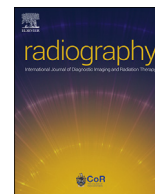




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COVID-19 follow-up: Chest X-ray findings with clinical and radiological relationship three months after recovery

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ABSTRACT

Introduction: To evaluate the radiological sequelae of coronavirus disease (COVID-19) in a mid-term follow-up and investigate their relationship with clinical-radiological findings.

Methods: This prospective study included COVID-19 patients who underwent a CXR three months after discharge. The relationship between CXR score at three months after discharge and clinical findings and previous CXR scores, at admission and before the discharge, were evaluated. Then, based on mid-term follow-up CXR score, patients were divided in Group A (score = 0) and Group B (score ≥ 1), and clinical-radiological findings were compared between two Groups. Finally, we calculated the CXR scores at admission and before the discharge with the highest sensitivity and specificity to predict normal and abnormal CXR score at mid-term follow-up.

Results: The study included 119 patients, mean age 65.9 ± 14.6 years. The oxygen saturation (SaO_2) ($p = 0.0006$), the days of hospitalization ($p < 0.0001$) and the CXR score before the discharge ($p = 0.0091$) were independent factors to predict the mid-term follow-up CXR score. The Group A, 59 (49.6%) patients, had CXR scores at admission and before the discharge lower than Group B. The CXR scores at admission and before the discharge with the highest sensitivity and specificity to predict normal and abnormal CXR score at mid-term follow-up were, respectively, 3 and 2 ($p < 0.0001$).

Conclusions: The radiological abnormalities were present in about half patients three months after discharge, which had higher age, previous CXR scores and longer hospitalization. The SO_2 , days of hospitalization and previous CXR scores were independent factors for predicting the CXR at three months.

Implications for practice: The radiologist with CXR could play a central role in mid to long-term follow-up of COVID-19, assessing the radiological sequelae of patients and identifying those who might require a closer follow-up.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1,2} Though most symptomatic patients have mild flu-like symptoms, a significant minority develop acute respiratory distress syndrome, leading to considerable morbidity and mortality.³ Despite chest computed tomography (CT) is the best modality to detect lung abnormalities,⁴ in case of a high number of hospitalized patients chest X-ray (CXR) is the most common radiological method to monitor the rapid course of COVID-19.^{5,6}

Moreover, some CXR scoring systems, including the Brixia Score, were developed to rate pulmonary involvement according to the type and the extension of lung abnormalities.⁷

Despite several previous studies reporting radiological temporal changes of COVID-19 in-patients until four weeks after the disease onset, most patients who have recovered still have residual abnormalities on CXR: a close follow-up during the hospitalization is essential but may not be enough.^{8–10} Indeed, some studies concluded that long-term follow-up is needed to evaluate the development of irreversible fibrosis.^{11–13} However, the optimal time for follow-up imaging is unknown; the American Thoracic Society does not recommend routine follow-up imaging for patients recovering satisfactorily from community-acquired pneumonia.^{14,15} Trying to solve this problem, George et al.¹⁴ provided a structure for long-term follow-up in COVID-19 patients. However,

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studies about COVID-19 patients after discharge reported different conclusions. According to Mo et al.,¹⁶ the impairment of diffusion capacity is the most common abnormality of lung function in COVID-19 patients and it is associated with the CT pneumonia severity score. Conversely, Frija-Masson et al.¹⁷ reported that more than half of patients exhibited abnormal lung function unrelated to CT severity 12 weeks post discharge.

Nevertheless, studies on a mid-term or long radiological follow-up of sequelae in COVID-19 are scarce.

Therefore, the aim of this study is to evaluate the radiological sequelae of COVID-19 patients in a mid-term follow-up (3 months) and to investigate their relationship with clinical and radiological findings.

Materials and methods

Study population

All procedures on studies involving human participants were performed in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The Institutional Review Board of our Hospital approved the study protocol (013087S). Written informed consent was obtained from all the patients.

In this prospective study from May 01 to June 31, 2021 we enrolled 122 consecutive patients with previous COVID-19 who underwent a follow-up with CXR three months after Hospital discharge.

The inclusion criteria were: COVID-19 infection at admission and COVID-19 resolution at discharge, confirmed by real-time reverse transcription polymerase chain reaction test using nasal and oropharyngeal swab specimens; the execution of a CXR exam at admission and before discharge. The exclusion criteria were: inaccessible clinical data and CXRs images ($n = 3$).

The final study population was composed by 119 patients.

For each patient sex, age and medical history (comorbidities and smoking) were collected.

Moreover, we retrospectively collected the clinical (fever, cough, dyspnea, myalgia, diarrhea, ambient air oxygen saturation, type of ventilation support during hospitalization) and laboratory data (value of lactate dehydrogenase, number of lymphocytes) at hospital admission, the number of days between disease onset and hospital admission, and the number of days of hospitalization. The date of disease onset was defined as the day when the first symptoms were noticed.

CXR evaluation

For each patient, two radiologists in consensus evaluated the CXR at admission, at discharge and at mid-term follow-up (3 months), using an 18-points score system.

In each CXR, lungs were divided into three equal parts: upper, middle and lower, for a total of six zones. A score (from 0 to 3) was assigned to each zone based on lung abnormalities detected on a frontal view, as follow:

0 – no abnormalities;

1 – interstitial infiltrates; defined as septal thickenings and focal or extensive opacity, with the evidence of extravascular structure;
2 – interstitial and alveolar infiltrates (interstitial predominance);
3 – interstitial and alveolar infiltrates (alveolar predominance).

The single scores of the six lung zones were added to obtain an overall CXR score ranging from 0 to 18. To minimize bias, two radiologists were blinded to patient histories.

Relationship of mid-term follow-up CXR score

The mid-term follow-up CXR score was correlated with age, ambient air oxygen saturation (S_{O_2}), days from disease onset to hospital admission, days of hospitalization, CXR scores at admission and before discharge.

Comparison of long-term follow up CXR score

Based on mid-term follow-up CXR score, the patients were divided in two Groups: Group A, with radiological complete recovery (CXR score = 0) and Group B, with radiological abnormalities (CXR score ≥ 1). Age, sex, oxygen saturation (S_{O_2}), days from disease onset to hospital admission, days of hospitalization, CXR scores at admission and before discharge, were compared between the two Groups.

Then we calculated the cut-off CXR score at admission and before discharge with the highest sensitivity and specificity to distinguish patients with normal (score = 0) and abnormal (score ≥ 1) CXR at mid-term follow-up.

Statistical analysis

A dedicated statistical software was used (MedCalc v19.1.6, MedCalc Software, Ostend, Belgium). Continuous variables were displayed as mean \pm standard deviation and categorical variables were reported as counts and percentages.

CXR score was evaluated at admission, before discharge and in a mid-term follow-up (three months after the discharge). Regression analysis was used to study the independent covariates for the mid-term follow-up CXR score. Regression coefficient (b) and partial regression coefficient (r) were calculated.

Mann–Whitney U test and χ^2 test were used to compare, respectively, continuous and categorical variables between the two Groups A and B. A receiving operating characteristic (ROC) curve with area under the curve (AUC) and the Youden's index were used to calculate the cut-off CXR score at admission and before discharge with the highest sensitivity and specificity to distinguish patients with normal (score = 0) and abnormal (score ≥ 1) CXR at mid-term follow-up.

$p < 0.05$ was defined as statistically significant.

Results

Study population

Our study population included 119 patients, 72 (60.5%) males and 47 (39.5%) females and mean age was 65.9 ± 14.6 [95% CI: 63.2–68.5]. Fever was present in 103 (86.6%) patients; it was the most frequent onset symptom. Hypertension was the most frequent comorbidity: it was present in 26 (21.8%) patients. Ambient air S_{O_2} was 88.6 ± 12.4 mm Hg [95% CI: 85.7–91.3]. Lactate dehydrogenase (LDH) was 312.5 ± 146.6 U/L [95% CI: 278.7–346.2] (normal value < 214); lymphocytes count was $1.0 \pm 0.5 \times 10^9$ L [95% CI: 0.9–1.1]. Among the 119 included patients, 11 (9.2%) needed of invasive ventilation during hospitalization.

Time from disease onset to hospital admission was 6.8 ± 3.5 days [95% CI: 6.1–7.4]. The number of days of hospitalization was 17.6 ± 13.1 [95% CI: 14.7–20.4].

The study population's characteristics are summarized in [Table 1](#).

CXR evaluation

A total of 357 CXRs, three CXRs per patient (at admission, before discharge and at mid-term follow-up) were evaluated and scored.

Table 1
Study population characteristics.

Parameters	Value
Epidemiological Data	
Sex – M/F	72 (60.5%)/47 (39.5%)
Age (years)	65.9 ± 14.6 [95% CI: 63.2–68.5]
Clinical Data	
Fever (n, %)	103 (86.6%)
Cough (n, %)	64 (53.8%)
Dyspnea (n, %)	29 (24.4%)
Diarrhea (n, %)	6 (5.0%)
Ambient air S _{O₂} (mm Hg)	88.6 ± 12.4 [95% CI: 85.7–91.3]
Ventilation support during hospitalization	
Face mask NIV	86 (72.3%)
Helmet NIV	22 (18.5%)
IV	11 (9.2%)
Laboratory Data	
LDH (U/L)	312.5 ± 146.6 [95% CI: 278.7–346.2]
Lymphocytes (L)	1.0 ± 0.5 × 10 ⁹ [95% CI: 0.9–1.1]
Comorbidities	
Hypertension (n, %)	26 (21.8%)
Diabetes (n, %)	8 (6.7%)
Neoplasia (n, %)	7 (5.9%)
Smoking (n, %)	17 (14.2%)

Abbreviations – S_{O₂}, oxygen saturation; NIV, non-invasive ventilation; IV, invasive ventilation; CI: confidence interval.

CXR score at admission was 6.1 ± 3.5 (95% CI: 5.2–6.8).
 CXR score before the discharge was 5.4 ± 3.1 (95% CI: 5.0–5.8).
 CXR score at mid-term follow-up was 1.8 ± 1.5 (95% CI: 1.1–2.0), and 59/119 patients (49.6%) had a CXR score of 0.
 CXR scores at admission and before discharge were not statistically different (p = 0.2682).
 CXR scores at admission and at mid-term follow up were statistically different (p < 0.0001).
 CXR scores at discharge and at mid-term follow up were statistically different (p < 0.0001).

Relationship of mid-term follow-up CXR score

Mid-term follow-up CXR score had a negative linear relationship with S_{O₂} (r = -0.6186, p = 0.0006) and a positive linear relationship with the number of days of hospitalization (r = 0.6351, p > 0.0001) and with CXR score before discharge (r = 0.5242, p = 0.0091). The multiple correlation coefficient was 0.8419; it was statistically significant (p < 0.0001). Relationship between mid-term follow-up CXR score and clinical and radiological findings is shown in Table 2.

Comparison of mid-term follow up CXR score

In Group A (CXR score = 0 at three months), composed by 59 (49.6%), age, days of hospitalization and CXR scores at admission and before the discharge were statistically lower than in Group B,

Table 2
Relationship between mid-term follow-up CXR score and clinical and radiological findings.

Clinical and radiological findings	Regression coefficients (b)	Partial correlation coefficient (r)	P
Age	0.2240	0.2126	0.1786
Ambient air S _{O₂}	-0.0572	-0.6186	0.0006
Days before admission	-0.0912	-0.2182	0.2589
Days of hospitalization	0.0864	0.6351	<0.0001
CXR at admission	-0.0051	-0.0116	0.8942
CXR at discharge	0.2242	0.5242	0.0091

Abbreviations – S_{O₂}, oxygen saturation; CXR, chest X-ray.

composed by 60 (50.4%), with a CXR score of 3.0 ± 2.6 (95% CI: 2.4–3.7) at three months. No statistical difference was observed in sex distribution, ambient air S_{O₂}, LDH, lymphocytes count and days between disease onset to hospital admission. In addition, the mean CXR scores at admission and before the discharge were lower in Group A than in Group B, respectively, 4.2 ± 3.6 vs 7.1 ± 2.3 (p = 0.0003) and 3.9 ± 3.1 vs 6.9 ± 3.1 (p < 0.0001). Comparison between the two Groups is illustrated in Table 3.

The cut-off CXR score at admission with the highest sensitivity (85.0%) and specificity (64.0%) to distinguish normal (score = 0) and abnormal (score ≥ 1) CXR at mid-term follow-up was 3 with AUC of 0.757 ± 0.041 (95% CI: 0.670–0.830, p < 0.0001).

The cut-off CXR score before discharge with the highest sensitivity (92.1%) and specificity (61.3%) to distinguish normal (score = 0) and abnormal (score ≥ 1) CXR at mid-term follow-up was 2 with AUC of 0.798 ± 0.043 (95% CI: 0.713–0.867, p < 0.0001).

The ROC curves and the Youden’s index are illustrated in Fig. 1. The Figs. 2 and 3 show the CXRs images of two patients of this study.

Discussion

COVID-19 has spread around the world, causing hundreds of thousands of deaths.²⁰ During the acute phase of the pandemic, many patients with severe COVID-19 were hospitalized and radiological temporal changes were evaluated with a close follow-up; it was necessary, but not sufficient because most patients who have recovered still had residual radiological abnormalities.^{8–10} Therefore, a mid-term follow-up is needed to show eventual clinical-radiological COVID-19 sequelae, such as irreversible fibrosis, and to understand if further diagnostic insights and therapeutic actions are needed.^{11–13} Therefore, we aimed to evaluate the radiological sequelae of COVID-19 patients in a mid-term follow-up and to investigate their relationship with clinical and radiological findings.

Our study enrolled 119 patients who underwent a CXR three months after hospital discharge. The multivariate regression analysis revealed that ambient air S_{O₂} at admission (p = 0.0006), the days of hospitalization (p < 0.0001) and the CXR score before discharge (p = 0.0091) are independent factors for predicting the mid-term follow-up CXR score at three months. In particular, ambient air S_{O₂} has a negative linear relationship, probably because its reduction reflects a higher radiological disease severity, as indicated in previous works.^{18–21} On the contrary, the number of days of hospitalization and CXR score before discharge have a positive linear relationship, probably because they reflect a higher radiological disease severity, which requests a longer recovery time.

Out of the 119 patients included, 59 (49.6%) had a CXR score of 0 (Group A) which indicated a complete radiological recovery 3 months post discharge; the remaining 60 (50.4%) had radiological abnormalities with a CXR score of 3.0 ± 2.6 (Group B). In Group A, age, days of hospitalization, CXR scores at admission and before discharge were statistically lower than in Group B (patients with radiological abnormalities). These results could have different possible explanations. First, we hypothesize that in severe COVID-19 healing takes more time and the probability of a complete recovery is lower; consequently, CXR score at three months is higher. Indeed, older age and a long hospitalization could represent indirect factors of severe COVID-19 infection. In fact, in a recent systematic review and meta-analysis, Del Sole et al.²² showed that patients with severe/complicated SARS-CoV-2 infection had a mean older age (7 years) compared to those with non-severe disease. Moreover, as suggested by previous authors, higher CXR scores at admission and before discharge can represent direct

Table 3
Comparison between Groups with different mid-term follow-up CXR score.

Findings	Group A (n = 59)	Group B (n = 60)	P
Male/Female	36/23	38/22	0.8511
Age (years)	61.8 ± 16.7 (95% CI: 57.5–66.2)	69.8 ± 10.1 (95% CI: 67.0–72.6)	0.0026
So ₂ (mm Hg)	89.8 ± 11.0 (95% CI: 86.4–93.2)	87.3 ± 13.6 (95% CI: 82.9–91.0)	0.3913
Lymphocytes (L)	1.1 ± 0.5 × 10 ⁹ (95% CI: 0.9–1.2)	1.0 ± 0.4 × 10 ⁹ (95% CI: 0.9–1.1)	0.1947
LDH (U/L)	282.9 ± 134.0 (95% CI: 236.7–329.1)	338.4 ± 153.4 (95% CI: 289.3–387.4)	0.1023
Days before admission	6.5 ± 3.5 (95% CI: 5.6–7.5)	7.0 ± 3.5 (95% CI: 6.0–7.0)	0.5404
Days of hospitalization	18.1 ± 12.3 (95% CI: 13.1–23.2)	26.2 ± 17.1 (95% CI: 21.1–31.2)	0.0409
CXR at admission	4.2 ± 3.6 (95% CI: 2.8–5.9)	7.1 ± 2.3 (95% CI: 6.2–7.9)	0.0003
CXR before discharge	3.9 ± 3.1 (95% CI: 3.1–4.7)	6.9 ± 3.1 (95% CI: 6.1–7.7)	<0.0001

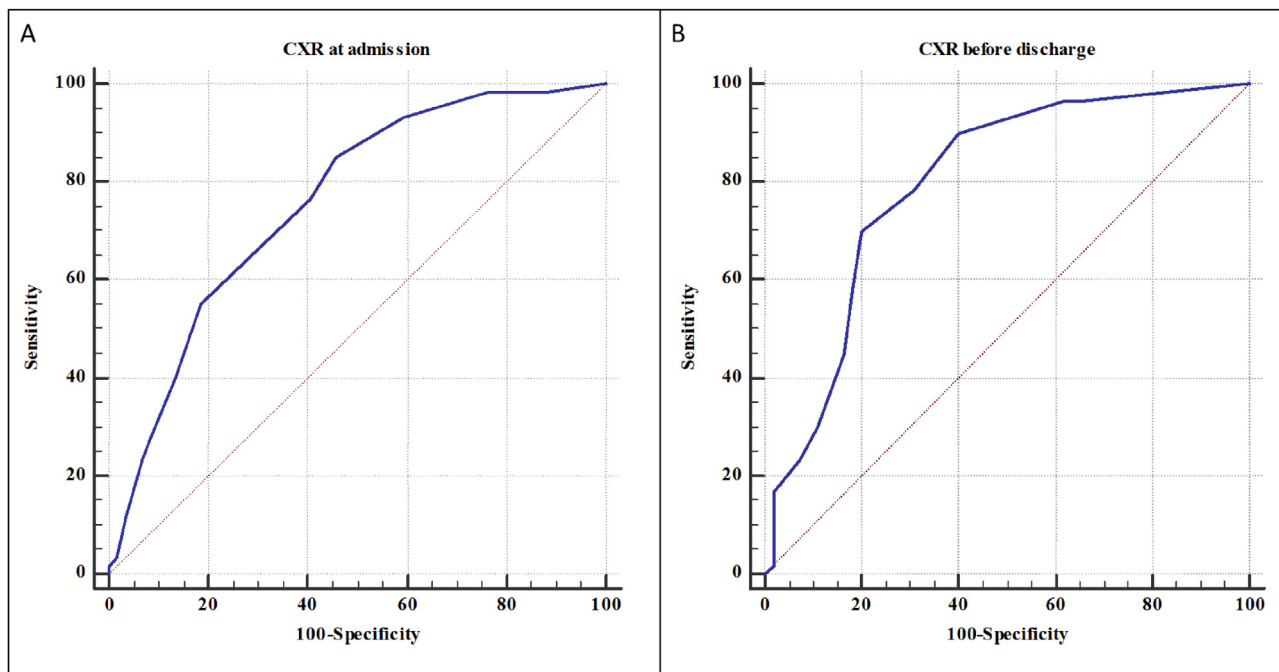


Figure 1. The cut-off CXR score at admission with the highest sensitivity and specificity to distinguish normal and abnormal CXR at mid-term follow-up was 3 (A). The cut-off CXR score before discharge with the highest sensitivity and specificity to distinguish normal and abnormal CXR at mid-term follow-up was 2 (B).

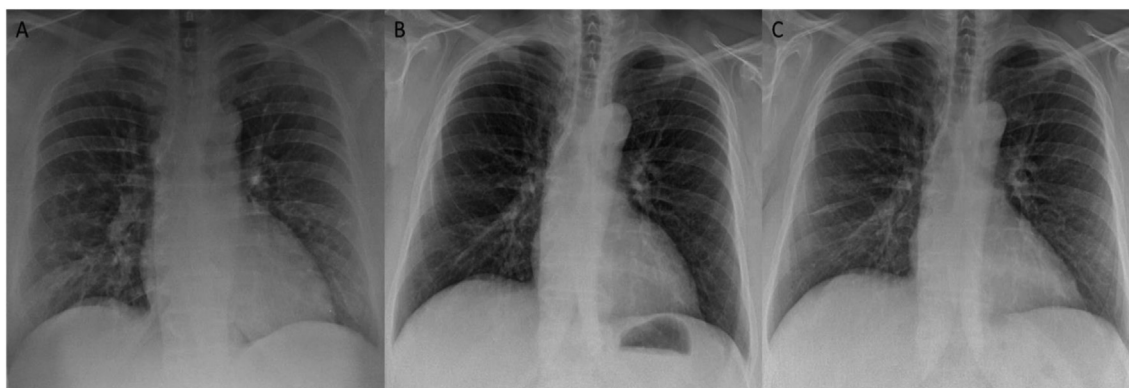


Figure 2. The figure shows the examples of patient with a CXR score of 3 at admission and CXR scores of 0 before the discharge and at three months follow-up.

elements of severe COVID-19 disease.²³ Second, we suppose that older age and longer hospitalization could reduce the physiological lung reserve and postpone the rehabilitative intervention,²⁴ increasing healing times and, consequently, mid-term follow-up CXR score at three months.

Interestingly, CXR score of 3 at admission and CXR score of 2 before discharge were the values with the highest sensitivity and specificity to distinguish the patients with normal (score = 0) and abnormal (score ≥ 1) CXR at mid-term follow-up. These score could be used, as cut-off values, to decide if the mid-term follow-up is

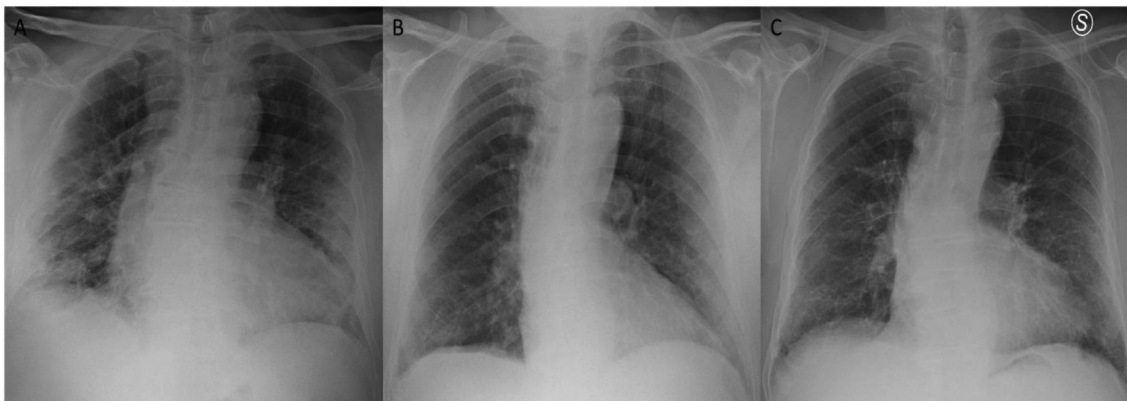


Figure 3. The figure shows the examples of patient with a CXR score of 6 at admission and CXR scores of 4 before the discharge and at three months follow-up.

necessary, avoiding, in this way, an excessive number of CXRs and giving priority to patients with more severe clinical and radiological findings.

An observational study of Zhao et al.¹⁸ evaluated the radiological sequelae of COVID-19 patients three months after discharge. They reported radiological abnormalities in 74.6% of patients and this value was higher than in our work (52.0%); however, they used a chest-CT to assess radiological sequelae and they had a smaller study population than ours (55 vs 119). Finally, similar to our work, they concluded that patients with abnormal radiological findings were generally older than patients with normal radiological images. Moreover, we carried out a literature review about radiological sequelae in similar pandemics induced by SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). In a study about SARS-CoV-1,²⁵ 36% of 110 patients had residual CXR abnormalities three months after discharge and similar results were obtained in MERS survivors.^{26,27} These results indicate that after three months approximately a half - two third of patients have a full CXR resolution.

George et al.¹⁵ proposed a structured long-term follow-up after discharge of patients with previous COVID-19 pneumonia. They suggested use of CXR as the first imaging modality to evaluate discharged COVID-19 patients and, only in the case of radiological abnormalities, they proposed to proceed with clinical assessment and CT evaluation, paying particular attention to patients with previous complicated COVID-19. Based on our results, we agree with this follow-up structure. CXR represents a rapid, widespread and low-dose method allowing evaluation of possible sequelae in COVID-19; it can be a useful and objective first step modality to decide whether to go further with more in-depth diagnostic and expensive exams, such as chest-CT.

Evaluation of clinical data, such as S_{O_2} and, above all, CXR scores at admission and before discharge, we might predict the CXR score at three months and, taking into consideration the patient's age, we could suggest a closer follow-up and a targeted management.

Until an effective vaccine for SARS-Cov-2 is developed, long-term follow-up should be performed to identify and proactively manage sequelae from infection and support patients through pulmonary rehabilitation with the goal of complete recovery.

This study has some limitations. First, it is a mono-centric study; further multi-centric works are needed to confirm our results. Second, CXRs were reviewed in consensus and the inter-observer agreement was not calculated. Third, patients included in the study have predominantly a mild to moderate disease.

Conclusions

Radiological abnormalities persist three months after discharge in a high proportion of COVID-19 patients. S_{O_2} at admission, days of hospitalization and CXR score before discharge are independent factors for predicting the CXR score at three months. Moreover, age, days of hospitalization, CXR scores at admission and before discharge were statistically higher in the Group with radiological abnormalities than in the Group with radiological complete recovery, three months after discharge. The radiologist has an essential role in the detection of the pathology but he also can play a central role in mid to long-term follow-up of COVID-19, assessing the radiological sequelae of patients and identifying those who might require a closer follow-up.

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Data statement

Data to support the findings of this study are not publicly available, however, data is available upon reasonable request from the corresponding author.

Conflict of interest statement

The authors declared no potential conflicts of interests associated with this study.

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None

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