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Laboratory data and broncho-alveolar lavage on Covid-19 patients with no intensive care unit admission

Correlation with chest CT features and clinical outcomes

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Abstract

Broncho-alveolar lavage (BAL) is indicated in cases of uncertain diagnosis but high suspicion of Sars-Cov-2 infection allowing to collect material for microbiological culture to define the presence of coinfection or super-infection. This prospective study investigated the correlation between chest computed tomography (CT) findings, Covid-19 Reporting and Data System score, and clinical outcomes in Coronavirus disease 2019 (Covid-19) patients who underwent BAL with the aim of predicting outcomes such as lung coinfection, respiratory failure, and hospitalization length based on chest CT abnormalities. Study population included 34 patients (range 38–90 years old; 20 males, 14 females) with a positive nucleic acid amplification test for Covid-19 infection, suitable BAL examination, and good quality chest CT scan in the absence of lung cancer history. Pulmonary coinfections were found in 20.6% of patients, predominantly caused by bacteria. Specific correlations were found between right middle lobe involvement and pulmonary co-infections. Severe lung injury (PaO_2/FiO_2 ratio of 100–200) was associated with substantial involvement of right middle, right upper, and left lower lobes. No significant correlation was found between chest CT findings and inflammatory markers (C-reactive protein, procalcitonin) or hospitalization length of stay. Specific chest CT patterns, especially in right middle lobe, could serve as indicators for the presence of co-infections and disease severity in noncritically ill Covid-19 patients, aiding clinicians in timely interventions and personalized treatment strategies.

Abbreviations: BAL = broncho-alveolar lavage, CO-RADS = Covid-19 Reporting and Data System, Covid-19 = Coronavirus disease 2019, CT = computed tomography, NAAT = nucleic acid amplification test, RML = right middle lobe.

Keywords: broncho-alveolar lavage, computed tomography, Covid-19, intensive care unit, outcome

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1. Introduction

Coronavirus disease 2019 (Covid-19), first detected in China, in December 2019, has been rapidly spreading around the world reaching pandemic proportions in March 2020.[1] Covid-19 caused more than 7 million deaths in 4 years (https://covid19.who.int/). The detection of SARS-CoV-2 nucleic acid by nucleic acid amplification test (NAAT) on nasopharyngeal swabs is still considered the gold standard technique (sensitivity 95–97% and specificity 99%) for a definitive diagnosis of Covid-19.[2,3] The excellent NAAT detection rate derives from the analysis of pooled nasal and throat swabs. Conversely, reported sensitivities of salivary, nasal, or throat swabs alone are of 85%, 86%, and 68%, respectively, indicating a higher risk of false negative results.[3] One more issue to be considered is the inadequate sensitivity to detect SARS-CoV-2 in a positive specimen with a low viral load. Therefore, it is recommended to repeat NAAT 24 to 48 hours later if the clinical suspicion of Covid-19 persists.[3] NAAT on broncho-alveolar lavage (BAL) specimens shows higher positive rate (93%) than nasal and pharyngeal swabs (63% and 32%, respectively).[4] Therefore, BAL is indicated in cases of uncertain diagnosis, e.g. negative upper respiratory tract samples and high suspicion of Sars-Cov-2 infection, when clinical and safety criteria are met, still considering the risk for both patients and healthcare staff related to the aerosol generated during the procedure.[5] Moreover, BAL permits the collection of material suitable for microbiological culture to define the presence of co-infection,[6] but it is not always feasible due to eventual contraindications to bronchoscopy and requires a relatively long time to be processed.[7,8]

The role of chest computed tomography (CT) in the management of Covid-19 pneumonia has been widely recognized since the beginning of the pandemic.[9] The Dutch Radiological Society developed Covid-19 Reporting and Data System (CO-RADS) to obtain a standardized assessment of the probability of pulmonary involvement by Covid-19. Subsequently, different scoring systems correlating with disease severity have been developed.[10–12] Although CT is currently considered a crucial tool to optimize patient management,[2] Covid-19 abnormalities on chest CT are nonspecific and such imaging technique shows only moderate sensitivity and specificity for disease severity prediction (75–88% and 46–80%, respectively).[13,14] Consequently, chest CT is reserved to symptomatic patients suspected of being Covid-19 positive and cases of positive NAAT, as well as to evaluate unrelated urgent/emergent conditions.[14]

Some studies tried to find a correlation between chest CT findings and clinical outcomes[15–18] in Covid-19 patients, while others investigated the correlation between BAL features and clinical outcomes,[19–21] but no article focused on BAL analysis performed in Covid-19 patients without admittance to the intensive care unit. Therefore, it seems worthy correlating the CO-RADS and chest CT scores for lobe involvement with the length of hospitalization, the presence of infectious organisms by BAL specimens and laboratory data including PaO_2/FiO_2 ratio (FiO_2 = oxygen inspiratory fraction; PaO_2 = oxygen partial artery pressure), C-reactive protein and procalcitonin levels.

On this background, the current prospective study aimed at investigating the correlation between chest CT findings and clinical outcomes, respiratory failure, and hospitalization length.

2. Materials and methods

The study was approved by the Ethical Review Board (# 18085/OSS and 18099/BIO) and conducted following institutional guidelines, including the Declaration of Helsinki. All patients gave their informed consent to undergo CT examinations and take part in this research protocol.

2.1. Case selection

From January to December 2021, all patients diagnosed with SARS-CoV-2 infection who underwent BAL at the Careggi University Hospital (Florence, Italy) were selected for this study. From the originally enrolled sample made up of 51 consecutive patients, some of them were left out according to the following exclusion criteria (Fig. 1): intensive care unit admission, no BAL data (specimen not suitable), no chest CT examination during hospitalization, poor CT image quality, previous thoracic

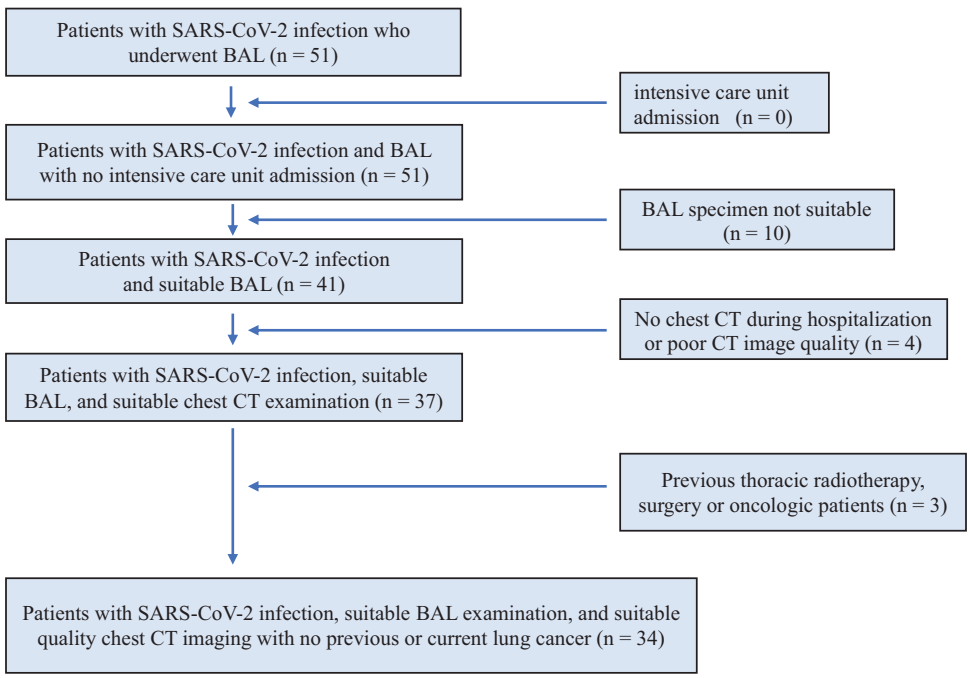

Figure 1. Flowchart of the selection criteria for enrolling patients. Notably, only patients with no intensive care unit admission were enrolled because of the imposition of local authorities that decided to avoid BAL procedures in critical patients. BAL: Broncho-alveolar lavage.

radiotherapy treatment, previous surgery for lung cancer, oncologic patient, underage patient (<18 years).

The final sample consisted of 34 patients (range 38–90 years old; 20 males, 14 females) with a positive NAAT test for Covid-19 infection, suitable BAL examination, and good quality chest CT scan in the absence of previous or current lung cancer. It is worth pointing out that the absence of patients admitted to the intensive care unit was a deliberate choice on behalf of the local authorities and medical doctors who decided not to per-form BAL on patients in critical condition.

2.2. Chest CT

CT examinations were performed using the same 128-row multidetector CT system with a single helical acquisition (Somatom Definition AS 128, Siemens, Erlangen, Germany) from the lower area of the neck to the diaphragm. Scans were carried out in full inspiration with the patient in the supine position. The following parameters were used: tube voltage 100 kV, current × exposure time 150 mAs, rotation time 0.5 s, pixel size 0.465 mm, both thickness and reconstruction intervals 1 mm, beam collimation 128 × 0.6 mm, and pitch 1.2 mm. Post-processing 1-mm-thick sections were obtained on axial, sagittal, and coronal planes using standard filtered back-projection for mediastinal study and very sharp reconstruction kernel (B70f) for parenchymal study. Lung window (window-width 1500 HU, window-level 500 HU) was used for image evaluation. All the images were stored in a picture archiving and communicating system (PACS) and displayed on a 24-inch medical monitor (2048 × 1536 resolution) with a 3-megapixel Barco display (Barco, Kortrijk, Belgium). The software programs originally provided with the systems were used for image assessment. No intravenous contrast agent was administered.

2.3. Image analysis

After assessing scan quality based on motion artifacts and inspiratory level, CO-RADS scores were assigned to define a level of suspicion of Covid-19 infection. CO-RADS is generally considered a tool to diagnose Covid-19 and does not necessarily reflect the severity of lung alterations. Therefore, high scores do not mean that pulmonary CT alterations are extensive but that chest CT findings correspond to a greater probability of patients being infected by Covid-19.[22] CO-RADS ranges from 1 to 5, with higher values representing an increase in the probability to have lung involvement related to SARS-CoV-2 infection, as follows[23]: 0, not interpretable; 1, very low probability; 2, low probability; 3, uncertain; 4, high probability; 5, very high probability. Based on the CO-RADS score, chest CT examinations of the 34 selected patients were evaluated by 2 general radiologists (V.R and G.Z.) with 5 years of experience and trained to establish a level of suspicion of Covid-19 infection.[23] CO-RADS scores were classified into 2 groups to differentiate no or equivocal findings for Covid-19 (scores 2 and 3) from typical findings for Covid-19 (scores 4 and 5). Additionally, the dominant chest CT pattern (consolidation, ground-glass opacity, or ground-glass opacities together with consolidations) and distribution (upper/lower lobes, multifocal, peripheral, or bronchocentric) were assessed. It is worth pointing out that the aforementioned features were assessed to aid in the assignment of the CO-RADS score, but the analysis of their correlation with outcomes was beyond the purpose of the present manuscript.

Finally, each CT examination was scored according to the chest CT score for lobe involvement ranging from 0 to 5 as follows: 0%; 1: <5%; 2: 5% to 25%; 3: 26% to 50%; 4: 51% to 75%; 5: >75%.[15,24] In the current study scores 0-1-2 and 3-4-5 were grouped, corresponding to a parenchymal involvement of 0 to 25% (mild extension of disease) and higher than 25%, (from moderate to severe extension of disease) respectively. A cutoff value of 25% for the differentiation between the 2 groups was chosen because CT abnormalities extended to more than 25% of pulmonary parenchyma need to be considered relevant in terms of pulmonary impairment.[25]

2.4. BAL collection and laboratory data

All bronchoscopies were performed for diagnostic purposes to detect potential coinfections, that are recognized to be simultaneous infections of a host by multiple pathogen species.[26] It shall be reminded that cytological study was not carried out because cytologic analysis during BAL examinations had not been planned yet by the Institution. Following the World Health Organization guidelines, a disposable bronchoscope, the aScopeTM 4 (Ambu A/S, Baltorpbakken, Denmark), was used. Stringent security protocols were strictly enforced, with only essential personnel participating in the endoscopic procedures. Personal protective equipment including respiratory protection (FFP3 masks), gloves, water-resistant gowns, and eye protection was consistently used. In case of unavailability of bronchoscopes, the personnel adhered to the standard High-Level Disinfection procedures for reusable bronchoscopes. BAL specimens were processed in a biosafety level 3 laboratory until inactivation. BAL underwent centrifugation at 400 g for 10 minutes at room temperature. Subsequently, it was treated with a 0.2% SDS and 0.1% Tween-20 solution, heated to 65 °C for 15 minutes, and stored at −20 °C until analysis. Notably, no complications arising from bronchoscopy were found. Hospitalization length of stay, BAL specimens and laboratory data including PaO_2/FiO_2 ratio, C-reactive protein, and procalcitonin levels were investigated.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS® v. 28.0 commercial software (IBM Corp., New York, NY). Numerical data were presented as mean ± standard deviation or median and interquartile range based on their normality. Categorical data were presented as percentages. Association between co-infection (yes vs no) with CO-RADS and chest CT score for lobe involvement, as well as between BAL and CT features with clinical outcomes and especially with predictive features of coinfection, was assessed using the Chi^2 test. Association between PaO_2/FiO_2, hospitalization length, C-reactive protein, and procalcitonin levels with CO-RADS and chest CT score for lobe involvement was assessed using the Mann–Whitney test or Kruskal–Wallis test. As previously mentioned, all chest CT examinations were analyzed by 2 radiologists with 5 years of experience in chest imaging and trained to examine chest CT of Covid-19 patients since the outbreak of the pandemic. The 2 readers were unaware of the NAAT results and disease severity and whenever came to a different conclusion, a discussion was held until they reached a consensus. Cohen's K coefficient was used to estimate inter-reader concordance for the categorical variables defined by the CO-RADS score and lobe involvement score.[27] K values of 0.01 to 0.20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, 0.81 to 0.99, and 1 corresponded to weak, poor, moderate, good, excellent, and perfect agreement respectively. For all the analyses, a *P*-value of <.05 was considered significant.

3. Results

3.1. Patients

Around half of patients had no or equivocal CT findings for Covid-19 and the other half of them had typical findings for Covid-19, since CO-RADS scores 2-3 and CO-RADS 4-5 were assigned in 44.1% and 55.9% of cases respectively. Individual scores were reported in Tables 1 and 2. Inter-reader agreement

was excellent as demonstrated by Cohen's K values, specifically 0.87 for CO-RADS score and 0.84 for lobe involvement.

3.2. Coinfections

Microbiological analysis of BAL specimens revealed the presence of coinfection in 7 out of 34 patients (20.6%); 5 out of 7 coinfected patients showed right middle lobe (RML) involvement. Bacterial coinfections were the more common infections with 4 cases, exactly 2 cases of *Klebsiella pneumonia*, 1 case of *Escherichia coli*, and 1 case of *Pseudomonas aeruginosa*. The other 3 cases were represented by viral and fungal coinfections, namely 1 case each of *Candida albicans*, *Aspergillus fumigatus*, and Cytomegalovirus (Table 3).

Coinfected patients generally showed lung abnormalities within the RML extending more than 25% of pulmonary parenchyma with a statistically significant association both considering the standard 5 degrees (*P*-value .021) and the 25% involvement cutoff (*P*-value .043) (Table 4).

3.3. Respiratory failure

Regarding the grade of respiratory failure, 3 patients (8.8%) showed a PaO_2/FiO_2 ratio > 300 indicating no or mild lung injury, 20 patients (58.8%) had values between 200 and 300 indicating moderate lung injury, whereas 11 patients (32.4%) presented a PaO_2/FiO_2 ratio between 100 and 200 corresponding to severe lung injury according to Berlin classification (27) (Table 3). No statistically significant result emerged from the analysis of the correlation between coinfection and chest CT severity score for the other lobes, as well as between CO-RADS score and both coinfection and PaO_2/FiO_2 ratio. Nevertheless, an involvement >25% of left lower lobe, right upper lobe, and RML was associated to severe respiratory failure consisting in PaO_2/FiO_2 ratio of 100 to 200 in 50.0% (*P*-value .046), 63.6% (*P*-value .016), and 61.5% (*P*-value .008), respectively (Table 5).

3.4. Hospitalization length of stay

Mean hospitalization length of stay was 9.1 days, ranging from a minimum of 2 days and a maximum of 20 days. No significant associations were found between CO-RADS or chest CT scores and C-reactive protein levels, procalcitonin levels, or hospitalization duration.

4. Discussion

In the current series, RML involvement >25% was related to greater disease severity and higher probability of pulmonary coinfection; 5 out of 7 coinfected patients showed RML involvement. No interesting correlations between CO-RADS or chest CT score for lobe involvement and C-reactive protein, procalcitonin, or hospitalization length of stay were found. The current study represented an attempt to correlate chest CT features of Covid-19 patients with clinical outcomes related to lung coinfection by BAL analysis, grade of respiratory failure, and hospitalization length of stay. As mentioned in the introduction, a significant advantage of BAL is the possibility to collect material suitable for microbiological culture to define the presence of co-infection or super-infection. In fact, the hyperinflammatory condition together with the pulmonary damage caused by Covid-19 pneumonia are important risk factors for the acquisition of secondary infections that affect patients' prognosis and mortality rate (6). *K pneumoniae* is the bacteria most frequently responsible of co-infections, followed by Enterococcus and coagulase-negative *Staphylococcus*, whereas *Candida*, *Aspergillus*, *Cryptococcus*, Cytomegalovirus, Herpes Simplex Virus, and Epstein–Barr Virus represent the main fungal and viral infective pathogens, respectively.[28] However, BAL is not always achievable due to specific contraindications to bronchoscopy including severe hypoxemia, current or recent myocardial ischemia, poorly controlled heart failure, significant hypotension or hypertension, exacerbation of asthma or chronic obstructive pulmonary disease, pregnancy, bradycardia or tachycardia, and life-threatening cardiac arrhythmias. Finally, NAAT requires a relatively long time to process, which is not ideal for managing such a rapidly spreading epidemic.[7,8] In this series, no patient was admitted to intensive care unit because the procedure risk was too high for such severely critical patients and the local authorities' regulations did not allow to perform BAL examinations. Slightly more than half of patients (55.9%) showed strong suspicion of Covid-19 infection since high CO-RADS scores corresponded to typical findings for Covid-19. In addition, as it is known in Covid-19 patients, severe extension of lung alterations on CT examinations was primarily observed in lower lobes.[29] BAL specimens demonstrated co-infection in one fifth of the patients (20.6%), almost 3 times the rate (6.9%) emerged from a systematic review by Langford et al.[30] Bacteria were the main cause of lung coinfection. A significant correlation was found between the extent of lung alterations observed in RML on chest CT examinations and coinfection (Fig. 2). Specifically, when a more relevant involvement of RML was found (>25%), there was a greater probability of coinfection and severe respiratory failure. This is rather surprising since RML is the smallest lobe and should contribute less to lung function. Moreover, it should be reminded that it shows deep pleural fissures and only scanty parenchymal bridges and so a difficult and scarce collateral ventilation.[31,32]

Table 1

Covid-19 diagnosis based on CO-RADS. Extension of lung disease was generally larger in lower lobes than upper lobes. Alterations lower and >25% of pulmonary parenchyma practically had the same frequency in the lower lobes.

CO-RADS	N (%)	CO-RADS grouped	N (%)
2	2 (5.9)	2–3	15 (44.1)
3	13 (38.2)		
4	10 (29.4)	4–5	19 (55.9)
5	9 (26.5)		
Total	34 (100)		34 (100)

Table 2

Chest CT score for lobes grouped for extension of lung alterations lower or >25%.

Chest CT score	LUL	LLL	RUL	RML	RLL
Disease extension	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
0–25 %	23 (67.6)	18 (52.9)	23 (67.6)	21 (61.8)	16 (47.1)
>25%	11 (32.4)	16 (47.1)	11 (32.4)	13 (38.2)	18 (52.9)
Total	34 (100)	34 (100)	34 (100)	34 (100)	34 (100)

LUL: left upper lobe. LLL: left lower lobe. RUL: right upper lobe. RML: right middle lobe. RLL: right lower lobe.

Table 3

Frequency of lung coinfection and respiratory failure in the study population. Coinfected patients generally showed lung abnormalities within the RML extending more than 25% of pulmonary parenchyma with a statistically significant association both considering the standard 5 degrees (*P*-value .021) and the 25% involvement cutoff (*P*-value .043).

Coinfection	N (%)
No	27 (79.4)
Yes	7 (20.6)
PaO_2/FiO_2	N (%)
>300	3 (8.8)
200–300	20 (58.8)
100–200	11 (32.4)
PaO_2/FiO_2 grouped	N (%)
100–200	11 (32.4)
>200	23 (67.6)
Total	34 (100)

Table 4

Association of lung coinfection and RML (right middle lobe) involvement.

		Coinfection, N (%)		
Chest CT score		**No**	**Yes**	**Total**
RML	0	0 (0)	1 (100)	1 (100)
	0–5%	11 (100)	0 (0.0)	11 (100)
	5–25%	8 (88.9)	1 (11.1)	9 (100)
	25–50%	4 (50.0)	4 (50.0)	8 (100)
	50–75%	3 (100)	0 (0)	3 (100)
	>75%	1 (50.0)	1 (50.0)	2 (100)
	P-value			.021
RML grouped	0–25%	19 (90.5)	2 (9.5)	21 (100)
	>25%	8 (61.5)	5 (38.5)	13 (100)
	P-value			.043
Total		27 (79.4)	7 (20.6)	34 (100)

Table 5

Association of respiratory failure and chest CT score for single lobe.

		PaO_2/FiO_2 grouped, N (%)		
Chest CT score		**100–200**	**>200**	**Total**
LLL grouped	0–25%	3 (16.7)	15 (83.3)	18 (100)
	>25%	8 (50.0)	8 (50.0)	16 (100)
	Total	11 (32.4)	23 (67.6)	34 (100)
	P-value			.046
RUL grouped	0–25%	4 (17.4)	19 (82.6)	23 (100)
	>25%	7 (63.6)	4 (36.4)	11 (100)
	Total	11 (32.4)	23 (67.6)	34 (100)
	P-value			.016
RML grouped	0–25%	3 (14.3)	18 (85.7)	21 (100)
	>25%	8 (61.5)	5 (38.5)	13 (100)
	Total	11 (32.4)	23 (67.6)	34 (100)
	P-value			.008

LLL: left lower lobe. RUL: right upper lobe. RML: right middle lobe.

Indeed, it emerged that RML is frequently associated with an extensive lung involvement, being an unfavorable prognostic finding as proved by Nardi et al on a very large sample of infected patients.[25] The intrinsic anatomical characteristics of RML make it difficultly reachable by infectious agents, and therefore involved only later than the other lobes. Furthermore, the difficult air drainage of the RML due to the small diameter, considerable length, and acute take-off angle of the right middle bronchus (Fig. 2) could make the RML parenchyma the ideal site for bacterial overlap.[31,32] Finally, the lesser collateral ventilation of the RML than the other lobes, owing to the higher pleural to non-pleural surface ratio, furtherly decreases mucus clearance thus favoring bacterial infections.[33,34]

One third of the patients (32.4%) showed low PaO_2/FiO_2 ratio (values from 100–200) indicating noteworthy lung injury. Such severe respiratory failure was observed in more than half of patients when lung alterations >25% involved left lower lobe (50.0%), right upper lobe (63.5%), and RML (61.5%). Nevertheless, patients investigated in the current study cannot be framed within the Adult Lung Injury Syndrome or Acute Respiratory Distress Syndrome since they were in a state of room air ventilation without ventilatory support.

No correlation was found neither between CO-RADS score and both coinfection and PaO_2/FiO_2 ratio nor between CO-RADS/chest CT severity score and C-reactive protein, procalcitonin, and hospitalization length. Interestingly, *S aureus* was never identified in BAL of recruited patients, even though it was proved to be the pathogen most frequently found in deep respiratory samples of Covid-19 patients.[35] Nonetheless, Gram-negative pathogens as *K pneumoniae*, *E coli*, and *P aeruginosa*, which were identified in this study, are also common microorganisms.[35]

Some interesting imaging-based markers identified in the current study on the prediction of clinical outcomes could be helpful in assisting clinicians during the decision-making process. First, when a more relevant involvement of RML is present, it should increase the suspicion of lung coinfection and therefore culture examination of BAL samples needs to be performed to confirm or exclude the coinfection and start appropriate anti-microbial therapy in order to rapidly improve the patients' health but also avoid the inappropriate use of antibiotics. Then, physicians should pay more attention to clinical conditions of patients in cases of abnormalities on chest CT >25% in left lower lobe, right upper lobe, and RML since respiratory failure could arise in those patients. This study presented 2 main limitations, both due to the small number of patients enrolled and the even smaller number of coinfections because of the restrictions imposed by the local authorities. Further studies analyzing BAL specimens in larger samples are needed to strengthen the findings of this research and improve the understanding of Covid-19 progression and management. Another weakness was that only virological and microbiological features were obtained by BAL. Cytological and immunological features and other biomarkers such as inflammatory indexes or alveolar cellularity defined by BAL cytofluorimetry were not investigated. We are coordinating with other partners of the Consortium for the detection of chest CT alterations in patients with a broader range of features derived from BAL specimens. A strength of this study was the inclusion of only those patients who were not admitted to the intensive care unit thus reducing possible variables associated with even more severe clinical conditions. Nevertheless, a topic of discussion for future research is to perform same or similar correlations in patients with intensive care unit admission by the addition of the death rate as clinical outcome.

5. Conclusions

In the current series of Covid-19 infected patients not admitted to intensive care unit who underwent BAL:

(1) One fifth of them was coinfected, mainly by bacteria. RML involvement was related to greater disease severity and higher probability of pulmonary coinfection than the other lobes.
(2) One third of them showed values of PaO_2/FiO_2 compatible with severe lung injury, usually associated with

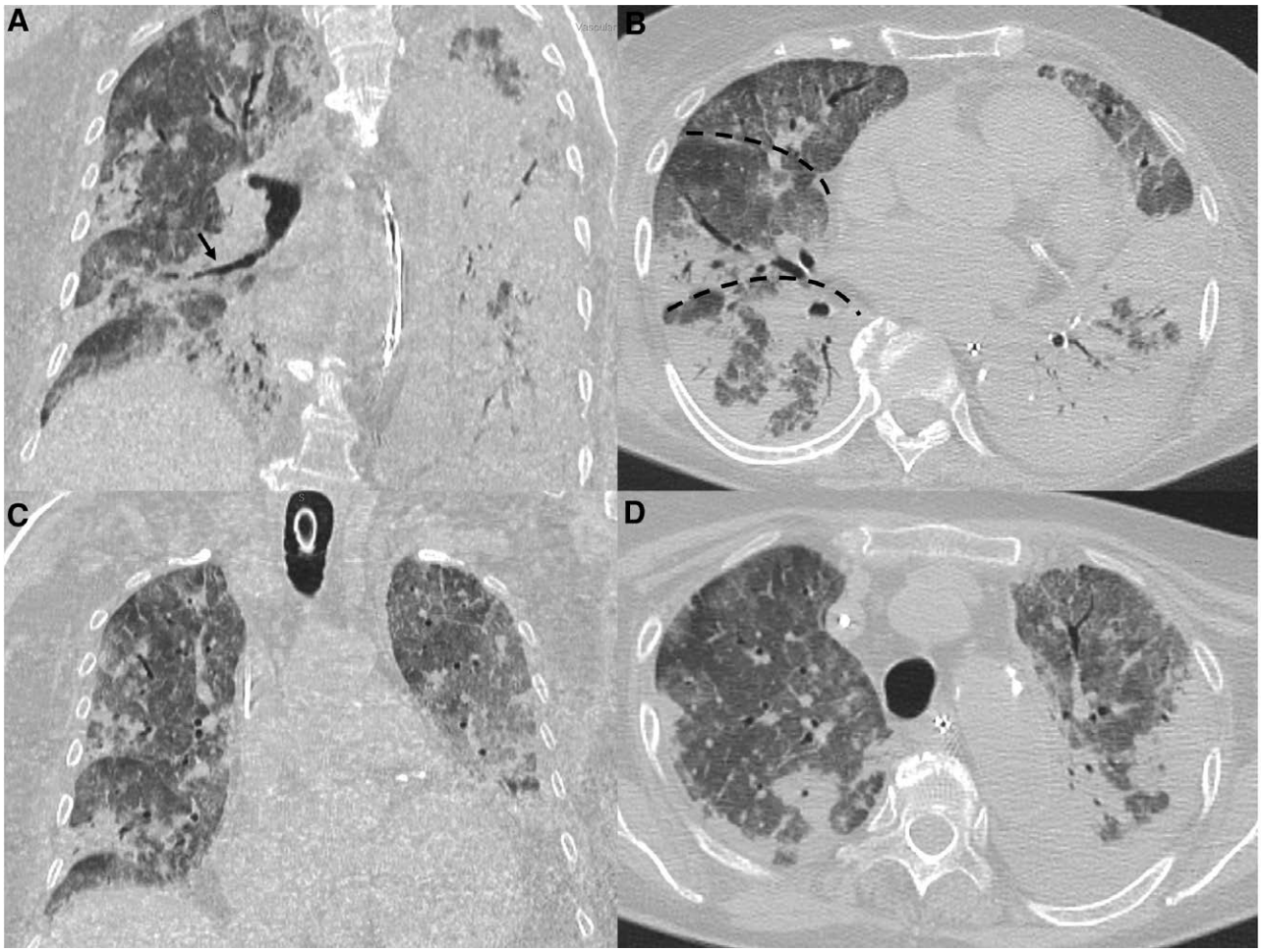

Figure 2. Extensive parenchymal involvement of the lungs including the right middle lobe. (A) Oblique coronal CT reconstruction focused on the right middle bronchus (black arrow) demonstrating its small diameter, length, and acute take-off angle. (B) Oblique axial CT reconstruction at the level of the right fissures of the right middle lobe (dashed black lines). (C and D) Coronal and axial CT reconstructions at the level of the superior vena cava and aortic arch respectively, showing bilateral extensive consolidation of lung parenchyma.

relevant involvement of RML, right upper lobe, and left lower lobe.

(3) No interesting correlations emerged between CO-RADS or chest CT score for lobe involvement and C-reactive protein, procalcitonin, or hospitalization length.

Author contributions

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