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Research Article

Diagnostic Utility of Different Respiratory Clinical Specimens in the COVID-19 Era and Risk of Nosocomial Transmission of SARS-CoV2 with Fibrobronchoscopy and Sputum Induction Procedures

Paola Mencarini[1], Gina Gualano[1*], Carlo Pareo[1], Annelisa Mastrobattista[1], Serena Maria Carli[1], Maria Angela Vittoria Licata[1], Assunta Navarra[2], Silvia D'Arezzo[3], Giulia Matusali[4], Maria Cristina Marini[5], Fabrizio Palmieri[1], On Behalf of ReCoVeRI Study Group[6]

[1]Respiratory Infectious Diseases Unit, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS; Rome, Italy

[2]Clinical Epidemiology Unit, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS; Rome, Italy

[3]Microbiology Department and Cell Factory, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS; Rome, Italy

[4]Virology Unit, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS; Rome, Italy

[5]Intensive Care Unit, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS;

[6]On Behalf of ReCoVeRI Study Group

[*]**Corresponding author:** Gina Gualano, Respiratory Infectious Diseases Unit, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS; Rome, Italy

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Abstract

We wanted to retrospectively examine a series of 229 patients hospitalized between March 2020 and January 2022 to evaluate the role of bronchoscopy and induced sputum for the diagnosis of SARS-CoV2 infection and other lung diseases. Furthermore, we wanted to evaluate the risk of nosocomial transmission of SARS CoV2 infection through the two procedures. Broncho alveolar lavage fluid and induced sputum have been shown to be valuable respiratory specimens for difficult or questionable SARS-CoV2 diagnoses and allow the diagnosis of concomitant respiratory infections in more severe patients.

At the same time, by applying an institutional protocol, which involves the use of negative pressure rooms and compliance with airborne, droplet and contact isolation during the execution of these procedures, we have not observed any cases of transmission among dedicated healthcare personnel and among non-COVID19 patients observed during the study period.

Since patients often present with multiple respiratory infections at the same time and given the usefulness of these respiratory specimens for their diagnosis, we believe that extending these precautions to all patients undergoing FBS and sputum induction is necessary, regardless of the clinical suspicion of SARS-CoV2 infection.

Keywords: SARS-CoV2; Fibrobronchoscopy; Sputum induction, Nosocomial transmission

Introduction

Current recommendations suggest that Fibrobronchoscopy (FBS) with Bronchoalveolar Lavage (BAL) in patients with COVID19 should be considered in emergencies and in selected cases, also due to possible procedural risks for the operator and the patient [1,2]. Furthermore, statements have been published according to which induced sputum (IS) is also contraindicated in COVID 19 positive or suspected patients due to the infectious risk [3,4]. When SARS-CoV2 infection is not confirmed by nasopharyngeal swab (NPS), as well as in some cases of persistent infection, the clinician may ask himself whether the symptoms presented by the patient can be attributed to the SARS-CoV2 virus or to other pathogens possibly present. Performing sputum induction and/or FBS with bronchoalveolar lavage allows to look for any persistence of the virus in the lower airways, document the inflammatory pattern of the cells in the alveolar cytogram and the presence/absence of other pathogens that can complicate patient's clinical picture during SARS-CoV2 infection. Cytological examination and bronchial and transbronchial biopsy broaden the diagnostic range of FBS for the purpose of diagnosing neoplastic or inflammatory lung diseases.

Four years after the COVID19 pandemic, a consensus has been reached on the safety of bronchoscopy with bronchoalveolar lavage for patients and operators if infection prevention control (IPC) measures are respected [5], while the position on the safety of induced sputum in COVID19 or suspected COVID19 patients remains negative or uncertain to date [4].

Objectives

We wanted to examine the contribution of BAL and IS for the diagnosis of SARS-CoV2 infection in a cohort of patients with respiratory diseases referred for hospitalization at INMI Spallanzani from March 2020 to January 2022. We also wanted to explore the usefulness of BAL in the diagnosis of other respiratory pathologies found in COVID19 and non-COVID19 patients. Finally, we assessed the risk of SARS-CoV2 transmission when performing FBS and induced sputum during the study period.

Materials and Methods

FBS procedure

Bronchoscopies were performed in the thoracic endoscopy service, in a dedicated negative-pressure ventilation room with 12 air exchanges per hour. The patients in the study were all hospitalized and had already undergone a molecular NPS upon admission, the result of which was known to the operators. Precautions for droplet and airborne transmission were also taken. The operators always wore personal protective equipment which includes gown, gloves, respiratory protection with FFP3 facial filters, and eye protection. FBS was performed with the patient under conscious sedation to improve comfort and tolerance of the examination. Precautions have also been taken to reduce the production of aerosols and droplets generated by the patient.

Induced sputum procedure

It was performed if the patient was unable to deliver a spontaneous sputum sample. In a dedicated room, at negative pressure with 12 air changes per hour, patients were subjected to an aerosol with an ultrasonic nebulizer with 15-20 ml of 3% hypertonic saline solution. If there was a history of asthma, the patient received salbutamol 200-400 mcg and is aerosolized with isotonic saline solution to prevent any bronchoconstriction. The sputum is collected in sterile containers and then sent for microbiological and cytological examination. The operator carrying out the exam will use Personal Protective Equipment (PPE): a) gloves; b) hydro-repellent gowns; c) FFP3 facial filter; d) protective glasses (goggles); e) headgear.

Population examined and results

We retrospectively collected clinical data from a sample of 229 patients who were referred for lung diseases at INMI Spallanzani from March 2020 to January 2022 (Tables 1 and 2): all these patients underwent FBS at least once; 7 patients with SARS-CoV2 infection repeated it twice. All patients performed a molecular NPS for SARS-CoV2 (NPS1) upon admission. A second NPS (NPS2) was performed: a) in case of NPS1 negativity at entry; b) during hospitalization to demonstrate the patient's negativity.

Variables	Total		Covid 19 pneumonia			Non Covid 19 pneumonia			p value
N° of patients	229		79			150			
Mean age (years)	58		61			56			0.075
Male sex	150 (66%)		55 (70%)			95 (64%)			0.341
Comorbidities	**140 (61%)**		**42 (53%)**			**98 (65%)**			IRR 0.8; 95%CI 0.55-1.18; p=0.26
COPD	11		1			10			
Asthma	1		1			0			
Hypertension	19		8			11			
Other cardiovascular diseases	15		4			11			
Diabetes	11		3			8			
Chronic kidney disease/renal failure	10		5			5			
Cirrhosis/liver failure	8		2			6			
HIV infection	30		2 (3%)			28 (19%)			Fisher's exact test; probability=0,00032
Immunity disorder	13		8			5			
Liver transplant	3		0			3			
Malignancy	19		8			11			
Hospitalization ward									
ICU	32 (14%)		21 (27%)			11 (7%)			RR=3.62 (95%CI: 1.84-7.13) p<0.001
Infectious diseases departments	197		58			139			
RT-PCR SARS-CoV2		**Diagnostic**	positive	negative	PCR nd	positive	negative	PCR nd	
NPS 1	229	**73 (92.4%)**	73	6	0	0	150	0	
NPS 2	210	**1**	32	43	0	0	135	0	
Induced sputum	125	**2**	18	11	24	0	56	16	
BAL	236	**3**	30	16	40	0	76	74	
Anti spike antibodies			positive	negative		positive	negative		
IgA	130		29	19		2	80		
IgM	130		20	28		1	81		
IgG	130		35	13		2	80		
IgG anti S	4		4	0					
IgG anti N	4		0	4					
Microbiological findings in BAL	**111 (48%)**		**41 (52%)**			**70 (48%)**			IRR 1.11; 95%CI 0.74-1.66; p=0.59
Haemophilus influenzae	3		1			2			
Streptococcus pneumoniae	2		1			1			
Mycoplasma pneumoniae	2		0			2			
Staphylococcus aureus	3		1			2			
Staphylococcus haemolyticus	1		0			1			
Stenotrophomonas maltophilia	2		1	8 (10%)		1	6 (4%)		RR=2.53; 95%CI 0.91-7.04; P=0.075
Pseudomonas aeruginosa	12		7			5			
Klebsiella pneumoniae	4		4			0			
Enterobacter aerogenes / K. aerogenes	3		2			1			
Klebsiella oxytoca	1		1	9 (11%)		0	5 (3%)		RR=3.41; 95%CI 1.19-9.85; P=0.0229
Enterobacter cloacae	1		0			1			
Citrobacter freundii	2		1			1			
Escherichia coli	3		1			2			
Acinetobacter baumanii	4		3			1			
Hafnia alvei	1		1			0			
Elizabethkingia meningoseptica	1		0			1			
Enterococcus faecium	2		1			1			
Enterococcus faecalis	1		1			0			
Actynomices	3		1			2			
Legionella pneumophila	1		0			1			
Mycobacterium tuberculosis	25 (11%)		5 (6%)			20 (13%)			
NTM	6		1			5			
Pneumocystis jirovecii	8		0			8			
Candida spp	2		2			0			
Aspergillus spp	17 (7%)		6 (8%)			11 (7%)			
Saprochaete clavata	1		0			1			
Lung neoplasms diagnosis	12		4			8			
Kaposi's sarcoma	2		0			2			
Squamous cell carcinoma	3		1			2			
Lung adenocarcinoma	5		1			4			
Metastasis	1		1			0			
Amartoma	1		1			0			
Respiratory diagnosis and complications	**394**		**186**			**208**			IRR=1.7 (95%CI 1.39-2.08; P<0.001
Interstitial pneumonia	101		79 (100%)			22 (15%)			Fisher's exact test; probability<0,0001
PCP	8		0			8			
CMV pneumonia	3		1			2			
Bacterial pneumonia	82		29 (37%)			53 (35%)			RR=1.04; 95%CI 0.72-1.49; P=0.84
Legionellosis	7		0			7			
Lung abscess	7		2			5			
Non-tuberculous mycobacteriosis	6		1			5			
Tuberculosis	26		5 (6%)			21 (14%)			RR=0.45; 95%CI 0.18-1.15; P=0.097
TB MDR	1		0			1			
LTI	13		2			11			Fisher's exact test; probability=0,23
Atelectasis /obstruction	17		15 (19%)			2 (1%)			Fisher's exact test; probability<0.001
ARDS	27		18 (23%)			9 (6%)			RR=3.8; 95%CI 1.79-8.06; P<0.001
Pleural effusion	10		3			7			
TEP	14		6 (8%)			8 (5%)			
PNX/pneumomediastinum	9		4			5			
Fibrosis	2		1			1			
Emphysema	2		0			2			
Bronchiectasis/displasia	10		0			10			
Hemoptysis	14		0			14			Fisher's exact test; probability=0,003
Sepsis	33		19 (24%)			14 (9%)			RR 2.58; 95%CI: 1.37- 4.86; P=0.003
COPD flare-up	2		1			1			
Outcome									
Exitus	23 (11%)		14 (22%)			9 (6%)			RR=2.95; 95% CI 1.34-6.52; P=0.007
Discharged	206		65			141			
Indications for bronchoscopy									
Pulmonary consolidation	48		17			31			
Atelectasis	4		3			1			
Orotracheal control	22		20			2			
Covid 19 suspicion	17		3			14			
TB/Mycobacteriosis suspicion	104		21			83			
Nodules	9		3			6			
Not specified	32		19			13			

Table 1: Study population and results.

SARS-CoV2 RNA has been researched in all respiratory samples with qualitative real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay.

Data relating to age; sex; hospitalization unit; indications for bronchoscopy; comorbidities; SARS-CoV2 research results on NPS, induced sputum and BAL; serology result for SARS-CoV2; other pathogens identified on BAL; lung neoplasms; diagnosis of respiratory diseases and complications; outcome, were collected from clinical documentation and reported in an Excel file for descriptive statistics (Epi info 7.2.5.0; https://www.medcalc.org/calc/) (Table 1).

Seventy-nine patients proved to be affected by SARS-CoV2 infection, whereas the others 150 were affected by other respiratory pathologies and tested negative (Table 2).

Variables	Total	SARS-CoV2 infected	SARS-CoV2 not infected	p-value
N° of patients	229	79 (34%)	150 (66%)	
Median age in years (interquartile range)	58 (46-70)	59 (53-74)	57 (44-68)	0.075
Male sex	150 (66%)	55 (70%)	95 (64%)	0.341

Table 2: Study population.

The frequency of comorbidities at admission was similar both in COVID and non-COVID patients (Table 1). Main comorbidities: hypertension with other cardiovascular diseases (34 cases), followed by HIV infection (30), neoplasms (19 cases), immune diseases (13), COPD and asthma (12), diabetes (11).

Of the 229 patients, 32 (16%) were hospitalized in intensive care: 21/79 (27%) among those suffering from COVID19 and 11/150 (7%) suffering from other lung pathologies, with a significant risk increase for COVID19 patients: RR=3.62 (95% CI: 1.84-7.13) p<0.001 (Table 1).

Overall, 800 respiratory samples were collected from 229 patients. 646 were tested for SARS-CoV2: NPS 439, of which 105 positive and 334 negative; IS 125, of which 85 tested for SARS-CoV2 (18 positive and 67 negative). There were 236 BALs, of which 122 tested for SARS-CoV2: 30 positive and 92 negative (Table 3).

RT-PCR SARS-CoV2		Covid-19 pneumonia				No Covid-19 pneumonia		
		Diagnostic	PCR positive	PCR negative	PCR not done	PCR positive	PCR negative	PCR not done
NPS1	229	73	73	6	0	0	150	0
NPS2	210	1	32	43	0	0	135	0
IS	125	2	18	11	24	0	56	16
BAL	236	3	30	16	40	0	76	74

Table 3: SARS-CoV2 RT-PCR on respiratory samples.

The diagnosis of SARS-CoV2 infection was possible in 79 cases: NPS1 tested positive in 73/79 COVID-19 patients; NPS2 tested positive in one of the 6 NPS1 negative patients; 2 other positive cases were identified by an induced sputum sample and 3 other cases tested positive for SARS-CoV2 on BAL (Table 3).

In COVID-19 patients, detection of SARS-CoV2 RNA in respiratory samples decreased proportionally to the collection time. Taking NPS1 as the initial time point, we classified respiratory samples from COVID-19 patients based on the day of their execution and documented (Figure 1) a range of positivity for SARS-CoV2 of NPS2 from day 1 to day 49 of hospitalization; of the IS from day 1 to 29; of BAL from day 1 to day 40. Negative samples were collected later than positive samples: NPS2 from day 1 to day 62; IS from 1st to 120th day; BAL from the 5th to the 125th day. In Figure 1 we illustrated the dispersion of these samples over time using the box plot method.

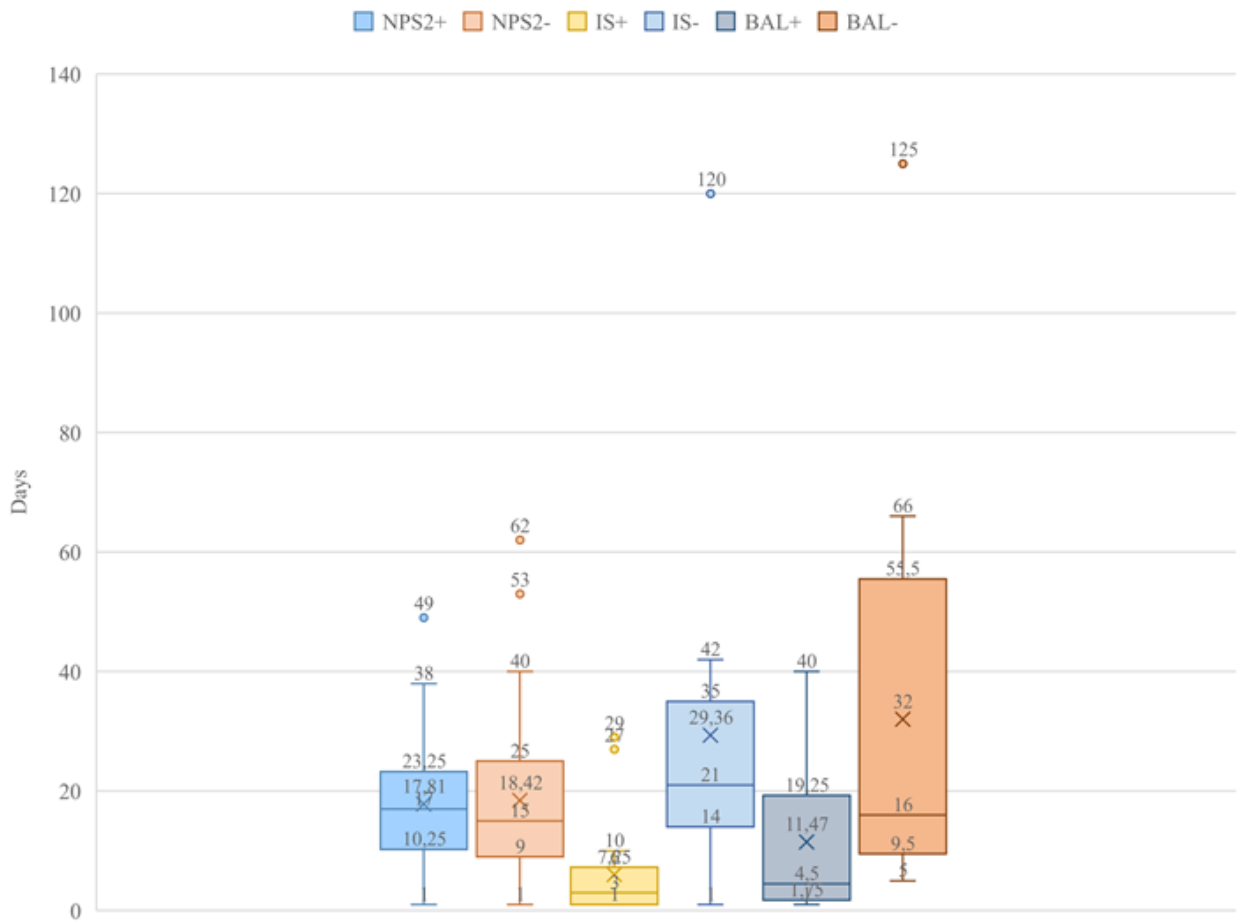

Figure 1: Respiratory samples tested for SARS-CoV2 in patients with COVID-19 pneumonia: time distribution of positive and negative results.

NPS1 testing at admission in our population presented a sensitivity of 92.4%, with specificity of 100% (Table 4). Five COVID-19 cases were negative at NPS1 because they were hospitalized in a late stage of the illness, in fact two were positive at IS and three with BAL. One more patient was negative at admission but developed COVID-19 infection during hospitalization.

	Covid-19 pneumonia	**No Covid-19 pneumonia**	TOTAL	sensitivity	92.4%	84.20% to 97.16%
TNF1 RT PCR +	73	0	73	specificity	100%	97.57% to 100.00%
TNF1 RT PCR -	6	150	156	PPV	100%	95.07% to 100.00%
	79	150	229	NPV	96.2%	92.05% to 98.18%

Table 4: Sensitivity, specificity, positive predictive value, and negative predictive value of NPS1.

NPS2 was diagnostic in only one NPS1 negative clinical case (Table 3). Induced Sputum (IS) was performed mainly for diagnostic purposes, to isolate bacteria, mycobacteria, or fungi. A search for SARS-CoV2 RNA was also performed on 85 samples, with positive results for 18/29 samples obtained from positive COVID19 patients. We illustrated the dispersion of these samples over time using box plots (Figure 1).

The search for SARS-CoV2 sequences in induced sputum proved to be highly specific, but less sensitive than NPS1 in the clinic (Table 5). However, it should be underlined that in two patients out of 79 (2.5%) the positivity of RT-PCR for SARS-CoV2 on IS allowed to make the diagnosis (Table 3).

	Covid-19 pneumonia	**No Covid-19 pneumonia**	**TOTAL**	sensitivity	62%	42.26% to 79.31%
IS RT PCR +	18	0	18	specificity	100%	93.62% to 100.00%
IS RT PCR -	11	56	67	PPV	100%	81.47% to 100.00%
	29	56	85	NPV	84%	76.17% to 89.02%

Table 5: Sensitivity, specificity, positive predictive value, and negative predictive value of induced sputum.

Thirty of 46 (65%) BALs performed on COVID-19 patients tested positive for SARS-CoV 2 RNA, of which 3/79 were diagnostic (3.8%) for three patients who tested negative for NPS. No BAL performed in 76 patients without COVID-19 pneumonia was positive for SARS-CoV2 (Table 3).

In 229 patients, 111 microorganisms were isolated with BAL (48% of cases), apart from viruses: 41 identified in the 86 BAL of COVID-19 patients (52%); 70 in the 150 BAL of non-COVID patients (48%) (Table 1). It should be noted that 9 (11%) of the 79 patients with COVID-19 pneumonia presented Enterobacteriaceae infection versus 5 (3%) of the 150 non-COVID patients (RR=3.41; 95%CI 1.19-9.85; P=0.0229). *Pseudomonas/Stenotrophomonas* infections were also more frequent: 10% vs 4% in COVID patients (RR=2.53; 95%CI 0.91-7.04; P=0.075).

Mycobacterial and *P. jirovecii* infections were more frequent in the non-COVID group. We documented positivity for Aspergillus in 17 cases, with a comparable frequency in the two groups. Remarkably, pulmonary tuberculosis was observed in both groups: 5/79 cases (6%) versus 21/150 cases non-COVID (14%) (RR=0.45; 95%CI 0.18-1.15; P=0.097).

We compared the incidence rate of respiratory disease diagnoses and complications per case (Table 1), and we saw that in the COVID-19 patients' group each patient had on average 2.4 diagnoses, compared to 1.4 diagnoses in the non-COVID group (186 diagnoses/79 COVID-19 positive cases versus 208 diagnoses/150 COVID-negative patients: IRR=1.7 (95% CI 1.39-2.08; P<0.001.

Sepsis was documented in 19/79 (24%) COVID-19 patients and in 14/150 (9%) non-COVID patients (RR 2.58; 95%CI: 1.37-4.86; P=0.003). Atelectasis / obstruction were more frequent in COVID-19 patients: 15/79 (19%) versus 2/150 (1%) of non-COVID (Fisher's exact test; probability<0.001) and ARDS 18/79 (23%) COVID-19 vs 9/150 (6%) in patients non-COVID (RR=3.8; 95% CI 1.79-8.06; P<0.001).

Hemoptysis was more frequent among non-COVID patients: (14/150 patients, 0/79 in COVID patients, Fisher's exact test; probability=0.003).

We believe this data correlates with the observed greater clinical severity of cases with COVID-19. In fact, if we look at the number of deaths, we find 14 deaths among the 79 cases (22%), versus 9 deaths (6%) among the 150 cases without COVID-19 pneumonia (RR=2.95; 95% CI 1.34-6.52; P=0.007).

Discussion

We examined a cohort of 229 patients, 79 with SARS-CoV2 infection and 150 without, all hospitalized for lung pathologies and subjected to bronchoscopy from March 2020 to January 2022. Our patients with COVID-19 pneumonia were characterized by a greater severity of clinical picture compared to non-COVID, evident both for the higher percentage of admissions to intensive care (27% vs 7%) and for the higher mortality observed during hospitalization (22% vs 6%).

The two groups differed significantly in the total number of respiratory disease diagnoses and complications, higher in the COVID19 group (2.4 vs 1.4 diagnoses/patient), interstitial pneumonia (100% vs 15%); atelectasis/obstruction (19% vs 1%); ARDS (23% vs 6%); sepsis (24% vs 9%) (Table 1).

In clinical practice, the NPS for SARS-CoV2 RT-PCR performed upon entry was confirmed to be very sensitive, testing positive in 92% of cases and allowing a diagnosis in 73 out of 79 cases. In one case a second NPS allowed the diagnosis of SARS-CoV2 infection. Induced sputum test for SARS-CoV2 in our study group had a sensitivity of 62%, allowing the diagnosis of 2 of the 79 cases (3%). BAL tested positive for SARS-CoV2 in 30/46 COVID positive cases (65%), being diagnostic in three of the 79 cases (4%).

NPS, tested with RT-PCR assay, is confirmed as the reference diagnostic test, because it is faster, easily repeatable, and sensitive. Induced sputum and bronchoscopy are often performed with a certain delay because they require dedicated spaces, specific equipment and trained medical personnel to avoid nosocomial transmission of infectious agents during their execution. Normally, the execution of induced sputum and FBS with BAL in COVID-19

patients is dictated by the need to identify concomitant respiratory pathologies. However, in our case series, these two types of respiratory sample allowed the diagnosis of SARS-CoV2 infection in 5 out of 79 COVID patients (7% of cases).

The time of collection of respiratory samples certainly influences the result of the PCR for SARS-CoV2. Wang and colleagues in 2020 [6] found SARS-CoV2 RNA in 14 out of 15 (93%) BAL samples but in only 126 out of 398 (32%) pharyngeal swabs from patients with COVID-19. We confirm their observation on BAL, because also in our series, out of 18 BAL performed within the 5th day of hospitalization of COVID patients, 16 tested positive for SARS CoV2 (89%). For IS it is almost the same thing, in fact out of 15 induced sputa collected within the fifth day of hospitalization, 13 tested positive for SARS-CoV2 RNA (86.7%). Regarding nasopharyngeal swabs, our data are quite different, probably because the technique for performing respiratory swabs has improved compared to the beginning of the pandemic. In fact, nasopharyngeal swabs have been shown to be more sensitive than nasal-only or throat-only swabs [7]. Furthermore, due to the development of a rapid referral system for hospitalization of COVID cases in our region, it is possible that the COVID-positive patients in our series were hospitalized at an earlier stage of the disease than in Wang's case series.

The research of SARS-CoV2 on other respiratory specimens such as BAL and IS is justified with the intent to definitively exclude the presence of SARS-CoV2 in doubtful cases and to document the elimination or persistence of the virus in the lower respiratory tract or compartmentalization [8], with the possibility of prolonging or repeating antiviral therapy, in other selected cases.

Furthermore, BAL allows to diagnose bacterial or fungal superinfections (52% in COVID-19 patients; 48% in non-COVID), allowing targeted treatment. Enterobacteriaceae lung infections and Pseudomonas / Stenotrophomonas infections were more frequent in COVID-19 patients: 11% vs 5% and 10% vs 4%, respectively.

We did not observe a significant difference between the two groups regarding the number of pulmonary aspergillosis and pulmonary thromboembolism. It should also be said that, following the appearance of COVID-19, radiological research of TEP and research of Aspergillus on BAL are performed much more frequently even in our non-COVID series.

Tuberculosis was diagnosed in 6% of patients hospitalized for COVID-19 by bronchoscopy, which is confirmed as the best procedure for diagnosing tuberculosis in patients who have difficulty producing spontaneous or induced sputum and in the non-cavitary pulmonary form. Bronchoscopy has been also crucial to manage tracheal complications and obstructive atelectasis, which have been frequently encountered among COVID-19 patients also in our series.

More than three years have passed since the appearance of the SARS-CoV2 epidemic and since then many things have changed, both in terms of diagnosis and in terms of prevention and treatment of the disease. The virus continues to circulate in the population, posing a continuous threat to the most vulnerable, who continue to fall ill and often require hospitalization. It also happens that the presence of asymptomatic infection is found in patients hospitalized for other pathologies, or who access outpatient services, with the risk that healthcare facilities become places of contagion for healthcare personnel and the patients themselves.

Since 2021, multiple Authors have documented how the negativity of NPS, administered to patients at low risk for COVID-19, is always corroborated by the negativity of BAL for SARS-CoV2 [9,10]. This finding supported the use of NPS tests, associated with symptom screening questionnaires, as an appropriate screening method for aerosol-generating procedures, like bronchoscopy and IS.

On the other hand, there are also numerous reports of symptomatic patients with NPS negative for SARS-CoV2, in which the BAL tested positive for SARS-CoV2 [11-13]. Indeed, we observed three symptomatic cases, NPS negative for SARS-CoV2, in which the BAL tested positive. It is therefore necessary to ask ourselves what the risk is that medical-health personnel run in carrying out the procedure on suspected or known positive patients and whether it is worth it.

Conclusions

Our case series documents a greater severity and clinical complexity of COVID-19 patients compared to non-COVID, with a greater need for diagnostic investigations, so we are of the idea that the best role for bronchoscopy in suspect COVID patients would be when less invasive testing to confirm SARS-CoV2 infection, as NPS1, NPS2, and IS, are inconclusive, or if there is suspicion for an alternative diagnosis that would impact clinical management, or when an urgent life-saving intervention is needed [3,14].

CDC Guidelines for Collecting and Handling of Clinical Specimens for COVID-19 Testing [4], in the last update of July 2022, do not recommend the induction of sputum in COVID-19 patients and they reiterate that "collection of specimens other than sputum from the lower respiratory tract may be limited to patients presenting with more severe disease, including people admitted to the hospital and/or fatal cases."

In our institution FBS and IS have proven to be safe for healthcare personnel and patients, thanks to the absolute compliance with respiratory, droplet and contact precautions and the availability of

negative pressure rooms for carrying out the procedures. In fact, from the beginning of the epidemic to today, we did not observe secondary cases of COVID-19 in our staff members and non-COVID patients undergoing FBS and IS. It should also be emphasized that precautions have been used universally for all patients, suspected or not for COVID-19, also because, in most cases, IS and FBS at INMI are performed to diagnose pulmonary infectious diseases, including tuberculosis and pulmonary mycobacteriosis, for which we are in favour of their generalization. Likewise, thanks to the development of an institutional internal protocol for IS adapted to the risk of airborne and droplet transmission, so far, no cases of COVID-19 have been observed in healthcare personnel and patients attributable to the sputum induction procedure.

Institutional procedures for performing sputum induction in hospitalized patients have proven effective in preventing nosocomial transmission of SARS-CoV2 and have therefore also been applied to outpatient cases, for example, to obtain control samples from patients being treated for pulmonary tuberculosis.

Consent for Publication

Written informed consent was obtained from patients for this paper to be published. A copy of the written consent is available for review by the Editor of this journal.

Authors Contributions

PC, MA, MP, GG, and FP conceived the study. MP wrote the paper. PC, MA, MP, MMC, LMAV, CS, D'AS and MG supplied the clinical data. FP, GG and AN reviewed the paper. All authors reviewed and approved the final version of the paper submitted to the journal.

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Ethical Approval

Epidemiological, demographic, clinical, and laboratory data and information on treatments and outcomes of all patients with a confirmed COVID-19 diagnosis were collected and recorded using a standardized electronic database (ReCOVery study). The study was approved by our local ethics committee.

Conflicts of Interest

All authors declare no conflict of interest.

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