Med Pregl 2026; LXXIX(3-6): 109-115. Novi Sad: mart-juni.

COMPARISON OF COLLAGEN AND ELASTIC FIBRE DISTRIBUTION IN THE LUNGS OF PATIENTS WITH SARCOIDOSIS AND HYPERSENSITIVITY PNEUMONITIS – A PILOT STUDY

POREĐENJE DISTRIBUCIJE KOLAGENIH I ELASTIČNIH VLAKANA U PLUĆIMA BOLESNIKA SA SARKOIDOZOM I HIPERSENZITIVNIM PNEUMONITISOM – PILOT STUDIJA

Mladen SAVANOVIĆ[1], Nikola GARDIĆ[1,2], Sonja GARDIĆ[1,2], Dejan MILJKOVIĆ[1,2] and Aleksandra LOVRENSKI[1,2]

ORCID NUMBER
Mladen Savanović – 0009-0008-0785-8313
Nikola Gardić – 0000-0002-1360-6103
Sonja Gardić – 0009-0006-0020-1576
Dejan Miljković – 0000-0002-7739-5202
Aleksandra Lovrenski – 0000-0002-5278-6194

University of Novi Sad, Faculty of Medicine Novi Sad[1]
Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica[2]

Original study
Originalni naučni rad
UDK 616.24:616-091.8
https://doi.org/10.2298/MPNS2606109S

Abstract

Introduction. Sarcoidosis and hypersensitivity pneumonitis are common interstitial lung diseases whose histopathological appearances may overlap, particularly when only bronchial biopsy specimens are available. This study aimed to examine differences in the distribution of collagen and elastic fibres between sarcoidosis and hypersensitivity pneumonitis. **Material and Methods.** Thirty-one histopathological slides from patients with sarcoidosis and hypersensitivity pneumonitis were analysed. Samples were obtained by transbronchial or surgical biopsy. Additional histological sections were stained using Masson Trichrome and Orcein methods. Following laboratory processing, representative microphotographs of alveolar tissue were obtained, and software-based image analysis was used to determine the surface areas occupied by collagen and elastic fibres, as well as by epithelium and the remaining interstitium. Clinical characteristics, including age, sex, smoking status, and occupation, were also recorded. **Results.** A higher density and proportion of collagen fibres were observed in hypersensitivity pneumonitis ($p<0.05$). The mean area occupied by collagen fibres was 0.63 ± 0.40 mm^2 in hypersensitivity pneumonitis, compared with 0.35 ± 0.47 mm^2 in sarcoidosis. The collagen proportion was 48.79% in hypersensitivity pneumonitis and 32.01% in the sarcoidosis group. No statistically significant difference in the density or proportion of elastic fibres was observed between the two diseases. Correlation analysis demonstrated a positive association between collagen and elastic fibres in sarcoidosis (rho = 0.632; p = 0.024). Sarcoidosis samples showed better preservation of alveolar tissue. **Conclusion.** Collagen fibre distribution is more pronounced in hypersensitivity pneumonitis than in sarcoidosis, whereas no difference in elastic fibre distribution was found between the two conditions.

Key words: Sarcoidosis; Lung; Lung Diseases, Interstitial; Extracellular Matrix; Collagen; Elastic Tissue; Biopsy

Sažetak

Uvod. Sarkoidoza i hipersenzitivni pneumonitis su česte intersticijumske bolesti pluća kod kojih postoje sličnosti u patohistološkim uzorcima pogotovu kada su dostupne isključivo bronhobiopsije. Cilj rada je ispitati razlike u distribuciji kolagenih i elastičnih vlakana kod sarkoidoze i hipersenzitivnog pneumonitisa. **Materijal i metode.** Za potrebe ove studije analiziran je 31 patohistološki preparat bolesnika obolelih od sarkoidoze i hipersenzitivnog pneumonitisa. Uzorci koji su korišćeni dobijeni su transbronhijalnom ili hirurškom biopsijom. Na dodatnim histološkim rezovima preparati su bojeni metodama *Masson Trichrome* i *Orcein*. Nakon laboratorijske obrade na dobijenim preparatima su načinjene reprezentativne mikrofotografije alveolarnog tkiva. Softverskom obradom mikrofotografija dobijene su površina kolagenih/elastičnih vlakana, kao i površine epitela i ostatka intersticijuma, nakon čega je izvršena statistička analiza dobijenih podataka. U statističku analizu bile su uključene i kliničke karakteristike poput starosti, pola, pušačkog statusa i zanimanja. **Rezultati.** Dokazana je veća gustina i udeo kolagenih vlakana u patohistološkim uzorcima bolesnika sa hipersenzitivnim pneumonitisom. Prosečna vrednost površine koju su zauzimala kolagena vlakna kod hipersenzitivnog pneumonitisa iznosila je $0,63 \pm 0,40$ mm^2, dok je kod sarkoidoze iznosila $0,35 \pm 0,47$ mm^2. Udeo kolagena kod hipersenzitivnog pneumonitisa iznosio je 48,79%, dok je kod sarkoidoze iznosio 32,01%. Gustina i udeo elastičnih vlakana nisu pokazali statistički značajne razlike između ova dva oboljenja. Korelacionom analizom utvrđena je proporcionalnost u distribuciji kolagenih i elastičnih vlakana kod sarkoidoze ($p < 0,05$). Takođe, primećena je bolja očuvanost alveolarnog tkiva na uzorcima sa sarkoidozom. **Zaključak.** Distribucija kolagenih vlakana u hipersenzitivnom pneumonitisu je značajnije izražena u odnosu na sarkoidozu. Razlike u distribuciji elastičnih vlakana nisu nađene.

Ključne reči: sarkoidoza; pluća; intersticijalna plućna bolest; ekstracelularni matriks; kolagen; elastično tkivo; biopsija

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology, the diagnosis of which remains somewhat arbitrary, non-standardised, and often unreliable [1,2]. The principal histopathological feature indicative of sarcoidosis is the presence of aseptic, typically non-caseating granulomas, often distributed lymphatically along the bronchovascular bundles of the pulmonary tree [1,3].

Hypersensitivity pneumonitis (HP) is defined as "an inflammatory and/or fibrotic disease affecting

✉ Corresponding author: Nikola Gardić, E-mail: nikola.gardic@mf.uns.ac.rs

Abbreviations

HP	– hypersensitivity pneumonitis
MGCs	– multinucleated giant cells
APCs	– antigen-presenting cells
HP group	– hypersensitivity pneumonitis – group
S group	– sarcoidosis - group
SB	– surgical biopsy
ACE	– angiotensin-converting enzyme
sIL	– 2R Soluble interleukin-2 receptor

the lung parenchyma and small airways, typically resulting from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals" [4]. Histopathological changes in HP are characterised by a triad comprising cellular bronchiolitis, interstitial pneumonia, and poorly formed non-necrotising granulomas [5–7].

From a differential diagnostic perspective, HP is often confused with sarcoidosis in the absence of specific histopathological features [2]. Nonetheless, specific differences can help distinguish the two entities: compared with sarcoidosis, granulomas in HP are smaller, poorly formed, less well-circumscribed, centred on the airways, and more commonly associated with multinucleated giant cells [8].

Sarcoidosis-associated pulmonary fibrosis results from fibroblast activation and proliferation, leading to increased collagen synthesis and deposition in the context of prolonged, chronic granulomatous inflammation [9]. A more prominent presence of collagen and fibroblasts at the periphery of the granuloma indicates that fibrosis in sarcoidosis begins peripherally before extending towards its central regions [9,10].

The structure of a sarcoid granuloma comprises a core containing aggregates of macrophages and epithelioid cells, along with a smaller number of multinucleated giant cells (MGCs), and an outer rim composed predominantly of T-lymphocytes with a minor proportion of B-lymphocytes [11]. Sarcoid granuloma formation begins with the phagocytosis of an antigen by monocytes, which subsequently differentiate into antigen-presenting cells (APCs) – specifically, macrophages and/or dendritic cells [11]. The antigen is then presented to T-lymphocytes by APCs, which accumulate and differentiate into epithelioid cells [11]. These cells then organise into cellular clusters to form an immature granuloma, within which inflammatory signals drive the fusion of macrophages and monocytes/dendritic cells, ultimately resulting in the formation of MGCs [11,12]. In most patients with sarcoidosis, granulomas regress spontaneously within a few years; in a significant proportion of patients, however, the disease instead becomes chronic and progressive, characterised by persistent granulomas and the formation of fibrotic lesions [12].

Granulomas and isolated MGCs are also present in most cases of acute/subacute HP and may contain cholesterol crystals or Schaumann bodies [4,7]. Schaumann bodies are a significant histopathological finding in the differential diagnosis of HP, as they can occur in any persistent granuloma, whereas in granulomatous infections they are rare or absent [4]. According to Churg, these structures also occur considerably more frequently in HP than in sarcoidosis [4]. Granulomas in HP are frequently described as poorly defined, reflecting the absence of fine concentric rings of fibrosis characteristic of sarcoid granulomas [4,8].

According to several studies [5,11,12], the presence of poorly formed granulomas in the acute and subacute forms of HP, alongside well-formed granulomas in sarcoidosis, is a characteristic feature distinguishing biopsy samples from these two diseases. Although granuloma morphology and distribution are traditionally regarded as important diagnostic features, they are not always clearly distinct, and considerable overlap may occur between sarcoidosis and hypersensitivity pneumonitis [2]. The identification of new markers, such as the specific distribution of collagen and elastic fibres, could contribute to more precise histopathological diagnosis, which in turn has implications for selecting the appropriate therapeutic approach.

Material and Methods

This retrospective study was conducted following approval by the institutional Scientific and Ethics Committee (Decision Nos. 46-2/8, 43-1/8, and 91/4, dated January 22, 2026). A total of 31 histopathological lung biopsies retrieved from the archives were analysed. Specimens were divided into two groups: 18 specimens from patients with hypersensitivity pneumonitis (HP group), and 13 from patients with sarcoidosis (S group).

Histopathological Tissue Preparation

The analysis included specimens obtained via transbronchial and surgical biopsy, with histologic and clinical confirmation of sarcoidosis or hypersensitivity pneumonitis.

Additional histological sections were stained using Masson's trichrome and Orcein methods, both performed according to previously validated laboratory protocols.

The Orcein solution was prepared by dissolving 0.1 g of Orcein in 100 mL of 70% ethanol, adding 1.35 mL of hydrochloric acid and 0.65 mL of distilled water. Slides were first rinsed in distilled water, then incubated in the Orcein solution for 60 minutes. Fol-

lowing staining, they were rinsed in 70% ethanol and running tap water. Counterstaining was performed using Hematoxylin for two minutes, after which the slides were rinsed again with water. Dehydration was performed using a graded series of alcohols (96% and 100% ethanol), followed by final clearing in xylene.

Masson's trichrome staining was performed by first rinsing the slides in distilled water, then incubating them in preheated Bouin's solution at 60 °C. After incubation, the slides were washed under running tap water and stained with Weigert's hematoxylin for five minutes, then rinsed again under running tap water.

Cytoplasmic structures were stained with 0.5% acid fuchsin for five minutes, then briefly rinsed in distilled water and treated with 1% phosphomolybdic acid for four minutes. Following a further rinse in distilled water, the slides were stained with 2.5% aniline blue for five minutes. Finally, dehydration was carried out through a graded series of alcohols (96% and 100% ethanol), followed by clearing in xylene.

Digital Image Analysis

Following laboratory processing, a single microphotograph containing alveolar tissue was captured at 200x magnification for each transbronchial biopsy specimen; for surgical biopsy (SB) specimens, three randomly selected microphotographs were captured at 200x magnification. Images were processed using QuPath software, version 0.7.0 (https://qupath.github.io/). Using segmentation and machine-learning methods, the software was trained to quantify elastin- and collagen-positive pixels **(Figure 1).** All microphotographs were subsequently analysed using the same principles and identical parameters. Absolute values per unit area were obtained for the fibres under evaluation, the remaining lung parenchyma, and the background. In addition, the proportion of evaluated fibres relative to the remaining lung parenchyma was calculated, with the background excluded from the analysis.

Clinical Characteristics

Patient clinical characteristics were retrieved from the Institute's information system, which recorded smoking status, occupation, biopsy specimen, sampling method, age, and sex.

Statistical Analysis

Statistical analysis was performed using JASP software, version 0.95.4.0 (https://jasp-stats.org). The normality of the data distribution was assessed using the Shapiro-Wilk test. Nominal variables were compared using the chi-squared test. The Mann-Whitney U test was used to compare non-normally distributed variables, and the Student's t-test was used for normally distributed variables. Correlations between numerical variables - the density of collagen and elastic fibres, analysed both across the combined groups and separately within each group, as well as fibre density across the total sample in relation to age - were assessed using Spearman's correlation coefficient. To evaluate effect size for the Mann-Whitney U test, the rank-biserial correlation coefficient was used, with absolute values greater than 0.5 indicating a large effect size; for the Student's t-test, Cohen's d was used to estimate effect size. A p-value of <0.05 was considered statistically significant.

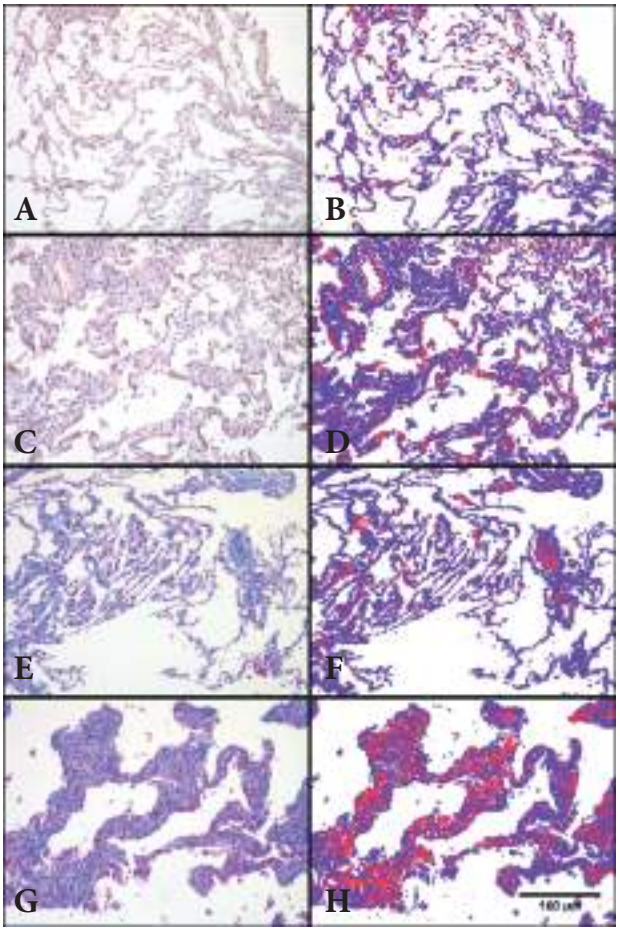
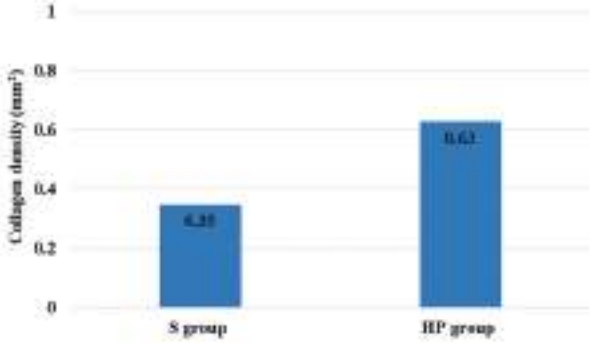


Figure 1. Display of segmentation and the result of pixel classification training for the purpose of quantifying the examined fibers; A and B – S group, Orcein, 200x; C and D – HP group, Orcein, 200x; E and F – S group, Masson's trichrome, 200x; G and H – HP group, Masson's trichrome, 200x.

Results

The mean age of patients in the S group was 49.15 years, compared with 56.77 years in the HP group; This difference was not statistically significant (t = 1.632; p = 0.113). Regarding sex distribution, a slightly higher proportion of females was observed in the



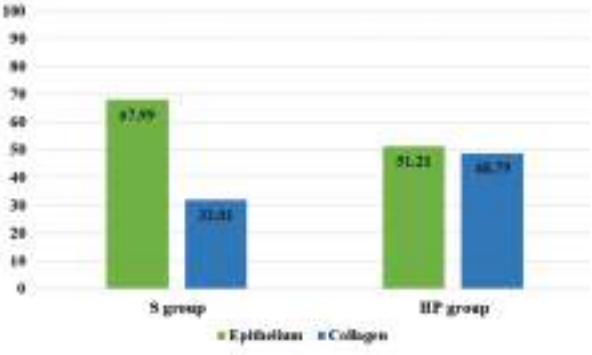
Graph 1. Collagen density across the study groups (U = 180.000; p = 0.018; rank-biserial = -0.539, 95% CI [-0.77, -0.182].

HP group. In contrast, male patients predominated in the S group, although this difference was not statistically significant (χ^2 = 1.454, p = 0.228). With respect to smoking status, 61.54% of participants in the S group were current or former smokers, compared with 38.89% in the HP group; conversely, non-smokers comprised 38.46% of the S group and 61.11% of the HP group**.** No statistically significant association was observed between disease group and smoking status (χ^2 = 1.551, p = 0.213).

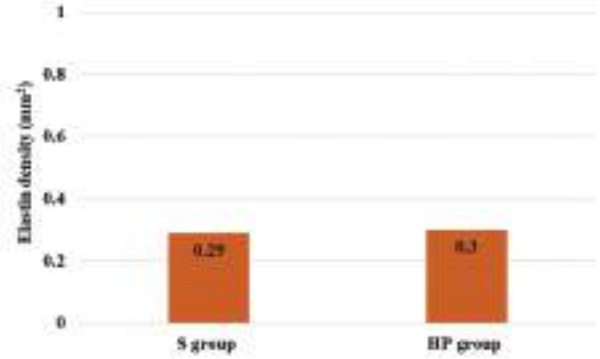
The most prevalent occupations were retirees (12.90%), homemakers (9.68%), and farmers (9.68%). Other occupations – including auto mechanic, economist, electrician, pharmacy technician, manual labourer, physiotherapist, hairdresser, tailor, nurse, painter, police officer, baker, security officer, salesperson, teacher, driver, and craftsman - were represented by only one or two patients, reflecting a heterogeneous distribution.

Bronchobiopsies and transbronchial biopsies accounted for a significantly higher proportion of the specimens (74.19%) than surgical biopsies (25.81%).

Analysis of collagen distribution revealed statistically significant differences between the groups. In terms of density, collagen was significantly more



Graph 2. Collagen-to-lung ratio between groups (U = 177.000, p = 0.016; rank-biserial correlation = -0.513)



Graph 3. Elastin density across the study groups (U = 133.000; p = 0.540; rank-biserial correlation = -0.137, 95% CI [-0.505, 0.274]).

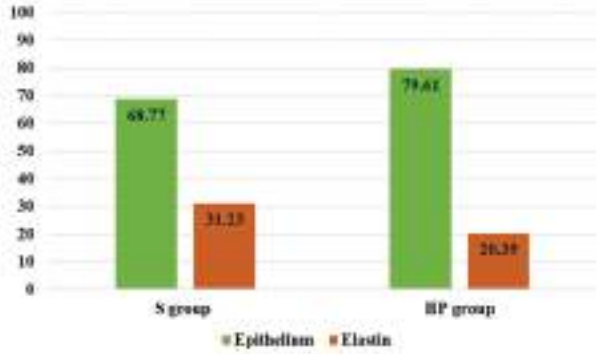
abundant in the HP group **(Figure 1, Graph 1).** The mean area occupied by collagen fibres was 0.63 ± 0.40 mm² in the HP group, compared with 0.35 ± 0.47 mm² in the S group (U = 180.000; p = 0.018; Rank biserial = -0.539, 95% CI [-0.77, -0.182].

Similar results were obtained for the proportion of collagen relative to the remaining tissue. In the HP group, collagen accounted for an average proportion of 48.79% **(Graph 2),** compared with a significantly lower average of 32.01% in the S group (U = 177.000, p = 0.016; rank-biserial correlation = -0.513).

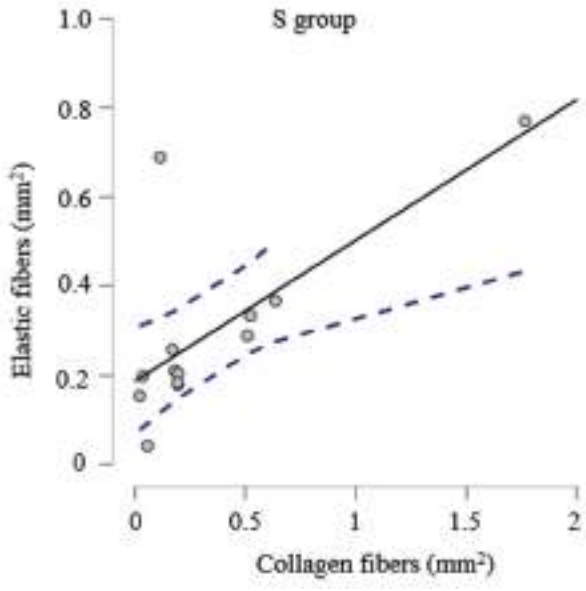
Unlike collagen, the distribution of elastic fibres showed no statistically significant differences between the groups **(Graph 3)**. The mean area occupied by elastic fibres was 0.3 ± 0.15 mm² in the HP group, compared with 0.29 ± 0.21 mm² in the S group (U = 133.000; p = 0.540; rank-biserial correlation = -0.137, 95% CI [-0.505, 0.274]).

The mean elastin content was 20.39% in the HP group and 31.23% in the S group **(Graph 4)**; this difference was not statistically significant (U = 106.000, p = 0.678).

Correlation analysis across the total sample revealed no statistically significant association between the density of collagen and elastic fibres when the two



Graph 4. Elastin-to-lung ratio between groups (U = 106.000, p = 0.678)



Graph 5. Correlation between collagen and elastic fiber density of S group (ρ = 0.632; p = 0.024; effect size [z] = 0.745)

study groups were pooled (ρ = 0.303; p = 0.098; effect size [*z*] = 0.313). In the S group, a statistically significant, strong positive correlation was observed between collagen and elastic fibre density (ρ = 0.632; p = 0.024; effect size [*z*] = 0.745, **Graph 5**). By contrast, no statistically significant correlation was found between collagen and elastic fibre density within the HP group (ρ = -0.108; p = 0.668; effect size [*z*] = -0.109). Within the HP group, there was also no statistically significant difference in collagen area (U = 55.000; p = 0.203) or elastin area (U = 55.000; p = 0.203) between the fibrotic and non-fibrotic forms of the disease. Correlation analysis further showed no statistically significant association between patient age and the density of either collagen (rho = -0.048; p = 0.797) or elastic fibres (rho = 0.140; p = 0.453) across the entire study sample.

Discussion

In the present study, analysis of collagen and elastic fibre distribution revealed a higher density and proportion of collagen fibres in specimens from patients with hypersensitivity pneumonitis than in those with sarcoidosis. Previous studies indicate that collagen fibre deposition and granuloma formation occur in both HP [4,6] and sarcoidosis [9,12], supporting the existence of potential histopathological overlap between the two conditions. Although granulomas in HP are typically smaller, poorly formed, and ill-defined [2,8] - in contrast to sarcoidosis, which predominantly features well-formed granulomas [11,12] - the development of diffuse fibrotic foci interspersed with areas of granulomatous inflammation in HP can mimic the histopathological appearance of sarcoidosis, thereby complicating precise diagnosis. Particularly in such borderline cases, the findings of this study may aid differential diagnosis by demonstrating that HP is characterised by a significantly higher density and proportion of collagen fibres than sarcoidosis. Given the demonstrably higher collagen density and proportion in the specimens analysed, quantitative measurements of the epithelial and interstitial areas suggest that pulmonary parenchymal remodelling is more pronounced in hypersensitivity pneumonitis than in sarcoidosis.

The analysis of elastic fibre distribution, by contrast, found no differences in density or proportion between the two conditions, suggesting that this marker is unlikely to be useful in differential diagnosis. Unlike collagen, the relatively stable distribution of elastic fibres suggests that more pronounced collagen deposition is the principal factor underlying interstitial remodelling. In principle, a more aggressive clinical course, with frequent acute exacerbations of HP, might be expected to cause destruction of elastic fibres and a corresponding reduction in their density; however, the results of this study did not support this, as elastin distribution did not differ from that observed in sarcoidosis. The lower collagen proportion observed in sarcoidosis in this study is consistent with the histological finding of preserved alveolar tissue. Indeed, histological examination of patients with sarcoidosis revealed relative preservation of alveolar tissue, even in areas with granulomas. In the sarcoidosis group, the correlation analysis further indicated that the deposition of connective fibres (collagen and elastic) occurs proportionally. In contrast, in the hypersensitivity pneumonitis group, that process appears asymmetrical, owing to substantially more pronounced collagen deposition. Taken together with previous studies [10,13,14] indicating that fibrosis in sarcoidosis begins at the periphery of the granuloma – reflecting an increased presence of fibroblasts and collagen fibres there - before spreading towards the centre, this specific morphological pattern, together with preservation of the surrounding alveolar tissue, provides clear support to a diagnosis of sarcoidosis and may considerably ease histopathological differentiation.

Analyses of clinical characteristics, including smoking status and occupation, as well as age and sex, revealed no significant differences between the groups.

HP can be divided into two forms: a non-fibrotic, acute/subacute (inflammatory) form, and a chronic (fibrotic) form [6]. Fibrotic HP is characterised by patchy fibrosis with a subpleural and paraseptal dis-

tribution, fibroblastic foci, honeycombing, and diffuse collagen fibrosis; the predominant involvement of the centrilobular and peribronchial regions by fibrosis helps to distinguish HP from other forms of interstitial pneumonia [6]. Although granulomas and multinucleated giant cells occur less frequently in chronic HP, they remain a significant histopathological finding and, unlike in the acute or subacute form, where they are typically located only peribronchially, may occur anywhere within the lung parenchyma [4]. The classification of HP into fibrotic and non-fibrotic forms is based on clinicopathological correlation. It may also reflect different stages in disease progression, particularly as lung biopsies are often obtained during the early phases of the disease. In our cohort, no statistically significant differences were observed in the density or proportion of collagen or elastic fibres between the fibrotic and non-fibrotic HP subgroups. These findings suggest that the inclusion of patients with fibrotic HP did not substantially influence the overall results and that the greater collagen fibre content observed in the HP group, relative to the sarcoidosis group, cannot be attributed solely to the presence of fibrotic HP cases.

In clinical practice, a wide array of diagnostic modalities is available for diagnosing sarcoidosis. Alongside clinical presentation, radiographic imaging, and bronchoalveolar lavage, serum biomarkers are also used, with angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) levels being the most frequently determined [15]. According to previous studies [15,16], measurement of ACE and sIL-2R levels is not recommended for the initial evaluation or diagnosis of sarcoidosis owing to insufficient sensitivity and specificity.

Given the limitations of serum markers in confirming a diagnosis of sarcoidosis and in cases lacking clear and specific clinical features, the final diagnosis often depends on biopsy findings. In this context, the results of this study may primarily assist in the histopathological differentiation of sarcoidosis from hypersensitivity pneumonitis and, potentially, from other diseases, based on the histopathological characteristics reported here.

A similarly wide range of diagnostic modalities is available for hypersensitivity pneumonitis [16]. These include the determination of specific IgG antibodies reactive to predefined antigens, as well as specific inhalation challenges involving controlled, metered exposure to such antigens, both of which contribute to an accurate diagnosis; however, their clinical use is not routine, and they carry certain limitations [17,18]. Consequently, despite the broad range of diagnostic methods available, including highly specific tests, histopathological evaluation remains essential for assessing and confirming this disease in a subset of cases. Based on the findings of the present study, higher collagen density and proportion can be added to the diagnostic features favouring HP over sarcoidosis in the differential diagnosis and, combined with the future identification of additional biomarkers, may help to differentiate HP and sarcoidosis from other interstitial lung diseases.

Conclusion

Analysis of baseline clinical characteristics, including smoking status, occupation, age, and sex, revealed no statistically significant differences between the study groups. Software-assisted image analysis and statistical evaluation demonstrated higher collagen fibre density and proportion in hypersensitivity pneumonitis specimens than in those from patients with sarcoidosis. In contrast, no significant differences were observed in the density or proportion of elastic fibres between the two conditions. Correlation analysis further showed that collagen and elastic fibre deposition progressed proportionally in sarcoidosis, whereas this relationship was not observed in hypersensitivity pneumonitis.

References

1. Popević S, Bukurović Sudić E, Uskoković Stefanović Ž, Dudvarski Ilić A, Stjepanović MI, Mihailović Vučinić V. Modern bronhoscopic diagnosis of sarcoidosis. Med Pregl. 2013;66(1):17-21.

2. Judson MA. Granulomatous sarcoidosis mimics. Front Med (Lausanne). 2021;8:680989.

3. Bonham CA, Strek ME, Patterson KC. From granuloma to fibrosis: sarcoidosis associated pulmonary fibrosis. Curr Opin Pulm Med. 2016;22(5):484-91.

4. Churg A. Hypersensitivity pneumonitis: new concepts and classifications. Mod Pathol. 2022;35(Suppl 1):15-27.

5. Castonguay MC, Ryu JH, Yi ES, Tazelaar HD. Granulomas and giant cells in hypersensitivity pneumonitis. Hum Pathol. 2015;46(4):607-13.

6. Varone F, Iovene B, Sgalla G, Cavello M, Calabrese A, Larici AR, et al. Fibrotic hypersensitivity pneumonitis: diagnosis and managment. Lung. 2020;198(3):429-40.

7. Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol. 1988;12(7):514-8.

8. Kawanami O, Basset F, Barrios R, Lacronique JG, Ferrans VJ, Crystal RG. Hypersensitivity pneumonitis in man. Light- and electron-microscopic studies of 18 lung biopsies. Am J Pathol. 1983;110(3):275-89.

9. Patterson KC, Hogarth K, Husain AN, Sperling AI, Niewold TB. The clinical and immunologic features of pulmonary fibrosis in sarcoidosis. Transl Res. 2012;160(5):321-31.

10. Asif H, Ribeiro Neto M, Culver D. Pulmonary fibrosis in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2023;40(3): e2023027.

11. Sakthivel P, Bruder D. Mechanism of granuloma formation in sarcoidosis. Curr Opin Hematol. 2017;24(1):59-65.

12. Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary sarcoidosis. Front Immunol. 2013;4:437.

13. Zhang C, Chan KM, Schmidt LA, Myers JL. Histopathology of explanted lungs from patients with a diagnosis of pulmonary sarcoidosis. Chest. 2016;149(2):499-507.

14. Tana C, Donatiello I, Caputo A, Tana M, Naccarelli T, Mantini C, et al. Clinical features, histopathology and differential diagnosis of sarcoidosis. Cells. 2021;11(1):59.

Rad je primljen 3. VI 2026.
Recenziran 11. VI 2026.
Prihvaćen za štampu 15. VI 2026.
BIBLID.0025-8105:(2026):LXXIX:3-6:109-115.

15. Li Y, Xu G. Diagnostic value of imaging and serological biomarkers in pulmonary sarcoidosis. Adv Respir Med. 2024;92 (3):190-201.

16. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis. An Official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020;201(8):e26-51.

17. Barnes H, Troy L, Lee CT, Sperling A, Strek M, Glaspole I. Hypersensitivity pneumonitis: current concepts in pathogenesis, diagnosis, and treatment. Allergy. 2022;77(2):442-53.

18. Millerick-May ML, Mulks MH, Gerlach J, Flaherty KR, Schmidt SL, Martinez FJ, et al. Hypersensitivity pneumonitis and antigen identification - an alternate approach. Respir Med. 2016;112:97-105.