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Accuracy of galactomannan testing on tracheal aspirates in COVID-19-associated pulmonary aspergillosis

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Abstract

Objective: Our aim was to evaluate the performance of two galactomannan (GM) assays (Platelia Aspergillus EIA, Bio-Rad®, and Aspergillus GM LFA, IMMY®) in tracheal aspirate (TA) samples of consecutive critically ill patients with COVID-19.

Methods: We included critically ill patients, performed GM-EIA and GM-Lateral Flow Assay (GM-LFA) in TA and followed them until development of COVID-19-associated pulmonary aspergillosis (CAPA) or alternate diagnosis. CAPA was defined according to the modified AspICU criteria in patients with SARS-CoV-2 infection. We estimated sensitivity, specificity, positive and negative predictive values for GM-EIA, GM-LFA, the combination of both or either positive results for GM-EIA and GM-LFA. We explored accuracy using different breakpoints, through ROC analysis and Youden index to identify the optimal cut-offs. We described antifungal treatment and 30-day mortality.

Results: We identified 14/144 (9.7%) patients with CAPA, mean age was 50.35 (SD 11.9), the median time from admission to CAPA was 8 days; 28.5% received tocilizumab and 30-day mortality was 57%. ROC analysis and Youden index identified 2.0 OD as the best cut-off, resulting in sensitivity and specificity of 57.1% and 81.5% for GM-EIA and 60% and 72.6% for GM-LFA, respectively.

Conclusions: The diagnostic performance of GM in tracheal aspirates improved after using a cut-off of 2 OD. Although bronchoalveolar lavage testing is the ideal test, centres with limited access to bronchoscopy may consider this approach to identify or rule out CAPA.

KEYWORDS
COVID-19, galactomannan, invasive aspergillosis, SARS-CoV-2 infection

1 | INTRODUCTION

Invasive pulmonary aspergillosis (IPA) is an emerging complication among critically ill patients with chronic lung disease, diabetes mellitus, corticosteroids and liver cirrhosis. The modified AspICU criteria were created to improve the diagnosis of IPA among critically ill patients, considering the limitations of the EORTC/MSG criteria. These criteria define putative invasive aspergillosis (IA) with a

positive serum or bronchoalveolar lavage (BAL) galactomannan (GM) result, a positive *Aspergillus* culture in BAL or histopathological evidence of IA.[1]

The COVID-19 pandemic has infected over 50 million people and caused more than a million deaths worldwide. Between 5% and 14% develop acute respiratory distress syndrome (ARDS) and most receive corticosteroids or immunomodulating agents. Since April 2020, COVID-19-associated pulmonary aspergillosis (CAPA) was described in several case reports and series with various definitions.[2–4] Also, aerosol-generating procedures (AGP) such as bronchoscopy are a potential hazard for healthcare workers in overburdened critical care units (ICU) with a shortage of personal protective equipment (PPE), limiting the availability of BAL sampling.[5] Currently, GM testing is not validated in tracheal or bronchial aspirates.

Our aim was to evaluate the performance of two methods (Platelia Aspergillus EIA, Bio-Rad® and Aspergillus GM LFA [IMMY®]) of GM detection in tracheal aspirate samples of consecutive COVID-19-infected patients with invasive mechanical ventilation (IMV) to diagnose CAPA and explore potential cut-offs.

2 | MATERIAL AND METHODS

2.1 | Patients and samples

In March 2020, this tertiary care centre in Mexico City was converted to a COVID-19-dedicated facility. The intensive care unit (ICU) was expanded from 14 to 42 beds. Tracheal aspirates (TA) from consecutive COVID-19-infected patients admitted to the ICU with IMV were included; all clinical samples were requested by the treating physician due to clinical worsening or suspected in-hospital or ventilator-associated pneumonia.

Data from the electronic medical record were collected through a standardised questionnaire. Patients were followed for 28 days to assess mortality and whether they developed CAPA. COVID-19 was confirmed in patients with compatible signs and symptoms and a SARS-CoV-2-positive nasopharyngeal swab by real-time reverse transcription-polymerase chain reaction (PCR; Applied Biosystems 7500 thermocycler; [Applied Biosystems] using primers and conditions described elsewhere).[6]

2.2 | Laboratory procedures

Tracheal aspirates were received at the Clinical Microbiology Laboratory and processed for bacterial and fungal cultures following standard practice. For fungal isolates, identification through microscopic and macroscopic morphology was confirmed through MALDI-TOF (Bruker Daltonics GmbH) Results were analysed in MALDI BioTyper 3.0 (commercial version, Filamentous Fungi Library 1.0; Bruker Daltonics) and interpreted according to manufacturer recommendations: score ≥2 correct genus and species identification, ≥1.7 correct genus identification and <1.7 unreliable identification. GM antigen (Platelia Aspergillus EIA, Bio-Rad; GM-EIA) was performed on 300 µl of TA following the manufacturer's instructions. Results ≥0.5 OD in serum were considered positive as per Schauwvlieghe et al[1] definition of putative IA.

Sona Aspergillus GM Lateral Flow Assay (GM-LFA; Immuno-Mycologics [IMMY]) was donated by IMMY and was performed on 300 µl of TA following manufacturer's instructions. Results were interpreted automatically with the LFA Cube Reader.

Tracheal aspirate GM-EIA and GM-LFA interpretation were blinded from clinical and standard culture results, TA samples were given a code without individual information, TA GM-EIA and GM-LFA results were not informed to the treating physicians, but culture and serum GM results were reported immediately as in normal clinical practice.

Galactomannan-EIA was performed in 144 TA samples and GM-LFA was performed on the 105 from 144 first consecutive TA samples. CAPA was considered in patients with SARS-CoV-2 infection according to the modified AspICU algorithm (1) considering a positive serum GM or *Aspergillus* spp. growth from a TA, since bronchoscopies were not performed at our institution due to safety concerns for healthcare workers.

2.3 | Statistical analysis

Descriptive analysis was performed using STATA V14 (College Station) Sensitivity, specificity, positive and negative predictive values of TA GM-EIA, GM-LFA alone or in combination were calculated by comparison to the definition of CAPA, as a reference standard. For GM-EIA and GM-LFA in TA samples, we compared different OD cut-offs (0.8-2.0 OD) through area under the curve (AUC) analysis and Youden index (provided in Table S1). IMMY had no access to clinical data nor participated on data analysis.

2.4 | Ethics

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. On admission, all patients sign an informed consent to allow the use of clinical samples taken during routine care for additional research studies.

3 | RESULTS

From 13 April to 1 June 2020, we included 144 critically ill patients with COVID-19 who required IVM and had at least one TA culture; 99 (68.8%) had two, and 66 (45.8%) had three serial TA's. Demographics and clinical characteristics are described in Table 1. GM-EIA and GM-LFA were performed on 296 and 181 individual TA samples, respectively. The first, second and third TA samples were

TABLE 1 Characteristics of patients with and without COVID-19-associated invasive pulmonary aspergillosis

	All *n* = 144 (%)	Without IA *n* = 115 (79.8%)	Putative IA (mAspICU) *n* = 14 (9.7%)	Putative IA (TAAspICU) *n* = 19 (20%)
Male sex	103 (71.5)	92 (80)	11 (78.5)	16 (84.2)
Age, mean (SD)	48.6 (11.5)	48.5 (11.5)	48.3 (11.7)	53.3 (12.25)
Comorbidities				
Obesity	82 (57)	73 (63.4)	9 (64.2)	12 (63.1)
Overweight	41 (28.28)	34 (29.3)	3 (23)	6 (31.5)
Hypertension	38 (26.3)	34 (29.3)	4 (30.7)	7 (36.8)
Diabetes	35 (24.3)	31 (26.7)	4 (30.7)	6 (31.5)
COVID-19 treatment				
Clq or HCQ	36 (25)	31 (26.7)	5 (38.5)	6 (31.5)
Tocilizumab	31 (21.5)	29 (23.2)	4 (30.7)	2 (10.2)
Remdesivir RCT	4 (2.7)	3 (2.6)	1 (7.1)	2 (10.5)
Steroids	15 (10.4)	14 (12)	1 (7.6)	0
Antifungal treatment	46 (32)	34 (29.5)	12 (85.7)	13 (68.4)
Voriconazole	24/46 (52.1)	14/34 (41.1)	10/12 (83.3)	11/13 (84.6)
Echinocandin	22/46 (47.8)	20/35 (57.1)	2/11 (15.3)	2/13 (15.3)
Antifungal duration, Mdn (IQR)	11 (4-14)	11 (4-14)	21 (5.75-42)	11 (5-35)
Reason for antifungal				
Empiric IFI	13/46 (28.2)	11/35 (31.4)	2/11 (18.2)	2/13 (15.3)
Empiric IA	12/46 (26)	12/116 (34.2)	0	5/13 (38.4)
AI putative	10/46 (21.7)	1/116 (2.8)	9/11 (81.8)	6/13 (46.1)
Candidemia	9/46 (19.5)	9/35 (25.7)	0	0
Serum GMN	1/46 (2.17)	0	1/	0
30-day mortality	64 (44.4)	56 (48.6)	8 (57.1)	14 (73.6)

Abbreviations: Clq, chloroquine; HCQ, hydroxychloroquine; IA, invasive aspergillosis; IFI, invasive fungal infection; mAspicu, modified AspICU criteria; TAAspICU, Tracheal aspirate with modified AspICU criteria.

obtained with a median of 3 days (IQR 2-6), 7 days (IQR 5-10) and 11 days (IQR 8.5-15.5) after intubation.

CAPA was diagnosed on 14/144 patients (9.7%), none met the EORTC/MSG host criteria. (Table 2). Four (28.5%) received tocilizumab and one (7.1%) corticosteroid. The median time from admission to CAPA diagnosis was 8.5 days (IQR 3-13). All had progressive bilateral diffuse infiltrates on chest X-ray; two had a chest CT at the time of CAPA diagnosis, with diffuse ground glass opacities in one and multiple consolidations with ground glass opacities in another. Nine (64%) had a TA culture with *Aspergillus* spp., six (42.8%) had a positive serum GM and one patient had both. More than one species of *Aspergillus* spp. were identified in two cases. The clinical isolates identified were *Aspergillus fumigatus* 6/11, *A flavus* 1/10, *Aspergillus niger* 1/10 and *Aspergillus* spp. 3/10.

Twelve patients (85.7%) received antifungal treatment, ten received voriconazole for treatment IPA and two anidulafungin for suspected candidemia. Twenty-eight-day mortality among patients with CAPA of 57.1% (8/14) was higher than patients without CAPA seen during the same period (57/131, 43.5%), although nonstatistically significant (OR, 1.7, CI, 95% 0.57-5.3).

Three patients with positive *Aspergillus* spp. TA cultures were considered colonisation. One grew *A fumigatus* and had a positive TA GM-EIA (7.2 OD) and GM-LFA (2.4 OD); one *A niger* grew and had negative TA GM-EIA (0.5 OD) and the other with *A flavus* with TA GM-EIA (9.367 OD) and GM-LFA (4.7 OD). Serum GM was not available for either. All were discharged and alive at 28 days without antifungal treatment.

3.1 | Tracheal aspirate galactomannan performance

Evaluation of cut-offs for GM-EIA showed sensitivity and specificity of 64.3% and 63% when using a cut-off of 0.8, a sensitivity and specificity of 64.3% and 68.5% when using a cut-off of 1, a sensitivity and specificity of 57.1% and 78.5% when using a cut-off of 1.5 and a sensitivity and specificity of 57.1% and 81.5%, respectively, when using a cut-off of 2 OD. Evaluation of cut-offs for GM-LFA showed a sensitivity and specificity of 80% and 41% when using a cut-off of 0.8, a sensitivity and specificity of 80% and 48.4% when

TABLE 2 Characteristics of patients with COVID-19-associated pulmonary aspergillosis

Comorbidities	Immunomodulatory treatment	Mycologic criteria	Treatment and outcome
55-year old female	—	Serum GM-EIA positive: 2.39 OD	Voriconazole 42 days
Obesity and Diabetes		TA GM-EIA 3.88 OD	Discharged
		GM-LFA: 1.19 OD	
		TA culture: negative	
32-year old male	—	Serum GM-EIA: NA	Voriconazole 42 days
Obesity		TA GM-EIA 2.3 OD	Discharged
		TA GM-LFA: 6 OD	
		TA culture: *Aspergillus versicolor*	
65-year old female	Tocilizumab	Serum GM-EIA negative: 0.04 OD	Voriconazole
Overweight and Hypertension		TA GM-EIA: 3.8 OD	5 days
		TA GM-LFA: 0.83 OD	Died
		TA Culture: *Aspergillus fumigatus*	
50-year old male	Tocilizumab	Serum GM-EIA: NA	No antifungal treatment
Obesity, Diabetes Hypertension		TA GM-EIA: Negative	Died
		TA GM-LFA: 0.8	
		Culture: *Aspergillus section* fumigati	
33-year old male	Tocilizumab	Serum GM-EIA positive:1.7 OD	Voriconazole for 28 days
Obesity		TA GM-EIA: Negative	Discharged
		TA GM-LFA: 2.4 OD	
		TA culture: *K pneumoniae*	
64-year old male		Serum GM-EIA positive: 1.15 OD	Voriconazole
Obesity		TA GM-EIA: 11.4 OD	3 days
		TA GM-LFA: 12.49 OD	Died
		TA culture: *Aspergillus flavus* & *Aspergillus fumigatus*	
40-year old male	Tocilizumab	Serum GM-EIA negative: 0.214 OD	Voriconazole 42 days
Obesity		TA GM-EIA: Negative	Discharged
		TA GM-LFA: 0.93	
		TA culture: *Aspergillus niger*	
40-year old male	—	Serum GM-EIA: NA	No antifungal treatment
Obesity		TA GM-EIA: 11.4	Died before culture growth
		TA GM-LFA: 21.4	
		TA culture: *Aspergillus fumigatus*	
55-year old male	—	Serum GM-EIA: NA	Voriconazole 10 days
Obesity, diabetes Hypertension		TA GM-EIA: 8.8	Died before isolate
		TA GM-LFA: NA	
		Culture: *Aspergillus fumigatus*	
68-year old female	—	Serum GM-EIA negative: 0.09 OD	Voriconazole 35 days
Obesity and hypertension		TA GM-EIA: 3.5	
		TA GM-LFA: 2.1	
		TA culture: *Aspergillus sp*	
46-year old male	—	Serum GM-EIA positive: 0.8 OD	Empiric Caspofungin
Overweight		TA GM-EIA: 5.8	Died
		TA GM-LFA: 1.6	
		TA culture: Negative	

(Continues)

TABLE 2 (Continued)

Comorbidities	Immunomodulatory treatment	Mycologic criteria	Treatment and outcome
47-year old male	—	Serum GM: NA	Voriconazole 5 days
Overweight and smoker		TA GM: 10.5	Died
		TA GM-LFA: NA	
		TA Culture: *Aspergillus fumigatus* & *Aspergillus flavus*	
46-year old male	Corticosteroids	Serum GM-EIA positive: 8.7 OD	Voriconazole 42 days
HIV+		TA GM-EIA: 2.1 OD	Discharged
		TA GM-LFA: 1.15 OD	
		TA culture: Negative	
64-year old male	Remdesivir vs pbo	Serum GM-EIA positive: 0.559 OD	Voriconazole 14 days
Obesity		TA GM-EIA: 7.7 OD	Died
		TA GM-LFA: NA	
		TA culture: Negative	

Abbreviations: GM-EIA, galactomannan antigen; TA, tracheal aspirate.

TABLE 3 Diagnostic performance galactomannan (GMN) and lateral flow galactomannan (LFA) on tracheal aspirate (TA)

Putative IA	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TA GM-EIA	57.1 (29-82)	81.5 (74-88)	94.6 (91-97)	25 (16-37)
TA GM-LFA	60 (26-88)	72.6 (63-81)	94.5 (89-97)	18.7 (11-30)
GM-EIA or LFA	81.2 (48-98)	63.1 (53-73)	96.7 (89.4-99)	20.4 (15-27.4)
GM-EIA and LFA	40 (12-74)	85.2 (77-91)	93.1 (89-96)	22.2 (10.4-41.2)

Abbreviations: TA GMN, Tracheal aspirate Galactomannan, TA GM-LFA, Tracheal aspirate Galactomannan lateral flow.

using a cut-off of 1, a sensitivity and specificity of 60% and 64.2% when using a cut-off of 1.5 and a sensitivity and specificity of 60% and 72%, when using a cut-off of 2. (See Table S1).

When both GM-EIA and GM-LFA were positive with a cut-off value of 2 OD, sensitivity was 40%, specificity was 85.2%, NPV was 93.1% and PPV was 22.2%. When either a TA GM-EIA or GM-LFA were positive using a cut-off value of 2 OD on the sensitivity was 81.2%, specificity was 63.1%, NPV was 96.7%, and PPV 20.4% (Table 3).

In patients with CAPA, 57.1% (8/14) had a positive TA GM-EIA with a median OD value of 8.5 (range 5.7-11.4), 60% (6/10) had a positive TA GM-LFA with a median value of 3.67 (range 2.4-12.5); three had a positive TA culture for bacteria, four had a positive TA culture for *Candida* spp. and five had *Aspergillus* spp.

Among 261 TA samples from 130 patients without CAPA, 33/261 (12.6%) had a positive GM-EIA [median OD 5.7, (range 3.3-10.4)], of which 13/33 (39.4%) had cultures positive for bacteria, 9/33 (27.3%) had cultures positive for *Candida* spp. and 2/33 (6%) had *Aspergillus* growth, one *A flavus* and one *A fumigatus*.

If tracheal aspirate GM-EIA and GM-LFA were used to fulfil the mycological criteria for putative IA, five additional CAPA cases would have been diagnosed (Table 1). Among these, all had progressive infiltrates in chest X-ray with ground glass opacities and consolidations, two had chest CT with nonspecific progressive infiltrates. Three had both GM-EIA- and GM-LFA-positive test results and two had positive GM-EIA only. The range of GM-EIA was 2-11.4, and the range of GM-LFA was 2.4-8.7. A single TA cultures was positive for *Candida albicans* and neither grew bacteria. Empirical antimicrobial treatment was given in 60% (3/5) and empirical voriconazole in 40% (2/5) for clinically suspected IPA. A higher 28-day mortality was seen compared to patients without CAPA (85% vs 40%).

4 | DISCUSSION

Invasive fungal diseases complicating viral infections is observed in a high number of patients with severe influenza and occasionally in SARS-CoV-1 and Middle East Respiratory Syndrome. Since the beginning of the SARS-CoV-2 pandemic, IPA has been recognised in patients with COVID-19 and ARDS.[7–9] In this study, we evaluated the performance of two GM assays in tracheal aspirate samples from consecutive critically ill patients with COVID-19 trough different cut-offs. Considering a cut-off of 2 OD, we found sensitivity of 57.1%-60%, specificity of 72.6%-81.5% and high NPV for both tests.

The optimal diagnostic algorithm for CAPA is not established. Traditional EORTC/MSG criteria are not applicable to ICU patients, since 65% do not meet the host criteria. Schauwvlieghe et al introduced the modified AspICU criteria to identify putative IA based

on the presence of clinical, radiological and mycological criteria.[1,10] The latter is met when histopathological evidence of septate hyphae with a positive culture for Aspergillus, a positive Aspergillus BAL culture, a BAL GM >1 or a serum GM >0.5.

A prospective cohort of IAPA showed 65% and 88% positivity for serum and BAL GM.[1,11]

Studies of CAPA showed BAL culture and GM had a sensitivity of 72.7% and 66.7%, while serum GM was positive in 21.4% of cases. In consequence, BAL GM testing is the reference standard.[5] Unfortunately, bronchoscopy is an AGP, requiring personnel with N95 respirators to perform BAL sampling. Due to N95 respirator shortage and concern for SARS-CoV-2 infection among healthcare workers, limited access to bronchoscopies occurred in our centre. Since TAs were the only available respiratory sample, we intended to validate GM testing.

Using the definition of putative IA as the reference standard,[1] we found a sensitivity for TA GM-EIA and GM-LFA of 57.1% and 60%, respectively, and specificity of 81.5% and 72.6%, respectively. Our findings are consistent with reported elsewhere for BAL GM-EIA and GM-LFA.[12–15] Aspergillus GM Lateral Flow Assay (IMMY) is a novel point of care test with sensitivity and specificity in BAL samples, of 83% and 87%, respectively, among haematological patients.[16] Jenks et al evaluated two GM lateral flow assays in BAL samples of non-neutropenic critically ill patients and found sensitivity ranging from 58% to 69% and specificity ranging from 68% to 75%.[13,17]

When different cut-off values were evaluated for GM lateral flow in BAL, Jenks et al described improved performance of LFA with higher cut-offs of 1 or 1.5.[15] In our study using TA samples, a cut-off of 2 for GM-EIA and GM-LFA showed a better performance. Using lower cut-offs in TA samples may lead to overestimating CAPA prevalence, since low grade avidity of *Candida* sp and Gram-negative bacteria in heavily colonised ICU patients with ventilator-associated pneumonia could result in cross reactivity with GM assays.[11,18,19] Also, false-positive BAL GM results may occur in up to 17.4% ICU patients colonised with Aspergillus. We found 6% cultures with filamentous fungi among false GM-EIA and GM-LFA positives.[20–22]

The combined use of GM with PCR and GM-LFA in BAL samples allows a higher sensitivity and specificity in studies with haematological patients. In this study, having a positive result of either GM-EIA or GM-LFA resulted also in improved sensitivity with moderate specificity.[17]

In this study, we found a prevalence of CAPA of 9.7% among consecutive patients with critical SARS-CoV-2 infection. Lamoth et al[23] reported a 3.3% prevalence among 118 ICU patients with COVID-19 and recognised reduced availability of bronchoscopies may lead to underestimation of cases. All their patients received tocilizumab, as 28.5% of ours. Fungal infections in rheumatological patients treated with tocilizumab is unusual.[24,25] A better definition of risk of IPA among anti-IL-6 recipients is needed. Other series found a higher 19%-30% CAPA prevalence.[2,3,20,26] Unlike these reports, our patients were younger and had a higher frequency of obesity, which has been previously described in our country.[27] We found a low prevalence of steroid use since dexamethasone was not yet a standard of care at the time of inclusion.

Patients with CAPA have elevated mortality rates (44%-83%) emphasising the need to establish an efficient surveillance system with early antifungal treatment.[5] Interestingly, the subgroup of patients ruled in by TA results had elevated, mortality compared to patients with and without putative IPA. However, we cannot exclude IPA among this subset of patients, in which GM in BAL testing may have helped clarify.

We acknowledge several limitations. Due to the unavailability of bronchoscopies and BAL GM, our mycological criteria definition of CAPA included serum GM and *Aspergillus* TA culture only. Ideally, TA GM should have been compared with BAL GM. Since serum GM among the critically ill population with IA is insensitive,[28] the true prevalence of CAPA may be underestimated. Also, not all patients had a chest CT, rendering abnormal chest X-ray findings as the only radiological criteria. Blot and colleagues broadened the radiological criteria in critically ill patients, to include diffuse reticular or alveolar opacities or nonspecific infiltrates and consolidations in chest X-rays.[29] We acknowledge this may lead to reduced specificity, which was a recognised limitation in the original description and subsequent modification by Schauwvlieghe et al.[1] In a recent study describing nine patients with CAPA in France, eight had typical COVID-19 findings in chest CTs as the only abnormality.[2] A major limitation of this study is one shared with many biomarker performance studies in IFIs where the lack of an ideal reference standard leads to uncertainty when classifying the presence or absence of the disease.

The strengths of the study include a prospective double-blind validation, the personnel performing GM-EIA and GM-LFA had no access to the results of cultures and clinical data, and investigators evaluating the outcome were blinded to the TA GM-EIA and GM-LFA results, reducing the risk of bias. Also, we used the modified AspICU criteria as a reference standard, which was developed in a similar population with IAPA. To our knowledge, this is the first study that evaluates GM testing in TA samples and provides useful information for centres with limited access to bronchoscopies. Although CAPA was not clinically suspected in most patients, a prospective validation including at-risk patients results in a real-world estimate of diagnostic accuracy.

Our results warrant additional validation, ideally comparing TA GM directly with BAL. However, in centre with no access to bronchoscopies, the use of TA GM with an optimal cut-off may be a reasonable alternative considering high NPV that would allow excluding CAPA.

We believe the elevated mortality in CAPA supports implementing bronchoscopies providing adequate PPE. A recent study described a bronchoscopy simulation model in intubated patients to evaluate droplet an aerosol release. The authors found several critical situations during the procedure such as opening the closed respiratory circuit, the continued operation of the ventilator and inserting and removal of the bronchoscope. In addition to appropriate

PPE, they suggest implementing measures to limit droplet an aerosol contamination which may be of value.[30]

5 | CONCLUSIONS

The diagnostic performance of GM in tracheal aspirates to identify CAPA was improved after using a cut-off of 2 OD. Although BAL testing is the recommended diagnostic method, centres with limited access to bronchoscopy may consider this approach to identify or rule out CAPA.

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CONFLICT OF INTEREST

APL reports personal fees from Gilead, Merck, Pfizer and Stendhal outside the submitted work and grants from Conacyt, grants from NIH, grants from Bill and Melinda Gates Foundation, outside the submitted work. JSO reports personal fees from Senosiain, Pfizer, Merck, Sharp and Dohme, bioMérieux, Sanofi Pasteur and Astra Zeneca outside the submitted work. MFGL reports personal fees from Pfizer, Grupo Biotoscana and Teva Pharmaceutical Industries outside the submitted work.

AUTHOR CONTRIBUTION

Carla M. Roman Montes: Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Areli Martínez-Gamboa:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Validation (equal); Writing-review & editing (equal). **Paulette Diaz-Lomeli:** Data curation (equal); Formal analysis (equal); Methodology (equal); Resources (equal); Validation (equal); Visualization (equal). **Axel Cervantes-Sanchez:** Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Writing-original draft (equal). **Andrea Rangel-Cordero:** Data curation (equal); Formal analysis (supporting); Methodology (equal); Validation (supporting); Writing-review & editing (supporting). **Jose Sifuentes-Osornio:** Formal analysis (supporting); Funding acquisition (lead); Investigation (supporting); Methodology (equal); Supervision (supporting); Validation (supporting); Writing-review & editing (supporting). **Alfredo Ponce-de-León-Garduño:** Conceptualization (equal); Investigation (equal); Project administration (equal); Resources (equal); Supervision (supporting); Writing-review & editing (supporting). **Maria Fernanda González-Lara:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (lead); Writing-original draft (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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