ORIGINAL ARTICLE

Chest x-ray resolution after SARS-CoV-2 infection

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ABSTRACT

Aim To analyse the resolution of chest X-ray findings in relation to laboratory parameters in patients infected with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a two- month follow-up. Analysis of chest X-ray findings in the first few months after the disease is the main goal of our work.

Methods Out of the total of 343 patients chest X-ray findings were followed in 269 patients. Patients were divided into groups according to the severity of findings. D-dimer, inflammatory markers, blood cell count, neutrophil lymphocyte ratio (NLR) were analysed. Chest X-ray was analysed during the hospitalization on the day of admission, on the third, the seventh and the fourteenth day (scoring method was used). After discharge chest X-ray was performed in a two-week follow-up, then after one and two months, and after three months if necessary.

Results Incomplete chest X-ray resolution was identified in 24 (39.34%) patients with severe, 27 (22.31 %) patients with moderate and in three (3.91%) patients with mild findings. Statistical significance was established in overall score by comparison between all groups ($p<0.001$), and in the moderate compared to the mild group ($p=0.0051$). The difference of NLR in the severe compared to the moderate group was observed ($p=0.0021$) and in the severe group compared to the mild group ($p=0.00013$).

Conclusion Chest X-ray findings persisted mostly in the severe group followed by the moderate and mild ones. Long-term follow-up is necessary for the appropriate treatment and prevention of fibrosis, and reduction of symptoms.

Key words: COVID-19, fibrosis, inflammation, lung

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INTRODUCTION

Infection caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is predominantly respiratory infection manifested most commonly as interstitial pneumonia, but also other organs can be involved (1). Vascular complications are very common in SARS CoV-2 disease (COVID-19) (2). Due to pathological changes in the blood vessels of the entire organism, COVID-19 can be presented as a disease involving several tissues and organ systems (3). The pathophysiology of disease can be analysed in two ways – mostly as an analysis of organ involved in the disease, or analysis of tissue involved in pathogenesis of the disease. The second approach seems to be more correct because of ubiquitous involvement of the vessels in the pathogenesis of COVID-19 (4). The second fact to be analysed in COVID-19 is a variant of the disease according to mostly impaired organ (5). According to recent literature, lung variant presented as interstitial pneumonia is present in approximately 85% of cases (5). Involvement of other organs can be seen in other 15% of cases, with or without lung involvement at the same time (7,8).

Pathogenesis of SARS CoV-2 pneumonia has many patterns, different than other known pneumonias. In an earlier phase of the disease, type 1 of the inflammation is presented as implying exudative patterns extensive exudation in interstitial lung tissue, as well as in alveolar space (9,10). Substantial part of lung tissue is out of the function (11). In such a stage of the disease, the usage of mechanical ventilation (non-invasive and invasive) should be considered (12-14). In the immunological pattern, a decrease of absolute number of lymphocytes, as well as an increase in neutrophil to lymphocytes ratio (NLR) predominates (15,16). Moreover, NLR was significantly higher in SARS CoV-2 patients, and this ratio was in correlation with the severity of the disease (16-18).

Chang revealed one of the first attempts for quantification of chest X-ray sequelae (21). At the beginning of the pandemic and as it continues, numerous questions remain unanswered (22). Which one of the clinical signs, laboratory parameters and/or chest X-ray findings are the most important for long time persistent sequelae after SARS CoV-2 infection still remains unknown. How the changes in blood cell count can influence the behaviour of inflammation? Which one of these parameters directs the inflammation towards type 1 (mostly exudative) or towards type 2 inflammation (with formation of granulomatous tissue)? What is the role of cytokines in directing inflammation to a specific type (type 1 or type 2) (23,24).

According to immunological patterns in pathophysiology of SARS CoV-2, type 1 inflammation is predominant (25,26). In late phases of the disease consolidations of lung parenchyma were seen. Condensation of lung tissue, seen on chest X-ray or CT scan, may be suspicious for lung fibrosis in the future. Occurrence of lung fibrosis is a irreversible process, refractory to treatment. However, condensation of lung tissue, seen in radiologic imaging, may be resolved by treatment (27).

Once started pulmonary fibrosis is a long-term process, lasting for several months. Condensation of the lung parenchyma seen in the acute phase of the disease does not imply fibrosis, but if left untreated, fibrosis may occur. Significant sequelae seen on chest X-rays, in the form of diffuse bright shadows, indicate the possibility of fibrosis occurrence (28). SARS CoV-2 infection has been present in the world for a relatively short period of time, about 14 months. For fibrous processes in the lungs, this is not a long period of time, so the findings and conclusions are subject to frequent changes (29).

Resolution of chest X-ray changes after SARS CoV-2 infection is most often effective and rapid, but sometime it is significantly slow (30, 31). Chest CT scan is much more sensitive for diagnosis of lung involvement in COVID-19 infection (32,33). Due to practical purposes repetitive chest CT scanning in post COVID-19 patients is inappropriate for follow up, chest X-ray with temporally combination of chest CT scan is more suitable (34,35).

In recently published literature, we did not find the topic regarding chest X-ray sequelae after COVID-19 infection. However, in our everyday clinical practice, we have observed many cases with prolonged sequelae detected on chest X-rays. A few scoring methods for X-ray analysis were described in recent literature (19,36).

The aim of this research was to find the most appropriate method for chest X-ray analysis suitable for comparison of changes on image findings during a follow-up period.

PATIENTS AND METHODS

Patients and study design

Patients with SARS CoV-2 infection treated at the Department of Pulmonology, Division for COVID-19 infection in General Hospital Tešanj, Bosnia and Herzegovina, were analysed. All 343 patients were divided in groups according to adopted method of classification (38): "mild group" with limited symptoms of upper respiratory tract, cough, sore throat, myalgia, fatigue; "moderate group" with productive cough, temperature >38 °C, prostration, chest X-ray signs of moderate, not severe pneumonia; "severe illness" with prostration, drop of systolic blood pressure below 100 mmHg, extensive chest X-ray findings, decrease of oxygen saturation (spO_2<92%). Original classification includes additional two groups, asymptomatic and critical illness, but these patients were not analysed in our study.

Methods

For all patients standard diagnostic protocol for SARS CoV-2 was performed. Laboratory parameters including complete blood cell count with leukocyte formula, erythrocyte sedimentation rate, arterial blood gas analyses, d-dimer and blood sugar levels, C reactive protein (CRP), lactate dehydrogenase (LDH), creatinine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, coagulation tests were performed. Real time PCR (RT PCR) for SARS CoV-2 infection was performed for all patients (29). The neutrophil-lymphocyte ratio (NLR) was calculated in all patients.

Chest X-ray was performed on the day of admission, on the third and seventh day of hospital stay and on discharge. Unscheduled chest X-rays were performed as it was needed. CT scan was performed in cases when the RT PCR SARS CoV-2 test was negative but suspicion of infection remained very high in order to confirm whether the infection is present or not, according to actual guidelines in use (34).

The method of semi-quantification of chest X-ray findings for the analysis of acute inflammatory changes in the lungs in patients with RT PCR-positive COVID-19 tests used in this research, was the same as the methodology previously used in Italy during SARS CoV-2 pandemic (20,37). The method was based on an analysis of six fields of the lung (18).

The scoring system is based on dividing chest x-ray image into six fields, all of which are analysed separately. Points belonging to each field were summarized as follows: no radiographically detected changes 0 points; changes with only reticular interstitial changes 1 point; appearance of clear radiopacity in less than 50% of the analysed field 2 points; a presence of radiopacity of more than 50% of the analysed field 3 points (20).

Statistical analysis

Data were analysed using descriptive statistics, ANOVA and correlation test. The results of chest X-ray scoring system in time-frame of follow up, CRP, NLR and hematologic parameters in the blood were analysed. Statistical significance was defined at the level of significance with $p<0.05$.

RESULTS

Out of the total of 343 patients, 151 (44.04%) were female and 192 (55.98%) male, 74 patients had no signs of inflammation on chest X-ray images and were excluded from further analysis.

Findings of chest X-ray images were followed up in the time frame of 60 days for 269 patients, 118 (43.87%) females and 151 (56.13%) males (Table 1).

Among the 269 patients in the group with mild disease, there were 77 patients, of which 34 (44.16%) were females and 43 (55.84%) males. In the group with the moderate disease, there

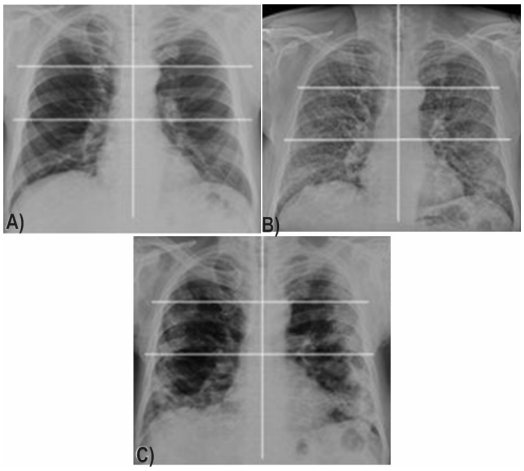

Figure 1. Chest X-ray scoring system. The first patient: A) on admission (score 4); B) after one month (score 7), C) after two months (score 6) (Prnjavorac B, 2021)

Table 1. Laboratory parameters according to the groups

Parameter (reference value)	Mean (± SD) (No of patients) in the group			
	Mild	Moderate	Severe	Total
Age	43.77 (18.93) (82)	62.89 (12.66) (176)	65.26 (13.52) (85)	58.91 (16.88) (343)
CRP (0-8mg/L)	32.28 (51.32) (67)	71.55 (64.8) (143)	133.60 (114.81) (74)	78.45 (78.53) (284)
pO2 (>70mmHg)	58.74 (8.66) (63)	55.17 (10.35) (137)	49.83 (10.5) (71)	54.60 (10.48) (271)
pCO2 (35-45 mmHg)	33.49 (4.40) (63)	30.40 (6.54) (137)	30.00 (5.58) (71)	31.01 (5.99) (271)
sO2 (>92 %)	91.57 (3.56) (27)	88.94 (7.03) (91)	83.83 (10.82) (42)	88.04 (8.22) (160)
Hb (145 (g/L)	151.20 (12.16) (81)	134.08 (17.80) (176)	134.46 (18.51) (84)	138.24 (16.42) (341)
Le (6-10 x106L)	6.53 (2.63) (82)	7.55 (8.21) (176)	7.71 (4.47) (86)	7.35 (6.42) (344)
Lymph (25-30 (%)	27.01 (11.78) (80)	19.66 (9.45) (157)	14.23 (8.56) (76)	20.22 (10.86) (313)
Mid (7-10 (%)	7.13 (1.96) (80)	7.29 (4.26) (156)	6.40 (2.38) (76)	7.08 (3.39) (312)
Gran (65-70%)	65.75 (12.47) (80)	73.18 (10.53) (156)	79.38 (9.09) (76)	72.78 (11.76) (312)
NLR (3-5)	3.21 (2.11) (80)	4.88 (3.03) (157)	8.34 (6.21) (76)	5.30 (4.29) (313)
Plt (150-300x109/L)	230.21 (76.69) (81)	234.64 (124.42) (174)	194.07 (73.17) (84)	223.53 (104.50) (339)
HTC (40-45%)	40.66 (11.81) (81)	40.07 (3.78) (174)	38.52 (5.18) (84)	39.23 (4.22) (339)

SD, standard deviation; CRP, C-reactive protein; pO2, partial pressure of oxygen; pCO2 partial pressure of pCO2; sO2, saturation of O2; Hb, haemoglobin; Le, leucocytes; Lymph, lymphocytes; Mid, monocytes; Gran, granulocytes; Plt, platelets in blood; HTC, haematocrit;

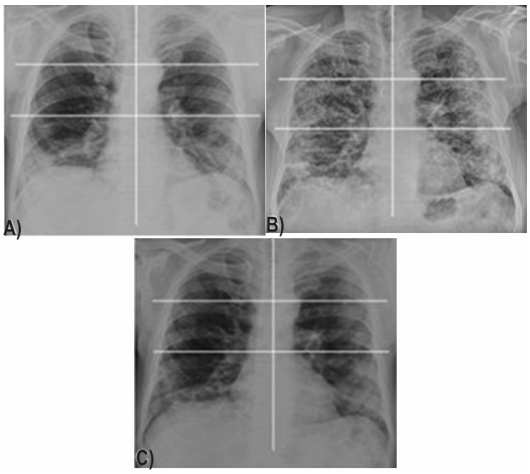

Figure 2. Chest X-ray scoring system. Second patient: A) on admission (score 5), B) after one month (score 13), C) after two months (score 6) (Prnjavorac B, 2021)

Table 2. Chest X-ray scoring according to severity of the disease during two-month follow-up

Disease classification	Score				
	At admission	After 7 days	After 14 days	After 30 days	After 60 days
Severe					
0	0	0	0	7	6
1-4	1	0	2	3	1
5-6	2	0	7	10	8
7-10	2	17	14	12	10
11-14	32	16	11	6	5
15-16	18	10	1	2	0
17-18	1	2	1	0	0
No data	5	16	25	21	31
Total	61	61	61	61	61
Moderate					
0	0	1	9	58	47
1-4	5	3	12	9	3
5-6	1	23	41	19	17
7-10	51	65	38	19	7
11-14	56	24	8	6	0
15-16	15	4	1	0	0
17-18	0	0	0	0	0
No data	3	11	22	20	57
Total	131	131	131	131	131
Mild					
0	0	21	48	44	31
1-4	30	31	11	5	1
5-6	25	10	7	2	2
7-10	18	4	4	1	0
11-14	0	0	0	0	0
15-16	0	0	0	0	0
17-18	0	0	0	0	0
No data	4	11	7	25	43
Total	77	77	77	77	77

were 131 patients, 63 (48.09%) and 68 (51.91%), and in the group with severe illness, there were 61 patients, 21 (34.42%) and 40 (65.58%) females and males, respectively (Table 1).

Statistical significance was established in radiological analysis scoring of the chest X-ray findings, by comparison between all groups ($p < 0.00$) (Figures 1, 2).

Significant negative correlation ($p<0.001$) was established between chest X-ray findings on the 7th day in severe and moderate group (Table 2).

Among other followed parameters in the analysis of haemoglobin, haematocrit, total white blood cell count there was no statistical significance. Platelet count was different only between mild and severe ($p=0.009$) (Table 1).

Neutrophil-lymphocyte ratio was different with statistical significance between mild and moderate group ($p=0.0051$), between mild and severe group ($p=0.00013$); the group with moderate illness was different in comparison with the severe one $p=0.0021$ (Table 1).

The correlation analysis identified negative statistical significance between CRP level and chest X-ray findings at admission and after seven days ($p<0.001$). Partial pressure of oxygen (pO_2) was significantly negatively correlated with CRP level ($p<0.05$).

Residual findings were identified in chest X-ray images in some patients even after 60 days of follow-up (Table 2).

In the group with mild disease in three (out of 77; 3.91%) patients, chest X-ray resolution was not complete. In the group with moderate disease complete resolution was not identified in 27 (out of 121; 22.31%) patients; in the group with severe disease incomplete resolution was identified in 24 (out of 61; 39.34%) patients (Table 2).

DISCUSSION

Late consequences of COVID- 19 infection have been a topic of interest in recent literature. According to the NICE guidelines used in the United Kingdom presence of symptoms related to COVID-19 disease "post COVID 19 syndrome" was defined as persistence of symptoms and signs 5 to 12 weeks after the disease, if it is not possible to relate them as manifestations of other diseases (34). "Long COVID" or post-COVID-19 syndrome are still new clinical entities. Therefore, guidelines for diagnosis and treatment are subject to frequent changes (39).

Our prevalence of post COVID-19 sequelae based on chest X-ray findings was substantially low as it is to be expected knowing that chest CT scan is much more sensitive and rarely performed.

In recently published guidelines chest CT scan is not routinely recommended for any case of SARS CoV-2 patient (12). If the diagnosis is with RT PCR test and chest X-ray findings undoubtedly confirm, there is no need for performing chest CT scan. This radiologic procedure is reserved for those patients with negative RT PCR SARS CoV2 test.

Radiography findings peaked in the time-frame 10-12 days after onset of the disease (40). According to the results of our study, worsening of overall clinical status was in correlation to the very quick progression in chest X-ray findings. Significant changes in the chest X-ray findings were recorded in some cases in a short period of time, approximately 48 hours. Sometimes the highest progression was identified in the end of the second week after admission to the hospital. Our patients were not admitted in the same phase of the disease development. Moreover, most of them were admitted in a later phase of the disease when chest x-ray findings were widespread.

Several studies have reported that NLR may differentiate between mild/moderate and severe/critical groups and probability of death in patients with COVID-19 infection.

A systematic review and meta-analysis of Li et al. (16) concluded that NLR had a good predictive value on disease severity and mortality in patients with COVID-19 infection. The use of NLR can also help clinicians identify potentially severe cases early, which may reduce the overall mortality of COVID-19. In terms of predicting the disease severity, the cut-off value in six studies covered with meta-analysis (17) was higher than 4.5 ("high cut-off value"); seven other studies used a lower cut-off value. Similarly, ten studies that reported the predictive value of NLR on mortality were divided into "high cut-off value" (cut-off$\geq$6.5) and "low cut-off value" (<6.5) subgroups (17). NLR is a marker of severe systemic inflammation and next ongoing studies should consider the question of utility of it for the prediction of COVID-19 disease severity. We applied it on patients in our study with the idea of determining the "cut-off" value for prediction of the disease severity. In our clinical practice we have seen a correlation of NLR and severity of the disease with statistical significance for mild and moderate cases and for severe cases as well. The mean cut-off value for severe cases in our study was 4.88 and 8.34 for moderate and severe cases, respectively.

Our findings in laboratory examinations overlap with worldwide findings in patients with COVID-19 (15), identifying the absolute value of peripheral white blood cells as most often normal or low, and lymphocyte count as decreased. However, in severe cases with COVID-19, the lymphocytes count decreases progressively, while the neutrophils count gradually increases, identifying the reason in excessive inflammation and/or immune suppression caused by SARS-CoV-2 (17).

As expected, in our patients, NLR was correlated with CRP, that is, with the intensity of inflammation. In the study of Yufei et al. among patients

confirmed to have COVID-19, the NLR and CRP of the moderate group were lower than those of severely ill patients (severe, critical and death groups), showing that the NLR, CRP, and lymphocyte percentages were independent risk factors for COVID-19 (18).

It should be noted that according to our study NLR was correlated with chest X-ray findings on the 14th day after admission. This is another confirmation of knowledge that the inflammation is mostly intense in the period of 7-12 days after the onset of the disease (41, 42).

According to the results of our study, chest X-ray imaging identified sequelae up to one year after the acute phase of disease. Chest X-ray imaging alone cannot accurately distinguish granulomatous changes, organized pneumonia and pulmonary fibrosis (43-44). Recovery after SARS CoV-2 disease is delayed in a very high percentage (45).

Among 190 patients recruited for the study of Sonnweber et al. at "zero date" (on discharge from hospital) (46) as many as 77% chest CT scan abnormalities on the first visit and 63% on the second were found. For inflammation and fibrosis chest CT scan is capable of making better differentiation, but due to practical purpose in everyday clinical praxis CT scan is not available, and these findings in our study were avoided (47,48).

Limitations of the study were a short period of follow-up, because the occurrence of fibrosis is a long process, and follow-up should be at least one year.

In conclusion, monitoring of changes in damaged tissue is of great importance for the treatment decision making in post COVID-19 period. Many aspects involved in post-COVID lung pathophysiology should be considered, like dynamic changes of profibrotic interleukin (TGF-β) as well as proinflammatory mediators.

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TRANSPARENCY DECLARATION

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