 93.8%, specificity = 51.1%). Among the CPPE and uCPPE markers, MLR demonstrated the best performance (AUC: 0.707; cut-off: 3.615; sensitivity: 87.5%; specificity: 77.8%), followed by NLR (AUC: 0.702) and PLR (AUC: 0.704), whereas SIRI and SII had modest utility. Although MLR showed superior accuracy, the addition of SII improved the sensitivity.

Conclusions: This study demonstrates that among hematological markers, CAGR is the most accurate for diagnosing PPE, while MLR best distinguishes CPPE from uCPPE. However, the limited specificity of CAGR highlights the need for the combined use of biomarkers. Prospective multicenter studies are warranted to validate and refine these findings.

KEYWORDS: Systemic immune inflammation index, Systemic inflammation response index, CRP-albumin-globulin ratio, Empyema, Monocyte lymphocyte ratio.

INTRODUCTION

Pleural effusion is characterized by pathological accumulation of fluid within the pleural space. While various conditions contribute to its etiology, the most prevalent are congestive heart failure, malignant effusion, and parapneumonic effusion (PPE)[1]. PPE occurs in ap-



Graphical Abstract. The diagnostic performance of hematological inflammatory markers, including CRP/albumin-globulin ratio (CAGR) and monocyte-to-lymphocyte ratio (MLR), in differentiating parapneumonic effusion (PPE) from other pleural effusion types and in distinguishing complicated PPE (CPPE) from uncomplicated PPE (uCPPE). Violin plots illustrate marker distributions across effusion subtypes, with key findings highlighting the superior diagnostic accuracy of CAGR for PPE identification and MLR for CPPE classification.

proximately 40% of patients with pneumonia[2]. Initially uncomplicated, PPE may progress to complicated parapneumonic effusion (CPPE) if inflammation advances and pathogens invade the pleural cavity. Close monitoring, antibiotic therapy, and, when necessary, repeated thoracentesis are essential. In CPPE cases, rapid drainage and potentially invasive interventions, such as intrapleural fibrinolytics, may be necessary to prevent empyema[3].

Although various inflammatory markers have been investigated in the context of PPE, none have demonstrated superiority over conventional pleural biochemical parameters in clinical practice. Therefore, pH, lactate dehydrogenase (LDH), and microbiological gram staining are essential[4,5]. C-reactive protein (CRP) and procalcitonin (PCT), which are easy to use and cost-effective, have been reported to play a role in distinguishing uncomplicated parapneumonic effusions (uCPPE) from CPPE in both serum and pleural fluids[6-9]. A serum CRP level greater than 100 mg/l demonstrated a sensitivity of 72% and a specificity of 89% in differentiating CPPE from uCPPE[9]. Although CRP and procalcitonin (PCT) are cost-effective and widely used, their limitations in reliably distinguishing CPPE from uCPPE highlight the need for additional inflammatory biomarkers. Hematologic indices such as the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), albumin-to-globulin ratio (AGR), and CRP-to-albumin-to-globulin ratio (CAGR) are recognized indicators of systemic inflammation, but their comparative utility in adult pleural effusion – particularly in differentiating CPPE from uCPPE – remains insufficiently studied[11-13]. This study examined the efficacy of inflammatory markers in distinguishing CPPE, uCPPE, and PPE from other types of effusion.

MATERIALS AND METHODS

This retrospective observational study was conducted in the Department of Chest Diseases at the Erciyes University Hospital, following approval by the Health Sciences Research Ethics Committee of Erciyes University, under protocol number 2024/116, dated August 4, 2024. The medical documentation of 141 patients diagnosed with pleural effusion who underwent thoracentesis for differential diagnosis between September 2016 and September 2024, was examined.

Patients with a history of trauma, recent surgery, blood transfusion, prolonged corticosteroid use (more than five days), connective tissue disease, chylothorax, thoracic surgery, sepsis, COVID-19 pneumonia, active malignancy under treatment, or severe hepatic or renal dysfunction were excluded from the study. Additionally, individuals with chronic inflammatory or autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, were also excluded to minimize confounding effects on serum CRP levels, as these conditions are known to independently elevate CRP and other inflammatory biomarkers. After applying the exclusion criteria, 94 patients with complete thoracentesis data were included in the final analysis.

The diagnostic workup for pleural effusion in our study followed a standard institutional protocol aligned with international guidelines, particularly the SEPAR (Sociedad Española de Neumología y Cirugía Torácica) recommendations[14]. At the time of presentation, all patients underwent both diagnostic thoracentesis and chest computed tomography (CT) to comprehensively assess the presence, extent, and complexity of pleural effusion. At the time of presentation, all patients underwent diagnostic thoracentesis under ultrasound (USG) guidance. Clinical management decisions, including the initiation of empirical antibiotic therapy and chest drainage, were made based on pleural fluid pH, LDH levels, and microbiological findings, following the criteria for CPPE as defined by current evidence-based standards.

Pleural effusions are classified into four etiological types: transudative, malignant, tuberculous, and parapneumonic. The classification of effusions as exudative or transudative was determined using Light's criteria and subsequently confirmed by expert clinicians (NAY and NT).

Parapneumonic effusion was defined as pleural fluid accumulation associated with pneumonia, presenting clinically with fever, purulent sputum, and radiological pulmonary infiltration without an alternative explanation. Parapneumonic effusion cases were further classified as uCPPE or CPPE according to established clinical and laboratory criteria. Uncomplicated parapneumonic effusion was defined by a pleural fluid glucose concentration greater than 60 mg/dL, a pH level exceeding 7.20, and an LDH level below 1,000 IU/L, with negative results for microbiological staining and culture, indicating no detectable microorganisms. In contrast, complicated parapneumonic effusion was characterized by a pleural fluid pH lower than 7.20 and/or an LDH level exceeding 1,000 IU/L. Additionally, the presence of microorganisms was confirmed by positive microbiological staining or culture of the pleural fluid.

Malignant effusion is characterized by the detection of cytologically confirmed malignant cells in pleural fluid.

Tuberculous effusion was diagnosed based on one or more of the following criteria: positive staining or culture for *Mycobacterium tuberculosis* in pleural fluid, sputum, or biopsy; histopathological evidence of granulomas with caseating necrosis in biopsy samples; or a pleural fluid adenosine deaminase (ADA) level >40 U/L accompanied by clinical improvement following antituberculosis therapy.

For all included patients, blood samples used for biomarker analysis were obtained at the initial presentation, before the initiation of antibiotic therapy. At the time of diagnosis, laboratory data were recorded, including serum CRP, albumin, globulin, LDH, PCT, and white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts. The derived inflammatory indices included the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (calculated platelet count × neutrophil/lymphocyte), and systemic inflammation response index (calculated neutrophil × monocyte/lymphocyte). In addition, the AGR and CAGR were calculated.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and as median (minimum-maximum) for non-normally distributed data, based on the results of the Shapiro-Wilk normality test. Categorical variables were presented as frequencies and percentages. Differences between groups were assessed using the one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. A p-value < 0.05 was considered statistically significant.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of systemic inflammatory markers – including SII, SIRI, CRP, NLR, PLR, MLR, AGR, and CAGR – in identifying PPE and in discriminating between uCPPE and CPPE. For each biomarker, the area under the curve (AUC) was calculated with 95% confidence intervals (CI), and optimal cut-off values were determined using the Youden index to maximize sensitivity and specificity.

All statistical analyses were conducted using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and laboratory characteristics

The study included 94 patients diagnosed with pleural effusion, categorized into four groups: transudative (n=12), malignant (n=25), tuberculosis (n=8), and PPE (n=49). Among the PPE cases, 29 patients were classified as having CPPE and 20 as having uCPPE. The mean age differed significantly across the groups ($p < 0.001$), with the highest mean age observed in the transudative group. No statistically significant differences in sex distribution were observed between groups ($p > 0.05$).

Markers of inflammation and immune responses varied significantly across the groups. The median SIRI values ranged from 1.79 in the tuberculosis group to 4.87 in the PPE group ($p = 0.021$). The median SII was highest in the PPE group, with a value of 2110 ($p = 0.029$).

WBC and neutrophil counts were markedly elevated in the PPE group, with median values of 11.5×10^9/L and 8.49×10^9/L, respectively (both $p < 0.001$). Lymphocyte counts also showed significant variation, with a median of 1.14×10^9/L overall ($p = 0.045$). Hemoglobin levels were the highest in the tuberculosis group, with a mean of 14.1 g/dL ($p = 0.014$). The monocyte and platelet counts were similar between the groups ($p > 0.05$).

NLR exhibited significant variation across groups ($p = 0.037$), whereas PLR and MLR did not ($p = 0.558$ and $p = 0.602$, respectively). Among the serum markers, albumin levels were significantly different between groups ($p = 0.027$), whereas PCT levels were markedly elevated in the PPE group ($p = 0.006$). Similarly, the CRP and CAGR levels were significantly higher in the PPE group (both $p < 0.001$).

The demographic and laboratory characteristics of the study population are summarized in Table I.

When we compared the PPE groups, the CAGR, AGR, CRP, PLR, and PCT levels were comparable between the two groups ($p > 0.05$). In contrast, SIRI and SII levels were significantly higher in the CPPE group than in the uCPPE group ($p = 0.011$ and $p = 0.028$, respectively), whereas lymphocyte counts were significantly lower ($p = 0.004$). Additionally, NLR and MLR levels were elevated in the CPPE group compared with those in the uCPPE group ($p = 0.028$ and $p = 0.018$, respectively).

ROC analysis for identifying parapneumonic effusions

ROC analysis demonstrated that CAGR had the highest diagnostic accuracy for PPE, with an AUC of 0.866 (95% confidence interval [CI]: 0.794-0.938, $p < 0.001$) and a cut-off value of 13.75. CRP also showed a high diagnostic accuracy, with an AUC of 0.843 (95% CI: 0.765-0.920, $p < 0.001$) and an optimal cut-off of 21.5, yielding a sensitivity of 93.8% and a specificity of 51.1% (Table II). PCT (AUC: 0.681, 95% CI: 0.574-0.788, $p = 0.003$) and SIRI (AUC: 0.672, 95% CI: 0.563-0.781, $p = 0.004$) had moderate diagnostic utility. SII, NLR, and MLR showed lower performance, characterized by lower AUCs. The ROC curve of markers used to distinguish PPEs from other types of effusion is shown in Figure 1. PLR and AGR did not significantly discriminate between PPE types ($p > 0.05$) (Figure 2).

ROC analysis for classifying parapneumonic effusions

Among all the biomarkers, MLR exhibited the highest diagnostic performance for differentiating CPPE from uCPPE, with an AUC of 0.707 (95% CI: 0.560-0.855, $p = 0.015$). At the optimal cut-off value of 3.615, MLR achieved a sensitivity of 87.5% and a specificity of 77.8%, indicating strong discriminative capacity. Similarly, NLR (AUC: 0.702; 95% CI: 0.550-0.854; $p = 0.018$) and PLR (AUC: 0.704; 95% CI: 0.548-0.860; $p = 0.017$) demonstrated moderate diagnostic utility. SIRI (AUC: 0.671; $p = 0.045$) and SII (AUC: 0.675; $p = 0.040$) demonstrated modest performance, whereas PCT, CRP, and AGR demonstrated lower diagnostic utility.

A graphical representation of the comparative diagnostic performance of MLR and CAGR is provided in the graphical abstract. Overall, MLR, with its optimal threshold, outperformed the other biomarkers in distinguishing CPPE from uCPPE (Figure 3 and Table III).

DISCUSSION

The primary finding of this study was that hematological inflammatory markers derived from routine blood tests may support the differentiation of infectious pleural effusions from other etiologies. Among these markers, CAGR showed the highest diagnostic accuracy for identifying PPE, with sensitivity and specificity of 93.8% and 51.1%, respectively. However, this moderate specificity indicates the potential for false-positive results, which may limit its diagnostic value. Combining CAGR with CRP, which also demonstrates high sensitivity, may improve diagnostic accuracy by reducing the risk of misclassification. In distinguishing CPPE from uCPPE, MLR achieved the best diagnostic performance, with an AUC of 0.707, sensitivity of 87.5%, and specificity of 77.8%. While MLR provides balanced accuracy,

Table I. Baseline demographic, clinical, and laboratory characteristics of patients with different types of pleural effusion. Data are presented as median (interquartile range) or number (percentage), as appropriate. Comparisons across groups were performed using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

	Transudative (n=12)	Malign (n=25)	Tuberculosis (n=8)	Parapneumonic (n=49)	Overall (N=94)	*p*
Age, Mean (SD)	74.4 (9.15)	63.3 (17.8)	43.4 (12.1)	59.2 (14.9)	60.9 (16.4)	<0.001[b]
WBC, Median [Min, Max]	6.32 [2.62, 17.9]	9.94 [3.63, 15.3]	6.72 [5.15, 10.2]	11.5 [3.15, 36.3]	10.0 [2.62, 36.3]	<0.001[a]
Neutrophil, Median [Min, Max]	4.71 [1.97, 17.1]	7.57 [2.39, 14.3]	4.36 [2.74, 6.30]	8.49 [1.15, 33.2]	7.43 [1.15, 33.2]	<0.001[a]
Lymphocyte, Median [Min, Max]	0.755 [0.430, 1.82]	1.00 [0.430, 2.81]	1.44 [0.820, 3.58]	1.16 [0.170, 4.63]	1.14 [0.170, 4.63]	0.045[a]
Hb, Mean (SD)	10.5 (2.08)	12.2 (2.35)	14.1 (2.03)	12.0 (2.49)	12.1 (2.48)	0.014[b]
Monocyte, Median [Min, Max]	0.455 [0.170, 1.59]	0.630 [0.0500, 1.82]	0.685 [0.300, 0.890]	0.760 [0.0700, 2.33]	0.690 [0.0500, 2.33]	0.054[a]
MPV, Mean (SD)	10.2 (1.64)	9.93 (1.17)	9.73 (1.39)	9.76 (1.17)	9.85 (1.24)	0.751[b]
Platelet, Median [Min, Max]	230 [151, 358]	286 [120, 620]	364 [218, 626]	306 [58.0, 637]	296 [58.0, 637]	0.174[a]
NLR, Median [Min, Max]	5.35 [1.24, 38.9]	5.94 [1.36, 26.1]	2.67 [1.76, 5.77]	6.65 [0.980, 55.1]	5.78 [0.980, 55.1]	0.037[a]
PLR, Median [Min, Max]	269 [166, 833]	264 [112, 883]	246 [82.4, 645]	225 [54.4, 923]	246 [54.4, 923]	0.558[a]
MLR, Median [Min, Max]	0.700 [0.240, 1.19]	0.490 [0.0800, 1.84]	0.485 [0.0800, 0.780]	0.540 [0.100, 2.65]	0.535 [0.0800, 2.65]	0.602[a]
Total protein, Mean (SD)	6.30 (1.02)	6.37 (0.550)	6.98 (0.825)	6.43 (0.950)	6.44 (0.864)	0.304[b]
Albumin, Mean (SD)	3.40 (0.483)	3.46 (0.471)	3.84 (0.510)	3.19 (0.698)	3.34 (0.628)	0.027[b]
Procalcitonin, Median [Min, Max]	0.0950 [0.0100, 2.63]	0.190 [0.0100, 3.72]	0.0500 [0.0200, 0.370]	0.285 [0.0200, 32.0]	0.190 [0.0100, 32.0]	0.006[a]
Globulin, Median [Min, Max]	2.68 [0.540, 4.36]	2.78 [0.0200, 4.26]	3.31 [2.33, 3.77]	3.26 [1.85, 5.12]	3.04 [0.0200, 5.12]	0.036[a]
CRP, Median [Min, Max]	12.5 [1.59, 130]	39.0 [4.00, 164]	39.5 [1.00, 135]	141 [4.71, 435]	68.0 [1.00, 435]	<0.001[a]
AGR, Median [Min, Max]	1.35 [0.890, 1110]	1.23 [0.630, 200]	1.13 [1.02, 1.71]	0.970 [0.260, 2.10]	1.13 [0.260, 1110]	0.004[a]
CAGR, Median [Min, Max]	9.98 [1.06, 100]	29.5 [0.0450, 159]	32.1 [1.12, 121]	161 [3.14, 609]	59.6 [0.0450, 609]	<0.001[a]
Serum LDH, Median [Min, Max]	304 [222, 1030]	298 [162, 1930]	330 [170, 640]	230 [121, 829]	261 [121, 1930]	0.012[a]
SIRI, Median [Min, Max]	3.33 [0.534, 12.1]	2.83 [0.577, 11.1]	1.79 [0.528, 4.39]	4.87 [0.634, 35.0]	3.59 [0.528, 35.0]	0.021[a]
SII, Median [Min, Max]	1130 [376, 4430]	1520 [371, 6760]	947 [519, 3010]	2110 [217, 14400]	1710 [217, 14400]	0.029[a]

[a]Kruskal-Wallis test, [b]ANOVA test. WBC: White blood count, MPV: Mean platelet volume, CRP: C-reactive protein, CAGR: CRP/albumin-globulin ratio, LDH: Lactate dehydrogenase, AGR: albumin-globulin ratio, SIRI: Systemic inflammation response index, SII: Systemic immune-inflammation index, NLR: neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

Table II. Diagnostic performance of systemic inflammatory biomarkers in identifying parapneumonic pleural effusion (PPE), based on ROC curve analysis. The table presents the area under the curve (AUC), 95% confidence intervals, optimal cut-off values, sensitivity, and specificity (as 1–specificity). Biomarkers with higher AUC values demonstrate better diagnostic accuracy.

Test result variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% confidence interval		Cut-off	Sensitivity	1-Specificity
				Lower bound	Upper bound			
NLR	.613	.059	.060	.499	.728	3.01	0.854	0.222
PLR	.436	.060	.289	.319	.553	152.32	0.771	0.178
MLR	.540	.060	.511	.422	.657	2.965	0.875	0.222
PCT	.681	.055	.003	.574	.788	0.097	0.771	0.467
CRP	.843	.039	.000	.765	.920	21.5	0.938	0.489
AGR	.276	.052	.000	.174	.379	1.135	0.313	0.378
CAGR	.866	.037	.000	.794	.938	13.75	0.938	0.489
SIRI	.672	.056	.004	.563	.781	3.9152	0.604	0.644
SII	.650	.058	.012	.537	.764	930.715	0.813	0.267

ROC: Receiver Operating Characteristic Curve, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, SIRI: Systemic Inflammation Response Index, SII: Systemic Immune-Inflammation Index, CRP: C-reactive protein, PCT: procalcitonin, AGR: Albumin-globulin ratio, CAGR: C-Reactive Protein/Albumin-globulin ratio.

SII, with an AUC of 0.675, may be more suitable in clinical situations where avoiding missed diagnoses is prioritized, despite its lower specificity. The combined use of MLR and SII may offer complementary strengths, enhancing diagnostic precision through their respective advantages.

CRP remains a commonly used acute-phase reactant for evaluating inflammatory disorders, including PPE[15]. In this study, CRP demonstrated substantial diagnostic accuracy (AUC: 0.843; 95% CI: 0.765-0.920), supporting earlier findings that pleural fluid CRP may outperform serum CRP in diagnosing PPE[16]. However, consistent with previous reports, CRP exhibited limited discriminative ability between CPPE and uCPPE when compared with classical biochemical markers such as pH, LDH, and glucose[7,8]. Previous scholars[16] have reported that PCT levels in pleural fluid are insufficient for the diagnosis of empyema, whereas a combination of CRP and presepsin provides greater diagnostic value. Although its sensitivity was high, the moderate specificity at the optimal threshold value (21.5 mg/L) restricted its utility in reliably distinguishing PPE types.

As a negative acute-phase protein, albumin decreases in infectious states, and albumin-based ratios have shown clinical value in evaluating systemic inflammation. Although the albumin-to-globulin ratio (AGR) also showed statistically significant differences across effusion types, its standalone diagnostic performance was limited, possibly due to the dominant influence of CRP in the composite ratio. Similarly, in patients with severe COVID-19, low serum albumin levels have been suggested as a marker of disease severity, and the CRP-to-albumin ratio has been found to be more predictive of prognosis than albumin alone[17]. In our study, CAGR proved to be the most reliable biomarker for identifying PPE, achieving an AUC of 0.866. A post-hoc power analysis confirmed the robustness of this finding, with a calculated power of 99.9%, thereby supporting its substantial diagnostic value in this context. These findings are consistent with recent studies in other infection-related settings. For example, Ji et al[18] demonstrated the diagnostic utility of CAGR in detecting periprosthetic joint infections, reporting an AUC of 0.780 with a cutoff value of 15.35, emphasizing its role as a systemic inflammatory marker. The clinical applicability of CAGR is further supported by its ease of calculation and cost-effectiveness, making it suitable for widespread clinical use, particularly in resource-limited settings. In our cohort, however, CAGR's ability to differentiate between CPPE and uCPPE was limited (AUC 0.707), with a corresponding post-hoc power of 52.2%, suggesting that its discriminatory power may vary according to the inflammatory spectrum. This highlights the potential value of combining CAGR with additional inflammatory markers to enhance diagnostic precision. While previous studies have reported that the CRP-to-albumin ratio is a stronger prognostic indicator than albumin alone in patients with severe COVID-19, the CAGR was not evaluated in this context[18]. Our study highlights the potential of CAGR as a novel and potentially superior biomarker in the diagnosis of inflammatory pleural effusions. Notably, as our analysis was based on serum samples, future investigations should assess whether pleural fluid-based calculations of CAGR may further enhance diagnostic accuracy.

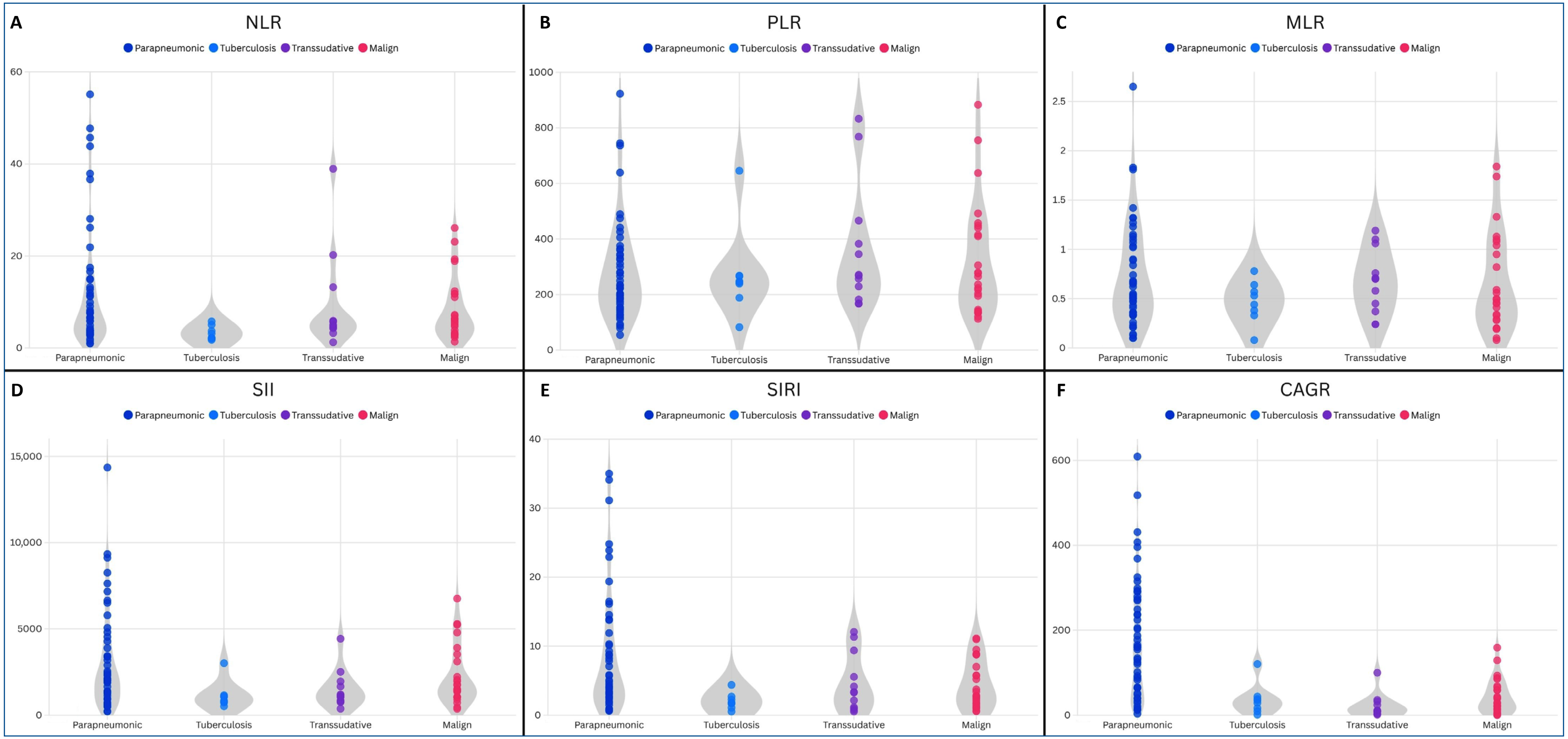


Figure 1. Violin plots illustrating the distribution and variability of systemic inflammatory biomarkers across different types of pleural effusion (transudative, malignant, tuberculosis-related, and parapneumonic). Each subplot represents a specific biomarker: **A**, NLR (Neutrophil-to-Lymphocyte Ratio); **B**, PLR (Platelet-to-Lymphocyte Ratio); **C**, MLR (Monocyte-to-Lymphocyte Ratio); **D**, SII (Systemic Immune-Inflammation Index); **E**, SIRI (Systemic Inflammation Response Index); **F**, CAGR (CRP/Albumin-Globulin Ratio). These plots allow visual comparison of median values, interquartile ranges, and distribution patterns of biomarkers among effusion subtypes.

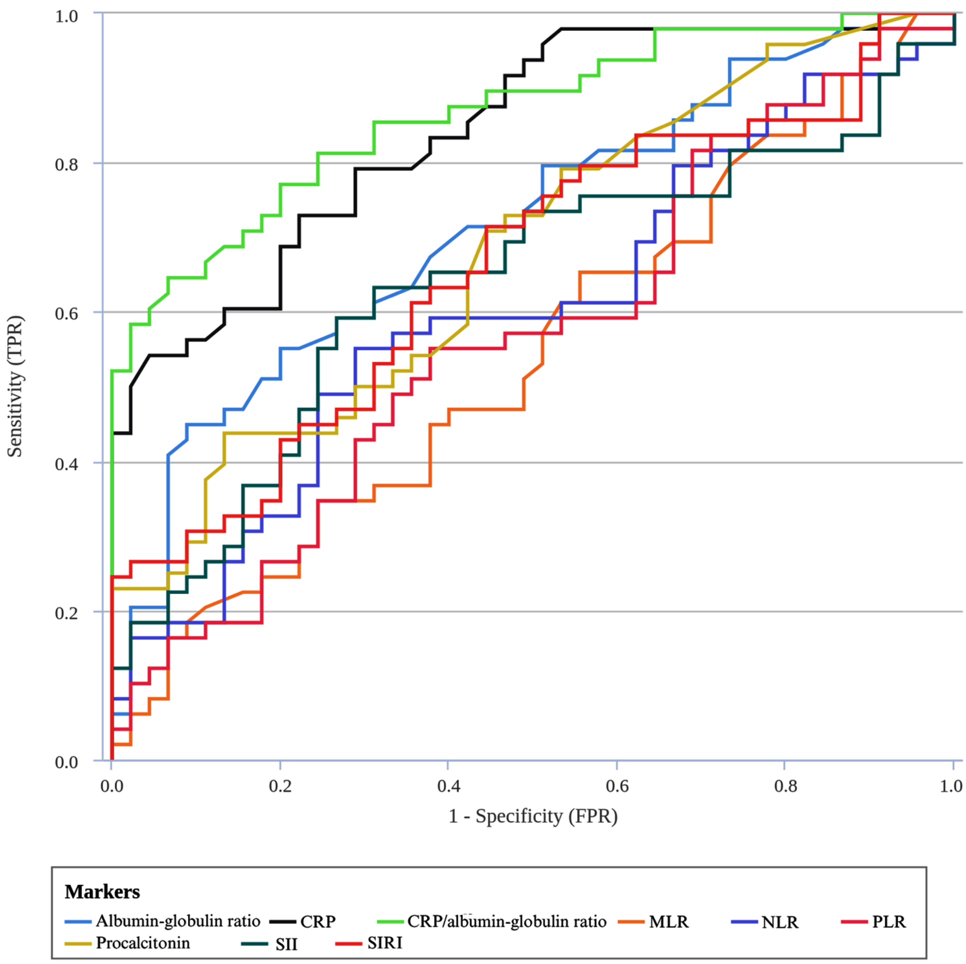


Figure 2. Receiver Operating Characteristic (ROC) curves of individual systemic inflammatory biomarkers for identifying parapneumonic pleural effusion (PPE) among all pleural effusion types. Each curve represents a biomarker's diagnostic performance, evaluated by the area under the curve (AUC), sensitivity, and specificity. CAGR demonstrated the highest discriminative ability for PPE.

Novel hematologic indices, such as the SII and SIRI, offer a broader perspective on systemic immune activation. Recent evidence highlights the diagnostic relevance of MLR in pneumonia-related complications, particularly as an independent predictor of stroke-associated pneumonia and a correlate of severity assessed by the pneumonia severity index score[19,20]. Consistent with these findings, our analysis – conducted in an extended adult cohort and incorporating additional indices such as SIRI – revealed that MLR outperformed other systemic inflammatory markers in distinguishing CPPE from uCPPE. These results reinforce the potential of MLR as a practical and robust adjunctive biomarker in the stratification of parapneumonic effusions.

Additionally, unlike PLR and NLR, which are predominantly influenced by systemic inflammatory responses, MLR may offer a more refined reflection of localized pleural inflammation. This interpretation aligns with previous studies that identified MLR as a robust biomarker of immune activity across a variety of pathological conditions, including tuberculosis and malignancies[21,22]. The superior sensitivity and specificity of MLR in detecting disease severity and complications in parapneumonic effusions may, therefore, be attributable to the distinct immunological role of monocytes.

In contrast to neutrophils and platelets – which are key effector cells in acute inflammation – monocytes are centrally involved in chronic inflammation and sustained immune responses. Their relatively longer lifespan and capacity for antigen presentation may contribute to the enhanced diagnostic performance of MLR, particularly in CPPE, which often exhibits features of prolonged or unresolved inflammation[23].

Although NLR ranked second in overall diagnostic performance, its utility as an adjunctive

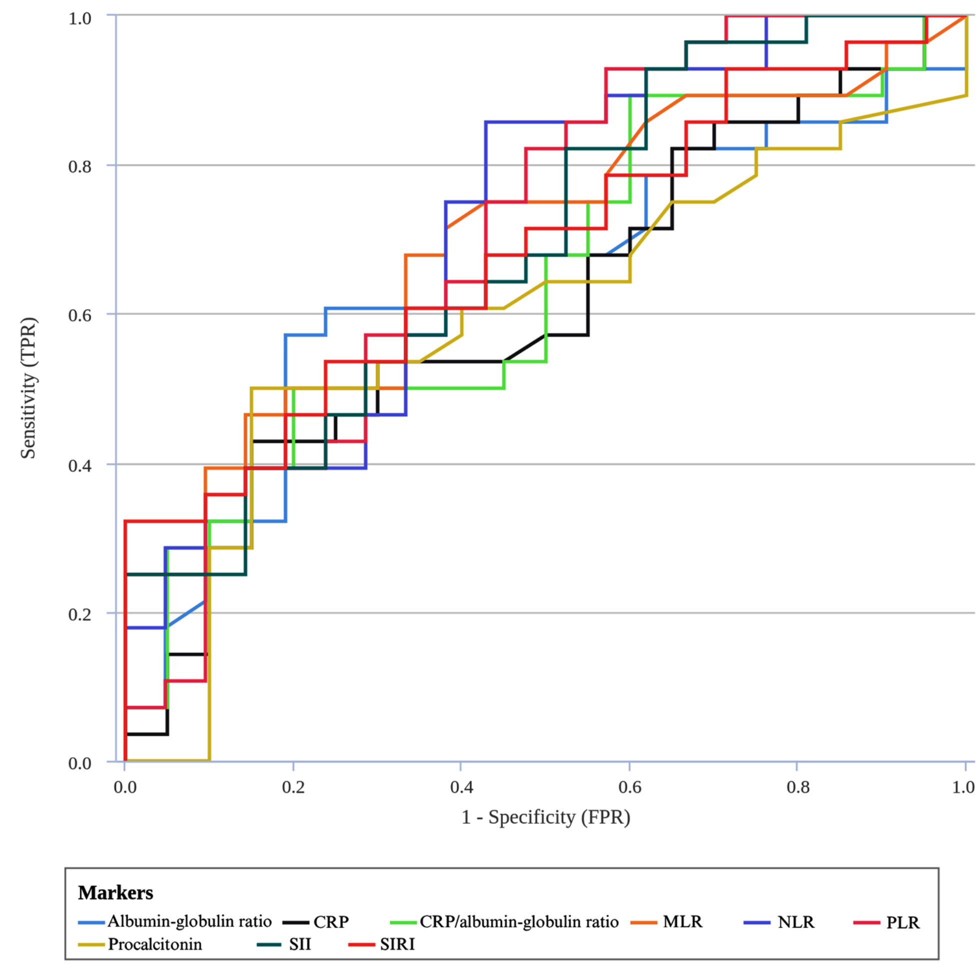


Figure 3. Receiver Operating Characteristic (ROC) curves of selected systemic inflammatory biomarkers for distinguishing complicated parapneumonic effusions (CPPE) from uncomplicated parapneumonic effusions (uCPPE). The figure illustrates the diagnostic performance of each biomarker based on area under the curve (AUC), with corresponding sensitivity and specificity values. Among the biomarkers analyzed, MLR showed the highest discriminative accuracy for identifying complicated cases.

Table III. Diagnostic performance of systemic inflammatory biomarkers in differentiating complicated parapneumonic effusions (CPPE) from uncomplicated parapneumonic effusions (uCPPE), based on ROC curve analysis. The table presents the area under the curve (AUC), 95% confidence intervals, optimal cut-off values, sensitivity, and specificity (expressed as 1–specificity). Higher AUC values indicate greater discriminative ability. MLR showed the highest diagnostic accuracy in this subgroup analysis.

Test result variable(s)	Area	Std. Error	Asymptotic Sig.[b]	Asymptotic 95% confidence interval		Cut-off	Sensitivity	1-Specificity
				Lower	Upper			
NLR	.702	.078	.018	.550	.854	0.525	0.679	0.3
PLR	.704	.080	.017	.548	.860	121.62	0.571	0.3
MLR	.707	.075	.015	.560	.855	3.615	0.71	0
PCT	.595	.084	.268	.429	.760	0.55	0.5	0.15
CRP	.610	.083	.198	.448	.772	215	0.5	0.2
AGR	.368	.082	.122	.208	.528	1.745	0.71	0
CAGR	.641	.081	.099	.482	.800	215	0.5	0.2
SIRI	.671	.077	.045	.520	.822	15.3234	0.321	0
SII	.675	.078	.040	.521	.829	930.715	0.929	0.65

ROC: Receiver Operating Characteristic Curve, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, SIRI: Systemic Inflammation Response Index, SII: Systemic Immune-Inflammation Index, CRP: C-reactive protein, PCT: procalcitonin, AGR: Albumin-globulin ratio, CAGR: C-Reactive Protein/Albumin-globulin ratio.

marker in the identification of CPPE remains noteworthy. Nevertheless, further prospective and multi-center studies are warranted to validate the clinical applicability of both MLR and NLR, especially when integrated into multimarker diagnostic algorithms.

PCT, a serum biomarker indicative of bacterial infection, demonstrated moderate diagnostic accuracy for PPE in this study. This finding is consistent with previous meta-analyses[24] reporting pooled areas under AUCs of 0.84 for serum PCT and 0.80 for pleural fluid PCT. However, its diagnostic performance was inferior to that of serum CRP and CAGR, thereby limiting its clinical utility in routine practice. As in earlier studies, PCT showed limited effectiveness in differentiating complicated from uncomplicated parapneumonic effusions, likely due to overlapping serum concentrations between these groups[25,26]. Furthermore, the strong correlation previously reported between serum and pleural fluid PCT levels suggests that concurrent measurement of both does not provide significant incremental diagnostic value[27]. In contrast to CRP, the diagnostic performance of PCT does not appear to improve substantially when included as part of a composite biomarker assessment.

Limitations

This study has several limitations. This retrospective single-center design restricts the findings' generalizability and precludes any causality inference. Although the sample size provided adequate statistical power, validating these findings requires prospective multicenter studies with larger and more heterogeneous populations. The exclusive reliance on serum-based biomarkers without parallel analysis of pleural fluid parameters may have limited the depth of diagnostic interpretation. A notable limitation of our study is the absence of comprehensive pleural fluid characterization and detailed radiological assessment, such as specific gravity, total protein levels, or imaging-based quantification of loculation or pleural thickness. The inclusion of such data could have allowed for a more robust correlation between systemic inflammatory markers and local pleural pathology. Future studies incorporating pleural fluid profiles and imaging features alongside systemic biomarkers may provide a more integrated diagnostic framework. Furthermore, the lack of adjustment for potential confounders, such as comorbid conditions or concurrent infections, and the absence of follow-up data hindered the evaluation of the prognostic relevance of the assessed biomarkers. These limitations underscore the need for future research involving more diverse cohorts and comprehensive biomarker profiling to confirm and extend the current findings.

CONCLUSIONS

In conclusion, this study identified CAGR as the most diagnostically accurate marker for detecting parapneumonic effusions and MLR as the most effective indicator for differentiating complicated from uncomplicated PPE. Although CRP remains a reliable marker for PPE diagnosis, its discriminatory capacity in distinguishing CPPE from uCPPE is limited. These findings emphasize the potential clinical benefit of integrating pleural fluid biomarkers with peripheral blood indices to improve diagnostic precision. Future prospective multicenter studies incorporating both serum and pleural fluid biomarker analyses are required to validate and expand upon these results.

Ethics Approval

Ethics approval was obtained by the Health Sciences Research Ethics Committee of Erciyes University, under protocol number 2024/116, dated August 4, 2024.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contribution

Nur Aleyna Yetkin: conceptualization, methodology, formal analysis, writing – original draft preparation, supervision, writing – review and editing.
Filiz Miraç Şimşek: data curation, investigation, validation.
Burcu Baran: methodology, visualization.
Bilal Rabahoğlu: data management, resources.
Nuri Tutar: supervision, writing – critical review.
İnci Gülmez: oversight, final approval of the manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because of institutional data protection policies and patient confidentiality requirements but are available from the corresponding author upon reasonable request.

ORCID ID

Nur Aleyna Yetkin: 0000-0001-5974-9129
Filiz Miraç Şimşek: 0009-0005-2343-8106
Burcu Baran: 0000-0002-6757-3140
Bilal Rabahoğlu: 0000-0002-1992-4073
Nuri Tutar: 0000-0003-3097-4896
İnci Gülmez: 0000-0002-4476-2213

Informed Consent

Due to the retrospective design of the study and the use of anonymized data, the requirement for written informed consent was waived by the Health Sciences Research Ethics Committee of Erciyes University (Protocol No: 2024/116, dated August 4, 2024).

REFERENCES

1) Jany B, Welte T. Pleural Effusion in Adults-Etiology, Diagnosis, and Treatment. Dtsch Arztebl Int 2019; 116: 377-386.
2) Light RW. Parapneumonic effusions and empyema. Proc Am Thorac Soc 2006; 3: 75-80.
3) Koppurapu V, Meena N. A review of the management of complex parapneumonic effusion in adults. J Thorac Dis 2017; 9: 2135-2141.
4) Kogan Y, Sabo E, Odeh M. Diagnostic Value of C-Reactive Protein in Discrimination between Uncomplicated and Complicated Parapneumonic Effusion. Diagnostics (Basel) 2020; 10: 829.
5) Saricam M. Efficiency of Lymphocyte-to-Monocyte Ratio in Differential Diagnosis of Parapneumonic Effusion and Thoracic Empyema. Surg Infect (Larchmt); 21: 891-894.
6) Li D, Shen Y, Qin J, Wan C, Zeng N, Chen L, Dong Y. Diagnostic performance of C-reactive protein for parapneumonic pleural effusion: a meta-analysis. Ann Transl Med 2019; 7: 1.
7) Chen SC, Chen W, Hsu WH, Yu YH, Shih CM. Role of pleural fluid C-reactive protein concentration in discriminating uncomplicated parapneumonic pleural effusions from complicated parapneumonic effusion and empyema. Lung 2006; 184: 141-145.
8) Porcel JM, Galindo C, Esquerda A, Trujillano J, Ruiz-González A, Falguera M, Vives M. Pleural fluid interleukin-8 and C-reactive protein for discriminating complicated non-purulent from uncomplicated parapneumonic effusions. Respirology 2008; 13: 58-62.
9) Watanabe N, Ishii T, Kita N, Kanaji N, Nakamura H, Nanki N, Ueda Y, Tojo Y, Kadowaki N, Bandoh S. The usefulness of pleural fluid presepsin, C-reactive protein, and procalcitonin in distinguishing different causes of pleural effusions. BMC Pulm Med 2018; 18: 176.
10) Porcel JM, Esquerda A, Vives M, Bielsa S. Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses. Arch Bronconeumol 2014; 50: 161-165. English, Spanish.
11) Mangalesh S, Dudani S, Malik A. The systemic immune-inflammation index in predicting sepsis mortality. Postgrad Med 2023; 135: 345-351.
12) Yetkin MF, Mirza M. Neutrophil to-lymphocyte ratio as a possible predictor of prognosis in recently diagnosed multiple sclerosis patients. J Neuroimmunol 2020; 346: 577307.
13) Xu JB, Xu C, Zhang RB, Wu M, Pan CK, Li XJ, Wang Q, Zeng FF, Zhu S. Associations of procalcitonin, C-reaction protein and neutrophil-to-lymphocyte ratio with mortality in hospitalized COVID-19 patients in China. Sci Rep 2020; 10: 15058.
14) Botana Rial M, Pérez Pallarés J, Cases Viedma E, López González FJ, Porcel JM, Rodríguez M, Romero Romero B, Valdés Cuadrado L, Villena Garrido V, Cordovilla Pérez R. Diagnosis and Treatment of Pleural Effusion. Recommendations of the Spanish Society of Pulmonology and Thoracic Surgery. Update 2022. Arch Bronconeumol 2023; 59: 27-35.
15) Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol 2018; 9: 754.
16) Watanabe N, Ishii T, Kita N, Kanaji N, Nakamura H, Nanki N, Ueda Y, Tojo Y, Kadowaki N, Bandoh S. The usefulness of pleural fluid presepsin, C-reactive protein, and procalcitonin in distinguishing different causes of pleural effusions. BMC Pulm Med 2018; 18: 176.
17) Ertekin B, Acar T. The relationship between albumin and its proportion to other markers in predicting mortality in severe COVID-19 patients. Eur Rev Med Pharmacol Sci 2023; 27: 6429-6436.
18) Ji W, Liu Z, Lin T. Diagnostic value of albumin/fibrinogen ratio and C-reactive protein/albumin/globulin ratio for periprosthetic joint infection: a retrospective study. PeerJ 2023; 11: e16662.
19) Calis AG, Karaboga B, Uzer F, Kaplan N, Karaca M, Gedik RB, Durmuş AA. Correlation of Pneumonia Severity Index and CURB-65 Score with Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio, and Monocyte/Lymphocyte Ratio in Predicting In-Hospital Mortality for Community-Acquired Pneumonia: Observational Study. J Clin Med 2025; 14: 728.
20) Cheng T, Zhu Y, Wang W, Wang Y. Monocyte-to-lymphocyte ratio as a predictor of stroke-associated pneumonia: A retrospective study-based investigation. Medicine (Baltimore) 2022; 101: e30663.
21) Güneylioğlu MM, Güngör A, Göktuğ A, Üner Ç, Bodur İ, Yaradılmış RM, Öztürk B, Şen ZS, Tuygun N. Evaluation of the efficiency of the systemic immune-inflammation index in differentiating parapneumonic effusion from empyema. Pediatr Pulmonol 2022; 57: 1625-1630.
22) Sibley L, Gooch K, Wareham A, Gray S, Chancellor A, Dowall S, Bate S, Marriott A, Dennis M, White AD, Marsh PD, Fletcher H, Sharpe S. Differences in monocyte: lymphocyte ratio and Tuberculosis disease progression in genetically distinct populations of macaques. Sci Rep 2019; 9: 3340.
23) Orozco SL, Canny SP, Hamerman JA. Signals governing monocyte differentiation during inflammation. Curr Opin Immunol 2021; 73: 16-24.
24) He C, Wang B, Li D, Xu H, Shen Y. Performance of procalcitonin in diagnosing parapneumonic pleural effusions: a clinical study and meta-analysis. Medicine (Baltimore) 2017; 96: e7829.
25) Wang CY, Hsiao YC, Jerng JS, Ho CC, Lai CC, Yu CJ, Hsueh PR, Yang PC. Diagnostic value of procalcitonin in pleural effusions. Eur J Clin Microbiol Infect Dis 2011; 30: 313-318
26) Porcel JM, Vives M, Cao G, Bielsa S, Ruiz-González A, Martínez-Iribarren A, Esquerda A. Biomarkers of infection for the differential diagnosis of pleural effusions. Eur Respir J 2009; 34: 1383-1389.
27) San José ME, Valdés L, Vizcaíno LH, Mora T, Pose A, Soneira E, Crecente C, González-Barcala FJ. Procalcitonin, C-reactive protein, and cell counts in the diagnosis of parapneumonic pleural effusions. J Investig Med 2010; 58: 971-976.