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CORRESPONDENCE

COVID-19 associated pulmonary aspergillosis: regional variation in incidence and diagnostic challenges

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We thank Rouze et al. for the thoughtful remarks [1] on our multinational study on pulmonary aspergillosis (CAPA) associated to coronavirus disease 2019 (COVID-19) [2].

We agree that diagnosis of CAPA is complex and requires incorporation of clinical presentation, imaging and mycological work-up with the additional challenge of possible diagnostic uncertainty in patients with acute respiratory failure. Further, diagnostic strategies vary widely between centers and systemic CAPA screening is rarely performed, as shown in our study where even serum galactomannan (GM) levels were available in less than half of patients (277/592) [2]. This scarce may be a result of low serum GM sensitivity (19%) [2] reflecting the primary airway invasive character of the disease with delayed angioinvasion, mirroring pathophysiology of aspergillosis in other non-neutropenic populations. Consequently, mycological evaluation of respiratory specimens is key for early diagnosis and successful management of CAPA. While bronchoalveolar lavage fluid (BALF) has been the benchmark specimen for diagnosing aspergillosis in the non-neutropenic host, BALF samples have not been widely available from COVID-19 patients due to safety concerns in the early phase of the pandemic (BALF was obtained in about half of our cohort [2]). Thus, other respiratory specimens such as non-bronchoscopic lavage and tracheal aspiration samples have been widely used for CAPA diagnosis. Although evaluation of clinical specificity was lacking, mycological evidence from these samples – often with GM cutoffs derived from BALF—have also been utilized for classification of CAPA according to modified Blot criteria. Emerging evidence indicates that GM testing from tracheal aspirates may be less discriminative between *Aspergillus* colonization and CAPA, and specificity may only improve once cutoffs are significantly increased (≥ 2.0 optical density index) [3]. Thereby CAPA classification efforts utilizing Blot criteria may have resulted in an overestimation of the real disease burden. These limitations of variations in early classification and CAPA overestimation where recently overcome by the more conservative 2020 ECMM/ISHAM CAPA consensus definitions. Compared to the modified Blot criteria, application of these new criteria resulted in a reduction of the mean incidence of probable/proven CAPA cases from 19% to 11.9% among evaluable cases[4], bringing the prevalence of CAPA cases closer to that suggested by autopsy studies. As an important strength, our study uniformly applied these more stringent ECMM/ISHAM criteria to all cases, resulting in an overall incidence of probable/proven CAPA of 15.4% (92/592), although incidence varied widely between participating centers [2]. This wide range may reflect local epidemiological variations that may be COVID-specific (e.g., non-uniform approaches to COVID-19 treatment) but may also be more generalizable, reflecting different burden of *Aspergillus* exposure, diagnostic accuracy and genetic predisposing risk factors.

Detailed evaluation of our cohort has indicated older age, need for invasive respiratory support and receipt of tocilizumab as independent risk factors associated with

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development of CAPA, and presence of CAPA represented an independent factor for reduced probability of ICU survival, even after controlling for underlying conditions [5].

Importantly our data reflect a real-life scenario with no predefined CAPA screening or fungal diagnostics strategies and despite enrolling prospectively, not all centers had CAPA and non-CAPA patients reported for the entire study period.

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Declarations

Conflicts of interest
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