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Immune Cell Response of the Spleen in COVID-19

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Summary

Objective. To study the morphometric characteristics and splenic immune cell response in patients with COVID-19.

Material and methods. A prospective observational study included 70 patients. Of these, 45 patients admitted to the infectious diseases hospital with Coronavirus infection caused by the SARS-CoV-2 virus diagnosis were included in the COVID-19 group, and 25 patients were included in the acute respiratory viral infection (ARVI) comparison group. Spleen linear dimensions, including length, width, and thickness were assessed using ultrasound imaging, and calculations of the spleen weight and spleen weight coefficient (SWC) were obtained. Additionally leukocyte count and formula, erythrocyte sedimentation rate (ESR) were estimated, and the leukocyte index (LI) and neutrophil-to-lymphocyte ratio (NLR) were calculated.

Results. Microsplenia was common in the acute period of COVID-19 with mean SWC value 1.6±0.2. In 17 (37.8%) patients the SWC varied from 1.0 to 1.5, and in 9 (20%) microsplenia was critical with SWC <1.0. Leukocyte count was lower, and ESR — higher in patients with COVID-19, compared to ARVI group (5.4±2.1×10^9/l and 10.8±4.8×10^9/l, respectively $P<0.00001$, and ESR — 36.1±13.8 mm/h and 23.0±5.1 mm/h, respectively $P=0.03$). The course of COVID-19 was characterized by a slight decrease in LI — from 0.29±0.02 to 0.22±0.01 ($P=0.19$), and significant increase in NLR from 3.7±0.1 to 4.3±0.12 ($P=0.002$). Opposite trends were documented in patients with ARVI. On Day 5 since initiation of treatment LI was significantly lower in the COVID-19 vs ARVI group (0.22 [0.16; 0.39] vs. 0.48 [0.29; 0.93], $P=0.003$), and NLR was significantly higher (4.3 [2.5; 6.1] vs. 2.1 [0.9; 2.9], $P=0.002$).

Conclusion. The course of coronavirus infection caused by the SARS-CoV-2 virus is characterized by significant immunological shifts. Microsplenia verified by ultrasonography stays as one of the pathognomonic signs. This phenomenon is explained by rapid «depletion» of the spleen as a secondary immune organ, and is associated with a high risk of developing acute immune deficiency.

Keywords: COVID-19, immune distress, inflammatory markers, spleen, respiratory failure

Conflict of interest. The authors declare no conflict of interest.

Introduction

All aspects of the pathogenesis and clinical course of COVID-19 infection caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) have been intensively studied. During the COVID-19 pandemic, a large body of scientific and clinical data was generated and is being rapidly updated with new information on diagnosis, treatment, and disease progression. Based on these data, risk factors for the development of COVID-19, diagnostic criteria for hyperimmune response («cytokine storm») and disease severity have been identified [1–3], and guidelines for respiratory therapy in acute respiratory failure have been developed [4].

The outcome of any infectious disease depends on the patient's immune status, which includes three important and interrelated aspects: susceptibility, intensity of the protective immune responses, and suggested immune dysregulation.

Previous infections and vaccinations build up an immune memory that provides full or partial immunological protection, manifested as a reduced risk of developing an infectious disease or a milder disease. The SARS-CoV-2 virus is an etiologic factor with no prior immune response. There is no immunologic memory against it, resulting in increased morbidity in the population, immune stress that may result in acute immunodeficiency, and adverse short- and long-term outcomes [5].

Severe COVID-19 is caused by extreme hypoxemia and hyperimmune response, with significant increases in IL-1β, IL-6, TNF-α, CXCL10/CXC, IP-10, MIP-1α, chemokines, and unbalanced levels of type I interferon (IFN-I) at different stages of the disease. IFN-I levels are low during acute COVID-19 but rise later in the disease [2, 6].

The most important receptor for viral entry is angiotensin converting enzyme 2 (ACE 2). A decrease in its production causes hypercytokinemia, which is linked to the severity of inflammation and disease [2, 4, 7]. SARS-CoV-2 RNA is found not only in the blood but also in internal organs like the lungs,

heart, spleen, liver, intestines, kidneys, and brain, indicating that the virus can bind to most cells via the ACE2 receptor [7]. As a result, COVID-19 causes impaired function in these organs [8]. The virus affects several organs and systems, causing changes in both specific and non-specific immune responses [9].

Experiments show that hypoxia and increased glucocorticoid production in critical illness significantly alter myelopoiesis and interfere with the migration of mature leukocytes from the bone marrow into the bloodstream, resulting in cellular changes in the blood and leukocyte infiltration of parenchymal organs [10].

Lymphoid cells, primary and secondary immune organs that actively respond to a variety of negative stimuli, including infection, are useful indicators of immune system function. The spleen is the largest peripheral immune organ and is frequently involved in the immune response which manifests as splenomegaly. However, splenomegaly is not detected in SARS-CoV-2 infection, typically associated with an inflammatory response [3], despite the fact that the virus has been found in the spleens of deceased patients [11].

COVID-19 is distinguished by the rapid onset of multiple organ failure, primarily immunologic, as evidenced by a significant decrease in T lymphocytes, including CD4, CD8, and NK cells, as well as regulatory T cells. Severe lymphopenia is an early warning sign of the disease [11] and is linked to lymph node and splenic atrophy.

The spleen of deceased patients exhibits cell degeneration, focal hemorrhagic necrosis, macrophage proliferation, and intense apoptosis. Immunohistochemical analysis of lymph nodes and spleen reveals a decrease in the number of CD4(+) and CD8(+) T cells [12, 13].

Thus, the spleen plays an active role in the immune response to SARS-CoV-2 coronavirus infection.

The aim of this study was to investigate the morphometric characteristics and the immune cell response in the spleen of patients with COVID-19.

Materials and Methods

The prospective observational study was approved by the Independent Ethical Committee of the Clinical Research Center of the Immanuel Kant Baltic Federal University (protocol of the IEC meeting No. 23 dated April 27, 2021) and was conducted in 2019–2021 at the Infectious Diseases Hospital of the Kaliningrad Region.

Initially, 75 patients were included in the study and divided into 2 groups: COVID-19 and ARVI (acute respiratory viral infection) (Fig. 1).

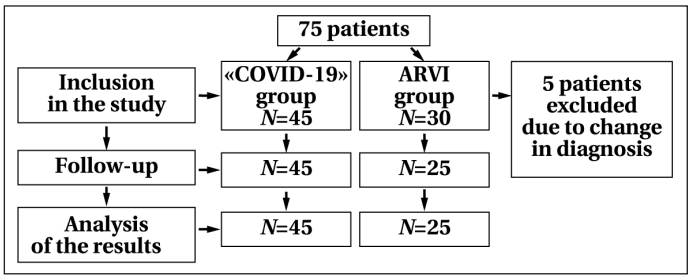

Fig. 1. The flowchart of the prospective clinical study.

Inclusion criteria for the COVID-19 group were clinical signs and laboratory confirmation of coronavirus infection caused by SARS-CoV-2 virus. The diagnosis was confirmed prior to hospitalization by polymerase chain reaction with detection of RNA fragment specific for SARS-CoV-2 coronavirus in the analyzed biological samples. The group was formed in 2021.

Inclusion criteria for the ARVI group were ARVI symptoms and negative viral tests. The group was formed in 2019, before the COVID-19 pandemic.

Medical history data were analyzed during the enrollment phase of the study. Patients with bacterial or fungal complications and decompensated chronic diseases were immediately excluded from the groups.

In all cases, outpatient treatment was ineffective and hospitalization in an infectious disease clinic was required.

The COVID-19 group included 45 patients admitted to an infectious disease clinic with a diagnosis of coronavirus infection caused by SARS CoV-2. All patients had acute onset of illness with fever up to 38–40°C, dry cough or cough with scanty sputum, dyspnea, chest tightness, sore throat, nasal congestion or moderate rhinorrhea, loss of smell, loss of taste, intoxication (fatigue, muscle pain, headache, vomiting, diarrhea). Patients did not receive steroids or anticytokine medications.

The ARVI group consisted of 25 patients with upper respiratory tract infection also characterized by acute onset, fever of 38–40°C, rhinorrhea, sore throat, cough (dry or wet) and fatigue.

The sample size was not predetermined.

Leukocyte count, leukocyte differential, and erythrocyte sedimentation rate were measured on admission (day 1, stage 1) and during treatment (day 5, stage 2). The blood test was performed on the 5diff MEK-8222K analyzer (Italy).

The leukocyte index (LI) was calculated using the formula: LI = lymphocytes/(band neutrophils + segmented neutrophils) [14].

The neutrophil-lymphocyte ratio (NLR) was determined using the formula: NLR = absolute neutrophil count / absolute lymphocyte count [15].

During lung ultrasound (LUS), we additionally performed linear measurements of spleen length, width, and thickness in two perpendicular planes. Based on the obtained morphometric data, we calculated spleen mass (Ms) and spleen weight coefficient (SWC) according to the method of O. Vozgoment et al.

The calculation of Ms was performed according to the formula:

Table 1. Characteristics of the studied groups, *M±SD*.

Parameter, units of measurement	Values in groups		*P* values
	COVID-19, *N*=45	ARVI, *N*=25	
Age, years	57.1±13.2	50.1±19.5	0.074
Body weight, kg	81.5±19.6	77.6±17.8	0.413
Height, cm	170,4±7.9	168.8±9.5	0.427
Duration of disease before hospitalization, days	7.6±3.6	7.1±2.5	0.646
Hypertension, *N* (%)	27 (60)	10 (40)	0.108
Coronary heart disease, *N* (%)	19 (42.2)	11 (44)	0.871
Diabetes mellitus, *N* (%)	5 (11.1)	2 (8)	0.688

Ms =0.34×L×2×h, where *L* is the length of the spleen, *h* is the thickness of the spleen (in cm).

SWC was calculated using the formula: 1000×m/body weight (in grams), where *m* is the mass of the spleen [16].

Statistical analysis was performed using the Statistica 10.0 software package (StatSoft Inc., USA). For normally distributed variables, arithmetic mean *(M)* and standard deviation *(SD)* were reported. The distribution of variables was tested using the Kolmogorov–Smirnov test with Lilliefors correction. For quantitative variables with non-normal distribution, the median *(Me)* and interquartile range *[Q1; Q3]* were calculated. Differences between two quantitative samples with non-Gaussian distribution were determined using the Mann–Whitney test, and the Wilcoxon test was used to compare paired samples. Qualitative data were analyzed by calculating the proportion (percentage) of each value. Qualitative variables were compared across the groups using Pearson's χ^2 test or Fisher's exact test. The two-tailed *P*-value was calculated. Differences were considered significant when $P \leqslant 0.05$. Pearson's parametric correlation test was used to analyze quantitative variables with normal distribution.

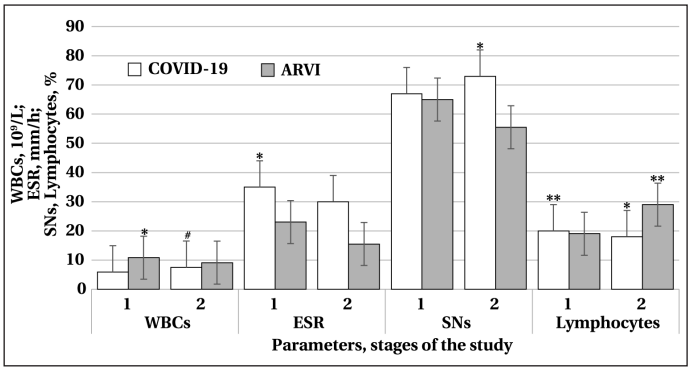

Fig. 2. Results of WBC differential and ESR measurements.
Note. * — $P<0.05$, significant differences between groups; significant differences at the stages of the study: # — $P<0.05$, in the COVID-19 group; ** — $P<0.05$, in the ARVI group. Stages 1,2 correspond to days 1 and 5 of treatment.

Results

The main clinical characteristics of the patients are shown in Table 1.

No significant differences were found between the groups in basic anthropometric parameters, age, duration of illness before hospitalization, and frequency of chronic comorbidities ($P>0.05$). All medical conditions of the participants were compensated.

Parameters of immune cell response are summarized in Fig. 2.

On hospital admission, significant differences between the groups were found in two parameters. The total leukocyte count was lower and the ESR was higher in the COVID-19 group than in the ARVI group ($P<0.001$ and $P=0.03$, respectively). Only in the COVID-19 group 14 (31%) patients had leukopenia on admission. There were no differences in segmented neutrophil and lymphocyte counts between groups ($P>0.05$).

In the COVID-19 group, the total leukocyte count increased significantly from 5.9×10^9/L to 7.5×10^9/L after 5 days of treatment ($P<0.001$), while the other parameters remained practically unchanged. In the ARVI group, the total leukocyte count and the ESR decreased slightly compared to day 1 of the study ($P>0.05$), there was a significant decrease in segmented leukocytes ($P=0.003$) and an increase in lymphocytes ($P=0.009$). In the intergroup analysis, we found that by day 5 of treatment, the percentage of segmented leukocytes was higher in the COVID-19 group and the percentage of lymphocytes was lower than in the ARVI group ($P=0.004$ and $P=0.039$, respectively).

The changes in LI over time are shown in Fig. 3, *a*.

At hospital admission, the median LI was 0.29 [0.18; 0.51] in the COVID-19 group and 0.27 [0.15; 0.48] in the ARVI group, with no significant differences ($P=0.521$). After 5 days of treatment, the leukocyte index showed multidirectional changes. In the COVID-19 group, it started to decrease with a value of 0.22 [0.16; 0.39] ($P=0.19$), while in the ARVI group, it increased 1.8 times compared to day 1, reaching 0.48 [0.29; 0.93] ($P=0.025$). On day 5 of treatment, the COVID-19 group had a significantly lower LI than the ARVI group ($P=0.003$).

At hospital admission, the median NLR was 3.7 [2.1; 6.5] in the COVID-19 group and 3.4 [1.9; 5.4] in the ARVI group (Fig. 3, *b*). There was no significant difference between the groups ($P=0.945$). On day 5 of treatment, the NLR changed in opposite directions. It increased to 4.3 [2.5; 6.1] in the

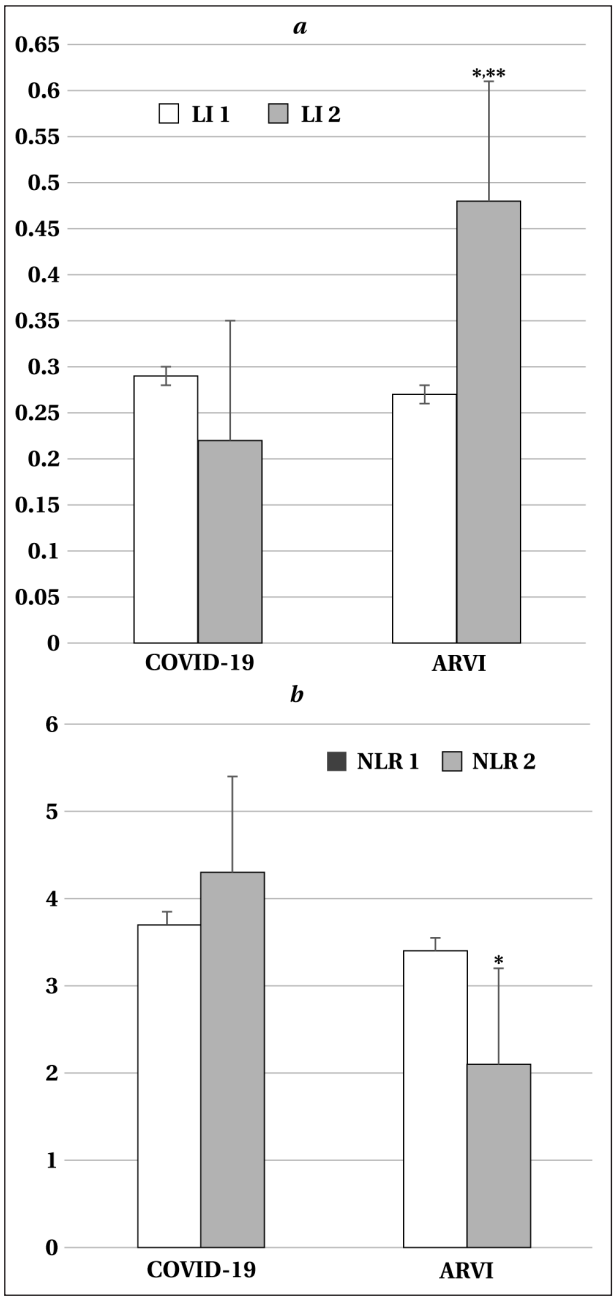

Fig. 3. Changes in leukocyte index (a) and neutrophil-lymphocyte ratio (NLR) (b) during treatment.
Примечание. * — $P<0.05$, significant differences between the groups on day 5; ** — $P<0.05$, significant differences in the ARVI group, compared to day 1. 1, 2 — stages of the study.

COVID-19 group and decreased to 2.1 [0.9; 2.9] in the ARVI group, indicating a significant difference between groups (P=0.002).

Table 2 shows the results of the ultrasonographic morphometric study of the spleen.

In patients in the COVID-19 group, all linear mean spleen dimensions (length, thickness, and width) were significantly smaller compared with the ARVI group ($P<0.001$). Based on the obtained linear dimensions, we calculated the mass and the spleen mass coefficient. The calculated spleen mass ranged from 52 to 138 g in the COVID-19 group and from 166 to 377 g in the ARVI group. The mean values of both spleen mass and SWC were 1.6 times lower in the COVID-19 group than in the ARVI group ($P<0.001$). The scatter plot of the spleen mass coefficient is shown in Fig. 4, *a*. Thus, patients in the COVID-19 group had reduced spleen size.

Previously, the SWC was shown to provide a detailed assessment of changes in spleen size and to allow the ranking of patients based on its value. An SWC value of less than 1.5 corresponds to microsplenia, the range of 1.6 to 3.9 to normal spleen size and more than 4 to splenomegaly [17].

Patients in both groups were ranked according to SWC (Fig. 4, *b*). We found that microsplenia corresponding to SWC less than 1.5 was significantly more frequent in the COVID-19 group compared to the ARVI group ($P<0.001$). Seventeen (37.8%) patients in the COVID-19 group had reduced spleen size with SWC in the range of 1.0 to 1.5, and 9 (20%) patients had critical microsplenia with a coefficient value of less than 1.0. A normal SWC value (1.6–3.9) was found in 18 (40%) patients in the COVID-19 group and 21 (84%) in the ARVI group. These differences were significant ($P<0.001$). Initial splenomegaly was detected in 1 (2.2%) case in the COVID-19 group and in 3 (12%) cases in the ARVI group. The differences were significant ($P<0.001$).

Only in the ARVI group a direct moderate correlation between SWC and WBC count was found (r=0.588; P=0.002).

In the COVID-19 group, 34 (75.6%) patients had moderate disease with bilateral interstitial pneumonia, 10 (22.2%) patients had severe disease and 1 (2.2%) patient had mild «ARVI-like» disease.

All patients in the ARVI group had moderate disease severity.

The distribution of patients by severity of acute respiratory failure (ARF) is shown in Table 3.

In the COVID-19 group, 29 (64.4%) patients had respiratory failure I–III. There was no evidence of ARF in the ARVI group. Significant differences in

Table 2. Measured and calculated morphologic characteristics of the spleen, *M±SD*.

Parameter	Values in groups		*P* value
	COVID-19, *N*=45	ARVI, *N*=25	
Length of the spleen, cm	9.5±1.5*	10.9±1.5	<0.001
Thickness of spleen, cm	3.9±0.9*	4.9±0.8	<0.001
Width of the spleen, cm	4.3±1.6*	5.8±1	<0.001
Weight of spleen, g	127.8±67.7*	204.3±81.6	<0.001
Spleen weight coefficient (SWC)	1.6±0.9*	2.6±1.1	<0.001

Note. Here and in Table 3: * — $P<0.05$, significant differences between groups.

this parameter were found between the groups ($P<0.001$). In all cases, the disease had a favorable course and no fatal outcomes were recorded. Most patients in both groups were discharged home. In the COVID-19 group, 6 (13.3%) patients required further treatment and were transferred to other hospitals.

Discussion

Hematologic parameters such as leukocyte count, segmented neutrophils, and ESR generally reflect the performance of the immune system in response to infection. In coronavirus infection caused by SARS-CoV-2 virus, leukopenia and elevated ESR are most prominent [18, 19]. Lymphopenia, elevated ferritin, fibrinogen, D-dimer, and troponin levels detected during hospitalization are considered predictors of mortality [18, 20, 21].

Integral markers can provide a more detailed assessment of immunologic changes and serve as predictors of disease progression [22, 23]. The LI reflects the balance between the cellular and humoral components of the immune system [24]. In the acute phase, LI decreased in both groups, indicating immunosuppression. This parameter changed differently in the two groups. While in patients with acute respiratory infections it returned to normal, i. e., an active inflammatory response occurred, in patients with COVID-19 the LI decreased only slightly, indicating further suppression of the immune system.

Lymphopenia and elevated NLR can predict a severe course of viral infection [18, 20, 24]. Both patients with COVID-19 and patients with ARVI had an increase in NLR in the acute phase, but its further changes differed between the two groups. While it decreased and then returned to normal in patients with acute respiratory viral infection, NLR grew further in COVID-19, indicating a persistent immune imbalance, as evidenced by low phagocytic activity and the dominance of specific immunological defense system.

Ultrasound revealed that the reduced spleen size is a pathognomonic sign of coronavirus infection caused by SARS-CoV-2 virus, which is consistent with previous research [25]. Pathologic and histologic studies have shown that coronavirus infection reduces the volume and cellular structure of the spleen and causes white pulp atrophy, resulting in an abnormal red/white pulp ratio [26, 27]. The number of lymphoid follicles is also significantly reduced or absent, although neutrophil infiltration or scattered plasma cells are occasionally seen. In some cases, macrophage proliferation and hemophagocytosis are observed. Lymphocyte necrosis and apoptosis, arteriolar thrombosis, and splenic

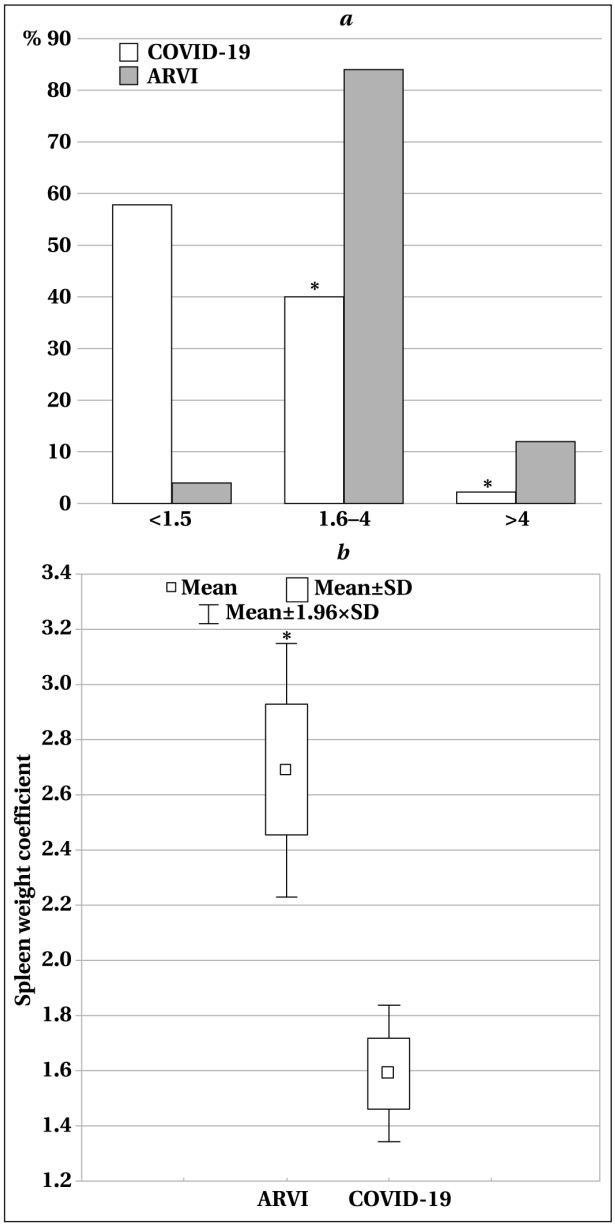

Fig. 4. Scatter diagram of the mean spleen weight coefficient *(a)* and ranking of patients according to its values *(b)*.

Table 3. Severity of respiratory failure and outcomes in patients with COVID-19 and ARVI.

Parameter, *N* (%)	Values in groups		*P* value
	COVID-19, *N*=45	ARVI, *N*=25	
ARF 0	17 (37.7)*	25 (100)	<0.001
ARF I	24 (53.3)*	0 (0)	<0.001
ARF II–III	5 (11.1)	0 (0)	0.085
Total ARF	29 (64.4)*	0 (0)	<0.001
Discharged	39 (86.7)	25 (100)	0.06
Transferred to other hospital	6 (13.3)	0 (0)	0.06

infarction are all characteristic. Immunohistochemical study [22] showed that the T and B lymphocyte counts decrease to varying degrees, and CD20 (+) B cells accumulate in the lymphoid tissue surrounding the splenic artery. The number of CD3(+), CD4(+) and CD8(+) T lymphocytes decreases, while the number of CD68(+) cells increases. J. Guet al. presented the results of a histological study of tissues from patients with ARDS caused by SARS-CoV-2 virus. In all cases, the virus was found in circulating lymphocytes and lymphoid organs, with atrophy of the spleen and lymph nodes [28]. Post-mortem, high viral loads were found in the lungs, followed by the liver and spleen, resulting in a significant reduction of the latter.

The SARS-CoV-2 virus targets several organs, including the spleen. Direct effect of the virus on all the structures of spleen causes active changes with a significant decrease in the lymphocyte population and the development of an acute immunodeficiency. Immunosuppression in the early stages can result in hyperacute disease [26, 28, 29]. In this regard, there is a need for early evaluation of splenic morphometric parameters using various radiologic techniques. A. Batur et al. demonstrated by computed tomography that in addition to lung damage, the spleen is also involved in the pathologic response. During the disease, it undergoes structural changes and shrinks, but the extent of this transformation is not related to the severity of lung damage. The spleen shrinks the most during the first two weeks of coronavirus infection [30], while the Hounsfield number (densitometric index) remains stable, indicating heterogeneous changes in the organ parenchyma. The observed changes could be attributed to the resulting cellular imbalance, proliferation, and response to hypoxia and necrosis [31]. L. Xie et al. using ultrasound imaging found that COVID-19 reduced the linear dimensions of the spleen. Patients with coronavirus infection had a mean spleen length of 89.57±11.49 mm, while healthy controls had a mean spleen length of 103.82±11.29 mm. This difference was significant ($P<0.001$). The study and control groups had a mean spleen thickness of 29.97±4.04 mm and 32.45±4.49 mm, respectively ($P<0.001$), indicating that the disease resulted in a reduced spleen size. Microsplenia is associated with a reduction in the T lymphocyte count [25].

In the acute period of COVID-19 against the background of systemic coagulation disorder, thrombosis of splenic arteries and veins may develop, leading to total ischemia of spleen [32]. The ultrasonographic morphology of splenic infarcts is highly variable. They can be both classic, wedge-shaped, or rounded, or irregularly shaped. In the recovery phase, new infarcts do not occur, but fibrosis and scarring appear in place of the existing ones, and the size of the organ remains reduced, which is manifested by changes in the ultrasound image of the spleen [33]. The formation of cysts is possible [34].

COVID-19, unlike ARVI, is characterized by a high frequency of bilateral interstitial pneumonia and acute respiratory failure, which is associated not only with direct viral damage to respiratory structures, but also with the development of immune distress as an early manifestation of multiple organ failure.

Study limitations. A representative sample was not pre-calculated during the planning of the study.

Conclusion

COVID-19 infection is characterized by significant immunological disturbances. This phenomenon is associated with a rapid «depletion» of the spleen as a secondary immune organ and a high risk of acute immune failure. One of the specific signs of the disease is microsplenia, which is diagnosed by ultrasound.

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