Features of the clinical course in lesions of the nose and paranasal sinuses in patients with postcovid syndrome.

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Summary: The management of COVID-19 in the early stages and in the post-COVID period is so different and has not yet found its final answer for all patients from mild, moderate to severe forms of the disease.

The purpose of the study is to determine the clinical manifestations of lesions of the nose and paranasal sinuses in patients who have undergone COVID-19.

Material and research methods. We examined 72 patients with diseases of the paranasal sinuses and their complications, frolicking in the first 2 months after undergoing COVID-19. SNP lesions manifested as necrotizing rhinosinusitis (NRS) with destruction of soft tissues and bone structures of the paranasal sinuses in all patients.

Research results. In the main group of 72 patients (100%), mild course of COVID-19 was observed in 9 (12.5%) patients, moderate course – in 23 (31.9%) patients, severe course – in 40 (55.6%) patients, while the percentage of lung tissue damage ranged from 12-60% at 95% CI: 10.1; 49.8%. HRS was accompanied by moderate edema of the periorbital region in 62 patients (86.1%), conjunctival injection was observed in all patients. All patients had a putrid odor. Nasal endoscopy revealed crusts and necrotic areas. Histological examination revealed fungal spores in 68 patients (94.4%). The ShiK reaction showed a positive result in 52 patients (72.2%). All patients had hyperglycemia more than 7 mmol /l.

Conclusions. The presence of anesthetized tissues in the nasal cavity may be the first diagnostic criterion for necrotizing rhinosinusitis. The presence of an immunodeficiency state (post-covid syndrome) is the basis for the development of necrotic rhinosinusitis.

Keywords: necrotizing rhinosinusitis, postcode syndrome, paranasal sinuses, hyperglycemia, fungal infection

The pandemic of a new coronavirus infection in 2020 caused by coronavirus 2 (SARS-CoV-2) has become a real challenge to humanity and the medical community and has raised a number of medical and social issues. The speed of infection in a short time gave rise to a large number of infected, associated with the high contagiousness of the viral infection and made it possible to distinguish groups of patients with mild, moderate and severe forms of the disease. Medicine is faced with an acute problem of diagnosing, treating and determining the manifestations of a large number of patients in critical conditions caused by COVID-19.

Morphological studies revealed ischemic and thrombotic changes in COVID-19 not associated with DIC or other thrombotic conditions. It is assumed that vasculitis develops as a pathological pattern with various clinical manifestations, but it is not yet considered a serious complication (Almashat Salma, 2020).

Biomarkers at an early stage of infection are very relevant to predict the outcome of coronavirus disease-19 (COVID-19) and determine the prognosis and treatment tactics. So Spanish research has identified SZC (zinc) as a new biomarker for predicting the outcome of COVID-19. Low levels of zinc promote the spread of the virus in SARS-CoV2 infected cells (Marina Vogel-Gonzalez, Marc Tallo-Parra, Victor Herrera-Fernández, Gemma Perez Vilaró, Miguel Chillon, Xavier Nogues, Silvia Gomez-Zorrilla, Inmaculada LopezMontesinos, Judit Villar, Maria Luisa Sorli- Redo, Juan Pablo Horcajada, Natalia Garcia Giralt, Julio Pascual, Juana Diez, Ruben Vicente, Robert Güerri-Fernández, 2020).

Management of COVID - 19, not only in the early stages but also in the post-COVID period, is so different and has not yet found its final answer for all patients from mild, moderate to severe forms of the disease.

The purpose of the study is to determine the clinical manifestations of lesions of the nose and paranasal sinuses in patients who have undergone COVID -19 .

Material and research methods

The work was completed in the period from 2019 to 2022. in on the basis of the Tashkent Medical Academy .

The basis of the work was 72 patients with diseases of the paranasal sinuses and their complications that manifested after COVID -19 in the first 2 months after the infection.

Criteria for inclusion in the main group were: SNP diseases - necrotizing rhinosinusitis, transferred by COVID -19. Exclusion criteria - age under 18, no history of COVID - 19; vaccination against COVID -19. The comparison group consisted of 20 CRS patients who did not have a history of COVID -19 and were not vaccinated. The choice of such a specific cohort of patients was due to the fact that we aimed to identify the specific features of SNP diseases in individuals who had undergone COVID -19, because. The pathogenesis of this infection is not fully understood, and the post- COVID consequences are very wide. We noticed that SNP diseases developed 3–8 weeks after the acute period of coronovirus infection and in all the applied patients (in 100%) they manifested themselves in the form of necrotic rhinosinusitis with the destruction of soft tissues and bone structures of the paranasal sinuses.

Age separation was carried out according to the generally accepted scheme of periodization of biological age [10] adopted in medicine and fixed by WHO (Issue No. 3 of 2017):

Analysis of the cohort of our patients in the observation group showed that the average age of patients was 57.0 ±1.2 years. The distribution of patients by sex and age showed a predominance of middle-aged and elderly males (Table).

Table 1.

Distribution of patients of the main group by sex and age

age	Men		Women		Total	
19-44 l	3	4.2	-	-	3	4.2
44-59 l	21	29.2	14	19.4	35	48.6
60-74 l	11	27.8	13	18.1	33	45.8
Over 75	1	1.4	-	-	1	1.4
	45	62.5	27	37.5	72	100

In the main group of 72 patients (100%), mild course of COVID -19 was in 9 (12.5%), moderate in 23 (31.9%), severe in 40 (55.6%) patients, while the percentage of lung tissue damage ranged from 12-60% at 95% CI: 10.1; 49.8%. The mean SPO 2 was 93.4±0.67% at 95% CI: 92.0; 94.8%. Bilateral polysegmental pneumonia was in 37 (51.4%) patients. The average length of hospital stay for treatment of COVID -19 was 7.1 ± 2.3 days, which was associated with the severity of the disease.

Out of 72 patients, the manifestation of SNPs within 3-4 weeks after COVID -19 was noted in 8 patients (11.1%), in the remaining 64 (88.9%) patients - at 5-8 weeks after COVID -19.

Special ENT examination included: examination of ENT organs (otoscopy, rhinoscopy, pharyngoscopy, posterior rhinoscopy); endoscopy of the nasal cavity and SNP, MSCT, study of the transport function of the ciliated epithelium (TFME) in the saccharin test.

The diagnosis of necrotic rhinosinusitis was established on the basis of the presence of foci of fusion of the SNP tissues, necrotic detritus, and violations of the integrity of the walls of the SNP. The diagnosis of chronic rhinosinusitis was established according to EPOS - 2012, on the basis of patient complaints and the results of endoscopic and MSCT studies. Note that MSCT was performed in all patients. According to the CRS classification recommended by EPOS-2012 [107], two CRS phenotypes were distinguished: CRS without nasal polyps and CRS with nasal polyps.

Special laboratory research methods included **lipid** profile parameters in blood serum (TG, total cholesterol, VLDL, HDL, LDL). We studied vascular - platelet hemostasis (determination of platelet count). From screening tests of the hemostasis system, activated partial thromboplastin time

(APTT) was determined; prothrombin time (PT) and international normalized ratio (INR); thrombin time (TV); fibrinogen; the number of platelets. Of the additional methods, D- dimer was used . Determination of the levels of IL-1 beta, IL-6, IFN-gamma, TNF-α in the blood serum of patients.

For a comparative assessment of the results of laboratory studies, a reference interval was used, as well as data obtained in the control group. The control group included 20 patients of the same age with planned surgical pathology (nasal septum deviated) without any deviations in somatic status.

Microbiological studies of the contents of SNPs - discharged and necrotic tissues included bacteriological cultures with the isolation of pure cultures of pathogens, determination of sensitivity to antibiotics and antifungal drugs.

Histological studies. Necrotic tissues taken during the operation were subjected to histological examination. At the same time, staining was carried out - with hematoxylin-eosin, the color combines basic and acid dyes, which makes it possible to identify almost all cells and many non-cellular structures. In this case, the nuclei acquire a blue-violet color, the cytoplasm - a yellowish-pink color. The hematoxylin used is prepared according to the Ehrlich method: it is oxidized to hematein with potassium alum.

To determine the fungal infection, histochemical research methods are carried out . The best results in the detection of fungi are obtained by stains designed to detect polysaccharides. Histochemical methods are based on a specific reaction between a chemical reagent and a certain component of the preparation. The resulting reaction product has a color different from that of the starting reagent. To determine the presence of polysaccharides in the test material, the PAS reaction is used using the Schiff-periodic acid reagent. Polysaccharides are contained in large quantities in the walls of the shell of mushrooms. This reaction is based on the oxidation of polysaccharides in the shell of mushrooms with iodic acid to form aldehyde groups, which are stained purple-red with fuchsin sulfuric acid. On the preparation, CHIC-positive components have a dark red color.

Research results.

The results of the study revealed that all patients were treated with numerous complaints in the facial area for progressive facial and periorbital edema, pain in the same part where the edema developed, nasal congestion, and visual impairment. Progressive discomfort nasal discharge and swelling in the palate, foul smell, black crusts from the nose, black spots on the palate, black spots around the eyes. We also determined a violation of smell, which was revealed in 95.8% of patients, it is worth noting that anosmia was observed in 65.5% despite the one-sidedness of the process.

Table 2

Characteristics of complaints in patients with rhinosinusitis after COVID -19 and who have not undergone COVID -19

	Main group		**Comparison group**	
complaints	**abs**	**%**	**abs**	**%**
swelling of the face	72	100	2	10.0
periorbital edema	58	80.6	0	0
pain	72	100	20	100
nasal congestion	67	93.1	20	100
nasal discharge	68	94.4	20	100
Changes in the palate (swelling, redness, necrosis)	49	68.1	0	0
Visual impairment	51	70.8	3	15.0
Smell impairment (hypo, -anosmia)	69	95.8	8	40.0

In patients with NRS+PKS (patients with necrotizing rhinosinusitis with post-covid syndrome), the process was unilateral in 61 patients, which accounted for 84.7%, bilateral in 11 patients, 15.3%. In the comparison group (CRS without PCC), the bilateral process was in 7 patients, which amounted to 35.0%, unilateral in 13 patients (65%). Such a difference shows that

HRS is only part of a systemic process with manifestation at the level of the nose and SNP. While the classic CRS is a manifestation of a local process without a pronounced systemic distribution.

The characteristics of the patients' complaints showed a significant difference in the manifestation of NCL+PCL in contrast to the classical CRS. So, with extensive lesions, complaints of headaches are not so pronounced in patients with HRS, signs of the spread of the process beyond the SNP are more pronounced (changes in the palate, periorbital edema, swelling of the face, etc.), while in classical CRS, symptoms during in all cases were limited to SNPs only. At the same time, headaches in terms of intensity in HRS were more intense without localization and were assessed on a VAS scale of 7.8 ± 1.2 points, while in classical CRS pain was assessed on a VAS of 3.9 ± 0.8 score and was noted in all patients with both types of SNP lesions.

Table 3

Rhinological characteristics of the manifestations of the disease

signs	Main group		Comparison group	
	abs	%	abs	%
swelling of the face	72	100	2	10.0
periorbital edema	58	80.6	0	0
Necrotic crusts	72	100	0	0
Purulent discharge	67	93.1	20	100
Bad (putrid) odor	67	93.1	1	5.0
Atrophy of the nasal mucosa	70	97.2	0	0
Hypertrophy of the nasal mucosa	0	0	20	100
Changes in the palate (swelling, redness, necrosis)	49	68.1	0	0
Injection conjunctiva	72	100	5	25.0

An objective examination revealed moderate swelling of the periorbital region in 62 patients (86.1%) in patients with HRS, exophthalmos was not observed in any patient (it is a sign of atrophy with necrosis and possibly thrombosis of the eye vessels), conjunctival injection was observed in all patients (72, 100 %). In the CRS group, edema of the face in 2 patients was characterized by slight pastiness of the side of maximum damage, while in the HRS group, a dense swelling of the face of a pronounced nature was observed. On examination, all patients with NRS had a putrefactive odor of varying severity, felt by the doctor. While with CRS, an unpleasant odor was observed only in one patient, whose CRS was associated with an inflammatory process in the teeth (of an odontogenic nature).

Nasal endoscopy revealed crusts and necrotic areas in all patients with NRS, while, depending on the prevalence of the process, the crusts spread in the lower, middle nasal passages up to the roof of the nasal cavity. The removal of the crusts was accompanied by unexpressed bleeding, while the mucosa was sharply atrophic , the cat's base thinned up to perforation on the nasal septum, with the absence of the walls of the SNP (maxillary, walls of the ethmoid labyrinth). In 12 patients, complete melting of all bone walls with exposure of the roof of the nasal cavity was noted. Mild thickening of the mucosa with no signs of invasive inflammation or bone erosion was observed in only 7 patients (9.7%) with HRS. In all other patients (65, 90.3%), various degrees of invasion and bone erosion of the walls of the nasal cavity and paranasal sinuses were determined with a sharp expansion of the nasal cavity. In classical CRS, the reverse picture was noted with thickening of the mucosa and its edema, severe hyperemia and liquid mucopurulent discharge, significant narrowing of the nasal passages, in some cases there were purulent crusts, no signs of necrotic black crusts were noted.

Histological examination in 68 patients (94.4%) revealed fungal spores, only in 4 patients (5.6%) no fungi were found. The ShiK reaction (Schiff with iodic acid) showed a positive result in 52 patients (72.2%), which indicated the presence of fungal elements and gave a negative result in

20 patients (27.7%), which, however, did not exclude the presence of fungal flora. Invasive fungal sinusitis was suspected clinically.

Bacterial seeding in patients with HRS showed poor data, only in 43.1% (n = 31) of patients it was possible to obtain data on the microflora, in the rest of the patients - due to necrotic melting, the flora was not determined.

Microflora was sown in our studies: Staphylacoccus aureus, Escherichia coli, Klebsiella pneumonia, Pseudamonas aeruginosa, Staphylococcus haemolyticus, Candida fungi. The causative agents of inflammatory processes were not only bacterial agents, but also fungal flora, which, without causing rapid clinical changes, most often exacerbates immunity disorders, both local and general. As can be seen, microorganisms belonging to pathogenic bacteria, as well as strains of fungi of the genus Candida , were isolated from patients . The average microbial load in patients varied widely from 1.27 to 18.28, averaging 2.94. The most common causative agent of HPC was Klebsiella pneumonia, which was sown in 48.4% of cases (n = 15), occupying a leading place among representatives of the monoflora, Pseudamonas was in second place aeruginosa (19.3% - n = 6), Candida fungi were detected in all patients. Escherichia were sown least of all coli (6.4%, n =2), Staphylacoccus haemolyticus (3.2% - n = 1), found only in isolation. When analyzing the polymorphic flora, microorganisms were found in the following associations: Staphylacoccus aureus and Klebsiella pneumonia 9.7 % (n =3), Staphylacoccus aureus and Pseudamonas aeruginosa - 12.9% (n = 4). Reveal the prevalence of the main pathogen both in monoflora and in seeding polyflora failed.

Hemodynamic parameters in 67 patients were stable (93.1%), the remaining 5 patients (6.9%) were in the intensive care unit with unstable hemodynamic parameters.

Attention was drawn to the fact that in all patients of the main group (100%), hyperglycemia of more than 7 mmol / l was detected in a biochemical blood test. At the same time, 49 (68.1%) patients had type 2 diabetes mellitus (DM2), and the remaining 23 (31.9%) patients had hyperglycemia that developed within 2 months after COVID -19, which was accompanied by an increase in glycated hemoglobin by more than 7%, which made it possible to confirm a stable long-term increase in blood glucose for at least 3 weeks and state DM2 (Fig. 1).

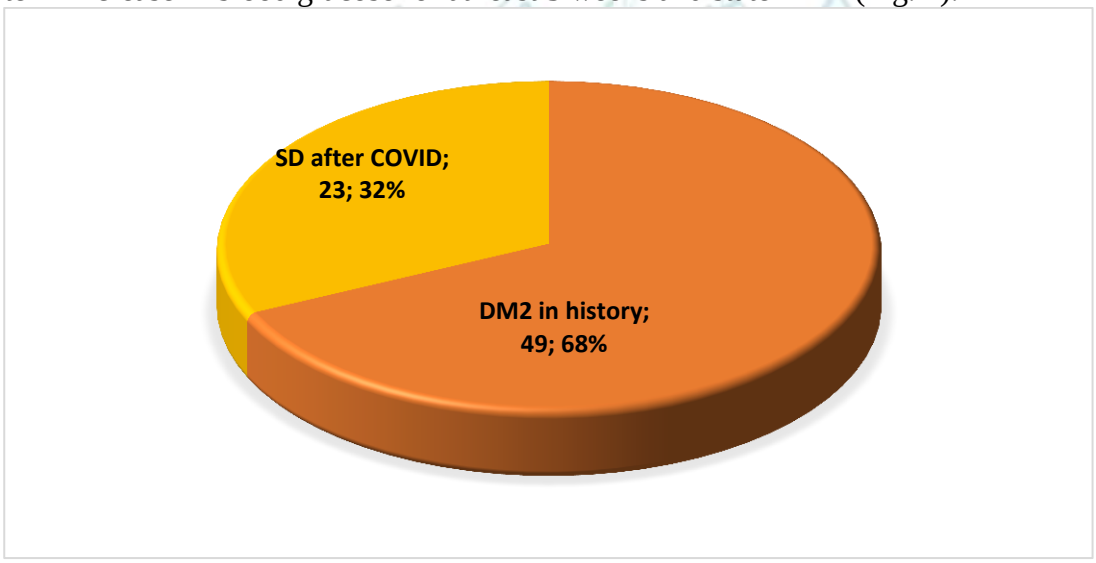
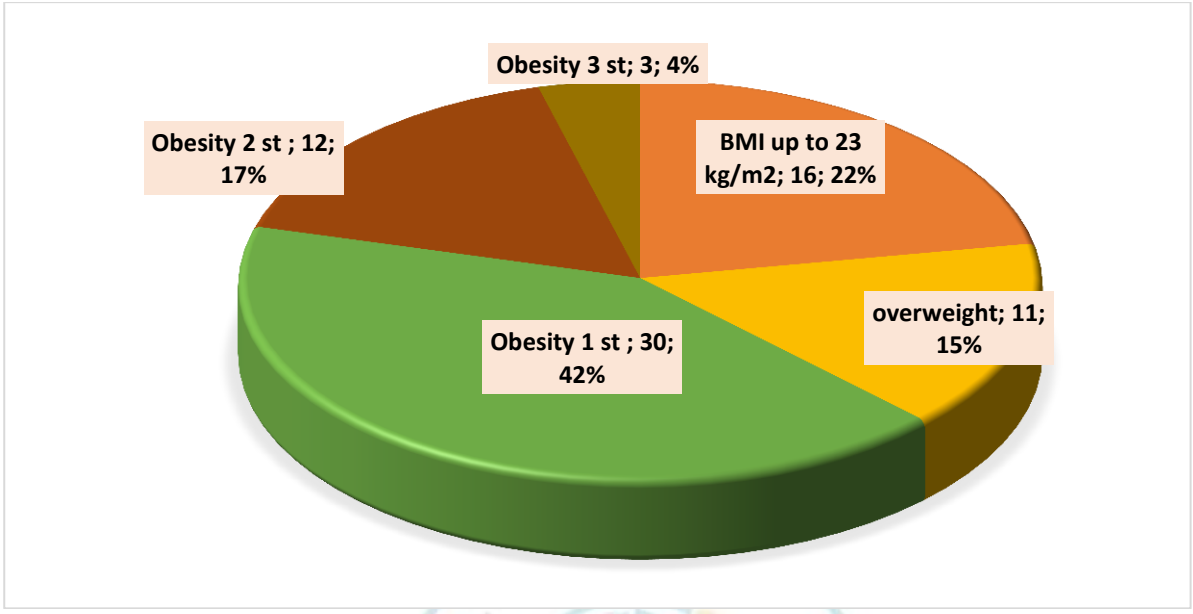


Fig. Distribution of patients depending on the DM2 manifestation

At the same time, there were 16 patients with normal weight (22.2%), with overweight (23.01-27.5 kg/m2) there were 11 (15.3 %), with obesity of the 1st degree (28.0-32 kg/ m2). m2) were 30 (41.7%), with 2nd degree obesity (32.0-37 kg/m2) - 12 (16.7%), with 3rd degree obesity (37.1 and more) - 3 (4, 2%) (Fig. 2).



Rice. 2.2. Distribution of patients by BMI

The study of the lipid spectrum in these patients showed the presence of dyslipidemia in the form of a decrease in HDL in 35 (48.6%) patients, hypertriglyceridemia in 55 (76.4%) patients, hypercholesterolemia in 43 (59.7%) patients.

The study of concomitant diseases showed that 44 of 72 patients (61.1%) had a history of cardiovascular diseases: 11 (15.3%) had arrhythmias, coronary artery disease, cardiomyopathy in anamnesis, 23 (31.9%) had arterial hypertension patients of the main group.

Conclusions.

The presence of anesthetized tissues in the nasal cavity may be the first diagnostic criterion for necrotizing rhinosinusitis .

The presence of an immunodeficiency state or disease is the basis for the development of necrotic rhinosinusitis , in our studies, this condition was a post- covid state. There is a wide range of life-threatening diseases that can be considered immunodeficient . conditions leading to the development of necrotic rhinosinusitis due to both fungal and bacterial infection.

Clinically, the presence of necrotic crusts was observed in all patients, while the mucosa was atrophic with multiple microthrombi, with swelling of the facial and periorbital areas, with a protracted course.

Species Klebsiella, Pseudomona aeroginosa combined with a fungal infection are the causative agents of necrotizing rhinosinusitis.

The diagnosis of necrotizing rhinosinusitis is based on clinical signs (chronic course with an unpleasant putrefactive odor), CT data (atrophic changes in the nasal mucosa with underlying bone resorption) and histology (presence of fungal spores with a positive CHIC reaction).

Aspergillus and mucor species are commonly associated with severe clinical presentation in neutropenic patients. Occasionally, the initial phase of invasive necrotizing sinusitis may be characterized by mild or non-specific symptoms, with minimal, subtle changes on CT, and thus delay treatment.

The presence of leukocytosis noted in some cases does not exclude a fungal infection. Long-term and high doses of steroids cause immunosuppression in patients and therefore increase susceptibility to fungal infections. Steroids may also be responsible for the increased white blood cell count.

The abundance of inflammatory cells and cultures of specific bacteria, especially Klebsiella and Pseudomonas species, point to a bacterial cause of necrotizing sinonasal infection.

Hyperglycemia occurred in 100% of cases in the main group, overweight and obesity - in 78.8% of cases. The study of the relative risk (RR) and the odds ratio of the development of necrotizing rhinosinusitis from the presence of comorbidity showed that in individuals who have

had SARS-CoV-2, necrotizing rhinosinusitis develops against the background of DM2 comorbidity in 100% of cases (RR = 73.7), overweight and obesity (RR=1.3), dyslipidemia (RR=2.3), an increase in the marker of left ventricular distension and a precursor of heart failure NTproBNP by 1.5 times relative to the control group ($p<0.05$), with a high incidence of CVD in history (RR=8.5).

Correlation analysis of the studied factors in the LRS group showed that the level of CRP correlated with the concentration of glucose ($r=0.76$, $p<0.01$), interferon gamma had correlations with the level of glycated hemoglobin, fibrinogen, IL-1beta: IFN-gamma/ HbA1c ($r=-0.57$, $p<0.05$), IFN-gamma/fibrinogen ($r=-0.46$, $p<0.05$), IFN-gamma/IL-1-beta ($r=-0\ .53$, $p<0.01$). IL-6 correlated with TNF-alpha ($r=0.77$, $p<0.0001$), and IL-6/LDL ($r=0.52$, $p<0.02$), IL-6/Cholesterol were found ($r=0.49$, $p<0.03$), IL-6/IL-1Beta ($r=0.62$, $p<0.0001$). The presence of IFN-gamma links with glycemic parameters indicates the contribution of DM-2 and hyperglycemia for more than 3 weeks to the formation of T-cell deficiency and a decrease in interferon production in SARS-CoV-2. The presence of links between IL-6 and lipid spectrum parameters indicates that dyslipidemia contributes to the escalation of inflammation, and this is also exacerbated by the hyperproduction of TNF-alpha, which has a wide range of damaging effects.

According to the results of bacteriological studies, fungi were found in biopsy specimens in 63 (87.5%), and mucormycotic was confirmed in 8 (11.1 %). Necro -inflammatory process with the destruction of bone and soft tissue structures of the SNP is characteristic of mucormycotic. Note that Mucor is an angioinvasive fungus, vascular invasion of hyphae leads to thrombosis and progressive tissue necrosis. An increase in the concentration of D- dimer in our patients may be due to this very reason. Moreover, mucor is sensitive to the availability of iron, an elevated level of which is indicated by an increase in ferritin found in patients in the observation group.

Thus, the study of COVID-19-associated factors revealed the following features: in individuals with necrotizing rhinosinusitis, inflammation is accompanied by hyperproduction of IL-6 and TNF-alpha cytokines, a high level of CRP against the background of an increase in thrombogenic activity, resulting in an increase in D - dimer , as well as accompanied by oxidative stress in view of the trigger pro- oxidant action of free iron against the background of an increase in the level of ferritin ; fungi are found, including Mucor ; there is thrombosis of the cavernous sinus and microthrombosis in the tissues of the SNP, which is the cause of necrosis and destruction of the bone and soft tissue structures of the paranasal sinuses. A decrease in the level of IFN-gamma may be due to the inhibitory effect of SARS-CoV-2 viral proteins and sharply reduces the immunoreactivity of the cell link, contributing to the attachment of an opportunistic infection in the form of mucormycosis. If this is confirmed, it can be argued that an alternative pathway for STAT-3 activation induced by SARS-CoV-2 proteins is triggered, which causes coagulopathy and thrombus formation, a pro- inflammatory state, and T- lymphocytopenia.