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REVIEW ARTICLE

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A review of significance of *Aspergillus* detection in airways of ICU COVID-19 patients

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Abstract

It is now well known that patients with SARS-CoV-2 infection admitted in ICU and mechanically ventilated are at risk of developing invasive pulmonary aspergillosis (IPA). Nevertheless, symptomatology of IPA is often atypical in mechanically ventilated patients, and radiological aspects in SARS-CoV-2 pneumonia and IPA are difficult to differentiate. In this context, the significance of the presence of *Aspergillus* in airway specimens (detected by culture, galactomannan antigen or specific PCR) remains to be fully understood. To decipher the relevance of the detection of *Aspergillus*, we performed a comprehensive review of all published cases of respiratory *Aspergillus* colonisation and IPA in COVID-19 patients. The comparison of patients receiving or not antifungal treatment allowed us to highlight the most important criteria for the decision to treat. The comparison of surviving and non-surviving patients made it possible to unveil criteria associated with mortality that should be taken into account in the treatment decision.

KEYWORDS
Aspergillus fumigatus, colonisation, COVID-19, intensive care unit, invasive pulmonary aspergillosis, mortality, SARS-CoV-2

1 | INTRODUCTION

Patients with severe pneumonia due to SARS-CoV-2 and hospitalised in the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS) may have an increased risk of coinfection with fungal and bacterial pathogens.[1] It is now well known that patients with severe influenza are at higher risk of developing invasive pulmonary aspergillosis (IPA).[2] Therefore, as a potentially severe

respiratory viral infection, SARS-CoV-2 infection may also be a risk factor for IPA. More and more cases in the literature report the presence of *Aspergillus* in airway specimens, for which the diagnosis of IPA seems unclear. There are several difficulties for the diagnosis: symptomatology is often atypical in ventilated intubated patients, and the radiological aspects are difficult to differentiate from those of SARS-CoV-2 pneumonia.

The first studies reported a widely variable incidence ranging from 2.4%[3] to 35%[4] depending on the screening protocols and used definition of IPA. Indeed, aspergillosis definitions were not consensual and were not necessarily in agreement with the definition of IPA in haematology.[5,6] As a reminder, the definition of IPA in ICU still remains non-consensual and unclear.[7] It is only recently that IPA definitions specifically, in the context of COVID-19, have been proposed.

One of the major issues is the significance of *Aspergillus* detection (culture, galactomannan antigen (GM) or specific PCR) in airways from intubated COVID-19 patients (colonisation or IPA) and thus the indication for an antifungal treatment. In an attempt to clarify this issue, we analysed all published cases of *Aspergillus* colonisation and IPA in ICU COVID-19 patients until 1 October 2020. Comparison of treated and non-treated patients allowed us to highlight the criteria leading the clinicians to a non-treatment decision. Comparison of survivor and non-survivor groups underlined the criteria associated with mortality that should help for treatment decision.

2 | SOURCES AND METHODS

We performed a review of literature until the 1 October 2020 on Pubmed database with the MeSH terms: “Aspergillosis” and “COVID” (Figure 1, Flow chart). Inclusion criteria were the description of SARS-CoV-2–infected patients in ICU under mechanical ventilation (35 publications). For statistical analysis, only 28 articles with individual patient information about diagnosis method, treatment and outcome were included. Quantitative data were compared with Student's *t* test or Mann-Whitney test when the distribution was not normal. Odds ratio with 95% confidence interval were calculated for selected quantitative variables. Qualitative data were compared with chi-square test or Fisher's exact test when an expected number was inferior to five. For each analysed parameter, patients with missing data were excluded of the statistical analysis. Variables with univariate *p*-values under .05 except those with too many missing data (such as *Aspergillus* PCR) were included in a multivariate linear regression model using R 3.6.3 software.

3 | ANALYSIS OF THE LITERATURE

A systematic review of the literature allowed us to select 35 studies (Figure 1), published between January 2020 and the 1 October 2020, gathering data from 182 COVID-19–associated pulmonary aspergillosis (CAPA) patients and 49 patients with *Aspergillus* colonisation Table 1. As showed in Table S1, 35 studies comprised 29 retrospective and 6 prospective ones, of which 4 were multicentre studies. Regarding the classification, eight different IPA definitions were used. A wide range of CAPA incidence (from 2.4%[3] to 35%[4]) among ventilated ICU patients with COVID-19 has been reported (Figure 2).

In the two largest multicentre prospective studies, including 108 and 122 patients, respectively, CAPA was associated with an overmortality. In Bartoletti et al.,[8] the 30-day mortality rate in ICU was 44% in the CAPA group vs 19% in the control group (p = .002). In White et al.,[9] among COVID-19 patients, the mortality rate in ICU was 53% in patients with fungal infection (including yeast infection) vs 31% in patients without fungal disease (p = .0387).

In order to analyse the criteria used for the decision of antifungal treatment, we selected the 28 publications for which individual data were available (Figure 1, Table S1). One hundred and thirty-four patients with CAPA or *Aspergillus* colonisation were included in these 28 studies (Table 2). Eleven CAPA patients were not treated because of pre- or post-mortem aspergillosis diagnosis and were thus excluded from the analysis. We compared the treated CAPA group (n = 96) vs the non-treated group with CAPA or *Aspergillus* colonisation (n = 27). Clinical decision not to initiate an antifungal treatment

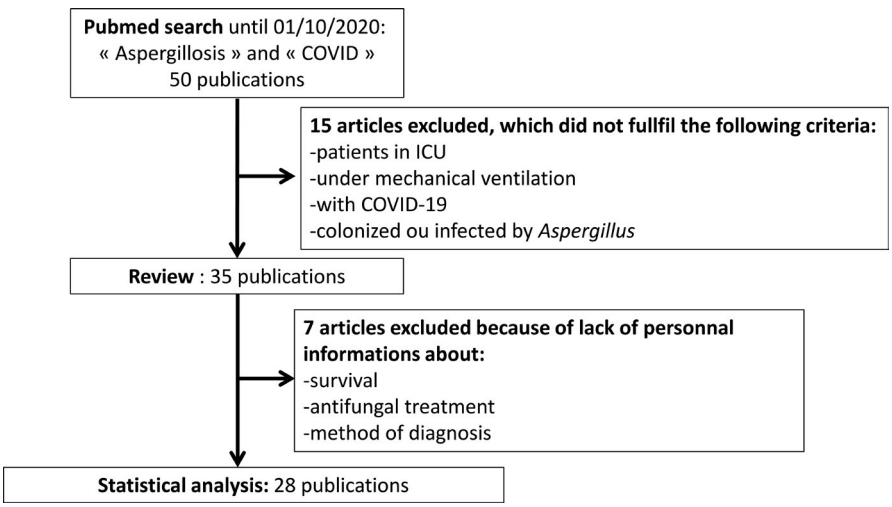

FIGURE 1 Flow chart

TABLE 1 Review of the 35 studies reporting COVID-19–associated pulmonary aspergillosis cases (CAPA) or respiratory *Aspergillus* colonisation in ICU COVID-19 patients

1st Author (ref)	Country	CAPA (/total number of described patients)	Colonisation (/total number of described patients)	Mortality rate in patients with CAPA
Abdalla, 2020[23]	Qatar	2/2	0/2	2/2
Alanio, 2020[15]	France	9/27 (33.3%)	0/27	4/9
Antinori, 2020[24]	Italy	1/1	0/1	1/1
Bartoletti, 2020[8c]	Italy	30/108 (27.8%)	5/108	16/30
Blaize, 2020[25]	France	1/1	0/1	1/1
Brown, 2020[26c]	United Kingdom	2/62 (3.2%)	4/62	NA
Dupont, 2020[27]	France	19/106 (17.9%)	0/106	7/19
Falces-Romero, 2020[28]	Spain	7/7[b]	0/7	5/7
Fekkar, 2020[14]	France	NA	2/2	0/2
Fernandez, 2020[29]	Argentina	1/1	0/1	1/1
Flikweert, 2020 [30]	The Netherlands	6/6	0/6	6/6
Gangneux, 2020[31]	France	7/45 (15.6%)	8/45	2/7
Ghelfenstein-Ferreira, 2020[32]	France	1/1	0/1	1/1
Helleberg, 2020[33]	Denmark	2/27 (7.4%)	0/27	2/2
Ichai, 2020[34a,c]	France	6/26 (23.1%)	2/26	4/6
Koehler, 2020[35]	Germany	5/5	0/5	3/5
Lahmer, 2020[36]	Germany	2/2	0/2	2/2
Lahmer, 2020[37]	Germany	11/32 (34.4%)	0/32	4/11
Lamoth, 2020[38]	Switzerland	3/80 (3.8%)	0/80	1/3
Lescure, 2020[1]	France	1/1	0/1	1/1
Meijer, 2020[39]	The Netherlands	1/1	0/1	1/1
Mitaka, 2020[40]	USA	4/7	3/7	4/4
Mohamed, 2020[41]	Ireland	1/1	0/1	1/1
Nasir, 2020[42]	Pakistan	5/23 (21.7%)	4/23	3/5
Prattes, 2020[43]	Austria	1/1	0/1	1/1
Rutsaert, 2020[4]	Belgium	7/20 (35.0%)	0/20	4/7
Santana, 2020[44]	Brazil	1/1	0/1	1/1
Sarrazyn, 2020[45c]	Belgium	4/4	0/4	4/4
Schein, 2020[3]	France	1/42 (2.4%)	12/42	1/1
Sharma, 2020[46]	Australia	1/1	0/1	0/1
van Arkel, 2020[47]	The Netherlands	6/31 (19.4%)	0/31	4/6
Van Biesen, 2020[48c]	The Netherlands	9/42 (21.4%)	1/42	2/9
Wang, 2020[49c]	China	4/15 (26.7%)[b]	0/15	NA
White, 2020[9]	United Kingdom	18/122 (14.8%)[b]	12/122	8/18
Yang, 2020[50a,c]	China	2/52 (3.8%)	0/52	N

Abbreviations:AMB, Amphotericin B; ANI, Anidulafungin; CAPA, COVID-19–associated pulmonary aspergillosis; CAS, Caspofungin; FLU, Fluconazole; GM, Galactomannan antigen; ICU, Intensive care unit; ISA, Isavuconazole; MIC, Micafungin; NA, Not available data; VOR, Voriconazole.

[a]Study in ICU where mechanical ventilation status was not precised.

[b]All the CAPA cases were not intubated and thus were not included in this review.

[c]Not included study because of lack of individual information.

was associated with a younger age (59.1 vs 68.8 years, $p = .001$) and a diagnosis based on a unique microbiologic criterion (culture, respiratory marker or blood marker) (81.5% vs 33.3%, $p < .001$), particularly on a unique respiratory marker (44.4% vs 11.5%, $p < .001$). In the non-treated group, positivity rates of *Aspergillus* isolation in culture ($P = .006$), of GM in non-BAL respiratory samples ($p = .03$) and of *Aspergillus* specific PCR in blood ($p < .001$) and in respiratory samples ($p = .01$) were significantly lower than in the treated group in univariate analysis. These results were confirmed in multivariate analysis except for *Aspergillus* isolation in culture (Table S2). We

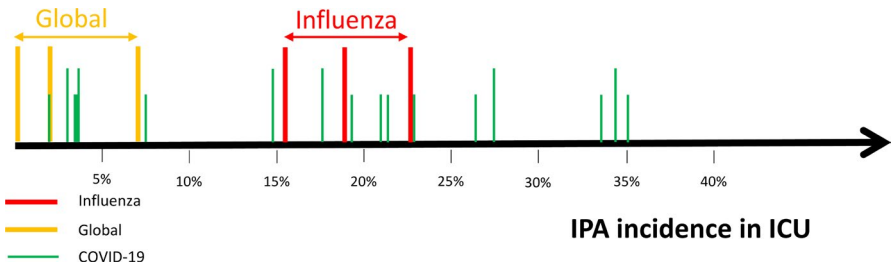

FIGURE 2 Schematic comparative representation of reported prevalence of IPA in ICU patients. Each green bar represents an individual study in COVID-19 patients (details in Table 2). A short and long bar represent a retrospective and prospective study, respectively. The three yellow bars represent the global prevalence in ICU non-COVID-19 and non-Influenza patients (0.3%–6.9%).[18,51,52] The three red bars represent the prevalence in the group of ICU patients with severe influenza (16%–23%).[10,53,54]

noted that a combination of positive culture and positive marker in respiratory sample was more frequent in the treated group (35.4% vs 11.1%, *P* =.02) (Table 2). Moreover, *Aspergillus* specific blood markers (GM and PCR) were more often positive in treated patients ($p = .02$). Interestingly, among *Aspergillus* species, *A niger* was more common in non-treated group (20% vs 2.6%, $p = .03$) and thus was more frequently considered as a contaminant. Concerning radiological data, although CT-scan results were reported only for 34 patients, the presence of typical aspergillosis imaging was correlated with the decision to treat ($p < .001$, data not shown). Besides, decision of non-treatment was not associated with an over-mortality (18.5% of fatality rate in non-treated group vs 56.3% in treated group, $p < .001$).

The overall mortality rate was 52.2% (70/134). In order to compare characteristics of survivor ($n = 64$) and non-survivor ($n = 70$) patients, we analysed the underlying diseases, the microbiological data and the antifungal treatment (Table 3). Non-survivor patients were older (70.8 vs 62.5 years, $p < .001$), were more likely to have chronic respiratory diseases (33.9% vs 11.8%, $p = .009$) and chronic obstructive pulmonary disease (COPD) (17.7% vs 2%, $p = .01$) in univariate analysis. However, the multivariate analysis did not confirm the positive association between COPD and mortality (Table S3). Of note, administration of systemic corticosteroids was not more frequent in non-survivor patients (48.0% vs 56.3%, $p = .5$, data not shown). Moreover, presence of a positive blood marker (PCR or GM) was more frequent in the non-survivor group (28.6% vs 9.4%, $p = .005$ and 27.1% vs 4.7%, $p < .001$, respectively) in univariate analysis. In multivariate analysis, positive GM was more frequent in the non-survivor group ($p < .006$). Patients with a positive blood GM or with any positive blood marker had an 11.67 (3.06–55.54)-fold or a 5.79 (1.98–16.93)-fold higher probability of death, respectively (Figure 3).

On the other hand, detection of *Aspergillus* spp. in the survivor group was more often based on a unique respiratory marker (PCR or GM), compared to non-survivors (25% vs 10%, $p = .02$).

4 | DISCUSSION

Currently, a major issue is the absence of consensual definition of IPA[6,7,10,11] in COVID-19 patients as shown in the literature review presented here, where at least 8 different definitions of IPA have been used in studies published between January and October 2020. To address this issue, an international working group is currently implementing new definition criteria. This categorisation into proven/probable/possible CAPA contains new criteria such as PCR in various samples and the taking into account of non-BAL respiratory samples, to classify as possible CAPA in case of positive culture and/or other positive markers.[12] Another issue is the high variability among studies concerning biological markers used for aspergillosis diagnosis. Indeed, few centres performed *A fumigatus* PCR in BAL or in serum. Moreover, there are no standardised recommendations nor diagnostic protocols, and some sampling procedures such as BAL were not always performed in COVID-19 patients due to the aerosolising nature of the procedure.[13]

This is, to our knowledge, the largest systematic literature review (covering a 9-month period) for which a statistical analysis of the data has been performed to clarify CAPA characteristics particularly in terms of decision to treat and of mortality criteria. This review clearly shows that the reported CAPA incidence is extremely variable, from 2.4%[3] to 35%.[4] The explanation for this variability remains unclear. The disparity among these results may be explained in part by the various screening methods for *Aspergillus* spp. detection in these studies and by the lack of consensual definition of IPA in COVID-19 patients until now.

Among the 134 cases analysed, there were 12 cases of colonisation and 122 IPA according to the authors' classification. Only 6.3% met the host factor required for classification as probable or putative IPA according to the EORTC [6] or Blot et al classification.[7] Of note, if the published cases were reclassified according to the most recent criteria of Kohler et al.,[12] based on the available data in the publications, 100 out of the 134 cases would have been classified as 6 proven, 92 probable and 2 possible CAPA. Nevertheless, as it was not possible to reclassify all the cases, we kept the classification given by the authors for our analysis.

Antifungal treatment was prescribed in 71.6% of cases. First, we compared the characteristics of treated patients versus untreated patients. We noted that the age and the number of microbiological criteria seemed to be key factors for treatment decision. As suggested in previous studies, the number of mycological criteria should be taken into account in further classification adapted for ICU COVID-19

TABLE 2 Comparison of antifungal treated and non-treated patients with CAPA or *Aspergillus* colonisation associated with COVID-19 infection in the 28 selected publications (*N* = 134)

Parameter	Total	Non-treated due to post-mortem diagnosis (NTd)	Non-treated due to clinical decision (NTc)	Treated (TT)	*p* NTc vs TT
Number of patients	134	11	27	96	
Age (years), mean (range)*	67 (38–87)	69 (47–86)	59.1 (38–79)	68.8 (38–87)	.001
Male gender, *n* (%)*	84 (72.4%)	8 (72.3%)	17 (77.3%)	62 (74.7%)	.8
Microbiology					
Positive Histology, *n/N*	6/13	1/1	0/0	5/12	-
Positive Culture, *n/N*	101/133	9/11	15/27	77/95	.006
With *A fumigatus*	87/101	8/9	11/15	68/77	.22
With TR34/L98 gene CYP51A mutation	3/87	1/8	0/11	2/68	1
With *A niger* complex	5/101	0/9	3/15	2/77	.03
With *A flavus*	6/101	1/9	0/15	5/77	.59
Others *Aspergillus* species	4/101	0/9	1/15	3/77	.52
GM positive in					
Serum (>0.5), *n/N*	22/76	2/5	1/15	19/56	.05
BAL (>1), *n/N*	26/33	0/1	3/6	23/26	.06
Other respiratory samples (>1), *n/N*	29/34	0/1	4/6	25/27	.03
PCR *A fumigatus* positive in					
Serum, *n/N*	9/31	0/1	0/14	9/16	<.001
Respiratory samples, *n/N*	36/48	2/5	8/15	26/28	.01
Positive beta D glucan, *n/N*	18/31	1/3	3/7	14/21	.38
Classification, *n* (%)[a]					
One positive result					
C−R−S−	1 (0.7%)	0	0	1 (1%)	1
C+R−S−	45 (33.6%)	7 (63.6%)	11 (40.7%)	27 (28.1%)	.24
C−R+S−	23 (17.2%)	0	12 (44.4%)	11 (11.5%)	<.001
Two positive results					
C−R−S+	3 (2.2%)	1 (9.1%)	0	2 (2.1%)	1
C+R+S−	39 (29.1%)	2 (18.2%)	3 (11.1%)	34 (35.4%)	.02
C+R−S+	4 (3%)	0	1 (3.7%)	3 (3.1%)	1
C−R+S+	6 (4.5%)	1 (9.1%)	0	5 (5.2%)	.58
Three positive results					
C+R+S+	13 (9.7%)	0	0	13 (13.5%)	.07
Positive blood marker[b], *n/N*	26/78	2/5	1/15	23/58	.02
Unique microbiologic criterion[c]	62 (46.3%)	8 (72.7%)	22 (81.5%)	32 (33.3%)	<.001
Outcome					
Death, *n* (%)	70 (52.2%)	11 (100%)	5 (18.5%)	54 (56.3%)	<.001
ICU length of stay (days), mean (range)**	24.2 (3–100)	11.9 (3–34)	28.9 (9–69)	25.4 (4–100)	.55
Time from ICU admission to diagnosis (days), mean (range)***	9.5 (1–48)	11.6 (4–25)	13.5 (2–38)	8.5 (1–48)	.24

Abbreviations: BAL, Broncho-alveolar lavage fluid; GM, Galactomannan antigen.

[a]Microbiological classification: C (culture) R (respiratory marker, PCR or GM) S (serum marker, PCR or GM), for example C+R−S− stands for a positive culture with negative respiratory and serum markers.

[b]Number of patients with positive blood marker including PCR and GM.

[c]Unique microbiologic criterion is fulfilled when the diagnosis was based on a unique mycological argument (culture, PCR or GM).

*18 patients not included (data not available),; **62 patients not included (data not available),; ***60 patients not included (data not available).

TABLE 3 Comparison of survivor and non-survivor patients with CAPA or *Aspergillus* colonisation associated with COVID-19 infection in the 28 selected publications (*N* = 134)

Parameter	Total	Survivor (S)	Non-Survivor (NS)	*p* S vs NS
Number of patients	134	64	70	
Age (years) mean (range) (18 NA)	67 (38-87)	62.5 (38-79)	70.8 (47-87)	<.001
Male gender, n (%) (18 NA)	84 (72.4%)	41 (75.9%)	46 (74.2%)	.83
Past medical history, *n* (%)				
Obesity	25 (19.7%)	14 (27.5%)	11 (17.7%)	.17
Diabetes	47 (37%)	21 (41.2%)	22 (35.5%)	.9
Hypertension	56 (44.1%)	25 (49%)	25 (40.3%)	.25
Hypercholesterolemia	8 (6.3%)	2 (3.9%)	6 (9.7%)	.46
Cardiovascular diseases	16 (12.6%)	8 (15.7%)	6 (9.7%)	.29
Solid cancer	9 (7.1%)	4 (7.8%)	5 (8.1%)	1
Hematological malignancy	5 (3.9%)	0	5 (8.1%)	.07
COPD	14 (11%)	1 (2%)	11 (17.7%)	.01
Asthma	9 (7.1%)	4 (7.8%)	5 (8.1%)	1
Chronic respiratory diseases	30 (23.6%)	6 (11.8%)	21 (33.9%)	.009
CKD	11 (8.7%)	7 (13.7%)	3 (4.8%)	.1
SOT	1 (0.8%)	1 (2%)	0	.44
Chronic steroid treatment	4 (3.2%)	2 (3.9%)	1 (1.6%)	.58
Host Factor EORTC[4]	8 (6.3%)	4 (7.8%)	4 (6.5%)	.73
NA[a]	7	13	5	
Microbiology, *n/N*				
Positive histology	6/13	3/3	3/10	.07
Positive culture with	101/133	45/64	56/69	.14
A fumigatus	87/101	40/45	47/56	.47
With TR34/L98 Gene CYP51A mutation	3/87	0/40	3/47	.25
A niger section	5/101	3/45	2/56	.65
A flavus	6/101	2/45	4/56	1
Others *Aspergillus* species	4/101	1/45	3/56	.63
GM positive in				
Serum (>0.5)	22/76	3/38	19/38	<.001
BAL (>1)	26/33	9/13	17/20	.39
Other respiratory samples (>1)	29/34	16/18	13/16	.65
A fumigatus PCR positive in				
Serum	9/31	4/22	5/9	.08
Respiratory samples	36/48	23/31	13/17	1
Positive beta-D-glucan	18/31	7/14	11/17	.41
Classification, *n* (%)[b]				
C−R−S−	1 (0.7%)	1 (1.6%)	0	.48
C+R−S−	45 (33.6%)	20 (31.3%)	25 (35.7%)	.58
C−R+S−	23 (17.2%)	16 (25%)	7 (10%)	.02
C−R−S+	3 (2.2%)	0	3 (4.3%)	.25
C+R+S-	39 (29.1%)	21 (32.8%)	18 (25.7%)	.37
C+R−S+	4 (3%)	1 (1.6%)	3 (4.3%)	.62
C−R+S+	6 (4.5%)	2 (3.1%)	4 (5.7%)	.68
C+R+S+	13 (9.7%)	3 (4.7%)	10 (14.3%)	.08

(Continues)

TABLE 3 (Continued)

Parameter	Total	Survivor (S)	Non-Survivor (NS)	*p* S vs NS
Number with positive blood marker[c]	26/78	6/39	20/39	<.001
Unique microbiologic criterion[d]	62 (46.3%)	31 (48.4%)	31 (44.3%)	.63
Antifungal treatment, *n* (%)				
Antifungal treatment:	96 (71.6%)	42 (65.6%)	54 (77.1%)	.14
Voriconazole	72 (53.7%)	34 (53.1%)	33 (47.1%)	.49
Isavuconazole	9 (6.7%)	4 (6.3%)	5 (7.1%)	1
Amphotericin B	22 (16.4%)	7 (10.9%)	14 (20%)	.15
Caspofungin	8 (6%)	5 (7.8%)	3 (4.3%)	.48
Micafungin	1 (0.8%)	1 (1.6%)	0	.48
Anidulafungin	15 (11.2%)	2 (1.6%)	9 (12.9%)	.06
Fluconazole	2 (1.5%)	3 (1.6%)	1 (1.4%)	.35

Abbreviations: BAL, Broncho-alveolar lavage fluid; GM, Galactomannan antigen; NA, not available data.

[a]The total is not equal to the sum of S and NS groups since in one publication[29] the past medical history was only available for the total of patients and not for S and NS subgroup.

[b]Microbiological classification: C (culture) R (respiratory marker, PCR or GM) S (serum marker, PCR or GM), for example C+R−S− stands for a positive culture with negative respiratory and serum markers.

[c]Number of positive blood marker included blood PCR and GM.

[d]Unique microbiologic criterion is fulfilled when the diagnosis was based on a unique mycological argument (culture, PCR or GM).

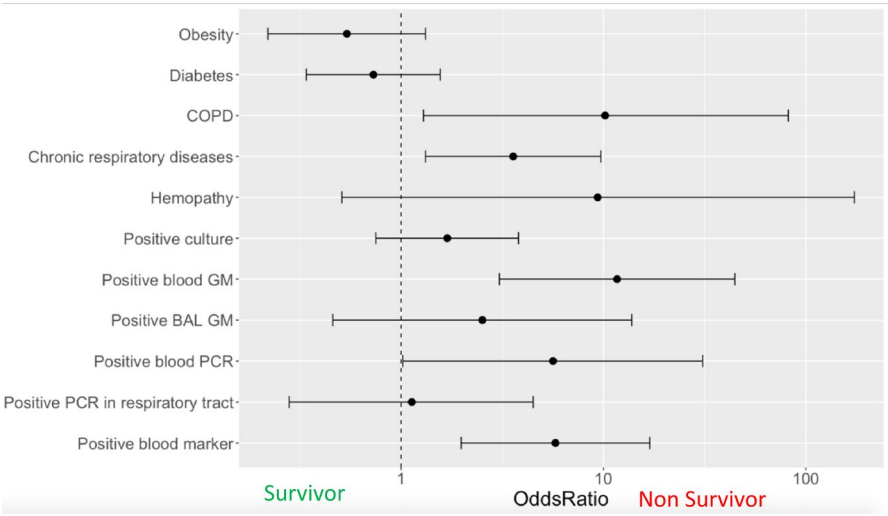

FIGURE 3 Mortality odds ratio of clinical and microbiological interest (calculated from Table 3). COPD: chronic obstructive pulmonary disease, GM, galactomannan antigen, Positive blood marker included both positive blood PCR and GM

patients.[14,15] Another important point revealed in our analysis is that the decision not to treat was not associated with excess mortality (18.5% vs 56.3% (p < .001)). The lower mortality rate in non-treated patients suggests that the presence of Aspergillus in respiratory tract may not be sufficient to diagnose IPA in a COVID-19 patient with a non-specific pulmonary imaging. The difficulty to differentiate colonisation from invasive infection among putative CAPA cases has been reviewed recently.[16] Finally, we compared the characteristics of surviving patients vs those of deceased patients. Criteria independently associated with mortality were high age, history of chronic respiratory disease and serum galactomannan index >0.5. Interestingly, COPD, which has been reported as a risk factor for both severe COVID-19[17] and IPA,[18] did not appear, using the multivariate analysis, as a prognostic factor of CAPA in this review. Regarding biomarkers, a positive galactomannan in serum seems to be a strong prognostic factor despite a low diagnostic sensitivity in ICU patients,[19] thus should prompt treatment. Although a positive GM in BAL was not associated with mortality, GM test remains interesting for diagnosis of IPA.[12] GM is generally detected by ELISA which is performed only twice/week in most laboratories. Lateral flow assay (LFA) is an alternative to ELISA that could decrease the time to diagnosis of IPA but it has been poorly evaluated in CAPA patients so far. In a study of non-bronchoscopic lavage or BAL from 23 patients with CAPA, the agreement between ELISA and LFA was excellent.[12,20] LFA has also shown good performance compared to ELISA for detecting GM in tracheal aspirates in a prospective study of patients with COVID-19–associated IPA.[21]

Before SARS-CoV-2 outbreak, influenza has been demonstrated as a risk factor of IPA in ICU patients with a reported incidence of IAPA

of 19% in a retrospective multicentre cohort study of 432 patients.[10] Nevertheless, some differences appeared between IAPA and CAPA. More patients fulfilled the EORTC host factor criteria in IAPA (43% according to Schauwvlieghe et al.[10]) than in CAPA (6.3% in this study). The mean delay between admission in ICU and the mycological diagnosis seems to be shorter in IAPA (2–3 days[22]) than in CAPA (9.5 days in this review). Finally, very few cases of tracheobronchitis form of aspergillosis[4] were described among CAPA compared with IAPA.[19] To decipher the risk factors for and characteristics of CAPA, it would be of major interest to design a study comparing COVID patients with non-COVID patients, in the same ICUs and same time period.

There are some limitations in the present review as many individual data were missing, especially concerning COVID-19 treatments that could increase the occurrence of CAPA. Particularly, corticosteroids are a known risk factor for IPA in ICU patients,[18] but their implication in CAPA remains to be established. Moreover, results of biological markers were not always reported (especially when negative) possibly leading to statistical bias.

The presence of *Aspergillus* in a pulmonary sample may not be sufficient to diagnose CAPA and to guide treatment onset. It seems therefore necessary to combine several mycological diagnostic tools in order not to overestimate the cases of CAPA. Analysis of the literature showed that age, COPD and a positive GM are the main prognostic factors in CAPA.

CONFLICTS OF INTEREST

During the past 5 years, Eric Dannaoui has received research grants from MSD and Gilead, travel grants from Gilead, MSD, Pfizer and Astellas, and speaker's fee from Gilead, MSD and Astellas. Marie-Elisabeth Bougnoux has received research grants from Astellas, and speaker's fee from Pfizer, MSD, Astellas and Gilead. Other authors have no conflict of interests.

AUTHOR CONTRIBUTIONS

Grégoire Pasquier: Data curation (equal); Formal analysis (equal); Writing-original draft (equal). **Agathe Bounhiol:** Data curation (equal); Writing-original draft (equal). **Florence Robert-Gangneux:** Writing-review & editing (equal). **Jean Ralph ZAHAR:** Conceptualization (equal); Writing-review & editing (equal). **Jean-Pierre GANGNEUX:** Conceptualization (equal); Writing-review & editing (equal). **Ana NOVARA:** Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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SUPPORTING INFORMATION

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

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