Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Mammadova A, Galata Z, Yaylçınkaya Z, et al. **Diagnostic value of pleural fluid and serum C-reactive protein/albumin ratio in exudate/transudate, infectious/non-infectious pleural fluid discrimination.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3060

Diagnostic value of pleural fluid and serum C-reactive protein/albumin ratio in exudate/transudate, infectious/non-infectious pleural fluid discrimination

Ayshan Mammadova,[1] Zuleyha Galata,[1] Zeynep Yaylçınkaya,[2] Nilgun Yılmaz Demirci[1]

[1]Department of Chest Diseases, Medical Faculty, Gazi University, Ankara; [2]Afyonkarahisar Central Community Health Center, Afyon, Turkey

Correspondence: Ayshan Mammadova, Department of Chest Diseases, Medical Faculty, Gazi University, Ankara, Turkey.
Tel.: +90 03122022000. Fax: +90 0312 221 32 02. E-mail: aysenmammadova665@gmail.com

Contributions: AM, NYD, designed and coordinated the study, participated in data acquisition and interpretation, and drafted the article; ZG, AM, ZY, participated in data collection; AM, NYD, participated in the interpretation of the data. All authors critically reviewed the article for important intellectual content and gave final approval for publishing the version.

Conflict of interest: the authors declare that they have no conflicts of interest.

Ethics approval and consent to participate: this prospective and single-center study was conducted with the approval of the Ankara City Hospital Faculty of Medicine Clinical Research Ethics Committee (date: 16.07.2020; decision no.: E1-20-918).

Informed consent: written consent forms were obtained from all patients included in the study. They are all available in the patient's hospitalization files.

Patient consent for publication: not applicable.

Availability of data and materials: this single-center prospective study of 160 patients was carried out by Gazi University Faculty of Medicine, Department of Chest Diseases. Upon reasonable request, data is available at this address.

Funding: this research received no specific grant from public, commercial, or non-profit funding agencies.

Abstract

As a new parameter, the C-reactive protein (CRP)/albumin ratio (CAR) has been shown to be more accurate than CRP and albumin alone in predicting the diagnosis and overall prognosis in cancer, sepsis, and vascular and non-vascular conditions. In this direction, we aimed to investigate the role of CAR in the differentiation of transudate/exudate and infectious/non-infectious in our study. A total of 160 patients who were examined for pleural fluid between August 2020 and February 2021 were included in our single-center prospective observational study. The study did not include those who could not undergo diagnostic thoracentesis and those under the age of 18. The presence of pleural effusion was determined by physical and radiological examinations [chest radiograph, thorax computed tomography, thoracic ultrasonography (US)]. Diagnostic thoracentesis was performed under the guidance of thoracic US after the patients who met the inclusion criteria signed an informed consent form.

A total of 160 patients, 117 (73.1%) male and 43 (26.9%) female, were included in the study. While exudate was detected in 101 (63.1%) cases and transudate was detected in 59 (36.9%) cases, 47 (29.4%) of these were due to infectious and 113 (70.6%) non-infectious causes. The mean pleural fluid CAR (46.38) and serum CAR (72.43) in the infectious group were found to be significantly higher than those in the non-infectious group (13.17 and 19.48, respectively) ($p<0.001$). The pleural fluid and serum CAR (31.79 and 49.68) were found to be significantly higher in the exudate-qualified group compared to the transudate-qualified group (7.76 and 9.97) ($p<0.001$). When the threshold value for the pleural fluid CAR is >15.65, it is 80.9% sensitive and 73.5% specific in predicting infectious fluid; when the threshold value was >9.48, it was found to be 71.3% sensitive and 71.2% specific in exudate-transudate discrimination.

In conclusion, in our study, we see that the pleural fluid and serum CAR are promising parameters in the differentiation of infectious/non-infectious pleural effusions and in the differentiation of exudate/transudate.

Key words: pleural fluid, exudate, transudate, CRP/albumin ratio.

Introduction

Pleural effusion is a pathology frequently encountered in daily practice, may develop due to many different diseases, and sometimes has diagnostic problems. Once the pleural effusion has been identified, the fluid needs to be analyzed. First, transudate and exudate should be differentiated, and thoracentesis should take a sample for this [1]. The exact etiology can sometimes be difficult despite all the examinations [2]. In recent years, the development of specific disease-specific biomarkers has opened the research area for common causes of pleural effusion. Many studies are carried out on inflammatory biomarkers, especially for the early detection of parapneumonic effusion and empyema, which may indicate emergency tube drainage.

There is a systemic physiological or metabolic complex response to infection, malignancy, or trauma in the body. These reactions reduce tissue damage, isolate and eliminate infective organisms, and activate repair mechanisms. C-reactive protein (CRP) is a positive acute phase reactant synthesized by the liver, and as a well-known acute phase reactant, its blood level increases within hours in response to inflammation and infection, which has so far been associated with a variety of diseases, including acute coronary syndrome, ischemic stroke, and facial palsy [3,4]. At the same time, it has been proven that there is a significant relationship between some types of cancer and CRP value [5,6]. Albumin synthesized by the liver is a negative acute phase reactant, and decreased albumin has been proven to be associated with an inflammatory response [7].

Studies conducted for many years have shown that the ratio of CRP/Albumin (CAR) has prognostic importance in determining inflammation. It has been shown to help determine the prognosis of many diseases, such as acute appendicitis, acute pancreatitis, sleep-disordered breathing, lung cancer, traumatic brain injury, and ulcerative colitis [8-10]. Although few studies evaluate the relationship between some inflammatory markers and pleural effusion, there has yet to be a study investigating the relationship between the CAR and the etiology of pleural effusion. In this prospective study, we aimed to examine the role of CAR in differentiating between transudative and exudative pleural effusion, as well as infectious and non-infectious pleural effusion.

Materials and Methods

This prospective observational and single-center study was conducted with approval of the Faculty of Medicine Clinical Research Ethics Committee (No: E1-20-918). A total of 160 patients with pleural effusion between August 2020 and February 2021 were included in the study. The study did not include those who could not undergo diagnostic thoracentesis and those under the age of 18. The presence of pleural effusion was determined by physical and

radiological examinations (chest radiograph, thorax computed tomography, thoracic ultrasonography (US)). Diagnostic thoracentesis was performed under the guidance of thoracic US [11] after the patients who met the inclusion criteria signed an informed consent form. 20-50 cc sample was taken at thoracentesis.

Serum and pleural fluid complete blood count, biochemical parameters, and CRP levels were measured simultaneously. Our study used the nephelometric measurement method as the CRP measurement method. Light's Criteria were used to differentiate exudate and transudate [12]. Additionally, pleural fluid culture, tuberculosis culture, and pleural fluid cytological examination were performed. In cases where diagnostic thoracentesis was insufficient to determine the cause of pleural effusion, additional tests such as bronchoscopy, closed pleural biopsy, Positron Emission Tomography (PET), and Thorax Magnetic Resonance Imaging (MRI) were conducted according to the preliminary diagnoses. The benign and malignant diagnoses were established based on clinical findings, pleural effusion analysis, microbiological examination, radiological findings, cytology of the pleural effusion, and/or histology of the pleural tissue. Patients for whom a diagnosis could not be reached despite undergoing all diagnostic procedures were followed up for at least one year [13].

Statistical analysis

Statistical analysis was performed using the IBM SPSS (Statistical Package for the Social Sciences) 26.0 package program. In descriptive statistical analyses, for continuous variables, mean ± standard deviation and median (minimum-maximum) were given according to their fitness for normal distribution; Numbers and percentages (%) were given for categorical variables. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test, and nonparametric tests were preferred according to the test result. Mann-Whitney U test was used to compare nonparametric data between the two groups. R.O.C. analysis was used to determine whether pleural and serum CAR values have diagnostic value for exudative and infectious pleural effusion and whether they can be used. The statistical significance level was accepted as $p<0.05$.

Results

A total of 160 patients, 117 (73.1%) male and 43 (26.9%) female, were included in the study. The mean age of the patients was 64.21±13.79 years. Exudate was detected in 101 (63.1%) cases and transudate in 59 (36.9%) cases, with 47 (29.4%) attributed to infectious causes and 113 (70.6%) to non-infectious causes. Among pleural effusions, the most common causes were empyema (11 cases, 6.9%), heart failure (28 cases, 17.5%), malignant effusion (16 cases, 10%), unknown etiology (27 cases, 16.9%), parapneumonic effusion (20 cases, 12.5%), tuberculosis

(TB) pleurisy (9 cases, 5.6%), and other miscellaneous causes (49 cases, 30.6%)(Table 1). Each group, categorized according to their diagnosis, was compared internally regarding pleural fluid (PF) and serum (S) CRP/Albumin Ratio (PF-CAR and S-CAR). While S-CAR values were elevated in all groups except for the 'others' category, they were notably highest in the empyema and parapneumonic effusion groups (Table 2).

The mean PF- CAR value was 31.79 and S- CAR value was 49.68 in the exudate group. The mean PF- CAR value was 7.76 and S- CAR value was 9.97 in the transudate group. Both PF-CAR value and S- CAR value was significantly higher in the exudate group than in the transudate group ($p< 0.05$, $p<0.001$). ROC curve analysis was performed to determine the PF-CAR cut-off level in the differentiation of exudate and transudate. When the cut-off was taken as 9.48, the sensitivity was 71.3%, the specificity was 71.2%, and the AUC was 0.79 (95% CI) (Figure 1).

We categorized the patients into two groups: those with pleural infection (Infectious: empyema, parapneumonic effusion, TB pleurisy) and those without pleural infection (Non-infectious: malignant effusion, unknown etiology, heart failure, and other causes. PF and S-CAR values between these two groups were compared. In the infectious group, the mean pleural PF- CAR (46.38) and S- CAR (72.43) were found to be significantly higher than those in the non-infectious group (13.17 and 19.48, respectively) ($p<0.001$)(Table 3). The threshold value for the PF- CAR >15.65 was found to be 80.9% sensitive and 73.5% specific in predicting the fluid of infectious origin (Figure 2).

Discussion and Conclusions

Our prospective study demonstrates that both the pleural fluid and serum CRP/Albumin ratios hold promise for distinguishing between infectious and non-infectious pleural effusions, as well as between exudative and transudative effusions.

CRP is a very inexpensive and easily applicable test that indicates inflammation due to various causes, such as infection, vasculitis, and trauma. Therefore, CRP has been the subject of many studies. Studies on serum CRP and pleural fluid levels have increased in recent years.

Transudative pleural effusion develops due to various etiological factors, which can vary between centers. Notably, the density of specific departments and the number of patients admitted influence this condition. In our center, we have a significant number of patients being monitored in the Nephrology and Cardiology departments, and cases of resistant pleural effusions are referred to our department. In our study, transudative fluid was detected in 36.9% of the included patients. Given that the likelihood of detecting transudative fluid is high in conditions such as heart failure and renal failure, thoracentesis was performed under the guidance of thoracic US when indicated.In this context, for patients diagnosed with heart or

renal failure who do not respond to diuretic therapy, the presence of symptoms such as side pain, fever, significant asymmetry of bilateral fluid, or excessive fluid on one side suggested the possibility of an underlying primary disease as well as a secondary condition due to an exudative pathology. Therefore, thoracentesis was deemed necessary. This process is critical for the accurate assessment of patients and the development of appropriate treatment plans [14].

CAR is a new prognostic score based on inflammation and has been shown to have a high predictive value in tumors such as pancreatic, ovarian cancer, or lung [15-17]. Also, this rate can be compared with other inflammation-based prognostic scores in predicting prognosis. A retrospective study showed that it **c**an be a prognostic indicator in determining the severity of the disease in patients with COVID-19, but it could not predict mortality [18].

Watanabe et al., in their study involving 132 patients with pleural effusion in Japan between 2015 and 2017, analyzed the CRP level, pleural fluid, and serum of patients [19]. As a result, CRP levels measured in pleural fluid were higher in empyema, parapneumonic effusion, and tuberculous pleurisy compared to malignant effusion and transudate, which was statistically significant. However, there was no significant difference between empyema and parapneumonic effusion. CRP levels measured in serum were found to be higher in the parapneumonic effusion group ($p<0.05$) [19]. In our study, the CAR measured in pleural fluid was statistically significantly higher in parapneumonic effusion compared to heart failure, malignant, and paramalignant effusion ($p<0.05$).

However, it was insignificant in distinguishing parapneumonic effusion from empyema ($p=1$, $p=0.37$). In the same study, PF-CRP levels were lower than S-CRP levels. Our analysis also observed that PF-CRP levels were lower than S-CRP levels. We found that PF-CAR and S-CAR levels showed a strong positive correlation in all patients ($p<0.01$) ($r=0.838$), regardless of their diagnosis. When the cut-off for PF-CAR levels was set at 15.65, the sensitivity was 80.9%, the specificity was 73.5%, and the AUC was 0.841 in distinguishing between infectious and non-infectious etiologies.

In a different study that included 233 patients between 2005 and 2008, they divided them into five groups and examined CRP levels in both pleural fluid and serum [20]. As a result of the study, it was found that the CRP values measured in pleural fluid and serum were statistically significantly higher in the parapneumonic effusion group compared to the other groups ($p<0.001$-0.006) [20].

Many studies have evaluated the PF-CRP level in differentiating between pleural fluid exudate and transudate. Ahmed et al. found statistically significant CRP levels in the pleural fluid to be higher in the exudate group ($p<0.01$) [21]. In our study, the PF-CAR was higher in the exudate group ($p<0.05$). When the cut-off for PF-CAR levels was set at 9.48, the sensitivity was 71.3%,

the specificity was 71.2%, and the AUC was 0.79 in separating exudate from transudate ($p < 0.001$).

Also, the synthesis of albumin, a negative acute phase reactant, is suppressed by inflammatory cytokines in the presence of inflammation [22]. Thus, albumin levels decrease in inflammation. For this reason, it is observed that the CAR increases in case of inflammation. However, the value of CRP and albumin has the advantage of reflecting not only the proinflammatory state but also the nutritional state. Therefore, it has prognostic value not only in the case of inflammation but also in healthy and malnutrition cases [23,24].

A prospective study hypothesized that an increased CAR indicates a higher inflammatory condition and may be superior to CRP and albumin alone in determining the prevalence and severity of coronary artery disease [25]. In a retrospective study of 256 patients, CAR as a prognostic marker based on inflammation in patients with pulmonary thromboembolism (PTE) was a useful prognostic marker for PTE, and these results reinforce the role of inflammation in PTE [26]. The strengths of this study include identifying CAR as an independent risk factor associated with 6-month mortality in patients with acute PTE [26]. Our study's most significant limitation was its single-center nature, as we were unable to obtain enough patients in each disease group that caused pleural effusion. Therefore, it has become apparent that supporting our results with studies involving a larger patient cohort would be appropriate.

In this study, we observed a strong positive correlation between PF and S-CAR regardless of the cause of pleural effusion. Additionally, PF-CAR was significant in distinguishing between infectious and non-infectious effusions, as well as exudative and transudative effusions.

References

1. Zocchi L. Physiology and pathophysiology of pleural fluid turnover. Eur Respir J 2002;20:1545-58.
2. Tokgöz F, Gökşenoğlu N, Bodur Y, et al. Retrospective analysis of 240 cases with pleural effusion. Eurasian J Pulmonol 2014;16:78-83.
3. Zhang X, Wang A, Zhang J, et al. Association of plasma C-reactive protein with ischaemic stroke: a Mendelian randomization study. Eur J Neurol 2020;27:565-71.
4. Cayir S, Hizli O, Kayabasi S. Is C-reactive protein to albumin ratio an indicator of poor prognosis in Bell's palsy? Eur Arch Otorhinolaryngol 2020;277:115-9.
5. Liu Z, Jin K, Guo M, et al. Prognostic value of the CRP/Alb Ratio, a novel Inflammation-based score in pancreatic cancer. Ann Surg Oncol 2017;24:561-8.
6. Zhou T, Zhan J, Hong S, et al. Ratio of C-reactive protein/albumin is an inflammatory prognostic score for predicting overall survival of patients with small-cell lung cancer. Sci Rep 2015;5:10481.

7. Esper DH, Harb WA. The cancer cachexia syndrome: a review of metabolic and clinical manifestations. Nutr Clin Pract 2005;20:369-76.
8. Gibson DJ, Hartery K, Doherty J, et al. CRP/albumin ratio: an early predictor of steroid responsiveness in acute severe ulcerative colitis. J Clin Gastroenterol 2018;52:e48-52.
9. Wang R, He M, Ou X, et al. CRP Albumin ratio is positively associated with poor outcome in patients with traumatic brain injury. Clin Neurol Neurosurg 2020;195:106051.
10. Hizli O, Cayir S, Coluk Y, et al. The novel indicators of moderate to severe sleep apnea: fibrinogen to albumin ratio vs. CRP to albumin ratio. Eur Arch Otorhinolaryngol 2021;278:851-5.
11. Dietrich CF, Mathis G, Cui XW, et al. Ultrasound of the pleurae and lungs. Ultrasound Med Biol 2015;41:351-65.
12. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507-13.
13. Ak G, Metintas S, Taskın AN, et al. Evaluation of exudative pleural effusions: a multicenter, prospective, observational study. Lung 2022;200:807-15.
14. Marel M. Epidemiology of pleural effusion. Eur Respir Mon 2002;22:146-56.
15. Arakawa Y, Miyazaki K, Yoshikawa M, et al. Value of the CRP-albumin ratio in patients with resectable pancreatic cancer. J Med Invest 2021;68:244-55.
16. Komura N, Mabuchi S, Shimura K, et al. Significance of pretreatment C-reactive protein, albumin, and C-reactive protein to albumin ratio in predicting poor prognosis in epithelial ovarian cancer patients. Nutr Cancer 2021;73:1357-64.
17. Ni XF, Wu J, Ji M, et al. Effect of C-reactive protein/albumin ratio on prognosis in advanced non-small-cell lung cancer. Asia Pac J Clin Oncol 2018;14:402-9.
18. Kalabin A, Mani VR, Valdivieso SC, Donaldson B. Does C reactive protein/albumin ratio have prognostic value in patients with COVID-19? J Infect Dev Ctries 2021;15:1086-93.
19. Watanabe N, Ishii T, Kita N, et al. The usefulness of pleural fluid presepsin, C-reactive protein, and procalcitonin in distinguishing different causes of pleural effusions. BMC Pulm Med 2018;18:176.
20. San José ME, Valdés L, Vizcaíno LH, et al. Procalcitonin, C-reactive protein, and cell counts in the diagnosis of parapneumonic pleural effusions. J Investig Med 2010;58:971-6.
21. Ahmed MM, Abdelhalim HA, El Kholy NA. Cut-off value of pleural fluid C-reactive protein in etiologic diagnosis of pleural fluid. Egypt J Chest Dis Tuberc 2014;63:617-23.
22. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. Semin Dial 2004;17:432-7.
23. Barbosa-Silva MC, Barros AJ, Wang J, et al. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr 2003;77:412-6.

24. Jeejeebhoy KN. Clinical nutrition: 2. Protein metabolism in stress and injury. CMAJ 2000;163:849-53.

25. Karabağ Y, Çağdaş M, Rencuzogullari I, et al. Relationship between C-reactive protein/albumin ratio and coronary artery disease severity in patients with stable angina pectoris. J Clin Lab Anal 2018;32:e22457.

26. Özcan S, Dönmez E, Yavuz Tuğrul S, et al. The prognostic value of C-reactive protein/albumin ratio in acute pulmonary embolism. Rev Invest Clin 2022;74:097-103.

Table 1. Causes of pleural effusion.

Groups	**n (%)**
Empyema	**11**
Heart failure	**28**
Malignant effusion	**16**
Tuberculosis pleurisy	**9**
Parapneumonic effusion	**20**
Unknown	**27**
Others	**49**
Dressler's syndrome	**7**
Hypoalbuminemia	**5**
Secondary to intra-abdominal event	**6**
Chronic kidney deficiency	**11**
Chronic fibrinous pleuritis	**2**
Lymphedema	**2**
Pericarditis	**5**
Pulmonary embolism	**2**
Rheumatoid pleurisy	**8**
Trauma	**1**
Total	**160**

Table 2. Pleural fluid and Serum CRP/Albumin ratio according to diagnoses.

Diagnosis	**PF- CAR**	**S- CAR**
Empyema (n=11)	52.6 (20.9-87.5)	92.1 (40.7-120.0)
Heart failure (n=28)	5.4 (1.0-16.6)	6.2 (0.7-26.5)
Malignant effusion (n=16)	14.7 (1.9-68.0)	29.2 (1.6-183.3)
Unknown (n=27)	7.4 (1.3-42.1)	9.6 (1.7-45.9)
TB pleurisy (n=9)	20.0 (1.2-44.1)	33.0 (0.8-110.0)
Parapneumonic effusion (n=20)	49.2 (2.7-118.4)	93.0 (4.0-165.9)
Others (n=46)	13.1 (1.1-89.9)	12.7 (1.3-123.8)

Data are presented as median (min-max). PF, pleural fluid, TB, tuberculosis; S, serum; CAR, CRP/albumin ratio.

Table 3. Laboratory values in infectious and non-infectious pleural effusion.

Laboratory findings	**Infectious**	**Non-infectious**	**p**
PF- CAR	46.38 (1.2-118.4)	13.17 (1.0-89.0)	**<0.001**
PF- CRP	82.0 (4.0-238.0)	14.0 (1.0-170.0)	**<0.001**
PF -Albumin	2.2 (0.5-3.5)	1.9 (1.1-3.6)	0.137
S- CAR	72.43 (0.8-165.9)	19.48 (0.7-183.3)	**<0.001**
S- CRP	173.0 (3.0-365.0)	30.0 (3.0-440.0)	**<0.001**
S- Albumin	3.1 (1.7-4.4)	3.3 (2.1-5.1)	**0.031**

Data are presented as median (minimum-maximum). CRP unit mg/L, Albumin unit g/dL. PF, pleural fluid; S, serum; CAR, CRP/albumin ratio.

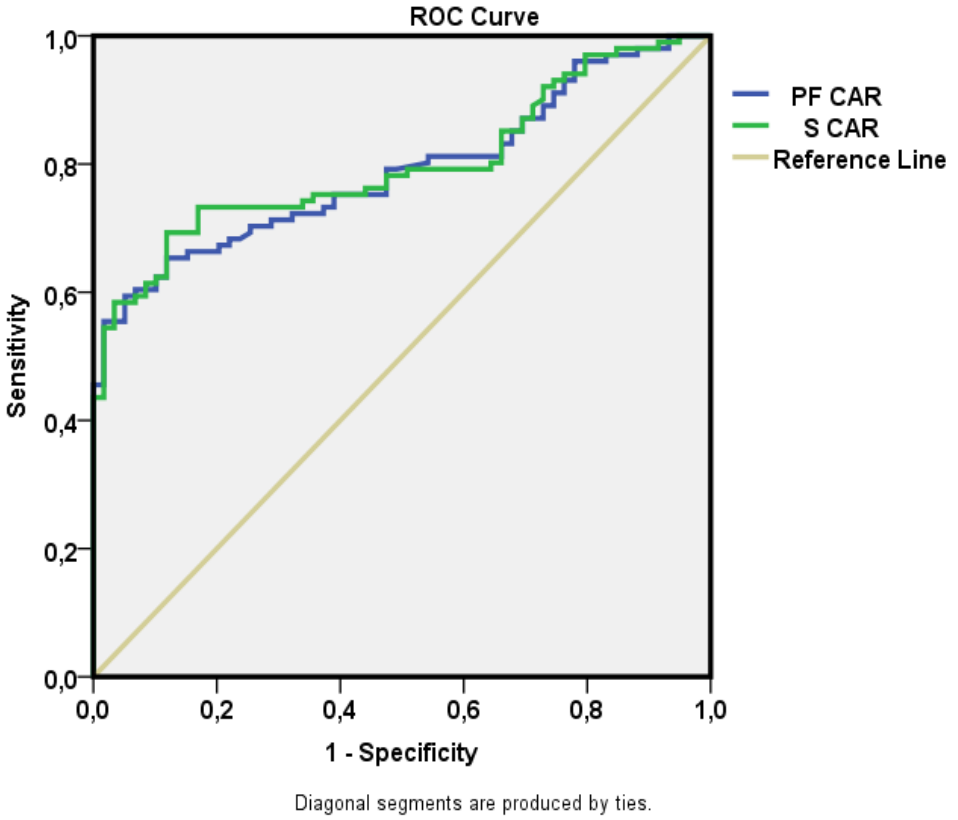

Figure 1. ROC analysis of PF-CAR and S-CAR values in exudate and transudate separation

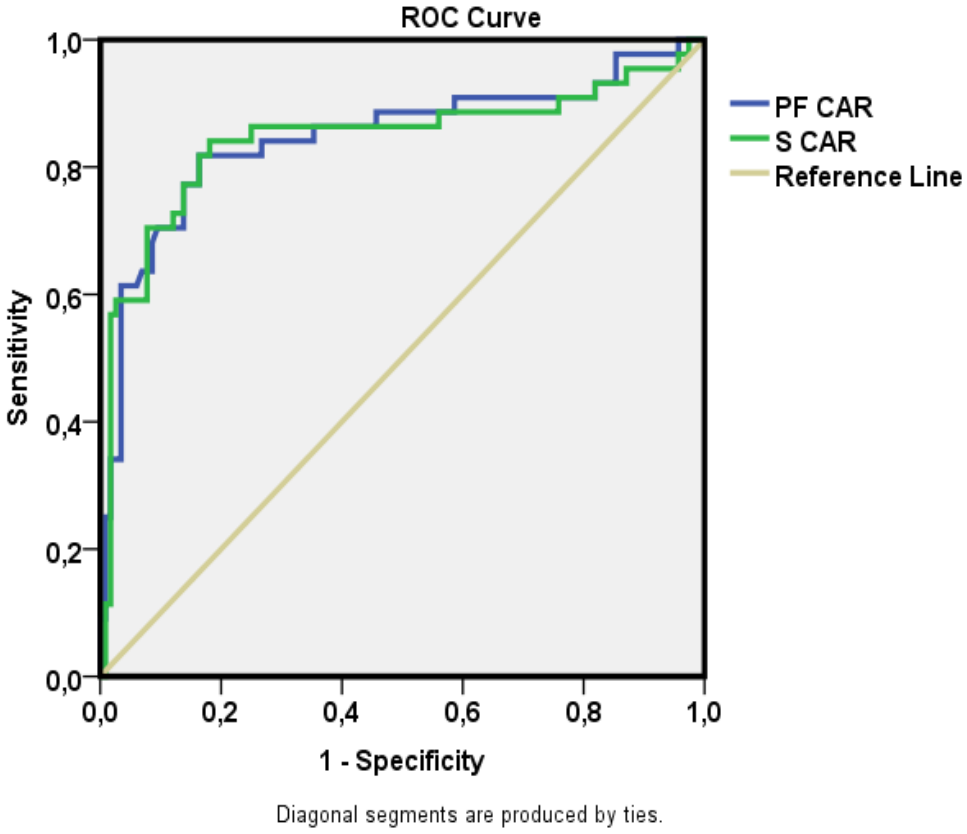

Figure 2. ROC analysis of PF-CAR and S-CAR values in differentiating infectious and non-infectious pleural effusion.