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Risk factors for COVID-19-associated pulmonary aspergillosis: a systematic review and meta-analysis

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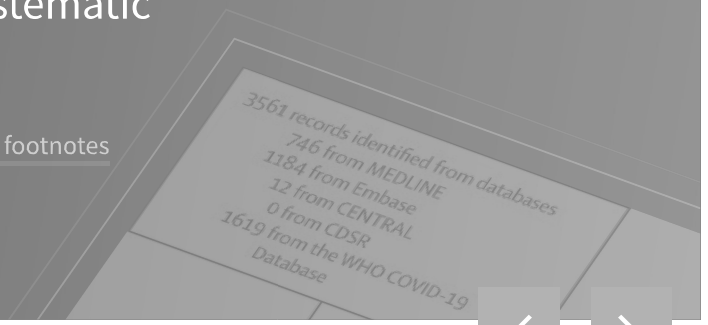

Summary

Background

COVID-19-associated pulmonary aspergillosis (CAPA) has been reported to be an emerging and potentially fatal complication of severe COVID-19. However, risk factors for CAPA have not been systematically addressed to date.

Methods

In this systematic review and meta-analysis to identify factors associated with CAPA, we comprehensively searched five medical databases: Ovid MEDLINE; Ovid Embase; the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials; and the WHO COVID-19 Database. All case-control and cohort studies in adults (aged >18 years) that described at least six cases of CAPA and evaluated any risk factors for CAPA, published from Dec 1, 2019, to July 27, 2023, were screened and assessed for inclusion. Only studies with a control population of COVID-19-positive individuals without aspergillosis were included. Two reviewers independently screened search results and extracted outcome data as summary estimates from eligible studies. The primary outcome was to identify the factors associated with CAPA. Meta-analysis was done with random-effects models, with use of the Mantel–Haenszel method to assess dichotomous outcomes as potential risk factors, or the inverse variance method to assess continuous variables for potential association with CAPA. Publication bias was assessed with funnel plots for factors associated with CAPA. The study is registered with PROSPERO, CRD42022334405.

Findings

Of 3561 records identified, 27 articles were included in the meta-analysis. 6848 patients with COVID-19 were included, of whom 1324 (19·3%) were diagnosed with CAPA. Diagnosis rates of CAPA ranged from 2·5% (14 of 566 patients) to 47·2% (58 of 123). We identified eight risk factors for CAPA. These factors included pre-existing comorbidities of chronic liver disease (odds ratio [OR] 2·70 [95% CI 1·21–6·04], p=0·02; I^2=53%), haematological malignancies (OR 2·47 [1·27–4·83], p=0·008; I^2=50%), chronic obstructive pulmonary disease (OR 2·00 [1·42–2·83], p<0·0001; I^2=26%), and cerebrovascular disease (OR 1·31 [1·01–1·71], p=0·05; I^2=46%). Use of invasive mechanical ventilation (OR 2·83; 95% CI 1·88–4·24; p<0·0001; I^2=69%), use of renal replacement therapy (OR 2·26 [1·76–2·90], p<0·0001; I^2=0%), treatment of COVID-19 with interleukin-6 inhibitors (OR 2·88 [1·52–5·43], p=0·001; I^2=89%), and treatment of COVID-19 with

corticosteroids (OR 1·88 [1·28–2·77], p=0·001; I^2=66%) were also associated with CAPA. Patients with CAPA were typically older than those without CAPA (mean age 66·6 years [SD 3·6] *vs* 63·5 years [5·3]; mean difference 2·90 [1·48–4·33], p<0·0001; I^2=86%). The duration of mechanical ventilation in patients with CAPA was longer than in those without CAPA (n=7 studies; mean duration 19·3 days [8·9] vs 13·5 days [6·8]; mean difference 5·53 days [1·30–9·77], p=0·01; I^2=88%). In post-hoc analysis, patients with CAPA had higher all-cause mortality than those without CAPA (n=20 studies; OR 2·65 [2·04–3·45], p<0·0001; I^2=51%).

Interpretation

The identified risk factors for CAPA could eventually be addressed with targeted antifungal prophylaxis in patients with severe COVID-19.

Funding

None.

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