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ORIGINAL ARTICLE

The evaluation of the association between the prevalence and patterns of computed tomography findings of cryptogenic organizing pneumonia, and neutrophil/lymphocyte and platelet/lymphocyte ratios

Zeynep Keskin[1] · Mihrican Yesildag[2]

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Abstract
Background Although rarely seen, organizing pneumonia (OP) is a quite characteristic clinicopathological picture among lung diseases.
Purpose Here, we aimed to investigate the relationship between neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios (PLR), among the parameters of complete blood count, and the patterns and severity of involvements of cryptogenic organizing pneumonia (COP) in thorax computed tomography (CT).
Materials and methods A total of 38 patients diagnosed as COP in our hospital between April 2011–February 2020 were included in the study. The patients' data were obtained and evaluated retrospectively from the hospital automation system. On CT images, the lobes involved, lesions, locations, focal or multifocal involvements, and patterns of the lungs were evaluated. Whether there was a correlation between CT scores, and NLR and PLR findings was also evaluated.
Results NLR was found significantly higher in those with Grade-2 severity scale than that in those with Grade-1 involvement in the Kruskal–Wallis test ($p=0.004$). NLR and C-reactive protein (CRP) values were significantly higher among patients with grade-3 involvement of severity scale than those having grade-1 involvement ($p=0.005$, $p=0.007$).
Conclusions In our study, NLR was evaluated as an appropriate parameter in correlation with the severity and prevalence of CT involvement in determining the disease severity in COP patients, and no significant association was found between the disease severity and PLR. Further studies including larger populations and more clinical evaluation parameters are needed to elucidate the entity.

Keywords Cryptogenic organizing pneumonia · Neutrophil-to-lymphocyte ratio · Platelet-to-lymphocyte ratio · Thorax computed tomography

Introduction

Although seen rarely, organizing pneumonia (OP) is of a very characteristic clinicopathological picture among lung diseases. If the etiological factor leading to OP is unknown, the condition is called cryptogenic organizing pneumonia (COP). On the other hand, if it occurs due to such reasons as infectious diseases, collagen vascular diseases, radiation, and drug therapy, OP is called secondary OP. To consider a case as COP, all reasons leading to secondary OP should be ruled out [1]. OP is diagnosed histopathologically by observing the buds of granulation tissue, also called Masson bodies, consisting of exudative materials, such as connective tissue components, fibrin, and fibroblasts in the alveolar ducts and alveoli [2]. OP also typically affects both genders in 60 years of age at an equal rate and usually presents with a relatively short subacute course (less than 3 months). Patients with OP may suffer from varying degrees of flu-like symptoms, dry cough, and dyspnea [3]. OP is also seen

✉ Zeynep Keskin
zkeskin@ymail.com

Mihrican Yesildag
mihricanysd@hotmail.com

1 Department of Radiology, Konya City Hospital, University of Health Sciences, Konya, Turkey

2 Department of Chest Diseases, Meram State Hospital, Konya, Turkey

as the nonspecific findings on radiography, and although usually observed as irregular bilateral alveolar patches, and recurrent and displaced consolidation areas, such findings are witnessed in different patterns and prevalence in the lungs. The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are both inexpensive and easily calculable indexes correlated with the prognosis of systemic inflammatory diseases. NLR and PLR have been discovered to be beneficial particularly in inflammatory and cardiovascular diseases, and cancers [4–7]. In the present study, we aimed to investigate the relationship between NLR and PLR as complete blood count parameters, and the patterns and severity of involvement in thorax computed tomography (CT) displayed by COP.

Materials and methods

Study population

To perform the present study, approval was received from the ethics committee, and the committee waived the need for consent from the participants due to the retrospective nature of the study. The study participants were composed of 38 patients diagnosed with OP in our hospitals between April 2011 and February 2020. The average age rate of the patients was 63 ± 12.28 years (ranging between 23 and 87 years of age). Of 38 participants, 12 and 26 patients were detected to be female and male, respectively.

Laboratory findings

The patients diagnosed with OP histopathologically with no secondary disorder were determined by scanning the hospital automation system, and the laboratory readings of the patients were investigated in detail. The values of C-reactive protein (CRP) (mg/dL), sedimentation (ESR) (mm/h) were obtained through biochemical analyses. Through the hemogram analyses, the counts of neutrophil (K/μL), lymphocyte (K/μL), thrombocyte (K/μL), eosinophil (K/μL), and the value of mean platelet volume (MPV) (fL) were obtained. CT and laboratory findings of the patients at the time of first admission were used in the study.

Additionally, while the value of NLR was calculated by dividing the number of neutrophils by the number of lymphocytes in peripheral blood samples, the value of PLR was determined by dividing the number of platelets by the number of lymphocytes. One score obtained from each patient only during one visit was included in the criteria, and whether there was a correlation between the CT score and the specified parameters was evaluated.

Evaluation of image analyses of thorax computed tomography scores

The first thorax CT images of the patients performed on admission were evaluated by the radiologist having no information over the clinical data. All images were stored in the digital imaging and communications in medicine (DICOM) format and are available in our hospital's picture archiving and communication system (PACS). To define the severity and prevalence of COVID-19 pneumonia more clearly, a scoring system of CT severity score (CT-SS) was developed, and this scoring system was utilized in investigating OP in our study. In this system, the involvement rate of the lobes of the lungs is defined semiquantitatively. Anatomically, both lungs are composed of five lobes and 18 segments. To achieve the standardization and maintain the symmetry, the evaluations were performed as if there were 20 lobes; so, while the upper lobe apicoposterior segment of the left lung was divided as apical and posterior segments, the lower lobe anteromedial–basal segment of the left lung was divided into anterior and basal segments. The lung opacities in all of the 20 lung regions were subjectively evaluated on chest CT images using a system attributing scores of 0, 1, and 2 if parenchymal opacification involved 0%, less than 50%, or equal to or more than 50% of each region, respectively. The CT was defined as the sum of the individual scores in the 20 lung segment regions, which may range from 0 to 40 points [8]. On CT images, the involvements of the lobes, the locations of the lesions, and the focal or multifocal involvements of the lungs were evaluated. Based on the evaluations, the patterns of the lesions were categorized as peripheral consolidation (Fig. 1A), nodule and mass (Fig. 1B), reversed halo sign (Fig. 2A), parenchymal bands (Fig. 2B), bronchial wall thickening, and dilatation (Fig. 3A), ground-glass opacity, reticulation (Fig. 3B), perilobular opacity, cavitation, mediastinal lymphadenopathy and pleural effusion (PE).

Statistical analysis

The statistical analyzes were performed using the statistical software of the Statistical Package for Social Sciences (SPSS) for Windows, version 25.0 program (SPSS Inc, Chicago, IL, USA). Numerical variables were expressed as mean ± standard deviation (SD) or number (rate of percentage) in terms of appropriateness. The appropriateness of the variables to normal distribution was examined by visual (histogram and probability graphics) and analytical methods through the Kolmogorov–Smirnov and the Shapiro–Wilk tests.

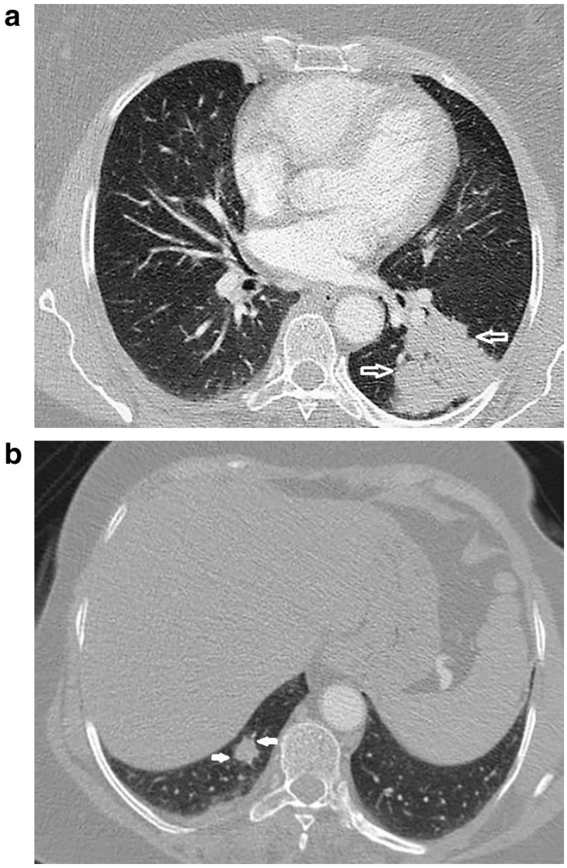

Fig. 1 Computed tomography (CT) scans of transverse thin section (section thickness of 1.0 mm) obtained from a 63-year-old female patient diagnosed with histopathologically organizing pneumonia. **A** Peripheral consolidation area where air bronchograms are observed is seen in the posterobasal segment of the left lower lobe of the left lung (white arrows). **B** Nodular pattern of organizing pneumonia is observed in posterobasal segment of the lower lobe of the right lung (white arrows)

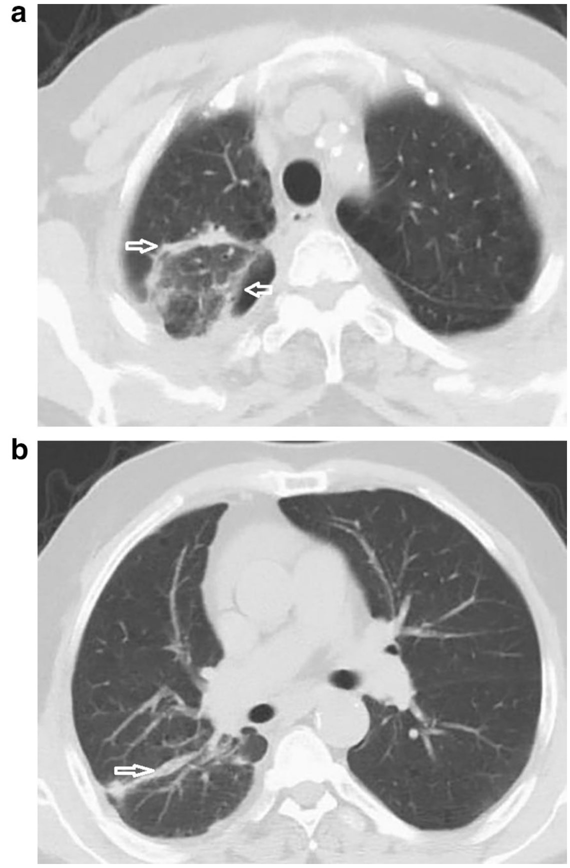

Fig. 2 CT scans of transverse thin-section (section thickness of 1.0 mm) obtained from a 71-year-old male patient who was diagnosed with histopathologically organizing pneumonia. **A** The oval area containing central homogeneous ground-glass opacities and smooth ring of consolidation (reversed halo sign) are seen in the upper lobe of the right lung (white arrows). **B** CT imaging shows a parenchymal band in the superior segment of the lower lobe of the right lung (white arrow)

The distributions within the normal limits were determined as mean and SD values. Since the values of lymphocyte and mean platelet volume (MPV) were determined to display normal distribution, the student's *t* test was used for the intergroup comparisons to determine whether there was an association between the lymphocyte and MPV values and the parameters including gender, peripheral consolidation, ground-glass opacity, perilobular opacity, reversed halo sign, nodule and mass, bronchial wall thickening and dilatation, reticulation, cavitation, mediastinal lymphadenopathy (LAP), PE, and parenchymal band. Since the rates of age, neutrophil, platelet, eosinophil, CRP, sedimentation, NLR, and PLR showed no normal distribution, the intergroup comparisons were performed using the Mann–Whitney *U* test to evaluate whether there was an association between the rates of age, neutrophil, platelet, eosinophil, CRP, sedimentation, NLR and PLR, and the parameters including gender, peripheral consolidation, ground-glass opacity, perilobular opacity, reversed halo sign, nodule and mass, bronchial wall thickening and dilatation, reticulation, cavitation, mediastinal LAP, PE, and parenchymal band. To determine whether there was the statistical significance between groups in terms of gender, peripheral consolidation, ground-glass opacity, perilobular opacity, reversed halo sign, nodule and mass, bronchial wall thickening and dilatation, reticulation, cavitation, mediastinal LAP, PE, and parenchymal band, the chi-square test was implemented.

However, the Kruskal–Wallis test was used to determine whether there was a significant relationship between age, neutrophil, platelet, eosinophil, CRP, sedimentation, and NLR and PLR values with no normal distribution, and the subtypes of severity and involvement scales. The pairwise comparisons were performed using the Mann–Whitney *U* test and evaluated through the Bonferroni correction. The correlation coefficients (CI) and statistically significant rates

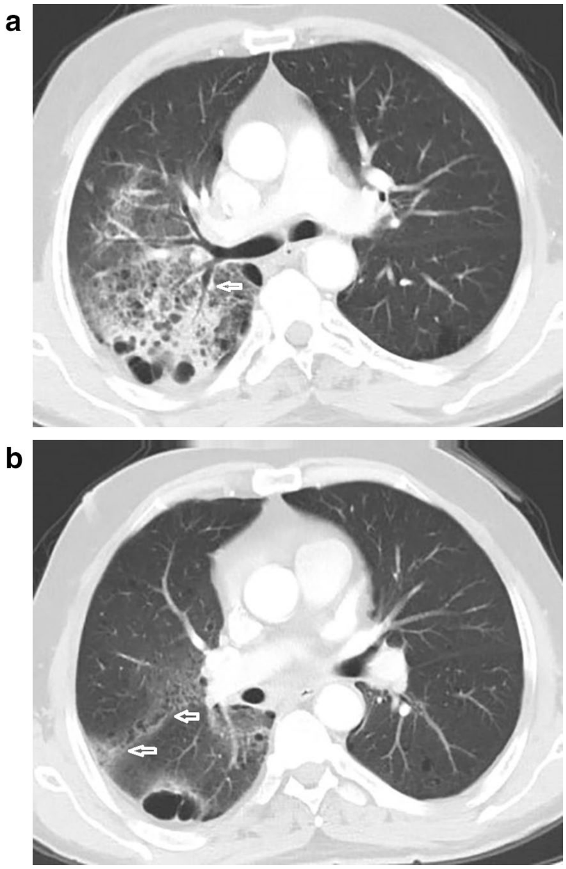

Fig. 3 CT scans of transverse thin-section (section thickness of 1.0 mm) obtained from a 70-year-old male patient who was diagnosed with histopathologically organizing pneumonia. **A** Bronchial wall thickening and dilatation accompanied by the consolidation area is observed in the posterior segment of the upper lobe of the right lung (white arrow). **B** Fine reticular lines accompanied by ground glass densities are observed in the posterior segment of the upper lobe of the right lung (white arrows)

for the variables, at least one of which was not normally distributed or ordinal, were calculated by the Spearman test. For statistical significance, the total type-1 error level was used as 5%, and the values with a p value less than 0.05 were considered statistically significant.

Results

According to Grade severity, the descriptive data in terms of neutrophil, lymphocyte, platelet, MPV, eosinophil, CRP, sedimentation, and NLR and PLR values are shown in Table 1. The upper, lower, and average values of NLR concerning the scores of the severity scale are presented in Fig. 4. The frequencies of the severity and involvement scales are presented in Table 2. According to the patients, the involvement frequencies of the findings in the lungs are also shown in Table 3.

Table 1 Descriptive information according to grade severity

	Minimum				Maximum				Mean				SD (±)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil (K/μL)	2.56	3.77	8.79	12.48	13.56	13.58	14.78	25.25	7.04	10.13	12.01	18.86	2.82	2.85	2.69	9,03
Lymphocyte (K/μL)	0.83	0.67	1.83	1.75	3.74	3.61	2.80	2.33	2.34	2.09	2.62	2.04	0.73	1.02	0.44	0.41
Platelet (K/μL)	54	116	186	515	564	737	713	881	305.45	303.92	465.25	698	105.45	173.96	223.77	258.80
MPV (fL)	7.3	7.01	7	8.9	11.8	12	10.5	9.6	9.39	9.79	8.57	9.25	1.21	1.42	1.45	0.49
Eosinophil (K/μL)	0	0	0.01	0.14	2.3	4.5	0.11	0.34	0.43	0.53	0.06	0.24	0.71	1.26	0.04	0.14
CRP (mg/dL)	3.02	3.14	19.4	125	53.2	44.5	189	159	13.04	18.74	94.97	142	14.14	15.46	71.62	24.04
Sedimentation (mm/h)	2	9	12	44	86	87	78	59	28.9	34.25	33.75	51.5	24.68	23.64	29.98	10.6
NLR	1	2	4	5	5	20	7	14	3.01	7.03	5.31	9.88	1.01	5.38	1.49	6.39
PLR	63	54.6	66.42	294.3	224.7	394.9	358.3	378	133.86	169.96	223.8	336.15	53.59	107.43	131.76	59.18

CRP C-reactive protein, *MPV* mean platelet volume, *NLR* neutrophil-to-lymphocyte ratio), *PLR* platelet-to-lymphocyte ratio, *SD* standard deviation

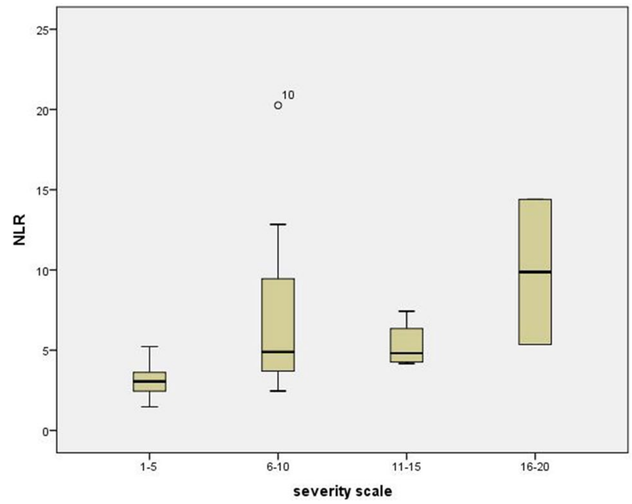

Fig. 4 Upper–lower and mean values of neutrophil-to-lymphocyte ratio (NLR) according to the scores of the severity scale

In the student's *t* test, the lymphocyte values were found to be significantly higher among the men, compared to those in women ($p = 0.049$). The lymphocyte values were also detected to be significantly higher in the patients with perilobular opacity, compared with those in the patients without perilobular opacity ($p = 0.005$). Given the values of MPV, those rates were also observed to be significantly higher in the patients without perilobular opacity than those with perilobular opacity ($p = 0.021$).

In the Mann–Whitney *U* test, the platelet values were found to be significantly higher in the patients with bronchial wall thickening and dilatation than those without ($p = 0.041$). Additionally, the sedimentation rates were also witnessed to be significantly higher in the patients with PE, compared to those without PE ($p = 0.001$). In light of the chi-square test findings, the values of bronchial wall thickening and dilatation, and reticulation were significantly higher in the patients with ground-glass opacity ($p = 0.028$ and $p = 0.026$, respectively). Bronchial wall thickening and dilatation were found to be significantly higher in the patients with nodules and masses ($p = 0.046$). Reticulation was also significantly higher in the patients with bronchial wall thickening and dilatation ($p = 0.037$). In those with reticulation, the parenchymal band was also found to be significantly higher ($p < 0.001$).

In the Kruskal–Wallis test, NLR was found significantly higher in the patients with the grade-2 involvement of the severity scale than those having grade-1 involvement ($p = 0.004$). However, the values of NLR and CRP were also observed to be significantly higher in the patients with the grade-3 involvement of the severity scale than those having grade-1 involvement ($p = 0.005$ and $p = 0.007$, respectively).

Table 2 Frequencies of severity and involvement scales

	Severity scale				Involvement scale						
	Grade-1	Grade-2	Grade-3	Grade-4	Right upper segment	Right lower segment	Right upper and lower segments	Left upper segment	Left lower segment	Left upper and lower segments	Bilateral
Total	20	12	4	2	8	4	4	5	2	2	13

Table 3 Frequencies of lung involvements

	Lung involvements										
	Peripheral consolidation	Ground-glass opacity	Perilobular opacity	Reversed halo sign	Nodule and mass	Bronchial wall thickening and dilatation	Reticulation	Cavitation	Mediastinal LAP	Pleural effusion	Paranchimal band
Yes	31	15	23	3	20	17	22	6	6	8	30
No	7	23	15	35	18	21	16	32	32	30	8

Discussion

COP is considered to arise from the incomplete healing of the inflammatory response that occurs in the alveoli as a result of unknown damage or more rarely, in the distal bronchioles [9]. The incidence rate is similar in both genders, and COP is commonly encountered in average 50–60 years of age [2, 10]. Of our 38 study participants, 12 and 26 cases were women and men, respectively, and compared to the rates in the literature, the incidence was significantly higher among men in our study. Such a gender difference may have been due to the low number of our cases. The average age of our patients was 63 years, as consistent with that in the literature. Although the basic radiological image is usually peripherally located multifocal airspace consolidation, the increasing number of case variation reports draw attention to the significance of CT in the diagnostic process and also the importance of including OP in differential diagnosis lists [11]. As well as displaying many variations in size, such a typical lesion can also vary qualitatively in a wide array from ground-glass opacity to the consolidation including air bronchograms, and is a condition encountered in 90% of the cases. Likewise, as the most common CT pattern, peripheral consolidations were observed in our cases (82%). In previous studies, such diffuse nodular lesions suggesting diffuse bilateral infiltration, solitary focal mass, or metastasis can also be observed less commonly [10, 12]. Radiological appearance can be seen as nodular structures at a rate of 10% [9]. As similar to the findings reported in previous studies, while the CT patterns were observed as parenchymal band (78%), perilobular opacity (60%), reticulation (57%), and nodules and masses ($n = 52$) in our study, other patterns were detected to be less frequent. It is also stated that a small amount of PE, usually bilateral and is more common, is seen in 10–35% of the patients with sufficient immunity [13]. In the study performed by Vasu et al., although PE was present in 60% of the patients with secondary OP, the researchers reported no PE in any of the patients with cryptogenic OP [14]. Contrary to the findings reported by Vasu et al. we determined PE in 21% of our cases albeit the presence of COP in all of our cases. We considered that the coexistence of such patterns as bronchial wall thickening and dilatation, reticulation, parenchymal band, and ground-glass opacity at a significantly higher rate may be associated with the inflammatory and fibrotic processes. To our knowledge, no previous studies have mentioned the frequency of the coexistence of bronchial wall thickening and dilatation, reticulation, parenchymal band, and ground-glass opacity. Although the reverse halo sign is witnessed in approximately 20% of the patients with COP [15], the rate was found as approximately 8% in our study. We consider that finding such a low rate in our study was due to the fact that our cases were diagnosed without any clinical and radiological modalities, and the majority of our cases were suspected to have malignancy.

NLR, PLR, and MPV have been defined as new potential markers to assess the inflammation in a variety of diseases, including oncological, cardiovascular, and cerebrovascular diseases, end-stage renal disease, and inflammatory diseases (e.g., ankylosing spondylitis, ulcerative colitis, appendicitis, and pelvic inflammatory disease) [16–19]. As an important advantage, the fact that NLR, PLR, and MPV can easily be measured via hemogram results without any additional fiscal burden makes them cost-effective, and therefore, the use of NLR, PLR, and MPV is becoming widespread. NLR, one of the systemic inflammation markers, has been accepted to be associated with the prognosis of different cancers [20]. NLR can demonstrate how the balance of neutrophils and lymphocytes is and reflect the immune function of the patients [21, 22]]. To our knowledge, no previous study has investigated whether there is a relationship between the CT patterns and CT involvement severity of COP, and NLR and PLR values. Although there was no significant difference between the rate of NLR and thorax CT patterns of COP in our study, we found that as the area of involvement increases in CT, the rate of NLR also increases significantly. NLR and CRP values were found significantly higher in the patients with the grade-2 and -3 CT involvements of the severity scale than those having grade-1 involvement. However, no significant difference was seen between the patients with grade-4 involvement and others with grade-1, -2, and -3 involvements. We consider that the reason we detected such a finding may have stemmed from the lower number of those with grade-4 involvement ($n = 2$) and not revealing a statistically significant result, meaning that as the involvement rate in CT increases, NLR also increases significantly, while there was no significant difference between PLR and the CT involvement. In other words, the increases in both NLR and rate of CT involvement suggest that a high level of involvement occurs in circulating inflammatory cells. Such an outcome also gives us preliminary information about the prognosis in patients. Our study has also some limitations. First, our study is of a retrospective design and was performed as a single-centered study. We consider that the retrospective design of the study may have limited the clinical evaluation of the presence of inflammation in patients. In this respect, further studies where clinical parameters are also included can contribute to the literature significantly. Additionally, the relatively small number of participants in the patient group and non-homogeneity of radiological CT patterns of the patient group in all patients are other limitations in our study. However, the fact that all diagnoses are histopathologically definitive provides valuable information.

In conclusion, it has been shown in clinical practice that such hemogram parameters as NLR, PLR, and MPV values are cost-effective and easy-to-use, and can be utilized as systemic inflammation markers in different diseases. Those simple biomarkers can be easily incorporated into routine clinical practice. To our knowledge, our study is the first to investigate such biomarkers in COP patients. In our study, NLR was evaluated as an appropriate parameter in correlation with the prevalence and severity of CT involvement in determining the disease severity in COP patients. We consider that studies with larger populations and also including clinical evaluation parameters are needed to elucidate the entity.

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Data availability The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors declare that they have no competing interests.

Informed consent All of the patients gave informed consent. Our study has not been published in another journal or presented at a congress.

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