VOLUME LXXVI, ISSUE 5 PART I, MAY 2023

ISSN 0043-5147
E-ISSN 2719-342X

Wiadomości Lekarskie
Medical Advances

Official journal of Polish Medical Association has been published since 1928

INDEXED IN PUBMED/MEDLINE, SCOPUS, EMBASE, EBSCO, INDEX COPERNICUS,
POLISH MINISTRY OF EDUCATION AND SCIENCE, POLISH MEDICAL BIBLIOGRAPHY

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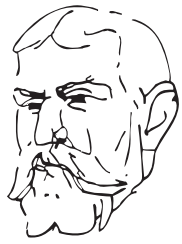

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The journal Wiadomości Lekarskie is cofinanced under Contract No.RCN/SN/0714/2021/1 by the funds of the Minister of Education and Science

Wiadomości Lekarskie
Medical Advances

Distribution and Subscriptions:
Bartosz Guterman prenumerata@wydawnictwo-aluna.pl
Graphic design / production:
Grzegorz Sztank www.red-studio.eu

Publisher:
ALUNA Publishing House
ul. Przesmyckiego 29,
05-510 Konstancin – Jeziorna
www.wydawnictwo-aluna.pl
www.wiadomoscilekarskie.pl
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ORIGINAL ARTICLE

MORPHOLOGICAL ASSESSMENT OF THE LUNGS IN POST-COVID-19 SYNDROME: ANALYSIS OF AUTOPSY MATERIAL

DOI: 10.36740/WLek202305120

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ABSTRACT

The aim was to reveal the morphological features of the lungs in post-COVID-19 syndrome.

Materials and methods: The material of the study was autopsy material – fragments of the lung tissue from 96 deceased (59 men and 37 women). During the lifetime, all patients had in anamnesis COVID-19 of varying severity, and after the treatment of this infection, they had various manifestations of respiratory failure until death. The average duration of the post-COVID-19 period was 148.6±9.5 days. Based on the severity of COVID-19 in anamnesis, all cases were divided into three groups. Group 1 included 39 cases with mild COVID-19 in anamnesis. Group 2 included 24 cases with moderate severity of COVID-19 in anamnesis. Group 3 included 33 cases with severe COVID-19 in anamnesis. Histological, histochemical, morphometric and statistical research methods were used.

Results: Morphological features of the lungs in post-COVID-19 syndrome were the presence of pneumosclerosis; focal-diffuse immune cells infiltration; emphysematous and atelectatic changes; degenerative-desquamatic changes in the alveolar epithelium; metaplastic changes of connective tissue; dystrophic calcification; dystrophic, metaplastic and dysplastic changes in the epithelial layer of bronchial tree; hemodynamic disorders. Pneumosclerosis, focal-diffuse immune cells infiltration, alterative changes in the alveolar epithelium, emphysematous and atelectatic changes, hemodynamic disorders increased with an increase the severity of COVID-19. Metaplastic changes of connective tissue, dystrophic calcification, dystrophic, metaplastic and dysplastic changes in epithelial layer of bronchial tree did not depend on the severity of the infection.

Conclusions: The changes identified by the authors help to explain pulmonary manifestations of post-COVID-19 syndrome. They should be the basis for the oncological alertness formation among doctors, the development of rehabilitation and treatment measures for such category of patients.

KEY WORDS: lungs, morphology, autopsy, post-COVID-19 syndrome

Wiad Lek. 2023;76(5 p.1):1030-1037

INTRODUCTION

After the COVID-19 pandemic, doctors of many specialties are now faced with a major global concern – post-COVID-19 syndrome [1]. The post-COVID-19 syndrome, according to some scientists, is the hidden part of a metaphorical iceberg that requires immediate interdisciplinary research [2].

Post-COVID-19 syndrome, according to the World Health Organization, includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of SARS-CoV-2 infection, lasting for at least 2 months and not attributable to alternative diagnoses [3]. Post-COVID-19 syndrome has an official disease status in the International Classification of Diseases (10th revision), where it is designated as a «post-COVID-19 condition» under the code U09.9 [4]. The impact of post-COVID-19 syndrome is enormous for patients, the healthcare system and economic development [5].

The prevalence of post-COVID-19 syndrome has varied across and within many countries: UK – 1.6-71%, Germany – 35-77%, China 49-76%, Africa – 68%, India –22%, Bangladesh – 16-46%, Denmark – 1%, Italy – 5-51%, USA – 16-53%, Norway – 61% [6].

The mechanism of the post-COVID syndrome is a debatable and not fully understood issue. Post-COVID-19 syndrome, according to many scientists, is a complex and multifactorial syndrome involving aberrant immune responses, virus-specific pathophysiological alterations, inflammatory damage in response to the acute infection and mechanisms of viral persistence in certain tissues, SARS-CoV-2 interactions with host microbiome/virome communities, clotting/coagulation issues and dysfunctional brainstem/vagus nerve signaling [7, 8].

Post-COVID-19 symptoms vary in intensity and duration and are not linear or sequential [9]. Post-COVID-19 syndrome may manifest by neurological, respiratory, car-

Table I. Pathological anatomy diagnoses and causes of death in the studied cases.

Pathological anatomy diagnosis	Cause of death	Number of cases	
		Absolute	Relative (%)
Myocardial infarction	Acute cardiac insufficiency	39	40.6
Atherosclerotic cardiosclerosis	Chronic cardiac /cardiopulmonary insufficiency	34	35.4
Cerebral infarction	Dislocation of the brain stem	12	12.5
Deep vein thrombophlebitis of the lower extremities	Thromboembolism of the pulmonary artery	7	7.3
Gangrene of the intestine	Intoxication	4	4.2

diovascular, hematologic, gastrointestinal and other symptoms, but the most common are respiratory disorders [1, 10]. Respiratory disorders include external respiration dysfunction, dyspnea, cough, reduced exercise tolerance, post-COVID-19 interstitial lung disease, pain in the intercostal space, pulmonary hypertension, etc. [1, 11, 12].

In the available literature, we did not find comprehensive morphological studies aimed at identifying the morphofunctional state of the lungs in patients with post-COVID-19 syndrome, which would make it possible to understand the morphological substrate of clinically observed signs of respiratory disorders in this category of patients.

THE AIM

The purpose was to reveal the morphological features of the lungs in post-COVID-19 syndrome.

MATERIALS AND METHODS

The material of the study was autopsy material – fragments of the lung tissue from 96 deceased (59 men and 37 women). Autopsies were performed on the basis of pathoanatomical department of Public nonprofit organization of the Kharkiv District Council «Regional Clinical Hospital» (Ukraine). During the lifetime, all patients had in anamnesis COVID-19 of varying severity, and after the treatment of this infection, they had various manifestations of respiratory failure until death. The average duration of the post-COVID-19 period was 148.6±9.5 days. In all cases, it was found the presence of immunoglobulin G antibodies to SARS-CoV-2 in diagnostic titers.

Based on the severity of COVID-19 in anamnesis, all cases were divided into three groups. Group 1 included 39 cases with mild COVID-19 in anamnesis. Group 2 included 24 cases with moderate severity of COVID-19 in anamnesis. Group 3 included 33 cases with severe COVID-19 in anamnesis.

An analysis of the causes of death and pathological anatomy diagnoses is given in Table I. In most cases the cause of death was acute cardiac or chronic cardiac/cardiopulmonary insufficiency.

Autopsy material was fixed in a 10% solution of neutral buffered formalin according to the generally accepted technique and embedded in paraffin. Serial sections of 3-4 μm thick were made from paraffin blocks. The slides were stained with hematoxylin and eosin, picrofuchsin according to van Gieson, according to Mallory. The slides were studied using an Olympus BX-41 microscope. A morphometric study was carried out using the Olympus DP-soft version 3.1 software.

The obtained digital data were statistically processed, using the Statistica 10.0 program. The average indicators in the groups were compared, using the nonparametric Mann-Whitney U test. Differences were considered significant at $p<0.05$.

RESULTS

Survey microscopy of the slides in all cases revealed pneumosclerosis, characterized by the excessive growth of connective tissue fibers perivascular and directly in the vessels walls of various calibers, around the bronchi and bronchioles or directly in their walls, in the interalveolar septa with its thickening, in the alveoli lumen (Fig. 1).

The results of a morphometric study also indicated sclerotic changes in the lungs. In all groups, in the lungs during morphometric study, the specific volume of the parenchyma, including the system of the bronchial tree and the system of the acini, and the stroma, represented by connective tissue fibers with vessels located between them, were determined (Fig. 2). In the direction from group 1 to group 3, the specific volume of the parenchyma decreased ($p<0.05$), and the specific volume of the stroma increased ($p<0.05$). These changes indicated an increase of pneumosclerosis with an increase of the infection severity.

Among the connective tissue fibers during Mallory staining a decrease in the number of elastic fibers and an increase in the number of collagen fibers in the direction from group 1 to group 3 were revealed, which also indicated about the sclerotic changes. In group 3, in a significant number of fields of vision, elastic fibers were practically not detected.

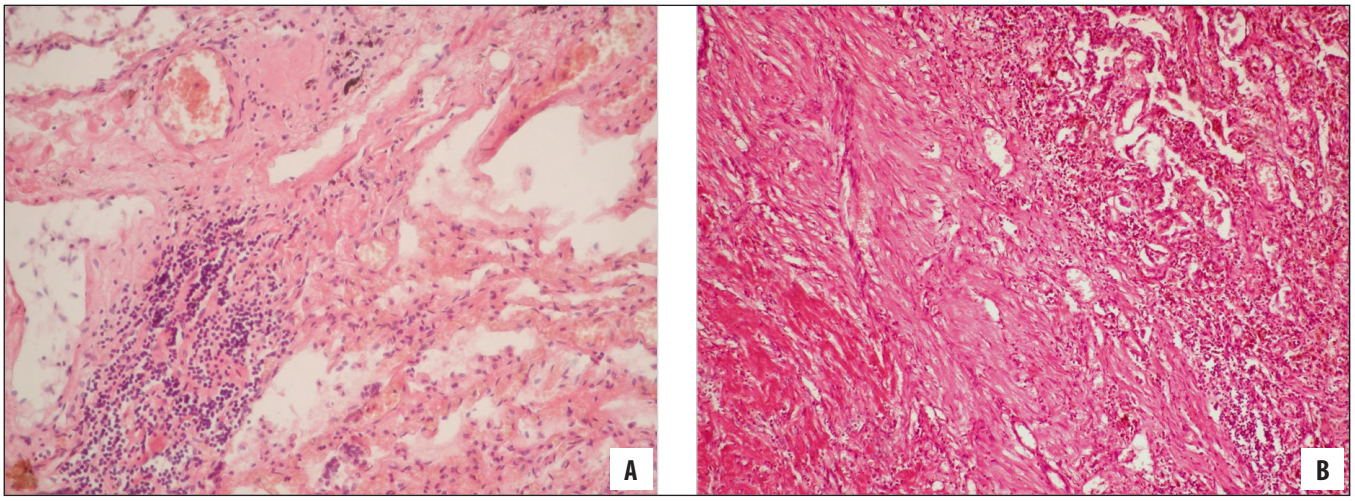

Fig. 1. Sclerotic changes in the lungs in groups 1 (a) and 3 (b). Immune cells infiltration in foci of pneumosclerosis. Stained with hematoxylin and eosin, a) ×200, b) ×100.

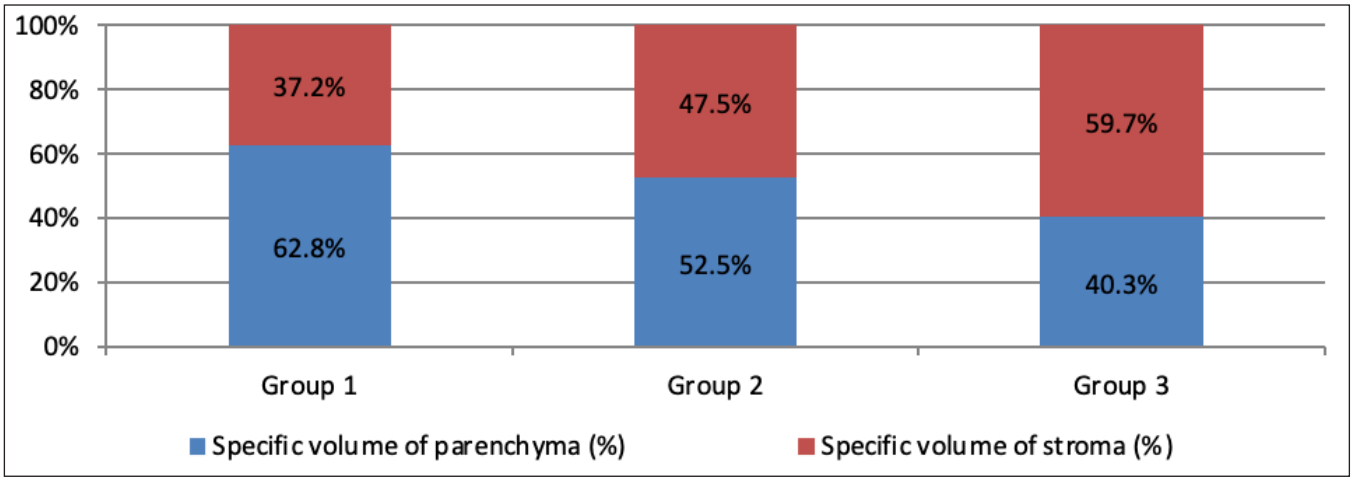

Fig. 2. The average values of the specific volumes of parenchyma and stroma in the lungs in groups 1-3.

In the foci of pneumosclerosis in all groups, focal-diffuse infiltration by immune cells was noted, which increased in the direction from group 1 to group 3 (Fig. 1).

Also, in the areas of pneumosclerosis, metaplastic changes of the connective tissue were detected, characterized by the presence of hyaline cartilage (Fig. 3), bone and adipose tissues (Fig. 4). These changes were identified in group 1 in 8 cases (20.5%), in group 2 – in 6 cases (25%), in group 3 – in 9 cases (27.3%). Comparative analysis did not reveal significant ($p>0.05$) differences between the numbers of cases with this microscopic finding in all groups.

Against the background of the changes described above in the areas of pneumosclerosis, foci with dystrophic calcification were also detected in group 1 in 7 cases (17.9%), in group 2 – in 4 cases (16.7%), in group 3 – in 6 cases (18.2%) (Fig. 5). The severity of dystrophic calcification did not depend on the severity of the infection.

In the deformed bronchial tree, due to sclerotic changes, we noted various general pathological processes in the epithelial layer. In all cases of groups 1-3, dystrophic changes in the epithelium were determined. Also in the epithelial layer in 8 cases (20.5%) of group 1, in 5 cases (20.8%) of group 2 and in 7 cases (21.2%) of group 3 metaplastic and dysplastic changes sometimes with the formation of adenomatous structures were detected (Fig. 6). The severity of the identified changes in the epithelium of the bronchial tree did not depend on the severity of COVID-19.

Microscopic examination of the lungs in all groups revealed focal degenerative-desquamatic changes in the alveolar epithelium, as well as unchanged alveoli, alveoli with ephysematous and atelectatic changes (Fig. 7). Alterative changes in the alveolar epithelium increased with an increase the severity of COVID-19. Morphometry identified that with an increase of the COVID-19 severity, the specific volume of unchanged alveoli (group 1 – (72.5±1.54)%, group 2 – (60.9±2.11)%,

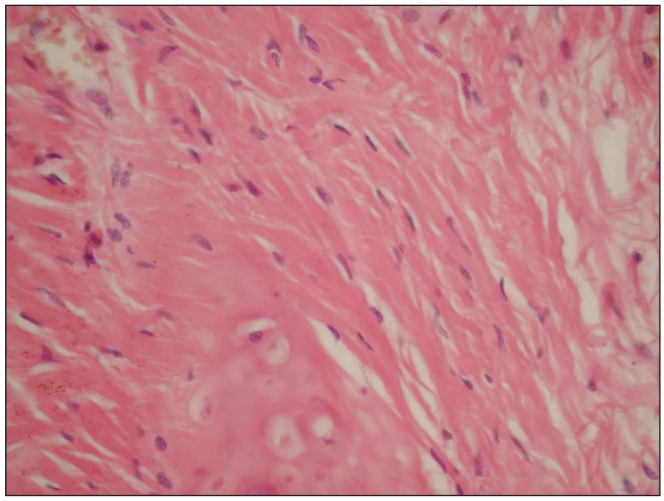

Fig. 3. Hyaline cartilage in the area of pneumosclerosis. Stained with hematoxylin and eosin, ×400.

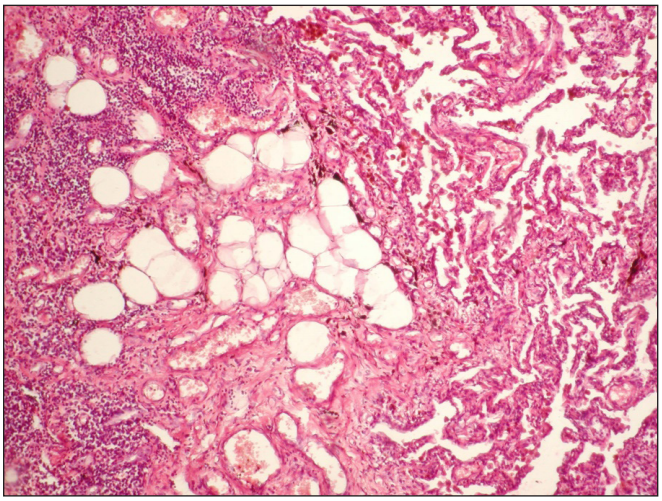

Fig. 4. Adipose tissue in the area of pneumosclerosis. Stained with hematoxylin and eosin, ×100.

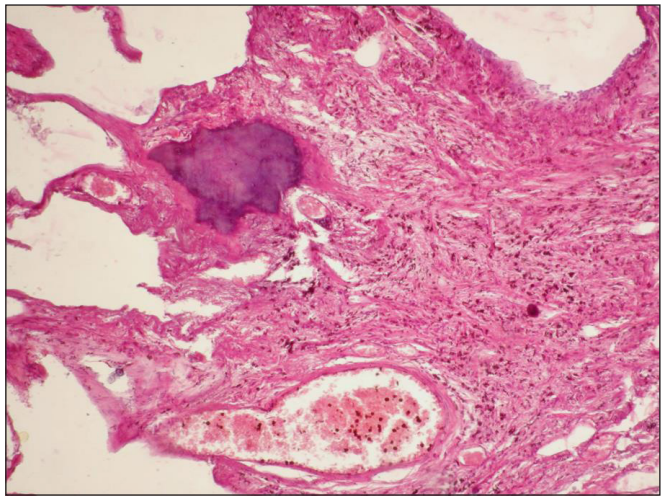

Fig. 5. Dystrophic calcification in the area of pneumosclerosis. Stained with hematoxylin and eosin, ×100.

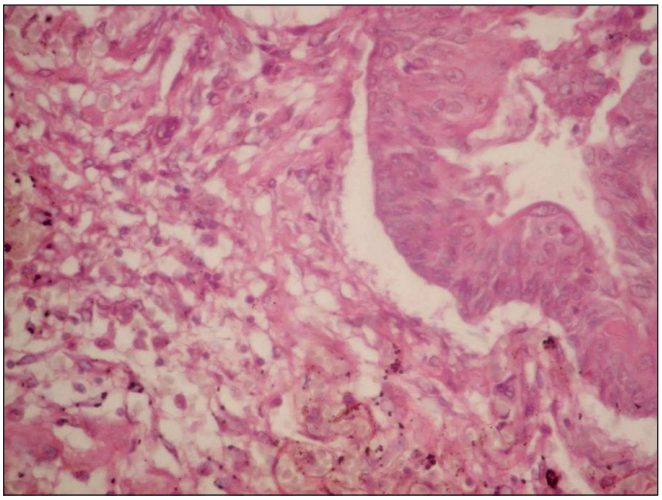

Fig. 6. Metaplastic and dysplastic changes in the epithelial layer of the bronchial tree in group 3. Stained with hematoxylin and eosin, ×400.

group 3 – (51.8±2.43)%) decreased ($p<0.05$), and the specific volume of emphysematous and atelectatically changed alveoli taken together (group 1 – (27.5±1.54)%, group 2 – (39.1±2.11)%, group 3 – (48.2±2.43)%) increased ($p<0.05$) (Fig. 8).

In all cases of groups 1-3, against the background of the described changes, we detected hemodynamic disorders that increased in the direction from group 1 to group 3 and were characterized by edema, vascular plethora, thrombosis, small-focal hemorrhages with hemosiderin deposition (Fig. 9).

DISCUSSION

The authors for the first time on autopsy material carried out a comprehensive morphological study of the lungs in post-COVID-19 syndrome, which makes it possible to explain the respiratory manifestation of this syndrome. This study revealed morphological changes in the parenchyma and stroma of the lungs in post-COVID-19 syndrome. Some preliminary results of this study were published by the authors earlier [13]. In this article, the authors publish the final results of the study.

The pneumosclerosis identified by the authors is the outcome of COVID-19, which has also been noted by many scientists [14]. Such pathological process is characterized by the replacement of parenchymal elements with connective tissue, the substitution of elastic fibers with collagen fibers, followed by a decrease in lung compliance, compression of the bronchial tree, which leads to the development of ventilation and parenchymal respiratory failure resulting in decreased quality of life, increased morbidity and mortality [15]. The authors noted an increase of pneumosclerosis with an increase the severity of the infection.

Sclerosis from the point of view of the reversibility of

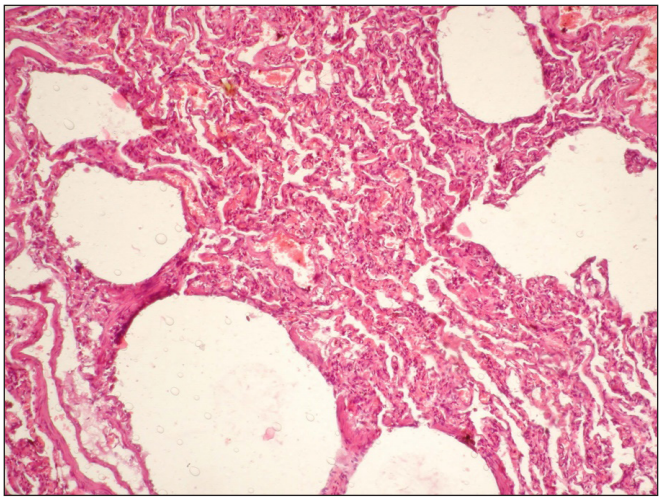

Fig. 7. Emphysematous and atelectatic changes in lung tissue in group 2. Stained with hematoxylin and eosin, ×100.

the process can be reversible (labile), partially reversible (stable), irreversible (progressive). In our study, among the connective tissue fibers, a decrease in the number of elastic fibers and their complete disappearance, an increase in the number of collagen fibers were revealed, which, from our point of view, indicates the irreversibility of the sclerotic process in such category of patients.

The pathogenesis of pulmonary fibrosis in post-COVID-19 period is a complex and not fully understood issue [15]. Most scientists associate the development of pneumosclerosis after COVID-19 with transforming growth factor beta (TGF-β), which is a multifunctional cytokine with profibrogenic, antiinflammatory and immunosuppressive effects that are elevated after COVID-19 [2].

Interestingly, one of the factors contributing to the development of pneumosclerosis is mechanical ventilation, which was used in the treatment of respiratory distress syndrome. Due to mechanical ventilation shear forces not only induce secretion of TGF-β but also activate collagen synthesis and inhibit collagenase production [2].

Some scientists assign the leading role in the development of pneumosclerosis after COVID-19 to endothelial-mesenchymal and epithelial-mesenchymal transformation. In the development of the latter, vascular endotheliocytes, alveolar epithelium (type II pneumocytes) can take part [16].

One of the factors triggering the endothelial-mesenchymal and epithelial-mesenchymal transformation can be hypoxemia [17].

Some scientists note the role of CD44 and metalloproteinase-9 in the development of pneumosclerosis after COVID-19. CD44 with hyaluronic acid activates the Phosphatidylinositol 3 Kinase/Protein Kinase B pathway, which induces the reduction in cellular apoptosis, increasing the survival of fibroblasts and myofibroblasts. Metalloproteinase-9 is expressed by alveolar epithelial cells, neutrophils, macrophages, and fibroblasts being able to activate TGF-β1, which contributes to the increase in the active TGF-β pool [18].

The infiltration by immune cells revealed by the authors in the foci of pneumosclerosis, which increased in parallel with sclerotic changes, indicates the participation of these cells in the development of pneumosclerosis.

In the foci of pneumosclerosis, the authors identified dystrophic calcification in 17 cases of groups 1-3, which is due to ongoing physicochemical changes in tissues, followed by the absorption of calcium salts from the blood and tissue fluid [19]. Also, in the areas of pneumosclerosis in 23 cases of groups 1-3, metaplasia of the connective tissue was noted with the formation of adipose, bone and cartilage tissues. In this case, before

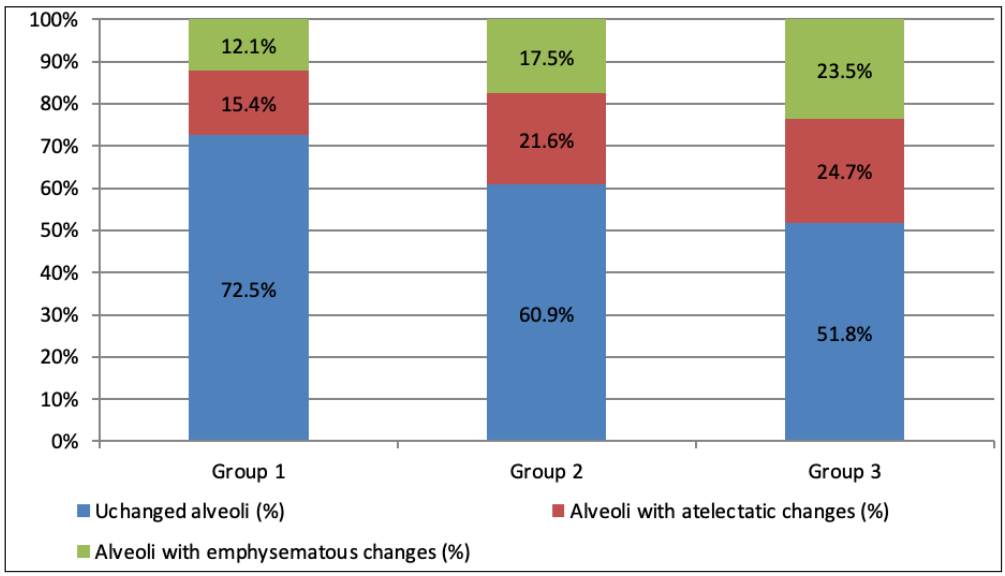

Fig. 8. The average values of the specific volumes of unchanged alveoli, alveoli with emphysematous and atelectatic changes in the lungs in groups 1-3.

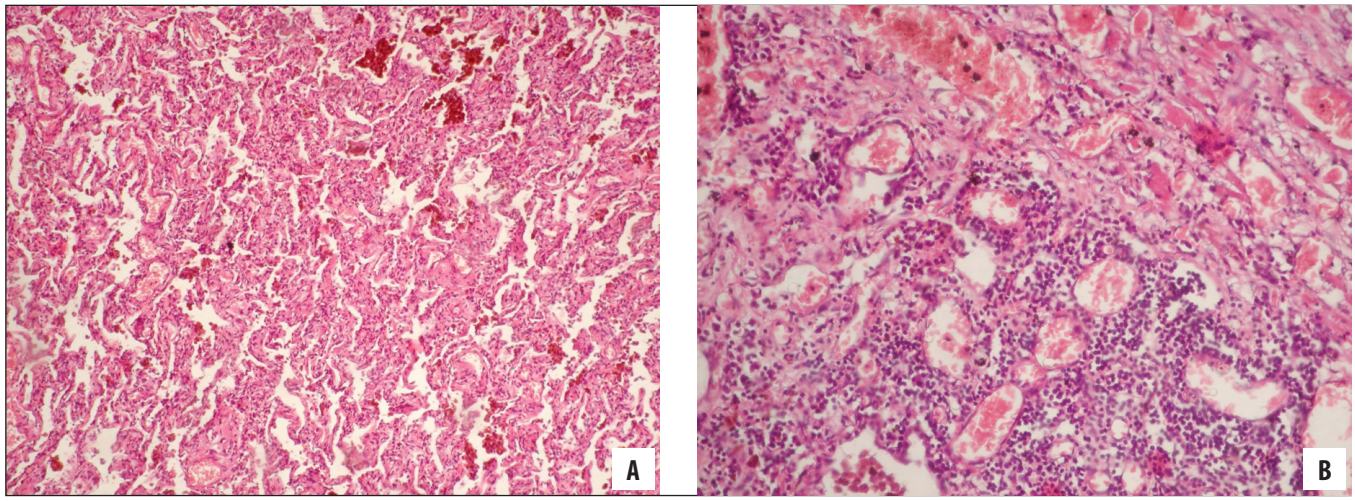

Fig. 9. Hemodynamic changes in the lungs in groups 2 (a) and 3 (b). Stained with hematoxylin and eosin, a) ×100, b) ×200.

the formation of adipose, bone, and cartilage tissues, proliferation of young cells of the connective tissue was noted, followed by differentiation into adipocytes, chondrocytes, and osteocytes. The changes in the connective tissue identified by the authors did not depend on the severity of the infection.

The sclerotic changes in the lungs identified by the authors led to a decrease of the parenchymal component, and with an increase of the severity of the infection, this pattern increased, which, accordingly, would lead to an increase the respiratory failure signs.

In all cases of groups 1-3, hemodynamic disorders were detected which depended on the severity of the infection and were characterized by edema, vascular plethora, thrombosis, small-focal hemorrhages with hemosiderin deposition. Similar changes have been described by scientists in the lungs during COVID-19 [20, 21].

Many scientists use the term COVID-19-associated interstitial lung disease (ILD) to describe pneumosclerosis as an outcome of COVID-19. Some scientists describe pulmonary aspergillosis as a manifestation of respiratory disorders of post-COVID-19 syndrome [22]. In our study, pulmonary aspergillosis was not detected. In our previous studies, we described chronic atrophic rhinosinusitis in patients in post-COVID-19 period caused by the association of bacteria and fungi. Among fungi, there were Aspergillus, Candida, Mucor and Coccidioides [23].

Sclerotic changes in the lungs were combined with damage of the parenchymal component. Damage of the latter was characterized, firstly, by focal degenerative-desquamative changes of the alveolar epithelium, which, together with the above described sclerotic changes of the basement membranes, leads to a violation of the morphofunctional state of the air-blood barrier and the development of parenchymal respiratory failure. Secondly, changes of the parenchymal component were characterized by a decrease of the specific volume of unchanged alveoli and an increase of the specific volume of emphysematous and atelectatically changed alveoli. The authors found an increase of these changes with increasing severity of COVID-19.

Also, changes of the parenchymal component of the lungs were characterized by damage of the epithelial layer of the bronchial tree, deformed due to sclerosis. In all cases of groups 1-3 the authors noted dystrophic changes. In 20 cases of groups 1-3 metaplastic and dysplastic changes sometimes with the formation of adenomatous structures were detected in the epithelial layer of the deformed bronchial tree. The changes in the bronchial epithelium identified by the authors did not depend on the severity of COVID-19.

Metaplasia and dysplasia are precancerous conditions [24, 25]. Therefore, the dysplastic and metaplastic changes identified by the authors in the epithelial layer of the bronchial tree, which did not depend on the severity of COVID-19, indicate that these patients are more likely to develop lung cancer in the future. It's just a hypothesis that requires years of research.

Some scientists in their studies also suggest that COVID-19 may be a risk factor for lung cancer [26].

There are studies in the literature that found that pneumosclerosis, immune cells infiltration, dysplastic and metaplastic changes in the epithelium of the bronchi are the basis for the development of peripheral lung cancer ("cancer in the scar") [27]. There are epigenetic and genetic alterations, abnormal expression of microRNAs, cellular and molecular aberrances such as an altered response to regulatory signals, delayed apoptosis or reduced cell-to-cell communication, along with the activation of specific signaling transduction

pathways, all these characterize the pathogenesis of pneumosclerosis and lung cancer [27].

Sadigov A. et al. showed in their studies that lung cancer most common was found at three months after lung infection, and most commonly incidence of lung cancer was observed in patients after surviving severe COVID-19 infection with severe acute respiratory distress syndrome in whom was developed massive and non-resolving fibrosis with history of cigarette smoking and most commonly type of the lung cancer was squamous cell lung cancer [28].

CONCLUSIONS

1. Morphological features of the lungs in post-COVID-19 syndrome are the presence of pneumosclerosis; focal-diffuse immune cells infiltration; emphysematous and atelectatic changes; degenerative-desquamatic changes in the alveolar epithelium; metaplastic changes of connective tissue; dystrophic calcification; dystrophic, metaplastic and dysplastic changes in the epithelial layer of bronchial tree; hemodynamic disorders.
2. Pneumosclerosis, focal-diffuse immune cells infiltration, alterative changes in the alveolar epithelium, emphysematous and atelectatic changes, hemodynamic disorders increased with an increase the severity of COVID-19. Metaplastic changes of connective tissue, dystrophic calcification, dystrophic, metaplastic and dysplastic changes in the epithelial layer of bronchial tree did not depend on the severity of the infection.
3. The changes identified by the authors help to explain pulmonary manifestations of post-COVID-19 syndrome. They should be the basis for the oncological alertness formation among doctors, the development of rehabilitation and treatment measures for such category of patients.

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Conflict of interest:
The Authors declare no conflict of interest

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Received: 12.10.2022
Accepted: 27.04.2023

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article