Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Incidence of invasive pulmonary aspergillosis among critically ill COVID-19 patients

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To the Editor,

The devastating pandemia of the novel Coronavirus Disease 2019 (COVID-19) resulting from the emergence of SARS-CoV-2 is of particular concern because of the development of acute respiratory distress syndrome (ARDS), which is associated with high mortality rates. Besides the impact of viral pneumonia itself, the prognosis can be affected by other infectious complications, such as ventilator-associated bacterial pneumonia or fungal infections. Previous reports of a significant risk of invasive pulmonary aspergillosis (IPA) among patients with severe Influenza raises questions about a similar association with COVID-19 [1]. IPA among ICU patients is often insidious, which results in delayed diagnosis and poor prognosis if not actively searched for.

At our center (Lausanne University Hospital), serial weekly monitoring of serum galactomannan was part of our standard of care procedure for all patients admitted in the ICU with confirmed COVID-19 (defined as a positive PCR on a nasopharyngeal swab or a lower respiratory sample: bronchial aspirate or broncho-alveolar lavage fluid [BAL]). Bronchial aspirates for detection of bacterial or fungal superinfections were regularly performed in patients under mechanical ventilation. Bronchoscopy and BAL were performed when clinically indicated. Fungal cultures were incubated for 7 days at 30°C on Sabouraud selective media. Galactomannan testing (Platelia *Aspergillus* EIA, Bio-Rad) was performed in serum and BAL considering a positive result for an optical density index of 0.5 and 1, respectively. Diagnosis of probable IPA was assessed according to the recent definitions of Influenza-associated IPA [2]. Because bronchoscopy and BAL sampling were minimized in the setting of COVID-19 unless clearly indicated (due to the risk of aerosolization), results of bronchial aspirates cultures were also considered for defining a putative IPA category (*Aspergillus* spp. recovered from culture of ≥2 consecutive bronchial aspirates in the absence of bronchoscopy and BAL sample). Cases with a single positive *Aspergillus* culture of bronchial aspirate were classified as colonization or "undetermined".

A total of 118 patients were admitted to ICUs with confirmed COVID-19 between March 6th and May 11th 2020, and 80 of them underwent mechanical ventilation. Among them, 3 (3.8%) patients fulfilled the criteria of IPA (one probable and two putative cases), as described in Table 1. There was no patient classified as colonization/undetermined.

None of the IPA patients had predisposing host conditions according to the definitions of the European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) [3]. However, they received tocilizumab for treatment of the COVID-19 inflammatory conditions within 4 days from IPA diagnosis. All three patients experienced worsening respiratory conditions despite broad-spectrum antibacterial therapy and no other pathogens were isolated in concomitant cultures except for one case (*Haemophilus influenzae*). All three patients were treated with voriconazole with a favorable outcome for two of them and a fatal issue for one of them. None of the other patients received empirical antifungal therapy for suspected IPA or anti-mold active prophylaxis.

The association of IPA with severe COVID-19 remains an important question to elucidate. A Dutch-Belgian study previously showed an incidence of IPA of 14% among non-immunocompromised ICU patients with severe Influenza compared to only 5% in those with non-Influenza community-acquired pneumonia [1]. Similarly, the lung injury and cytokine storm observed in COVID-19 could predispose to IPA. The

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Table 1
Characteristics of patients with COVID-19 and subsequent invasive pulmonary aspergillosis (IPA)

Age/sex Underlying conditions	Timing of IPA (days) from: COVID-19 diagnosis[1]/ICU admission/Start of mechanical ventilation	Clinical criteria	Radiological criteria (chest CT)	Mycological criteria[2] and IPA classification	Antifungal therapy outcome
55 y.o./male Hypertension, obesity, type 2 diabetes	7 days/7 days/6 days	Worsening respiratory conditions after initial improvement despite broad-spectrum ABT	Multiple consolidations	Culture (asp): *A. fumigatus* (3 consecutive samples) PCR[3] (asp): *A. fumigatus* (1.5E6 cp/ml) Putative IPA	Voriconazole Alive at day 17 (discharged from hospital)
65 y.o./male Hypertension, obesity, pulmonary fibrosis	8 days/3 days/3 days	Persistent fever and worsening respiratory conditions despite broad-spectrum ABT	Interstitial infiltrates and ground glass opacities	Culture (asp): *A. fumigatus* (5 consecutive samples) Positive serum GM (0.73) Positive serum BDG: 360 pg/ml Probable IPA	Voriconazole Death at day 22
66 y.o./male Asthma	13 days/8 days/6 days	Worsening respiratory conditions despite broad-spectrum ABT	Multiple consolidations	Culture (asp): *A. fumigatus* (2 consecutive samples) Putative IPA	Voriconazole Alive at day 28 (discharged from hospital)

IPA: invasive pulmonary aspergillosis, y.o.: years old, ICU: intensive care units, ABT: antibacterial therapy CT: computed tomography, asp: bronchial aspirate, GM: galactomannan (results expressed in optical density index).
[1] Date of first positive PCR for SARS-CoV-2 from nasopharyngeal swab or lower respiratory sample.
[2] Mycological criteria were adapted from definitions of Influenza-associated IPA [2]: i) probable IPA: positive galactomannan in serum (≥0.5), or positive galactomannan in bronchoalveolar lavage (BAL) fluid (≥1.0), or positive culture for *Aspergillus* spp. In BAL, ii) putative IPA: positive culture for *Aspergillus* spp. in ≥2 consecutive bronchial aspirates, in the absence of bronchoscopy or BAL, iii) colonization/undetermined: positive culture for *Aspergillus* spp. in a single bronchial aspirate.
[3] Specific *Aspergillus fumigatus* quantitative PCR, results expressed in copies (cp) per ml.

occurrence of probable/putative IPA among ICU COVID-19 has been previously reported among smaller cohorts of patients under mechanical ventilation (N = 13 to 31) with a prevalence of 19% to 35% [4–7].

Our larger cohort of consecutive COVID-19 patients requiring mechanical ventilation (n = 80) suggests a much lower incidence (3.8%), which did not differ from that observed in the population of ICU patients with community-acquired pneumonia of all causes except Influenza in the Dutch-Belgian study [1]. However, the actual incidence is difficult to assess because IPA diagnosis can be missed in this setting. The screening strategy in our cohort included weekly monitoring of galactomannan in serum, which provided positive results in only one case. A limitation was that bronchoscopy and BAL were performed in a relatively small proportion of patients (28%). Therefore, the diagnosis of putative IPA was also considered in two patients with repeated positive fungal cultures of bronchial aspirates in the absence of BAL sampling. The fact that these patients experienced worsening clinical and radiological respiratory conditions despite broad-spectrum antibacterial therapy argues against simple colonization. Some IPA cases could have been missed in the absence of BAL sampling and galactomannan testing in BAL.

The role of tocilizumab (monoclonal antibody targeting the interleukine-6 receptor) in favoring IPA can be questioned. The three IPA cases reported here received tocilizumab, as it was the case for most patients of the present cohort. While tocilizumab is frequently use for the treatment of auto-immune diseases, no association with IPA has been previously reported in the literature.

Further prospective studies are warranted to assess the actual incidence, risk factors and impact of IPA in severe COVID-19.

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Authors' contributions

F. Lamoth: conceptualization, methodology, formal analysis, investigation, writing original draft.

E. Glampedakis: formal analysis, investigation, writing (review-editing).

N Boillat-Blanco: investigation, writing (review-editing).

M. Oddo: investigation, writing (review-editing).

J. L. Pagani: formal analysis, investigation, writing (review-editing).

Ethical statement

COVID-19 patients were included in an institutional registry for the purpose of epidemiological description, which was approved by the "Commission d'éthique du Canton de Vaud" (2020-0401).

Transparency declaration

All authors: none to declare with respect to the present work.

F. Lamoth reports personal fees from Gilead, outside the submitted work.

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