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Clinical, Radiological And Laboratory Predictors Of Postcovid Interstitial Pulmonary Disease

Anvar Dalimov Arabboyevich
Doctor Of The Andijan Branch Of The Republican Specialized Medical Center For Emergency Care, Uzbekistan

Dilfuzahon Mamarasulova Zakirjanovna
Md, Associate Professor, Head Of The Department Of Oncology And Medical Radiology, Andijan State Medical Institute, Andijan, Uzbekistan

Nodirbek Ilkhomjon Ogli Yakubov
Assistant, Department Of Oncology And Medical Radiology, Andijan State Medical Institute, Andijan, Uzbekistan

ABSTRACT

The Fergana Valley model was used to study the risk of postcovid interstitial lung disease in patients who have had COVID-19 associated pneumonia with 50% or more of the pulmonary parenchyma affected. Predictors of the formation of postcovid pulmonary fibrosis were determined and a risk assessment scale was developed. It was found that the use of ultrasound scanners in the early postcovid period is informative and is not inferior in terms of predicting fibrosis by serial MSCT.

KEYWORDS

COVID-19, postcovid fibrosis, predictors, ultrasound scanners.

INTRODUCTION

COVID-19 has acquired a pandemic character due to extremely high contagiousness. The social significance of the disease is increasing, in addition to its widespread prevalence, extremely high mortality and a high incidence of life-threatening complications, such as severe pneumonia (10% of patients), acute respiratory distress syndrome in adults (5%) and thrombotic complications. A study of survivors from the COVID-19 pandemic in Italy found that up to 45% still complained of shortness of breath during follow-up visits, an average of 60 days (standard deviation 13.6 days) after the symptom first appeared. A follow-up study by Zhao et al. [8,9,10,11] of pulmonary function and radiology in 55 patients who survived COVID-19 3 months after recovery showed that 71% had residual CT abnormalities, including evidence of interstitial thickening in 27%.

A retrospective analysis by Xiong et al. [4,5,6,7] followed by imaging at 11.6 days of 42 COVID-19

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survivors, 83% showed signs of progression with opacification, interstitial thickening and fibrous streaks. The severity of opacities assessed at initial CT was significantly associated with progression at subsequent CT (P = 0.001). The recent autopsy study by Schwenen et al. [1,2,3] was the first study to document the detection of advanced pulmonary fibrosis involving large areas of disrupted architecture with fibromuscular organization and collagenized fibrosis. Cells and reconstruction similar to those found in idiopathic pulmonary fibrosis were also seen.

MATERIALS AND METHODS

During the first stage of the study, 102 patients were examined, immediately after discharge from the infectious diseases hospital, where they were hospitalized due to COVID-19 associated interstitial pneumonia with pulmonary tissue damage of 50% or more, severe and extremely severe course of the disease. By the time of inclusion in the study, all patients with PCR had a negative SARS-CoV-2 RNA test. The average age of the patients was 49.60 ± 1.15 years. As a control group (CG), 20 healthy volunteers (mean age 51.90 ± 2.53 years) were examined, without signs of respiratory pathology from the cardiovascular systems, including neurogenic ones.

The duration of the febrile period was in the average for the group was 19.93 ± 0.58 days; the average duration of hospitalization in an infectious diseases hospital was 19.78 ± 0.45 days. Upon admission to an infectious diseases hospital, the average volume of pulmonary parenchyma lesions was 67.57 ± 1.15%; by the time of inclusion in the study, MSCT demonstrated a significant decrease in the volume of lung lesions by 65.35 ± 2.25% (to 23.29 ± 1.47 %, p <0.001 reliability of the difference with the initial data). However, despite the recovery, the patients assessed their functional status on the PCFS scale by an average of 2.66 ± 0.09 points. All patients underwent rehabilitation measures, including physiotherapy exercises, antiplatelet therapy, according to indications (in the case of a blood dimer D concentration above 1 ng / l) - anticoagulant therapy and (in the case of a CRP concentration above 4 normal) - anti-inflammatory therapy. By the end of the 2nd month of observation, there was a further decrease in the volume of the affected pulmonary parenchyma (up to 18.38 ± 1.22%, p <0.01 reliability of the difference with the data at the time of inclusion in the study).

RESULTS AND DISCUSSION

Saturation in the patients included in the study was significantly reduced, both in comparison with the conditional norm (93%) and in comparison with the CG (84.90 ± 0.80% versus 97.20 ± 0.21%, p <0.001).

In patients who underwent COVID-19 with a lesion of 50% or more of the pulmonary parenchyma, even after discharge from the hospital, a high concentration of pro-inflammatory markers was observed compared with CG. Thus, the concentration of CRP was 36.75 ± 2.06 mg / l versus 2.80 ± 0.35 mg / l in the CG (p <0.001), ferritin - 206.99 ± 3.34 ng / ml versus 100.00 ± 0, 44ng / ml (p <0.001).

Hematological examination revealed a significant decrease in the concentration of hemoglobin in the peripheral blood in patients who underwent COVID-19: 112.80 ± 1.38 g / l versus 132.40 ± 3.47 g / l (p <0.001), which can

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be explained by the redistribution mechanism of iron deficiency anemia, since iron is used in the molecules of lysosomal enzymes in the effector cells of inflammation. The number of platelets was also reduced in patients who underwent COVID-19: 214.18 ± 7.26 * 109 / L versus 264.90 ± 11.54 * 109 / L in the CG (p <0.001), possibly due to excessive consumption platelets in the process of intravascular thrombus formation, characteristic of this pathology. The activation of thrombus formation is also confirmed by the high concentration of D dimer, which persists despite the ongoing anticoagulant therapy: 0.92 ± 0.05 mg / L versus 0.42 ± 0.05 mg / L (p <0.001).The total number of leukocytes was comparable in the experimental group and in healthy individuals (4.69 ± 0.09 * 109 / l and 4.91 ± 0.09 * 109 / l, respectively, intergroup differences - nd), although within the leukocyte pool in of patients who underwent COVID-19, the relative number of neutrophils increased due to a decrease in the relative proportion of lymphocytes: neutrophils by 74.92 ± 0.63% versus 66.85 ± 1.55% in the CG (p <0.001) and lymphocytes 22.51 ± 0.57% versus 29.30 ± 1.15% (p <0.001). This finding may be explained by the fact that in patients with severe and extremely severe SARS-CoV-2 infection, even by the time of elimination of the infectious agent, inhibition of specific immunity with simultaneous hyperactivation of nonspecific immunity, characteristic of this infectious process, remains.

In the course of the study, a hypothesis was formulated about the diagnostic value of ultrasound in the aspect of diagnosis and dynamic monitoring of the evolution of pulmonary parenchyma lesions in patients with COVID-19 associated interstitial pneumonia. All patients included in the study underwent ultrasound examination after discharge from the infectious diseases hospital and after two months of rehabilitation. Initially, the scoring of the compaction of the pulmonary parenchyma according to the results of ultrasonography was 14.57 ± 0.57 points, after 2 months of rehabilitation, the score decreased by 48.75 ± 3.14% and amounted to 6.88 ± 0.39 points (p <0.001 significance of the difference with the baseline data).

In the course of the study, the correlation relationship of the studied parameters with the volume of the affected pulmonary parenchyma at the time of inclusion in the study based on the results of CT and ultrasound imaging was studied, as well as with the concentration of CRP in the peripheral blood (Table 1). A significant positive strong relationship was revealed between the concentration of CRP and ferritin in the peripheral blood (r = 0.85, p <0.01), which is explained by the fact that both of these parameters are pro-inflammatory markers and are expressed by hepatocytes in response to an increase in the concentration of pro-inflammatory cytokines. Also, a positive average relationship was found between the volume of lung lesions according to the CT scan and ultrasound scan (r = 0.62, p <0.01). The ferritin concentration significantly and directly correlated to a moderate degree with the volume of lung lesions according to CT (r = 0.62, p <0.01) and to a very weak degree with the volume of pulmonary lesions according to ultrasound data (r = 0.29, p <0 , 01). The concentration of CRP was significantly and directly correlated to a weak degree with the volume of pulmonary lesion according to CT data (r = 0.40, p <0.01) and to a very weak degree - with the volume of pulmonary damage according to ultrasonography data (r = 0.21, p < 0.05). The saturation value also

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significantly negatively correlated with the volume of pulmonary lesion (to a weak extent according to CT, r = -0.34, p <0.01, and to a very weak extent according to ultrasound scan, r = -0.29, p <0 , 01), which is logically explained by the main functional role of the pulmonary parenchyma - blood oxygen saturation. But also pathogenetically important is the detected negative very weak relationship between the concentration of CRP and the saturation index (r = -0.22, p <0.05), which confirms the role of inflammation in reducing the functional capacity of the lung tissue.

Significant relationship between the concentration of the marker of intravascular thrombus formation and the volume of pulmonary lesion according to ultrasound scan data (r = 0.27, p <0.01), but not with CT and not with the concentration of CRP.

The duration of the febrile period, the significance was positively weakly correlated with the volume of pulmonary lesion according to CT data (r = 0.42, p <0.01) and the concentration of CRP (r = 0.32, p <0.01), while no correlation was found between the duration of hospitalization and the parameters under study. The relative proportion of lymphocytes significantly negatively and very weakly correlated with the concentration of CRP (r = -0.42, 0 <0.05), which confirms the position of the continuing inhibition of specific immunity in patients with the severity of the activity of systemic inflammation. Accordingly, the total number of leukocytes also negatively correlated with the volume of pulmonary lesion according to CT data (very weak, r = -0.26, p <0.01) and the concentration of CRP (weak, r = -0.33, p <0.01). The relative proportion of neutrophils significantly positively correlated with the volume of pulmonary lesions according to CT data (very weakly r = 0.21, p <0.05), according to USDP data (weakly, r = 0.35, p <0.01) and CRP concentration (weak, r = 0.38, p <0.01).

The relative dynamics of the volume of the pulmonary lesion negatively correlated with the average strength with the volume of the pulmonary lesion at the end of the infectious period (r = -0.45, p <0.01). The volume of residual pulmonary lesion by the end of the 2nd month of rehabilitation correlated reliably directly with the average strength with the volume of pulmonary lesion at the end of the infectious period according to CT (r = 0.31, p <0.01) and USIL (r = 0.38 , p <0.01) and CRP concentration (r = 0.44, p <0.01).

Thus, the study showed that the activity of systemic inflammation was associated with the retention of low activity of specific immunity in patients even after the end of the infectious period of COVID-19 and a large volume of pulmonary lesion according to CT and USDP data.

Table 1.

Coefficients of correlation of the studied parameters with the volume of lesions of the pulmonary parenchyma and the activity of systemic inflammation.

Lethality	correlated with KTreab,%	correlated with USDP reab, score	correlated with CRP, mg / l
USIL reab, score	0,62**		

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Saturation,%	-0,34**	-0,29**	-0,22*
CRP, mg / L	0,40**	0,21*	
Ferritin, ng / ml	0,62**	0,29**	0,85**
d dimer, mg / L	0,18	0,27**	0,19
Leukocytes, * 109 / l	-0,26**	-0,17	-0,33**
Platelets, * 109 / l	-0,13	-0,17	-0,08
Hemoglobin, g / l	-0,12	-0,08	-0,13
Lymphocytes,%	-0,18	0,10	-0,24*
Neutrophils,%	0,21*	0,35**	0,38**
PCFS, score	-0,12	-0,09	-0,05
fever duration, days	0,42**	0,10	0,32**
hospital infectious disease duration, days	-0,10	-0,15	0,08
Age, years	-0,14	0,02	0,16
CT scan 2 months,%	0,31**	0,38**	0,44**
Relates dynamics CT 2 months,%	-0,45**	-0,17	0,11

Note: * reliability of the Pearson correlation coefficient. One sign - p <0.05, two signs - p <0.01.

PREDICTORAL MARKERS OF THE DEVELOPMENT OF POSTOCOUS PULMONARY FIBROSIS AND THE RISK ASSESSMENT SCALE

All patients included in the first stage of the study were retrospectively distributed depending on the formation of fibrosis of the pulmonary parenchyma. The groups were compared according to the studied parameters (Table 2). It was found that the F + and F- groups did not differ in age and duration of hospitalization in an infectious diseases hospital, as well as in the score of functional status impairment (PCFS); however, in the F + group, the duration of the febrile period was significantly longer than in the F- (p <0.001), reflecting the longer duration of the inflammatory response.

It was found that the formation of fibrosis of the pulmonary parenchyma during the rehabilitation period of SARS-CoV2 infection is associated with a large amount of damage to the pulmonary parenchyma during the infectious period (the significance of the difference between the groups is p <0.001), as well as by the time of elimination of the infectious agent (p < 0.001) and by the end of the 2nd month of the rehabilitation period (p <0.001). A decrease in the volume of pulmonary parenchyma lesions by the end of the rehabilitation period was significant in both groups (p <0.001 significant difference with the initial data in both groups), although the

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relative dynamics of the volume of pulmonary parenchyma lesions according to CT data by the end of the infectious period was significantly greater in patients in whom resolution of pneumonia was not accompanied by the formation of pathological fibrosis (-73.50 ± 4.11% versus -59.87 ± 2.33%, p <0.01 - the significance of the difference in the relative dynamics between the groups). By the end of the second month of rehabilitation, the volume of pulmonary lesion according to CT data in the F- group decreased by another -31.09 ± 11.76% (p <0.001 reliability of the difference with the data at the end of the infectious period), while in the F + group it increased insignificantly by 23.25 ± 13.94% (reliability of difference in the volume of pulmonary parenchyma lesion according to CT data: p> 0.05 with data at the end of the infectious period, p <0.001 with initial data, reliability of difference in relative dynamics between groups F + and F- p <0.01).

The volume of pulmonary parenchyma lesion according to USIL data also significantly differed between the groups of patients depending on the tendency to fibrous remodeling of the pulmonary parenchyma: In the F + group, the USIL score at the time of inclusion in the study was higher than in the F- group (p <0.001). During 2 months of rehabilitation, the USDP score significantly decreased in both groups (p <0.001 significance of the difference between the USDP score by the end of the 2nd month of rehabilitation with the baseline data in both groups), however, the relative dynamics was significantly higher in the F- group (-69.61 ± 3.79%) compared with the F + group (-36.44 ± 3.73%, the significance of the difference in the relative dynamics between the groups is p <0.001).

Reflecting the volume of interstitial lung tissue damage and the corresponding degree of gas exchange disturbance, peripheral blood saturation measured at the time of inclusion in the study was significantly lower in the F + group compared to the F- group (p <0.001).

In order to determine the contribution of systemic inflammation to the formation of pulmonary parenchymal fibrosis, the study determined the differences in the concentration of pro-inflammatory markers and the ratio of the proportions of neutrophils and lymphocytes in the composition of the leukocyte pool. It was revealed that in patients of the F + group, the concentration of CRP and ferritin after the end of the infectious period of COVID-19 remained higher than in the F- group (p <0.001 for both indicators). The content of leukocytes in the blood of patients in the F + group was significantly lower with inhibition of the lymphocytic lineage (a decrease in the relative proportion of lymphocytes and an increase in the proportion of neutrophils) compared with the F- group (the reliability of the intergroup difference for the concentration of leukocytes and the relative proportion of neutrophils - p <0.001, for the relative the proportion of lymphocytes p <0.01).

The concentration of hemoglobin in the blood was also significantly lower in patients with a tendency to fibrous remodeling of the pulmonary parenchyma (p <0.05), which, together with a high level of ferritin, indicates the development of redistribution anemia.

By the end of the infectious period, patients with a tendency to develop pulmonary fibrosis compared with patients of the F-group had a significantly higher concentration of d-dimer (p

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<0.001), which indicates ongoing intravascular thrombosis, despite the ongoing anticoagulant therapy. This finding confirms the role of hemocoagulation disorders in the fibrous transformation of the pulmonary parenchyma in response to viral damage. The number of platelets between the F + and F- groups did not differ, indicating the endothelium as the primary link in intravascular thrombosis. The role of endothelium is also supported by in-situ thrombosis characteristic of COVID-19, rather than thromboembolic events.

Table 2

Comparative characteristics of lung damage, systemic inflammation activity and blood composition in the period of early rehabilitation after SARS-CoV2 infection with lung damage of 50% or more, depending on the tendency to fibrous remodeling of the pulmonary parenchyma.

indicator	F+ (n=61)	F- (n=41)	median
CT inf stat,%	71,59±1,20	61,59±1,90***	70,00
CT reab,%	28,79±1,68^^^	15,12±2,11^^^***	20,00
CT 2 months,%	25,57±1,20	7,68±1,16^^***	
USI reab, score	16,79±0,59	11,27±0,90***	16,00
USI 1 month, score	9,61±0,29^^^	2,83±0,26^^^***	7,50
Saturation,%	80,05±1,01	86,12±1,09***	80,00
CRP, mg / L	54,23±2,29	27,29±2,05***	45,00
Ferritin, ng / ml	227,48±3,51	181,68±3,37***	210,50
d dimer, mg / L	1,20±0,06	0,75±0,06***	0,90
Leukocytes, * 109 /l	4,42±0,11	5,09±0,13***	4,65
Platelets, * 109 / l	197,18±9,80	214,73±10,57	176,00
Hemoglobin, g / l	105,85±1,47	113,56±2,50*	108,00
Lymphocytes,%	19,87±0,65	23,12±0,95**	21,00
Neutrophils,%	79,18±0,69	72,51±0,89***	78,00
PCFS, score	2,59±0,12	2,76±0,14	3,00
duration lichor, days	21,57±0,78	17,49±0,73***	21,00
lasts hospital infectious disease, days	20,25±0,52	19,10±0,81	21,00
Age, years	49,80±1,33	48,17±2,07	47,00

Note: * - reliability of intergroup differences, ^ - reliability of differences with the initial data.

One sign - p <0.05, two signs - p <0.01, three signs - p <0.001.

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predictor significance of the detected markers (Table 3.). As can be seen, the presence of these markers is associated with an increased risk of developing fibrosis of the pulmonary parenchyma. Thus, the relative risk of fibrous remodeling of the pulmonary interstitium in patients with a volume of pulmonary lesion in the infectious period of 70% or more is 2.13, with a volume of pulmonary lesion by the end of the infectious period of 20% or more - 2.76, the relative dynamics of the volume of the affected pulmonary parenchyma to at the end of the infectious period 70% or less - 2.04, etc.

Table 3.

Predictor significance of different risk markers for postcovid pulmonary fibrosis

Indicator	Predictor (median)	Frequency of adverse events in patients in the presence of a predictor, number of events / number of individuals with a predictor (%)	Frequency of adverse events in patients with no predictor, number of events / number of persons with no predictor (%)	Xi square	OR of events in the presence of a predictor
CT scan,%	>70	42/52 (80,77%)	19/50 (38,00%)	19,43***	2,13
CT reabil,%	>20	47/56 (83,93%)	14/46 (30,43%)	30,06***	2,76
Relative dynamics of CTreab,%	<70	42/53 (79,25%)	19/49 (38,76%)	17,37***	2,04
USI reab, score	>16	42/52 (80,77%)	19/50 (38,00%)	19,43***	2,13
USI 2 months, score	>7,5	51/51 (100%)	10/57 (19,61%)	68,60***	5,10
Relates the dynamics of ultrasound for 2 months,%	>55%	45/52 (86,54%)	16/50 (32,00%)	31,57***	2,70
Saturation,%	<80%	39/55 (70,91%)	22/47 (46,81%)	6,15*	1,51
CRP, mg / L	>45	49/53 (92,45%)	12/49 (24,49%)	48,91***	3,78

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Ferritin, ng / ml	>210	47/54 (87,04%)	14/48 (29,17%)	35,42***	2,98
D dimer, mg / L	>0,9	42/59 (71,19%)	19/43 (44,19%)	7,55**	1,61
Leukocytes, * 109 / l	<4,65	39/51 (76,47%)	22/51 (43,14%)	11,83***	1,77
Hemoglobin, g / l	<108	37/52 (71,15%)	24/50 (48,00%)	5,72*	1,48
Lymphocytes,%	<21	44/64 (68,75%)	17/38 (44,74%)	5,71*	1,54
Neutrophils,%	>78%	48/59 (81,36%)	13/43 (30,23%)	27,02***	2,69
Fever duration, days	>21	39/53 (73,58%)	22/49 (44,90%)	8,75**	1,64

Note: * - reliability of the chi square test. One sign - p <0.05, two signs - p <0.01, three signs - p <0.001.

The most significant (with high RR) markers were: MSCT at the end of the infectious period 20% or more (RR - 2.76), the concentration of CRP 45 mg / L or more (RR - 3.78) and the relative proportion of neutrophils in the leukocyte population of peripheral blood 78% or more (RR - 2.69). Based on the above analysis, during the study, a scale was developed to assess the risk of developing postcovid fibrous transformation of the pulmonary parenchyma (Table 4). each marker is worth 1 point. In our study, the number of patients with a score according to the developed scale 2 and 3 was 56 people, of the bottom fibrosis developed in 54 (96.43%), among patients with a score of less than 2 (46 patients) fibrosis developed in 7 people (15.22 %, chi square = 69.27, p <0.001). Thus, in patients with a score of 2 or more, the relative risk of fibrous transformation of the pulmonary parenchyma is 6.34 compared with patients with a total score of less than 2. The sensitivity of the proposed scale in terms of the risk of developing postcovid pulmonary fibrosis is 88.52%, specificity is 81, 25%, diagnostic efficiency - 91.18%.

Table 4

Scale for assessing the risk of developing postcovid pulmonary fibrosis (the sum of points is taken into account)

Indicator	criterion	point
CT reabil	>=20%	1
CRP	>=45мг/л	1
neutrophils	>=78%	1

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The sensitivity of the proposed scale in terms of the risk of developing postcovid pulmonary fibrosis is 88.52%, specificity - 81.25%, diagnostic efficiency - 91.18%.

CONCLUSIONS

Thus, The study revealed significantly more pronounced pathological changes that persist even after the elimination of the infectious agent, characterizing hypercoagulation, systemic inflammatory response and depression of specific immunity, in patients with a tendency to fibrous remodeling of the pulmonary parenchyma induced by SARS-CoV2 infection.

A correlation was found between the volume of pulmonary lesion remaining at the end of the infectious period and the concentration of markers of intravascular thrombosis, inflammatory activity and lymphocytopenia.

Based on the results obtained, a risk scale was developed based on the available indicators and allowing to predict the development of postcovid disease lungs with an efficiency of more than 90%.

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