Role of the Bronchoalveolar Lavage in Noncritically Ill Patients during the SARS-CoV-2 Epidemic

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Background. Bronchoalveolar lavage (BAL) is currently not recommended in noncritically ill patients for the diagnosis of SARS-CoV-2 infection. Indeed, the diagnosis is based on the RT-PCR test on a nasopharyngeal swab (NPS) and abnormal findings on the chest CT scan. However, the sensitivity of the NPS and the specificity of the chest CT scan are low. Results of BAL in case of negative NPS testing are underreported, especially in the subgroup of immunocompromised patients. Objectives. The added value of BAL in the management of unstable, but noncritically ill patients, suspected of having SARS-CoV-2 infection despite one previous negative NPS and the side effects of the procedure for the patients and the health-care providers, were assessed during the epidemic peak of the COVID-19 outbreak in Belgium. Methods. This multicentric study included all consecutive noncritically ill patients hospitalized with a clinical and radiological suspicion of SARS-CoV-2 infection but with a negative NPS. BAL was performed according to a predefined decisional algorithm based on their state of immunocompetence, the chest CT scan features, and their respiratory status. Results. Among the 55 patients included in the study, 14 patients were diagnosed with a SARS-CoV-2 infection. Interestingly, there was a relationship between the cycle threshold of the RT-PCR and the interval of time between the symptom onset and the BAL procedure (Pearson’s correlation coefficient = 0.8, p = 0.0004). Therapeutic management was changed in 33 patients because another infectious agent was identified in 23 patients or because an alternative diagnosis was made in 10 patients. In immunocompromised patients, the impact of BAL was even more marked (change in therapy for 13/17 patients). No significant adverse event was noted for patients or health-care staff. All health-care workers remained negative for SARS-CoV-2 NPS and serology at the end of the study. Conclusions. In this real-life study, BAL can be performed safely in selected noncritically ill patients suspected of SARS-CoV-2 infection, providing significant clinical benefits that outweigh the risks.

1. Introduction

A novel coronavirus outbreak (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) is spreading all over the world [1]. The diagnosis of this new virus infection is based on the identification of viral RNA on nasopharyngeal swabs and typical abnormal findings on chest CT scan [2]. To date, bronchoalveolar lavage (BAL), which is a cornerstone exam in the setting of respiratory infections [3], is not recommended in noncritically ill patients because the...
virus is highly contagious and the procedure could increase the risk of transmission to health-care providers [4]. If a patient is highly suspected for SARS-CoV-2 infection despite a negative nasopharyngeal swab, it is recommended to repeat the nasopharyngeal swab [5].

There are, however, several drawbacks to this recommendation. First, the sensitivity of the nasopharyngeal swab and the specificity of the chest CT scan for the diagnosis of SARS-CoV-2 infection are low [6, 7]. A number of external factors may affect the viral nucleic acid detection including the adequacy of the nasopharyngeal swab as well as the timing of sampling related to the disease stage (i.e., higher viral loads early in the course of the infection) [8, 9]. Second, the turn-around time for reverse transcriptase polymerase chain reaction (RT-PCR) results was initially quite long (several days), potentially leaving patients without a diagnosis. Finally, this paradigm may not apply to immunocompromised patients, who are at higher risk of developing opportunistic infections [10], which could present with the same radiological expression as SARS-CoV-2 infection. Indeed, there could be overlap of CT imaging features between SARS-CoV-2 and other pulmonary potentially treatable diseases [9].

By establishing a definite or alternative diagnosis, we hypothesize that the expected benefits of BAL could outweigh the potential side effects of the bronchoscopic procedure and the risks for the health-care team in a subset of noncritically ill patients.

The main purpose of our study was therefore to assess the added value of BAL in the management of unstable, but noncritically ill patients, suspected of having SARS-CoV-2 infection despite at least one previous negative nasopharyngeal swab during the epidemic peak in Belgium [11]. We developed a decisional algorithm, allowing an a priori selection of patients eligible for the BAL procedure. We also aimed to evaluate the additional information provided by BAL fluid analysis, as well as the side effects of the procedure for the patients and the health-care providers.

2. Materials and Methods

2.1. Study Design. This retrospective study was conducted at Erasme University Hospital and Iris Sud Hospital in Brussels, Belgium, from March, 13th, 2020 to April, 30th, 2020. This period corresponds to the epidemic peak of the SARS-CoV-2 infection in Belgium [11]. The study protocol was approved by the ethics committees of both participating hospitals (Ref. Nr.: P2020/230) with a waiver of informed consent.

2.2. Population. Consecutive patients were considered for inclusion in the study if they fulfilled the following criteria: age over 18 years and clinical features requiring hospital admission for suspected SARS-CoV-2 infection with a first negative nasopharyngeal swab and a chest CT scan performed within the last 48 hours. Patients requiring intensive care unit (ICU) admission were excluded.

Suspicion of SARS-CoV-2 infection was defined as typical clinical presentation (more than one of the following signs or symptoms: fever, cough, dyspnea, hypoxemia, and flu-like syndrome) associated with any abnormal findings on chest CT scan [12].

Typical chest CT scan features of a SARS-CoV-2 infection included the presence of peripheral bilateral ground glass opacities with or without consolidations and intralobular septa thickening. Atypical chest CT scan manifestations, including bronchial wall thickening, pleural effusions, lymphadenopathy, and pulmonary nodules, were suggestive of another more likely diagnosis than SARS-CoV-2 infection [12].

BAL was performed in patients who were suspected to have SARS-CoV-2 infection but who had at least one previous negative nasopharyngeal swab, according to a predefined decisional algorithm (Figure 1), which took into account the patient’s state of immunocompetence/immunosuppression, the typical or atypical presentation on chest CT scan, and the clinical stability/instability of the patients with regard to supplemental oxygen therapy. So, BAL procedures (rather than repetitive nasopharyngeal swabs) were performed in patients requiring increased oxygen need, suggesting worsening of the respiratory function; patients with atypical CT scan suggestive of an alternate diagnosis than SARS-CoV-2 infection; and immunocompromised patients with atypical CT scan. Clinical outcomes were followed for at least 4 weeks after the BAL procedure.

2.3. Endoscopic Interventions. BAL was performed under local anesthesia with lidocaine 1% [13]. The exams were performed by experienced bronchoscopists, at bedside in a SARS-CoV-2 isolation room, using a disposable video-bronchoscope (Ambu® aScope™, Ballerup, Denmark). Airborne precautions, including FFP2 mask and personal protective equipment, were used. BAL was performed according to standard procedures [14]. Briefly, at least 100 ml and a maximum of 150 ml of sterile isotonic saline, divided in 50 ml syringes, were instilled through the working channel of the bronchoscope into the most affected segment of the lung. The aliquot aspirated after the first syringe injected was always sent for cytological examination. The subsequent aspirated aliquots were put into sterile containers for further laboratory testing.

2.4. Laboratory Testing. Microbiological analysis included microscopic examination; standardized fungal, viral, and bacterial cultures; acid-fast stain; and Mycobacterium tuberculosis PCR and culture. The positive cut-off for bacterial culture was 10,000 colony-forming units per milliliter [15].

For SARS-CoV-2 detection, viral RNA extraction was performed by the m2000 mSample Preparation SystemDNA Kit (Abbott, Chicago, IL, USA) using 1000 μl of a manually lysed sample (obtained from a 700 μl sample + 800 μl lysis buffer from a kit) eluted in 90 μl of elution buffer. A quantitative (q)RT-PCR internal control was added at each extraction. qRT-PCR was performed using 10 μl of the extracted sample in the RealStar® SARS-CoV-2 RT-PCR Kit (Altona-Diagnostics, Hamburg, Germany) with a cut-off set at a cycle threshold (Ct) value of 40. Since quantitative results were not available, the Ct was used as a relative measurement of the target concentration in the PCR reaction—the Ct value being inversely correlated with the amount of RNA present. A Ct value of less than 40 was defined as a positive test result.
indicating a significant viral load in the specimen [8]. A customized TaqMan array card (TAC) was also used for the detection of a larger panel of respiratory pathogens, as described previously [16].

Aspergillus galactomannan assay was performed using the one-stage commercialized immunoenzymatic sandwich microplate assay (Platelia Aspergillus Ag; Bio-Rad, Temse, Belgium) according to the manufacturer’s instructions.

2.5. Endpoints of the Study. The primary endpoint of the study was the impact of BAL results on patient management and outcome. Change of therapeutic management is defined as the initiation or a change in antimicrobial therapy, the start of steroid treatment, and/or the transfer of a patient out of the SARS-CoV-2 isolation ward.

Secondary endpoints included the yield of BAL, defined as the rate of positive detection of SARS-CoV-2 infection and/or the identification of another pathogen that could explain the patient’s clinical features and evolution; the proportion of coinfections, specifically in the subgroup of immunocompromised patients; and the occurrence of adverse events in patients and health-care staff following the endoscopic procedure. Each health-care staff had a nasopharyngeal swab and a blood sample with SARS-CoV-2 immunoglobulin G (IgG) serology within 4 weeks after inclusion of the last patient of our study.

2.6. Statistical Methods. Continuous variables are presented as means with standard deviation (SD) or median with interquartile range (IQR) depending on their distribution and compared with the Mann–Whitney U test. Categorical variables are expressed as number (%) and compared by the chi-square test or the Fisher exact test. The correlation between the SARS-CoV-2 viral load expressed as the Ct value obtained by RT-PCR and the interval of time between the day of symptom onset and the day of the BAL procedure was determined by the Pearson correlation test.

A p value of less than 0.05 was considered statistically significant. The yield of BAL was characterized by the values of sensitivity and accuracy.

3. Results

3.1. Patients’ Characteristics. Between March, 13th, 2020 and April, 30th, 2020, 261 consecutive noncritically ill patients with suspicion of SARS-CoV-2 infection, with a first negative nasopharyngeal (NP) swab were hospitalized in dedicated isolation wards.

BAL was performed in 55 patients (33 men/22 women, mean age 62 ± 16 years), 35 in Erasme Hospital (center 1) and 20 in Iris Sud Hospital (center 2) (Table 1). No statistically significant differences was noted between both centers regarding demographic and baseline patients’ characteristics except for an older age (70 ± 13 vs. 58 ± 16 years, p = 0.006) and a higher number of patients under antibiotic treatment at the time of the procedure (9 patients vs. 5 patients, p = 0.022) in center 2 (Table 1). Twenty-four patients (44%) had 2 negative nasopharyngeal swabs before the BAL.

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**Figure 1:** Decisional algorithm followed for indication of bronchoalveolar lavage (BAL) in noncritically ill patients with suspicion of SARS-CoV-2 infection, with a first negative nasopharyngeal (NP) swab. Stable respiratory status means that the patient has no increase of oxygen need in the past 48 hours. Abbreviations: NP—nasopharyngeal; BAL—bronchoalveolar lavage; HRCT—high-resolution chest CT scan.
Typical symptoms of SARS-CoV-2 infection include the presence of peripheral bilateral ground glass opacities with or without consolidations and intralobular septa thickening.

Fourteen out of 55 patients (25%) with at least 1 initial negative nasopharyngeal swab and who underwent BAL had a positive SARS-CoV-2 RT-PCR at the end of the workup. Thirteen patients (13/14, 93%) were diagnosed through BAL fluid analysis and 1 patient (1/14, 7%) was diagnosed through a further nasopharyngeal swab performed 2 days after the BAL procedure. Using any of these positive RT-PCR results as reference standard, sensitivity and yield of BAL for SARS-CoV-2 diagnosis were 93% (13/14) and 84% (46/55), respectively.

Of the 14 specimens positive for SARS-CoV-2, only 1 patient (7%) was also positive for an additional respiratory pathogen (Serratia marcescens) (Table 2).

The average time from initial disease onset to the first nasopharyngeal swab was $5.3 \pm 5.1$ days and to the BAL procedure was $9.1 \pm 6.9$ days (Table 1). Figure 2 shows the relationship between the viral load, assessed by the Ct of the RT-PCR on BAL obtained from 13 patients infected with SARS-CoV-2, and the time interval between symptom onset and the BAL procedure. A positive correlation ($\text{Pearson's correlation coefficient} = 0.8$, $p = 0.0004$) was observed, suggesting that higher viral loads (inversely related to the Ct value) were detected earlier after the symptom onset in specimens obtained from the lower respiratory tract.

### Table 1: Demographic and baseline characteristics. Typical symptoms of SARS-CoV-2 infection correspond to the presence of more than one of the following signs or symptoms: fever, cough, dyspnea, hypoxemia, or flu-like syndrome. Typical chest CT scan features of a SARS-CoV-2 infection include the presence of peripheral bilateral ground glass opacities with or without consolidations and intralobular septa thickening.

| Comorbidities (%) | All (n = 55) | Center 1 (n = 35) | Center 2 (n = 20) | p value* |
|-------------------|-------------|------------------|------------------|---------|
| Age (y)           | 62.5 ± 15.8 | 58.1 ± 15.9      | 70.1 ± 12.7      | 0.006   |
| Male n (%)        | 33 (60%)    | 20 (57%)         | 13 (65%)         | 0.775   |
| Chronic pulmonary diseases | 14 (25%)   | 8 (23%)          | 6 (30%)          | 0.751   |
| Cardiovascular diseases | 26 (47%)   | 18 (51%)         | 8 (40%)          | 0.575   |
| Diabetes          | 8 (14%)     | 5 (14%)          | 3 (15%)          | >0.999  |
| Digestive diseases | 8 (14%)     | 6 (17%)          | 2 (10%)          | 0.696   |
| Kidney diseases   | 8 (14%)     | 6 (17%)          | 2 (10%)          | 0.696   |
| Immunocompromised n (%) | 17 (31%)   | 14 (40%)         | 3 (15%)          | 0.072   |
| Typical symptoms of SARS-CoV-2 infection n (%) | 31 (56%) | 19 (54%) | 12 (60%) | 0.781 |
| Typical SARS-CoV-2 chest CT features n (%) | 29 (53%) | 17 (49%) | 12 (60%) | 0.575 |
| Number of patients with 2 negative NP swab before BAL n (%) | 24 (44%) | 16 (46%) | 8 (40%) | 0.781 |
| Time between the symptom onset and the BAL (days ± SD) | 9.1 ± 6.9 | 9.1 ± 6.7 | 9.1 ± 7.3 | >0.999 |
| FiO2 (%) | 29.4 ± 10.6 | 30.4 ± 11.5 | 27.6 ± 8.7 | 0.349 |
| Treatment at the time of the BAL n (%) | 30.8 ± 14.7 | 31.6 ± 16.1 | 27 ± 3 | 0.637 |
| Nonimmunocompromised | 28.7 ± 8.4 | 30 ± 7.4 | 27.4 ± 9.3 | 0.183 |
| Antibiotics | 14 (25%) | 5 (14%) | 9 (45%) | 0.022 |
| Hydroxychloroquine | 17 (31%) | 10 (29%) | 7 (35%) | 0.767 |
| Antiviral | 0 | 0 | 0 | NA |

*p value: difference between center 1 and center 2. Abbreviations: NP—nasopharyngeal; SD—standard deviation; y—years; BAL—bronchoalveolar lavage; NA—not applicable.

3.2. BAL Fluid Analysis

#### 3.2.1. SARS-CoV-2 Infection

Fourteen out of 55 patients (25%) with at least 1 initial negative nasopharyngeal swab who underwent BAL had a positive SARS-CoV-2 RT-PCR at the end of the workup. Thirteen patients (13/14, 93%) were diagnosed through BAL fluid analysis and 1 patient (1/14, 7%) was diagnosed through a further nasopharyngeal swab performed 2 days after the BAL procedure. Using any of these positive RT-PCR results as reference standard, sensitivity and yield of BAL for SARS-CoV-2 diagnosis were 93% (13/14) and 84% (46/55), respectively.

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#### 3.2.2. Non-SARS-CoV-2 Infection

Twenty-three out of the 55 patients (42%) were diagnosed with a non-SARS-CoV-2 infection using BAL fluid analysis. Specific infectious agents identified in these patients are summarized in Table 2.

In 18 out of the 55 patients (33%), no specific pathogen was detected in BAL fluid either by RT-PCR or by culture. Among these 18 patients, there was a more likely alternative diagnosis in 10 patients (18%). Indeed, 4 patients presented with a cardiogenic pulmonary edema, 2 with a cryptogenic organizing pneumonia exacerbation, 1 with a rheumatoid arthritis-associated interstitial lung disease exacerbation, 1 with a hepatic pulmonary syndrome, 1 with hypersensitivity pneumonitis, and 1 with sarcoidosis exacerbation. Each patient had at least one additional negative nasopharyngeal swab for SARS-CoV-2 after the BAL procedure. All these patients received specific treatment with good outcomes.
The final diagnosis remained undetermined in the 8 remaining other patients. In 7 (88%) of them, BAL was performed while they received antibiotics. All of them improved under antibiotic treatment and could return home at the end of antibiotic treatment. We assumed that those patients had bacterial pneumonia based on consistent clinical history and good outcome under antibiotic treatment but, indeed, the BAL results had no impact on their therapeutic management.

3.3. Comparison between Immunocompromised and Immunocompetent Patients. The characteristics of immunocompromised patients are summarized in Table 3. No significant difference was observed between the immunocompetent and the immunocompromised group, especially regarding disease severity evaluated by the FiO₂ (Tables 1 and 3), typical or atypical patterns on chest CT, mortality, ICU admission, and discharge rates (data not shown).

Among the 17 immunocompromised patients, only 2 patients (12%) were diagnosed positive for SARS-CoV-2 compared to 32% (12/38) among immunocompetent patients (Table 3). All patients with a negative BAL for SARS-CoV-2 infection (15 patients, 88%) had at least one further negative nasopharyngeal swab for SARS-CoV-2 after the BAL procedure.

3.4. Impact of BAL Results on Patient Management and Outcome. BAL results changed the therapeutic management in 33 patients (60%) because another infectious agent was identified in 23 patients (42%) or because an alternative diagnosis was provided in 10 patients (18%). Among the patients in whom a specific infectious agent was found, the change of therapeutic management consisted in the administration of an antimicrobial treatment and a transfer out of the isolation ward. All patients with an alternative final diagnosis received a specific treatment with a good outcome.

Even more importantly, among the immunocompromised patients, BAL results changed the therapeutic management in 13 patients (76%) because another pathogen was identified in 8 patients (47%) and an alternative diagnosis was made in 5 patients (29%). In the 4 remaining patients, 2 of them were diagnosed with SARS-CoV-2 infection by BAL fluid analysis followed by a slow and progressive improvement of their clinical status and 2 patients with an undetermined diagnosis had good clinical outcome.

3.5. Adverse Events. Transient increasing of FiO₂ (up to a maximum of 60% with no need of ICU admission or invasive ventilation) was the only adverse event related to the BAL procedure in our population. No health-care provider involved in the BAL procedures (8 physicians and 10 nurses) reported any signs or symptoms suggestive of a potential SARS-CoV-2 infection within 4 weeks after inclusion of the last patient of our study, and none tested positive for SARS-CoV-2 on nasopharyngeal swab or for anti-SARS-CoV-2 IgG serology.

4. Discussion

Several scientific pulmonology societies have issued a general recommendation against the use of bronchoscopy in
nonintubated SARS-CoV-2-suspected patients [4]. In our pulmonology department, a well-equipped bronchoscopy suite is run by several pulmonologists specialized in interventional bronchoscopy. From the outset of the SARS-CoV-2 pandemic, we considered that bronchoscopy with BAL could be of added value in the subset of noncritically ill patients suspected of SARS-CoV-2 infection, but who had at least 1 negative nasopharyngeal swab, and selected for BAL procedure because of (1) unstability from a respiratory point of view (increasing FiO₂), (2) atypical CT scan suggestive of an alternative diagnosis, or (3) immunodepression and atypical CT scan. We devised an a priori decisional algorithm and hypothesized that, in this subgroup of patients, the benefit of bronchoscopy with BAL would outweigh the side effects for the patients and the risks for the health-care team.

We applied our algorithm to all consecutive noncritically ill patients suspected of SARS-CoV-2 infection, but with at least 1 negative nasopharyngeal swab, and selected for BAL procedure because of (1) unstability from a respiratory point of view (increasing FiO₂), (2) atypical CT scan suggestive of an alternative diagnosis, or (3) immunodepression and atypical CT scan. We devised an a priori decisional algorithm and hypothesized that, in this subgroup of patients, the benefit of bronchoscopy with BAL would outweigh the side effects for the patients and the risks for the health-care team.

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FIGURE 2: Cycle threshold of the RT-PCR for SARS-CoV-2 in BAL fluid by the interval of time from onset of symptoms at time of BAL procedure in 13 SARS-CoV-2-positive patients. The Pearson correlation coefficient was 0.8, p = 0.0004. Dots and triangle represent the patients alive and dead, respectively, 4 weeks after the BAL. Red markers represent the patients admitted to the ICU. Abbreviations: BAL—bronchoalveolar lavage; RT-PCR—reverse transcriptase polymerase chain reaction.

Interestingly, and for the first time on BAL samples, we have shown a correlation between the viral load and the time
of sampling from symptom onset. The Ct values gradually increased with time interval from symptom onset suggesting that the viral loads in BAL fluid gradually decreased over time with less potential for transmissibility.

Patients with SARS-CoV-2 disease were found to be infrequently coinfected with other respiratory pathogens as shown in a large series of 99 cases from China [20]. Our results are in line with this previous study as the rate of coinfection in SARS-CoV-2-positive noncritically ill patients was 7% (1/14), significantly lower than in SARS-CoV-2-negative patients (23/41, 56%, \( p = 0.002 \)).

In our study, the diagnosis remained undetermined after the BAL procedure in 8 patients. We assumed that these patients could have bacterial pneumonia, with no specific pathogen identified in BAL fluid, but with a favorable clinical and radiological outcome under antimicrobial therapy. In a study including 35 heart transplant recipients [21], the diagnostic accuracy of bronchoscopic samples in bacterial pneumonia was low, most likely due to empiric antibiotic therapy that was used widely before bronchoscopy, as was the case in 7 out of our 8 patients.

Some limitations of this study should be acknowledged. First, the study included consecutive patients but results were analyzed retrospectively. The sample size was relatively small even after the involvement of 2 centers. This is probably due to the strict indications for BAL procedures following a decisional algorithm, during a limited period of time. However, currently, only case reports have been published on the usefulness of BAL fluid analysis after negative nasopharyngeal swab for SARS-CoV-2 [22–25]. A second limitation is that RT-PCR results for SARS-CoV-2 on BAL samples were used as reference to calculate the sensitivity and accuracy of the test. Finally, our patients were highly selected with mild-to-moderate disease, preventing generalization of our results.

In conclusion, our data and analysis have shown in a real-life study during the SARS-CoV-2 pandemic that BAL samples, obtained through bronchoscopy, can be performed in noncritically ill patients suspected of SARS-CoV-2 infection.

### Table 3: Characteristics of immunocompromised patients.

| Patients | Age (y) | Gender | Origin of immunodepression | Other comorbidities | \( \text{FiO}_2 \) at the time of BAL | Microbiological results | Final diagnosis |
|----------|---------|--------|---------------------------|---------------------|-----------------|------------------------|------------------|
| 1        | 53      | M      | Glucocorticoids           | RA-ILD              | 28              | —                      | RA-ILD exacerbation |
| 2        | 61      | F      | Liver transplant          | CKI, HT             | 21              | Haemophilus influenzae  | Haemophilus influenza pneumonia |
| 3        | 63      | M      | Kidney transplant         | CKI, HT, cardiac failure | 30 | Pneumocystis jirovecii | Pneumocystis jirovecii infection |
| 4        | 20      | M      | Heart transplant          | Cardiac failure     | 21              | Influenza A            | Influenza A infection |
| 5        | 35      | M      | Glucocorticoids           | Ulcerative colitis  | 80              | —                      | COP               |
| 6        | 53      | F      | Glucocorticoids           | Acute alcoholic hepatitis, liver failure | 80 | Influenza A            | Influenza A infection |
| 7        | 68      | F      | Glucocorticoids           | Sarcoidosis, HT, diabetes | 35 | SARS-CoV-2            | SARS-CoV-2 infection |
| 8        | 71      | M      | Kidney transplant         | HT, multiple myeloma | 24 | Metapneumovirus        | Metapneumovirus infection |
| 9        | 48      | M      | Untreated HIV             | HT                  | 27              | —                      | Undetermined       |
| 10       | 81      | M      | Chemotherapy              | CML, CKI            | 30              | —                      | Undetermined       |
| 11       | 41      | F      | Combination of immunosuppressive agents | Ankylosing spondylitis | 25 | Chlamydia pneumoniae | Chlamydia pneumoniae infection |
| 12       | 74      | F      | Heart transplant          | CKI, HT, diabetes   | 21              | SARS-CoV-2             | SARS-CoV-2 infection |
| 13       | 58      | F      | Glucocorticoids           | Severe asthma       | 24              | Aspergillus fumigatus  | Invasive aspergilosis |
| 14       | 38      | F      | Glucocorticoids           | Acute alcoholic hepatitis, liver failure | 21 | —                      | Hepatopulmonary syndrome |
| 15       | 71      | M      | Chemotherapy              | CLL, CKI            | 30              | Herpes simplex virus   | Herpes simplex virus infection |
| 16       | 71      | M      | Liver transplant          | HT, AF              | 35              | —                      | Cardiogenic pulmonary edema |
| 17       | 64      | M      | Sarcoidosis               | Emphysema           | 50              | —                      | Sarcoidosis exacerbation |

Abbreviations: M—male; F—female; HIV—human immunodeficiency virus; RA-ILD—rheumatoid arthritis-associated interstitial lung disease; CKI—chronic kidney injury; HT—hypertension; CML—chronic myeloid leukemia; COP—cryptogenic organizing pneumonia; CLL—chronic lymphoid leukemia; AF—atrial fibrillation.
with clinical benefits that outweigh the risks with the condition of properly selecting the patients. We suggest to nuance international recommendations that BAL may be useful in the setting of suspected SARS-CoV-2 infection in selected patients. Further studies on a larger series of patients are necessary to validate the proposed decisional algorithm aimed at selecting the patients who will benefit the most.

Abbreviations

BAL: Bronchoalveolar lavage  
Ct: Cycle threshold  
ICU: Intensive care unit  
IgG: Immunoglobulin G  
IQR: Interquartile range  
RT-PCR: Reverse transcriptase polymerase chain reaction  
qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction  
SD: Standard deviation  
TAC: TaqMan Array card.

Data Availability

All the data are available on request from the authors.

Ethical Approval

The study protocol was approved by the ethics committees of both participating hospitals (Ref. No.: P2020/230) with a waiver of informed consent.

Conflicts of Interest

All the authors declare no conflict of interest in relation with this work.

Authors’ Contributions

OT, EP, BB, CK, SVL, AB, and DL performed the BAL and participated in the writing of this manuscript. DM, IM, MLD, and KE performed different laboratory tests and participated in the writing of this manuscript.

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References

[1] WHO, Novel Coronavirus—China, 2020, January 2020, http://www.who.int/ncov/en/.
[2] T. Li, “Diagnosis and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0),” Emerging Microbes & Infections, vol. 9, no. 1, pp. 582–585, 2020.
[3] K. C. Meyer, “Bronchoalveolar lavage as a diagnostic tool,” Seminars in Respiratory and Critical Care Medicine, vol. 28, no. 5, pp. 546–560, 2007.
[4] M. M. Wahidi, C. Lamb, S. Murgu et al., “American Association for Bronchology and Interventional Pulmonology (AABIP) statement on the use of bronchoscopy and respiratory specimen collection in patients with suspected or confirmed COVID-19 infection,” Journal of Bronchology & Interventional Pulmonology, vol. 27, no. 4, pp. e52–e54, 2020.
[5] X. Xie, Z. Zhong, W. Zhao, C. Zheng, F. Wang, and J. Liu, “Chest CT for typical Coronavirus Disease 2019 (COVID-19) pneumonia: relationship to negative RT-PCR testing,” Radiology, vol. 296, no. 2, pp. E41–E45, 2020.
[6] Y. Li, L. Yao, J. Li et al., “Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19,” Journal of Medical Virology, vol. 92, no. 7, pp. 903–908, 2020.
[7] D. Caruso, M. Zerunian, M. Polici et al., “Chest CT features of COVID-19 in Rome, Italy,” Radiology, vol. 296, no. 2, article 201237, pp. E79–E85, 2020.
[8] L. Zou, F. Ruan, M. Huang et al., “SARS-CoV-2 viral load in upper respiratory specimens of infected patients,” New England Journal of Medicine, vol. 382, pp. 1177–1179, 2020.
[9] T. Ai, Z. Yang, H. Hou et al., “Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases,” Radiology, vol. 296, no. 2, article 200642, pp. E32–E40, 2020.
[10] J. A. Fishman, “Infection in organ transplantation,” American Journal of Transplantation, vol. 17, no. 4, pp. 856–879, 2017.
[11] Sciensano, “COVID-19—Bulletin épidémiologique hebdomadaire du 29 mai 2020,” https://epistat.wiv-isp.be/covid.
[12] S. Salehi, A. Abedi, S. Balakrishnan, and A. Gholamrezanezhad, “Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients,” American Journal of Roentgenology, vol. 215, no. 1, pp. 87–93, 2020.
[13] P. A. Mainland, A. S. Kong, D. C. Chung, C. H. S. Chan, and C. K. W. Lai, “Absorption of lidocaine during aspiration anesthesia of the airway,” Journal of Clinical Anesthesia, vol. 13, no. 6, pp. 440–446, 2001.
[14] N. Radhakrishna, M. Farmer, D. P. Steinfort, and P. King, “A comparison of techniques for optimal performance of bronchoalveolar lavage,” Journal of Bronchology & Interventional Pulmonology, vol. 22, no. 4, pp. 300–305, 2015.
[15] J. Chastre, J. Y. Fagon, M. Bornet-Lecso et al., “Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia,” American Journal of Respiratory and Critical Care Medicine, vol. 152, no. 1, pp. 231–240, 1995.
[16] D. Steensels, M. Reyners, P. Descheemaeker et al., “Clinical evaluation of a multi-parameter customized respiratory ‘Taq-Man’ array card compared to conventional methods in immunocompromised patients,” Journal of Clinical Virology, vol. 72, pp. 36–41, 2015.
[17] C. Huang, Y. Wang, X. Li et al., “Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China,” The Lancet, vol. 395, no. 10223, pp. 497–506, 2020.
[18] W. Wang, Y. Xu, R. Gao et al., “Detection of SARS-CoV-2 in different types of clinical specimens,” Journal of the American Medical Association, vol. 323, no. 18, pp. 1843–1844, 2020.
[19] P. K. C. Cheng, D. A. Wong, L. K. L. Tong et al., “Viral shedding patterns of coronavirus in patients with probable severe
acute respiratory syndrome,” *The Lancet*, vol. 363, no. 9422, pp. 1699-1700, 2004.

[20] N. Chen, M. Zhou, X. Dong et al., “Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study,” *The Lancet*, vol. 395, no. 10223, pp. 507–513, 2020.

[21] J. T. Lehto, V. J. Anttila, J. Lommi et al., “Clinical usefulness of bronchoalveolar lavage in heart transplant recipients with suspected lower respiratory tract infection,” *The Journal of Heart and Lung Transplantation*, vol. 23, no. 5, pp. 570–576, 2004.

[22] P. Winichakoon, R. Chaiwarith, C. Liwsrisakun et al., “Negative nasopharyngeal and oropharyngeal swabs do not rule out COVID-19,” *Journal of Clinical Microbiology*, vol. 58, no. 5, article e00297, 2020.

[23] P. Zhang, Z. Cai, W. Wu et al., “The novel coronavirus (COVID-19) pneumonia with negative detection of viral ribonucleic acid from nasopharyngeal swabs: a case report,” *BMC Infectious Diseases*, vol. 20, no. 1, p. 317, 2020.

[24] G. Gualano, M. Musso, S. Mosti et al., “Usefulness of bronchoalveolar lavage in the management of patients presenting with lung infiltrates and suspect COVID-19-associated pneumonia: a case report,” *International Journal of Infectious Diseases*, vol. 97, pp. 174–176, 2020.

[25] K. J. Ramos, S. G. Kapnadak, B. F. Collins et al., “Detection of SARS-CoV-2 by bronchoscopy after negative nasopharyngeal testing: stay vigilant for COVID-19,” *Respiratory Medicine Case Reports*, vol. 30, p. 101120, 2020.