Effect of glucocorticoids on the development of COVID-19-associated pulmonary aspergillosis: a meta-analysis of 21 studies and 5174 patients

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Effect of glucocorticoids on the development of COVID-19-associated pulmonary aspergillosis: a meta-analysis of 21 studies and 5174 patients

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**SUMMARY**

**Objective:**
COVID-19-associated pulmonary aspergillosis (CAPA) remains a high mortality mycotic infection throughout the pandemic, and glucocorticoids (GC) may be its root cause. We aimed to evaluate the effect of systemic GC treatment on the development of CAPA.

**Methods:** We systematically searched the PubMed, Google Scholar, Scopus, and Embase databases to collect eligible studies published until December 31, 2022. The pooled outcome of CAPA development was calculated as the log odds ratio (LOR) with 95% confidence intervals (CI) using a random effect model.

**Results:** A total of 21 studies with 5174 patients were included. Of these, 20 studies with 4675 patients consisting of 2565 treated with GC but without other immunomodulators (GC group) and 2110 treated without GC and other immunomodulators (controls) were analyzed. The pooled LOR of CAPA development was higher for the GC group than for the control group (0.54; 95% CI: 0.22, 0.86; p<0.01). In the subgroups, the pooled LOR was higher for high-dose GC (0.90; 95% CI: 0.17, 1.62; p=0.01) and dexamethasone (0.71; 95% CI: 0.35, 1.07; p<0.01) but had no significant difference for low-dose GC (0.41; 95% CI: -0.07, 0.89; p=0.09), and non-dexamethasone GC (0.21; 95% CI: -0.36, 0.79; p=0.47), treated patients versus controls.

**Conclusion:** GC treatment increased the risk of CAPA development, and the risk was particularly associated with the use of high-dose GC or dexamethasone treatment.

**Keywords:** Glucocorticoids; COVID-19-associated pulmonary aspergillosis; Meta-analysis

**PROSPERO Registration Number:** CRD42022341633.
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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), represents the most devastating pandemic in modern history, causing one of the largest health crises worldwide. It has been documented to claim >6.0 million deaths across the globe since its inception in 2019, but the real death toll may be double or even quadruple of this official count.\(^1\) Importantly, not only SARS-CoV-2 infection by itself but also superinfections caused by fungal or other microbial pathogens have contributed to these devastating mortality numbers.\(^2\)\(^-\)\(^5\)

Among fungal superinfections, invasive pulmonary aspergillosis remained a potential cause of morbidity and mortality in intensive care unit (ICU) patients with severe COVID-19 throughout the pandemic years, and the disease was named COVID-19-associated pulmonary aspergillosis (CAPA).\(^6\)\(^,\)\(^7\) Recent studies have shown a cumulative incidence of CAPA ranging from 3% to 35%, with a higher incidence in severe COVID-19 patients with acute respiratory distress syndrome (ARDS) requiring ICU care.\(^7\)\(^,\)\(^8\) The independent contribution of CAPA to the devastating mortality of approximately 55% of COVID-19 has been reported in multiple studies.\(^7\)\(^-\)\(^11\) Since COVID-19 is still continuing in several parts of the world, including China and India, and additional waves of the pandemic may follow in the future, it is of paramount clinical importance to understand the root cause of the development of CAPA to improve the management and outcome of the disease.

Glucocorticoids (GC) have been consistently used worldwide as a standard treatment for COVID-19 since the publication of the preliminary report of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial on 22 June 2020, demonstrating the efficacy of dexamethasone (Dexa) in controlling hyperinflammation and reducing mortality in patients.\(^12\)\(^,\)\(^13\) However, in addition to reducing inflammation, GC also act as potent immunosuppressants inhibiting innate and adaptive cellular immunity responsible for protective immune responses against fungal and other microbial pathogens.\(^14\)\(^,\)\(^15\) These properties of GC raise serious concerns about whether systemic GC treatment of COVID-19 could increase the risk of CAPA development. Although there are reports on the association of systemic GC treatment with
CAPA 8,10,11,16,17: a meta-analysis with detailed systemic evidence is still lacking on this issue. Therefore, to address this knowledge gap, we conducted a meta-analysis of available studies to synthesize real-life evidence of GC treatment on the development of CAPA.

METHODS

Study Protocol and Registration:

We carried out this study in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (www.prisma-statement.org), and the protocol of the study is registered with the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/prospero) under registration number CRD42022341633.

Search strategy and selection criteria:

We performed a comprehensive advanced literature search of four electronic databases, including PubMed/MEDLINE, Google Scholar, Scopus, and Embase, to identify all studies reporting CAPA and GC from inception to December 31, 2022. The search was independently carried out by two authors (NKT and ZH) using the following Boolean combinations of MeSH terms: (("Coronavirus disease-2019" OR "COVID-19" OR "Coronavirus-2" OR "SARS-CoV-2") AND ("Aspergillus Infection" OR "Aspergillosis")) AND ("Steroids" OR "Glucocorticoids" OR "Corticosteroids" OR "Prednisone" OR "Prednisolone" OR "Methylprednisone" OR "Methylprednisolone" OR "Dexamethasone") with appropriate search limits such as full text, article type, English language and search period. In addition, we manually searched the reference list, similar studies, and citations of included studies as other or extra sources to identify any additional studies missed in the electronic search.

We included studies fulfilling the following criteria: (i) full-text prospective or retrospective observational cohort, case–control, or cross-sectional study or case-series published in the English language in a peer-reviewed journal, (ii) reporting CAPA in hospitalized adult (>18 years of age) COVID-19 patients, (iii) comparative data of COVID-19 patients treated with GC and no GC therapy and frequency of development of CAPA as outcome measures, and (iv)
diagnosis of CAPA made using standard definitions or diagnostic algorithms.\textsuperscript{18-23} We excluded (i) studies published in non-English language or a nonpeer-reviewed journal, (ii) reviews, case reports, opinion articles, meta-analyses, editorials, and conference abstracts, (iii) studies reporting CAPA in nonadult (<18 years of age) patients, and (iv) studies with no clear comparative data of GC therapy or CAPA development as an outcome measure.

To select eligible studies, we first removed duplicate records from the total identified studies using EndNote (version 20) and manual checks. The remaining studies with no duplicates were subjected to two-level systems to select eligible studies. In the first level, two authors (NKT and ZH) independently screened the identified studies by titles and abstracts to select relevant full-text articles. In the second level, the same authors independently reviewed the full texts of the relevant studies in light of eligibility criteria to select the eligible studies for inclusion in the meta-analysis. Any disagreement between the two author reviewers was resolved by mutual discussion to reach a consensus. Any disagreement between the two authors was arbitrated by a third author (AK).

The quality of studies was assessed using the Newcastle–Ottawa scale (NOS) to detect the adequacy of the selection of exposed and nonexposed cohorts, comparability of groups, and adequacy of outcome assessment.\textsuperscript{24,25} The quality of the studies was independently analyzed by two authors (ZH and NKT), and any discrepancy was resolved by mutual discussion or discussion with the third author (AK).

\textbf{Data extraction and analysis:}

Data extraction from the included studies was performed by two authors (NKT and ZH) using a predesigned MS Office Excel worksheet. Any disparity between the extracted data of the two authors was re-examined, and a consensus was achieved following the discussion. In addition, the extracted data were independently reviewed by an additional author (AK). The following data from the text and supplementary information of each included study were collected and recorded. First author name, publication year, country, study design, setting, sample size, GC
treatment, number of patients in the GC treated patients and control group, and number of CAPA in the GC and control groups.

Several of the included studies used various other immunomodulators (IM), such as tocilizumab, sarilumab, anakinra and anti-IL1 antibody, along with GC. To evaluate the effect of GC alone on the risk of CAPA development, we excluded IM treated CAPA and noCAPA patients from such studies. Thus, patients who received standard of care (SOC) and GC but no other IM before CAPA diagnosis were categorized as the GC group, while those who received only SOC but not GC and IM were categorized as the control group.

Based on the dose and type of GC treatment, the included studies were also categorized into low-dose GC and high-dose GC and Dexa and non-Dexa GC subgroups for analysis against their respective control counterparts. For GC dosing, hydrocortisone potency was taken as the standard, and the intervention was classified as high or low dose according to whether the dose was greater or less than or equal to 400 mg of hydrocortisone per day. If any cumulative dose due to prolonged GC treatment was higher than the total cumulative dose regimen for 10 days (i.e., >4000 mg of HC), it was considered a high dose (i.e., cumulative high dose). The conversion of any mg/kg dose into total daily dose was performed taking the weight of the patient 75 kg as the standard. We also subcategorized the included studies using the ECMM/ISHAM definition for the diagnosis of CAPA.

STATA 17.0 software (Stata Corp. 2019; Stata Statistical Software: Release 17. College Station, TX: StatCorp LLC) was used for statistical analysis. We calculated the pooled log odds ratio (LOR) with a 95% confidence interval (CI) as the outcome measure using a random effect model. The LOR is a natural logarithm transformation of the odds ratio. It is a new tool for statistical pooling of data for meta-analyses with heterogeneity, as in the present study, to obtain a more accurate comparison of effect size across the studies. In addition, the LOR is more stable than other effect-size measures and thus produces more reliable results. A LOR ratio greater than zero with a positive 95% CI is considered to be significantly higher, while that having a negative 95% CI is not statistically significant. Publication bias or asymmetry of
the included studies was assessed qualitatively using funnel plots and quantitatively using Egger’s regression test. Heterogeneity in the studies was determined using I²-test, Cochran's Q-test, Tau-square (τ²) test, and H²-test. The values of I²-test: >50%, Cochran's Q-test p value: <0.05, τ²: >0, and H²-test: >1.0 were considered to show heterogeneity. A p value of <0.05 and LOR value of >0 with a positive 95% CI were considered statistically significant.

RESULTS

We identified a total of 2256 studies through different electronic databases and manual searches (Table-S1). Of these, 57 studies were removed as duplicates, and 2156 studies were excluded for having irrelevant titles and abstracts or being reviews, case reports, or editorials. The remaining 43 studies were selected for full-text screening for eligibility. Of these, 22 studies not meeting the eligibility criteria were excluded. Thus, 21 cohort studies were eligible and were included in the meta-analysis. The PRISMA flow chart depicting the literature search and selection of eligible studies is shown in Fig. 1.

Among these 21 included studies, 13 studies were from Europe, 6 were from Asia, and 2 were from North America. They comprised 15 retrospective observation studies (8 single-center, 6 multicenter, and 1 multicenter and multinational), one prospective observational study (multicenter), two ambispective observational studies (1 single-center and 1 multicenter), two retrospective case series (single-center), and one descriptive study (single-center). All included studies used standard diagnostic definitions/criteria for diagnosing CAPA. Thirteen studies used only ECMM/ISHAM criteria, while three studies used ECMM/ISHAM criteria along with other definitions, including practice guidelines, IAPA, and AspICU. Two studies used only EORTC-MSG criteria, while two other studies used a combination of EORTC-MSG and IAPA or AspICU and modified AspICU criteria. One study used a combination of the AspICU and IAPA criteria (Table 1). Details of the GC treatment and number of CAPA in the GC and control groups of the included studies are shown in Table 2. The included studies were of high quality (average NOS score: 7.8 [range: 7–9]) (Table S2). The studies of the GC versus control group had no publication bias, as shown by the visual symmetry of the funnel plot and values
of Egger’s regression test ($\beta_1$=0.87; $p=0.10$) (Fig. S1). However, the studies had heterogeneity ($I^2$ value: 45.46, $p=0.01$, $p=0.01$).

Out of 21 included studies, 11 used GC as well as other IM treatments. We excluded IM-treated CAPA and noCAPA cases from these 11 studies to obtain patients treated with or without GC alone. (Table-S3). After exclusion of IM-treated cases, one study had no GC group and was excluded. The remaining 10 studies after IM exclusion and 10 studies using only GC but no IM treatment were combined together for subsequent analyses. These 20 studies included in the analysis had a total of 4675 patients consisting of 2565 GC-treated patients and 2110 controls (Fig. 2). For subanalyses, we categorized these studies into four subgroups based on GC dose and type used in the treatment of the patients. Any study having no defined GC dose or type was excluded from these subgroups (Table-S4).

The pooled LOR of CAPA development was significantly higher for the GC group than for the controls (0.54; 95% CI: 0.22, 0.86; $p<0.01$) (Fig. 3). In GC dose-based subgroups, the pooled LOR had no difference for low-dose GC-treated patients versus controls (0.41; 95% CI: -0.07, 0.89; $p=0.09$), but it was significantly higher for high-dose GC-treated patients versus controls (0.90; 95% CI: 0.17, 1.62: $p=0.01$). In GC type-based subgroups, the pooled LOR was significantly higher for Dexa-treated patients versus controls (0.71; 95% CI: 0.35, 1.07; $p<0.01$), but there was no difference for non-Dexa-GC-treated patients versus controls (0.21; 95% CI: -0.36, 0.79; $p=0.47$) (Fig. 4).

Out of 20 analyzed studies, 16 used the ECMM/ISHAM definition for the diagnosis of CAPA (Table-S5). The poled LOR for CAPA development was also significantly higher for the GC group versus controls (0.49; 95% CI: 0.15, 0.83; $p<0.01$) in these studies (Fig. S2).

There was no publication bias ($\beta_1$: 0.76, $p=0.13$), but heterogeneity ($I^2$: 46.61, $p=0.01$) was present in the analyzed studies (Table-S6).
DISCUSSION
The present meta-analysis aimed to explore the real-life effect of GC treatment on the risk of developing CAPA. The main findings of this meta-analysis include that systemic GC treatment of COVID-19 patients was associated with an increased risk of CAPA development, and this effect of GC was independent of treatment with other IMs. The risk of CAPA was significantly associated with the use of high-dose GC or dexamethasone as the GC regimen, while there was no significant association with low-dose GC or non-Dexa GC. To the best of the authors' knowledge, this is the first meta-analysis in the literature to date reporting the effect of GC treatment on the risk of the development of CAPA.

Our data show that COVID-19 patients are at risk of developing CAPA, even in the absence of treatment with GCs. SARS-CoV-2 infection targets the respiratory system and causes significant immune dysregulation involving hyperinflammation (cytokine storm) and depletion of CD4+ and CD8+ T cells and NK cells. The direct damage to the respiratory epithelium due to hyperinflammation and an immunosuppressed state due to immune dysregulation together create an optimal opportunity for the occurrence of CAPA in COVID-19 patients who were immunocompetent before SARS-CoV-2 infection and had no GC pretreatment or traditional risk factors such as neutropenia or immunodeficiency. These pathological features of COVID-19 patients concur with our results of CAPA in patients with no GC therapy treatment. A recent meta-analysis and several research studies reporting CAPA in immunocompetent patients with no underlying risk factors suggest that severe COVID-19 is by itself a risk factor for the development of CAPA.

Since the publication of the preliminary report of the RECOVERY trial in June 2020, low-dose dexamethasone treatment (6 mg/day for up to 10 days) dampens cytokine storms and reduces 28-day mortality in severe COVID-19 patients with hypoxemia. As a result, GC treatment has been widely used worldwide as a first-line therapy for COVID-19 to reduce hyperinflammation (cytokine storm) and improve the outcome of the disease. However, the RECOVERY trial demonstrated the impact of dexamethasone treatment on COVID-19 overall mortality only but did not study its effect on the risk of developing secondary infections,
including CAPA. Many clinical trials after the RECOVERY trial also reported the impact of GC on COVID-19 mortality but with conflicting results, and there are limited data concerning the effect of GC on the risk of CAPA. In addition to immunomodulation, GCs are also potent immunosuppressive agents, and they quantitatively and qualitatively affect cells of the innate and adaptive immune systems, making patients prone to developing secondary infections. In patients with COVID-19, who are inherently immunocompromised and have defective antifungal immunity, GC treatment may further impair antifungal immunity and thereby increase susceptibility to developing CAPA. A previous meta-analysis on the outcome of CAPA reported that long-term GC treatment of COVID-19 is a risk factor for CAPA. In addition, GC therapy adversely affects glucose metabolism, causing hyperglycemia and new onset of diabetes, which is a common comorbidity in patients with COVID-19 and a well-recognized risk factor for CAPA. All these adverse effects further support the notion that GC therapy may be associated with an increased risk of CAPA development.

Approximately half of our included studies had used various other IMs, including tocilizumab (anti-IL6 receptor monoclonal antibody), sarilumab (IL6 receptor antagonist), anti-IL1 monoclonal antibody, and anakinra (IL1-receptor antagonist), along with GC in the treatment of patients, and these IMs may also be a risk factor for the development of CAPA. After exclusion of other IM-treated CAPA and noCAPA cases, our analysis showed that the association between GC treatment and CAPA is independent of other IM treatments.

The results of our subanalyses showed that the risk of CAPA development was significantly associated with high-dose GC treatment. A recent meta-analysis on comparative clinical characteristics and mortality of CAPA has reported that COVID-19 patients receiving long-term GC treatment may be particularly predisposed to CAPA. Similarly, a retrospective chart review demonstrated significantly increased secondary infections, including aspergillosis, in GC-treated patients. Although the exact dose and duration of GC therapy were not mentioned, the overall findings of these studies parallel our observations of increased CAPA risk in high-dose GC-treated patients.
Since dexamethasone and non-dexamethasone GCs have different pharmacologic characteristics\textsuperscript{60}, we categorized the included studies into these two subgroups to evaluate the effect of these GC types on the risk of CAPA development. Our results showed that dexamethasone treatment was significantly associated with the development of CAPA, whereas the use of non-dexamethasone regimens did not show a significant association. Although there are no comparative data on the effect of these GC types on the development of CAPA, there are indications in the literature supporting the superiority of non-dexamethasone regimens such as methylprednisolone. A meta-analysis of three randomized controlled trials reported significantly fewer adverse events, including hyperglycemia and secondary infections, in non-dexamethasone GC-treated COVID-19 patients than in dexamethasone-treated COVID-19 patients.\textsuperscript{61} An \textit{in vitro} study reported that dexamethasone inhibits the phagocytic bactericidal activity of neutrophils, while an equivalent dose of methylprednisolone does not have such adverse effects, indicating a diminished risk of infection with the use of this non-dexamethasone GC.\textsuperscript{62} The treatment of COVID-19 patients with methylprednisolone compared to dexamethasone has been shown to have a shorter length of ICU stay and fewer episodes of nosocomial sepsis.\textsuperscript{63} In addition, there are studies in the literature indicating the superiority of non-dexamethasone GCs over dexamethasone GCs in the treatment of COVID-19.\textsuperscript{64-67}

This meta-analysis has certain limitations. First, most of the studies included in the meta-analysis were retrospective observational studies and may have confounding factors. Second, there was inevitable heterogeneity across the included studies in this meta-analysis, including variation in the definition of CAPA\textsuperscript{58}. Importantly, most studies included in our analysis (16/20) used ECMM/ISHAM consensus criteria for defining CAPA, and in a subanalysis focusing only on these 16 studies with homogenous case definitions, we observed a similar significant association of GC treatment with the risk of CAPA (p<0.01). Finally, owing to the very limited number of studies on low and high doses of dexamethasone and non-dexamethasone GCs, we could not directly analyze the effect of low versus high doses of these GC types on the risk of CAPA development. However, despite these limitations, the results of this meta-analysis are strengthened by the rigorous study design, high level of acuity of the patient population with well-defined CAPA and appropriately accounted for statistical analysis,
including use of LOR, yielding an accurate estimation of the outcome. Further clinical evidence using high-quality and large-sized studies may be needed to generalize and validate the implications of this meta-analysis for clinical practice.

In conclusion, our meta-analysis shows that GC therapy independent of other IM treatments was associated with an increased risk of CAPA development, and this risk was significantly associated with the use of high-dose GC or dexamethasone as the GC regimen. Further clinical evidence using high-quality and large-sized studies, taking into account other clinical variables, may be needed to generalize and validate the implications of this meta-analysis for clinical practice.

Author Contribution:
ZH: Conceptualization, data analysis, review, and final approval of the article; AN: Interpretation of data, critical revision, and final approval of the article AK1: Data collection, revision and final approval of the article MG: Data collection, revision and final approval of the article RC: Data collection, revision and final approval of the article AK2: Data analysis and interpretation, and final approval of the article; RKD: Overall supervision, interpretation of data and final approval of the article; MH: Interpretation of data, critical revision, and final approval of the article, and NKT: Conceptualization and study design, format analysis, writing of original draft, critical revision for intellectual contents, and final approval of the article.

Funding source:
There was no funding source for this study.

Ethics statement:
This study was a meta-analysis of previously published studies with no direct involvement of human subjects or animals; hence, no ethical approval was applicable.

Declaration of Interest: None
REFERENCES:


Table 1: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Country</th>
<th>Type</th>
<th>Setting</th>
<th>Sample size</th>
<th>CAPA definition (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hashim et al; (3)</td>
<td>2022</td>
<td>India</td>
<td>Ambispective Observational Study</td>
<td>Single center</td>
<td>1161</td>
<td>ECMM/ISHAM (19), and Practice guidelines (20)</td>
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<td>2. Koukaki et al; (27)</td>
<td>2022</td>
<td>Greece</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
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<td>ECMM/ISHAM (19)</td>
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<td>3. Leistner et al; (28)</td>
<td>2022</td>
<td>Germany</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
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<td>ECMM/ISHAM (19)</td>
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<tr>
<td>4. Erami et al; (29)</td>
<td>2022</td>
<td>Iran</td>
<td>Descriptive study</td>
<td>Single center</td>
<td>119</td>
<td>ECMM/ISHAM (19)</td>
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<td>5. Gangneux et al; (30)</td>
<td>2022</td>
<td>France</td>
<td>Ambispective Observational Study</td>
<td>Multicenter</td>
<td>426</td>
<td>ECMM/ISHAM (19)</td>
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<td>6. Bentvelsen et al; (31)</td>
<td>2022</td>
<td>Netherlands</td>
<td>Retrospective Observational Study</td>
<td>Multicenter</td>
<td>123</td>
<td>ECMM/ISHAM (19)</td>
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<td>7. Permpalung et al; (32)</td>
<td>2022</td>
<td>Thailand</td>
<td>Retrospective Observational Study</td>
<td>Multicenter</td>
<td>396</td>
<td>ECMM/ISHAM (19)</td>
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<td>8. Sovik et al; (33)</td>
<td>2022</td>
<td>Norway</td>
<td>Retrospective Observational Study</td>
<td>Multicenter &amp; Multinational</td>
<td>155</td>
<td>ECMM/ISHAM (19)</td>
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<td>9. Prattes et al; (34)</td>
<td>2022</td>
<td>European Countries, USA and Pakistan</td>
<td>Retrospective Observational Study</td>
<td>Multicenter &amp; Multinational</td>
<td>585</td>
<td>ECMM/ISHAM (19)</td>
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<td>10. Fekkar et al; (4)</td>
<td>2021</td>
<td>France</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
<td>145</td>
<td>EORTC/MSG (18)</td>
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<td>11. Paramythiotou et al; (35)</td>
<td>2021</td>
<td>Greece</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
<td>179</td>
<td>ECMM/ISHAM (19)</td>
</tr>
<tr>
<td>12. Pintado et al; (36)</td>
<td>2021</td>
<td>Mexico</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
<td>83</td>
<td>ECMM/ISHAM (19)</td>
</tr>
<tr>
<td>13. Reizine et al; (37)</td>
<td>2021</td>
<td>France</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
<td>49</td>
<td>ECMM/ISHAM (19)</td>
</tr>
<tr>
<td>14. Bartoletti et al; (38)</td>
<td>2021</td>
<td>Italy</td>
<td>Prospective Observational Study</td>
<td>Multi center</td>
<td>103</td>
<td>AspICU (19), and IAPA (23)</td>
</tr>
<tr>
<td>15. Delliere et al, (39)</td>
<td>2021</td>
<td>France</td>
<td>Retrospective Observational Study</td>
<td>Multicenter</td>
<td>108</td>
<td>EORTC/MSG (18), and IAPA (23)</td>
</tr>
<tr>
<td>16. Xu et al; (40)</td>
<td>2021</td>
<td>China</td>
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<td>Multicenter</td>
<td>335</td>
<td>ECMM/ISHAM (19), and IAPA (23)</td>
</tr>
<tr>
<td>17. Jansen et al; (41)</td>
<td>2021</td>
<td>France, Belgium</td>
<td>Ambispective Observational Study</td>
<td>Multicenter &amp;</td>
<td>488</td>
<td>ECMM/ISHAM (19)</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Study Setting</td>
<td>Case Number</td>
<td>Additional Details</td>
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<tr>
<td>18. Shadrivova et al; (42)</td>
<td>2021</td>
<td>Russia</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
<td>131</td>
<td>ECMM/ISHAM (19)</td>
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<tr>
<td>19. Fortarezza et al; (43)</td>
<td>2021</td>
<td>France</td>
<td>Retrospective Case Series</td>
<td>Single center</td>
<td>45</td>
<td>ECMM/ISHAM (19)</td>
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<tr>
<td>20. Chauvet et al; (44)</td>
<td>2020</td>
<td>France</td>
<td>Retrospective Observational Study</td>
<td>Single center</td>
<td>46</td>
<td>EORTC-MSG (18), AspICU (21), and modified AspICU (22)</td>
</tr>
<tr>
<td>21. Wang et al; (45)</td>
<td>2020</td>
<td>China</td>
<td>Retrospective Case Series</td>
<td>Single center</td>
<td>104</td>
<td>EORTC/MSG (18)</td>
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</table>

**Abbreviations:** CAPA: COVID-19-associated pulmonary aspergillosis.
<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>GC and other IM treatment</th>
<th>Total CAPA in Patients</th>
<th>CAPA in GC (IM in some)</th>
<th>CAPA in No GC (IM in some)</th>
<th>CAPA in GC (No IM)</th>
<th>CAPA in controls (No GC or IM)</th>
</tr>
</thead>
</table>
| 1. Hashim et al; 2022 (3) | • GC: Dexa 6mg or equivalent MP daily up to 10 days; and MP pulses 125mg daily for three days.  
• IM: Tocilizumab | 74/1161 | 62/943 | 12/218 | 56/853 | 12/218 |
| 2. Koukaki et al; 2022 (27) | • GC: Dexa 20mg daily for >10 days.  
• IM: Tocilizumab | 14/178 | 11/64 | 3/114 | 2/14 | 2/114 |
| 3. Leistner et al; 2022 (28) | • GC: Dexa 6mg daily up to 10 days.  
• IM: None | 47/215 | 41/169 | 6/46 | 41/169 | 6/46 |
| 4. Erami et al; 2022 (29) | • GC: Not defined.  
| 5. Gangneux et al; 2022 (30) | • GC: Dexa: dose not defined.  
• IM: None | 57/426 | 34/202 | 23/224 | 34/202 | 23/224 |
| 6. Bentvelsen et al; 2022 (31) | • GC: Not defined.  
• IM: None | 58/123 | 9/19 | 49/104 | 9/19 | 49/104 |
| 7. Permpalung et al; 2022 (32) | • GC: Total dose of PS 120-160mg, MP 160-245mg; HC 425-500 mg; or Dexa 36-50 mg (in three to six days). Patients received two or more GC type in overlap.  
• IM: Tocilizumab | 39/396 | 26/178 | 13/218 | 17/106 | 13/218 |
| 8. Sovik et al; 2022 (33) | • GC: Dexa 6mg daily for 11 days.  
• Other IM: Anakinra | 5/155 | 5/72 | 0/83 | 5/67 | 0/59 |
| 9. Prattes et al; 2022 (34) | • GC: Not defined  
• IM: Tocilizumab | 109/585 | 68/346 | 41/239 | 53/307 | 41/239 |
| 10. Fekkar et al; 2021 (4) | • GC: Dexa 20mg daily for 10 days.  
• IM: Anti-IL6 and anti-IL1. | 6/145 | 0/24 | 6/121 | 0/14 | 6/121 |
| 11. Paramythiotou et al; 2021 (35) | • GC: Dexa 6mg daily for 10 days.  
• IM: None | 6/179 | 6/144 | 0/35 | 6/144 | 0/35 |
| 12. Pintado et al; 2021 (36) | • GC: PS 1.3mg/kg daily; duration not defined.  
• IM: Tocilizumab | 16/83 | 2/24 | 14/59 | 2/24 | 2/4 |
| 13. Reizine et al; 2021 (37) | • GC: Dexa 6mg daily x 10 days.  
• IM: None | 10/49 | 7/22 | 3/27 | 7/22 | 3/27 |
| 14. *Bartoletti et al; 2021 (38) | • GC: PS 100-107mg daily for five to seven days.  
• IM: Tocilizumab | 30/103 | 18/52 | 12/51 | 0/0 | 8/24 |
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>GC:</th>
<th>IM:</th>
<th>GC: PS 60 mg daily; duration not defined.</th>
<th>IM:</th>
<th>GC: PS cumulative dose 5.36 mg/kg.</th>
<th>IM:</th>
<th>GC: MP &gt;20-40 mg daily; duration not defined.</th>
<th>IM:</th>
<th>GC: Dexa cumulative dose of &gt;1000 mg.</th>
<th>IM:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delliere et al, 2021</td>
<td>GC: Dexamethasone;</td>
<td>Tocilizumab, Sarilumab, and Eculizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Xu et al; 2021</td>
<td>GC: MP &gt;20-40 mg daily</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Jansen et al; 2021</td>
<td>GC: Prednisolone</td>
<td>Tocilizumab and Anakinra</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Shadrivova et al; 2021</td>
<td>GC: Prednisolone</td>
<td>Tocilizumab and Anakinra</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Fortarezza et al; 2021</td>
<td>GC: Dexamethasone</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Chauvet et al; 2020</td>
<td>GC: Dexamethasone</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Wang et al; 2020</td>
<td>GC: Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab</td>
<td>Pseudoephedrine therapy</td>
<td>Tocilizumab</td>
<td>Methylprednisolone</td>
<td>Tocilizumab</td>
<td>Dexamethasone cumulative dose of &gt;1000 mg.</td>
<td>Tocilizumab</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- CAPA: COVID-19-associated pulmonary aspergillosis
- Dexa: Dexamethasone
- GC: Glucocorticoids
- IM: Immunomodulators
- HC: Hydrocortisone
- MP: Methylprednisolone
- PS: Prednisolone

*Study not included in analysis due to no patients in the GC group after IM exclusion.

**Note:** GC group includes patients treated with GC in ICU as part of COVID-19 care.
Studies identified through Database Search:
- PubMed: 105
- Embase: 445
- Scopus: 731
- Google Scholar: 970

Studies Identified Through Manual Search: 405

Total Studies Identified: 2256

Duplicate Studies Removed: 57

Studies Screened by Title and Abstract for the Qualification of Full-text Screening: 2199

Studies with Inadequate Title & Abstract Removed: 2156

Studies Screened by Full-text for the Assessment of Eligibility Criteria: 43

Studies with Ineligible Data Excluded:
- No control group: 12
- No data on GC therapy & CAPA: 07
- No standard CAPA definition: 02
- Outlier study: 01

Studies Included in the Meta-analysis: 21

Fig. 1
Total Included Studies/Patient: 21/5174

Studies/Patients with GC and IM Treatment: 11/3380

Studies/Patients with GC but no IM treatment: 10/1794

Exclusion of IM treated CAPA and noCAPA patients from studies

Studies/Patients with GC treatment: 11/2905

One study excluded due to no GC group after IM exclusion

Studies/Patients with GC treatment: 10/2881

Studies/Patients with GC treatment: 10/1794

Total Studies/Patients with GC Treatment Analyzed: 20/4675 (GC group: 2565 patients, and Control group: 2110 patients)
<table>
<thead>
<tr>
<th>Study</th>
<th>GC treated</th>
<th>Controls</th>
<th>Log odds-ratio with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashim et al., 2022</td>
<td>56</td>
<td>797</td>
<td>0.19 [-0.45, 0.83]</td>
<td>8.93</td>
</tr>
<tr>
<td>Koukaki et al., 2022</td>
<td>2</td>
<td>12</td>
<td>2.23 [ 0.19, 4.28]</td>
<td>2.08</td>
</tr>
<tr>
<td>Leistner et al., 2022</td>
<td>41</td>
<td>128</td>
<td>0.76 [-0.17, 1.69]</td>
<td>6.42</td>
</tr>
<tr>
<td>Erami et al., 2022</td>
<td>6</td>
<td>14</td>
<td>1.23 [ 0.09, 2.38]</td>
<td>5.02</td>
</tr>
<tr>
<td>Gangneux et al., 2022</td>
<td>34</td>
<td>168</td>
<td>0.57 [ 0.00, 1.14]</td>
<td>9.69</td>
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<tr>
<td>Bentvelsen et al., 2022</td>
<td>9</td>
<td>10</td>
<td>0.01 [-0.97, 0.99]</td>
<td>6.05</td>
</tr>
<tr>
<td>Permpalung et al., 2022</td>
<td>17</td>
<td>89</td>
<td>1.10 [ 0.34, 1.87]</td>
<td>7.77</td>
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<tr>
<td>Sovik et al., 2022</td>
<td>5</td>
<td>62</td>
<td>2.35 [-0.57, 5.27]</td>
<td>1.11</td>
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<tr>
<td>Prattes et al., 2022</td>
<td>53</td>
<td>254</td>
<td>0.01 [-0.44, 0.46]</td>
<td>10.94</td>
</tr>
<tr>
<td>Paramythiotou et al., 2021</td>
<td>6</td>
<td>138</td>
<td>1.20 [-1.70, 4.10]</td>
<td>1.12</td>
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<tr>
<td>Fekkar et al., 2021</td>
<td>0</td>
<td>14</td>
<td>-0.49 [-3.42, 2.44]</td>
<td>1.10</td>
</tr>
<tr>
<td>Pintado et al., 2021</td>
<td>2</td>
<td>22</td>
<td>-2.40 [-4.83, 0.04]</td>
<td>1.54</td>
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<tr>
<td>Reizine et al., 2021</td>
<td>7</td>
<td>15</td>
<td>1.32 [-0.18, 2.82]</td>
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<td>Deliere et al., 2021</td>
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<td>1.23 [-0.64, 3.10]</td>
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<tr>
<td>Xu et al., 2021</td>
<td>47</td>
<td>104</td>
<td>0.88 [ 0.35, 1.41]</td>
<td>10.08</td>
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<tr>
<td>Jansen et al., 2021</td>
<td>31</td>
<td>237</td>
<td>-0.26 [-0.79, 0.27]</td>
<td>10.08</td>
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<tr>
<td>Shadrivova et al., 2021</td>
<td>20</td>
<td>61</td>
<td>-0.33 [-1.50, 0.84]</td>
<td>4.86</td>
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<tr>
<td>Fortarezza et al., 2021</td>
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<td>19</td>
<td>1.97 [-0.21, 4.15]</td>
<td>1.87</td>
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<tr>
<td>Chauvet et al., 2020</td>
<td>3</td>
<td>6</td>
<td>1.73 [-0.09, 3.56]</td>
<td>2.53</td>
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<tr>
<td>Wang et al., 2020</td>
<td>6</td>
<td>57</td>
<td>0.72 [-0.93, 2.37]</td>
<td>2.96</td>
</tr>
</tbody>
</table>

**Overall**

Heterogeneity: $\tau^2 = 0.19$, $I^2 = 46.61\%$, $H^2 = 1.87$

Test of $\theta_i = \theta_j$: $Q(19) = 37.76$, $p = 0.01$

Test of $\theta = 0$: $z = 3.29$, $p < 0.01$

Random-effects REML model
Figure

(a) Study | Low-dose-GC Yes | Low-dose-GC No | Controls Yes | Controls No | Log odds-ratio with 95% CI | Weight (%)
---|---|---|---|---|---|---
Hashim et al. 2022 | 36 | 567 | 12 | 206 | 0.09 [-0.59, 0.76] | 16.01
Leistner et al. 2022 | 41 | 128 | 6 | 40 | 0.76 [-0.17, 1.69] | 12.45
Sovik et al. 2022 | 5 | 62 | 0 | 59 | 2.35 [-0.57, 5.27] | 2.41
Paramythiotou et al. 2021 | 6 | 138 | 0 | 35 | 1.20 [-1.70, 4.10] | 2.43
Pintado et al. 2021 | 2 | 22 | 2 | 2 | -2.40 [-4.83, 0.04] | 3.31
Reizine et al. 2021 | 7 | 15 | 3 | 24 | 1.32 [-0.18, 2.82] | 7.10
Xu et al. 2021 | 47 | 104 | 28 | 150 | 0.88 [0.35, 1.41] | 18.19
Jansen et al. 2021 | 31 | 237 | 32 | 188 | -0.26 [-0.79, 0.27] | 18.20
Shadrivova et al. 2021 | 20 | 61 | 5 | 11 | -0.33 [-1.50, 0.84] | 9.73
Fortarezza et al. 2021 | 8 | 19 | 1 | 17 | 1.97 [-0.21, 4.15] | 3.99
Wang et al. 2020 | 6 | 57 | 2 | 39 | 0.72 [-0.93, 2.37] | 6.17

Overall Heterogeneity: $\tau^2 = 0.25$, $I^2 = 49.55\%$, $H^2 = 1.98$
Test of $\theta_i = \theta$: $Q(10) = 22.59$, $p = 0.01$
Test of $\theta = 0$: $z = 1.69$, $p = 0.09$

Random-effects REML model

(b) Study | High-dose-GC Yes | High-dose-GC No | Controls Yes | Controls No | Log odds-ratio with 95% CI | Weight (%)
---|---|---|---|---|---|---
Hashim et al. 2022 | 17 | 274 | 12 | 206 | 0.06 [-0.70, 0.82] | 30.92
Koukaki et al. 2022 | 2 | 12 | 2 | 112 | 2.23 [0.19, 4.28] | 9.82
Permpalung et al. 2022 | 17 | 89 | 13 | 205 | 1.10 [0.34, 1.87] | 30.83
Fekkar et al. 2021 | 0 | 14 | 6 | 115 | -0.49 [-3.42, 2.44] | 5.38
Delliere et al. 2020 | 2 | 3 | 15 | 77 | 1.23 [-0.64, 3.10] | 11.28
Chauvet et al. 2020 | 3 | 6 | 3 | 34 | 1.73 [-0.09, 3.56] | 11.77

Overall Heterogeneity: $\tau^2 = 0.29$, $I^2 = 39.66\%$, $H^2 = 1.66$
Test of $\theta_i = \theta$: $Q(5) = 8.03$, $p = 0.15$
Test of $\theta = 0$: $z = 2.43$, $p = 0.01$

Random-effects REML model
Fig. 4
Legend to Fig. 1:
The PRISMA flow-diagram showing selection of eligible studies
Legend to Fig. 2:
Flow Chart showing selection of included studies for meta-analysis

Abbreviations:
CAPA: COVID-19-associated Pulmonary aspergillosis, GC: Glucocorticoids,
Legend to Fig. 3:
Forest plot showing pooled LOR of the CAPA outcome between GC treated patients and controls. A LOR value of >0 with positive 95% CI was considered to be significant.

Abbreviations:
**Legend to Fig. 4:**

Forest plots showing pooled LOR of CAPA development between GC dose and type based subgroups. The LOR is (a) low for low-dose-GC treated patients versus controls, (b) high for high-dose-GC treated patients versus controls, (c) high for dexamethasone (Dexa) treated patients versus controls, and (d): low for Non-Dexa-GC treated patients versus controls. A LOR value of >0 with positive 95% CI was considered to be significant.

**Abbreviations:**

CAPA: COVID-19-associated Pulmonary aspergillosis, Dexa: Dexamethasone, GC: Glucocorticoids, LOR: Log odds ratio, CI: Confidence Interval
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryAppendix.pdf