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Letter to the Editor

The association between corticosteroids and aspergillosis among COVID-19 patients

Dear Editor,

We read with great interest the multicenter, observational, retrospective study, which investigated the impact of dexamethasone on the superinfection in 157 mechanically ventilated patients with COVID-19.[1] Compared with the patients without superinfection, those with superinfection had more often received corticosteroid (66% [44/67] versus 32% [28/88], $p < 0.0001$). Among them, eight patients had invasive fungal infections, including five pulmonary aspergillosis, and all of them had received dexamethasone.[1] Additionally, Borman et al.[2] further demonstrated that COVID-associated pulmonary aspergillosis (CAPA) could be associated with a longer length of hospital stay and higher mortality than the matched critically ill patients without fungal infection. These findings[1,2] raised the serious concern about whether systemic corticosteroid could increase the risk of aspergillosis. Therefore, we conducted this retrospective cohort study to assess the risk of aspergillosis among COVID-19 patients receiving corticosteroid.

This study was conducted using TriNetX research platform. TriNetX is a global research network, which can provide the de-identified electronic medical record data on diagnoses, laboratory and diagnostic tests and results, procedures, and treatments from more than 120 healthcare organizations (HCOs) in 19 countries.[3] Initially, the patients with COVID-19 positive cases were identified by either a positive laboratory test or a COVID-19 diagnostic code on January 17, 2023, as previously described.[4,5] Then, only adult patients (aged $\geq$ 18 years) with hospitalization due to COVID-19 were included. In the meanwhile, we excluded those ever diagnosed with influenza and prior diagnosed with aspergillosis within prior three months before the index date. The index date of the case cohort was the date of COVID-19 diagnosis or a positive PCR test. This study only included patients whose HCO records were between March 1, 2020, and September 30, 2022, to ensure that the enrolled patients completed one-month of follow-up. Thereafter, we divided the patients into two cohorts - COVID-19 with oral or injectable corticosteroid (study group) and those without systemic corticosteroid (control group). Furthermore, we used TriNetX built-in propensity score matching algorithm to create two matched cohorts by age at index, race, gender, and comorbidities. The primary study outcome was the incidence of aspergillosis (ICD-10 code B44) within one month after the index date. The secondary outcomes included invasive pulmonary aspergillosis (B44.0), and disseminated aspergillosis (B44.7) during the follow-up period.

All statistical analyses were calculated using the TriNetX platform. Cox proportional hazard regression was implemented to compare the matched cohorts, and the proportional hazard assumption was tested with the generalized Schoenfeld approach. Hazard ratios (HRs) were calculated to investigate the risk ratio of aspergillosis between the study and control groups. All analyses were conducted using 95% confidence intervals (CIs) to determine statistical significance. Kaplan-Meier analysis was used for the cumulative incidence of aspergillosis during the follow-up period.

In total, 776,845 hospitalized adult COVID-19 patients from 66 HCOs in four countries were identified, including 255,844 patients receiving corticosteroid and 521,001 patients without corticosteroid. Using propensity score matching, we formed the study and control cohorts ($n = 252,169$ in each cohort). The basic characteristics of the study and the control cohorts before and after propensity score matching are shown in Table 1. Before matching, the study group were predominantly women and were older than the control group, and the ethnicity distribution also differed between groups. With regard to comorbidities, the study group had more neoplasms, HIV diseases, hypertension, diabetes mellitus, chronic lower respiratory disease, rheumatoid arthritis, immunocompromised condition, hyperlipidemia, kidney disease, overweight and obesity than the control group (Table 1). In addition, the study group had higher levels of interleukin-6 (IL-6), C-reactive protein (CRP), erythrocyte sedimentation (ESR), ferritin than the control group (Table 2). After matching, these differences in demographic characteristics, and comorbidities between the two groups became nonsignificant, and the groups were thus well-matched.

During the follow-up one months, COVID-19 patients with corticosteroid were associated with an increased risk of aspergillosis compared with control group (HR, 2.378; 95% CI, 1.871–3.023). In addition, the study group had high risk of invasive pulmonary aspergillosis than the control group, but the difference did not reach statistical significance (HR, 1.619; 95% CI, 0.849–3.086). Finally, ten patients had disseminated aspergillosis and all of them had received corticosteroid. Fig. 1 presents the results of the Kaplan–Meier curves of the probability of aspergillosis. The risk of aspergillosis in COVID-19 patients with corticosteroid was higher than that of the patients without corticosteroid (using a log-rank test, $p < 0.05$)(Fig. 1).

Based on the analysis of this large-scale retrospective cohort study, it indicated that the use of corticosteroid for hospitalized patients with COVID-19 could increase the risk of aspergillosis. Although systemic corticosteroid was recommended for hospitalized patients with severe COVID-19f for lowering mortality,[6] aspergillosis could be associated with high morbidity and mortality.[7] Therefore, clinicians keep alert the high risk of aspergillosis among hospitalized patients receiving systemic corticosteroid. Through this way, we can make early diagnosis and adminis-

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Table 1
Baseline characteristics for the study group with corticosteroid and control group without corticosteroid before and after matching.

	Before matching			After matching		
	Study group	Control group	Std diff	Study group	Control group	Std dff
Number	255,844	521.001		252,169	252,169	
Age; mean ± SD, year	58.2 ± 18.1	54.4 ± 19.7	0.201	58.1 ± 18.1	58.1 ± 18.3	0.004
Female; n (%)	132,928 (52.0)	299,742 (57.5)	0.112	132,205 (52.4)	131,961 (52.3)	0.002
Race; n (%)						
White	160,790 (62.8)	322,356 (61.9)	0.020	158,806 (63.0)	159,177 (63.1)	0.003
Black or African American	35,471 (13.9)	93,533 (18.0)	0.112	35,430 (14.1)	36,646 (14.5)	0.014
Hispanic or Latino	27,051 (10.6)	52,265 (10.0)	0.018	26,649 (10.5)	25,522 (10.1)	0.012
Comorbidities; n (%)						
Essential hypertension	109,035 (42.6)	188,272 (36.1)	0.133	107,230 (42.5)	108,356 (24.2)	0.009
Neoplasms	70,171 (27.4)	112,699 (21.6)	0.135	68,813 (27.3)	70,422 (27.9)	0.014
Diabetes mellitus	60,602 (23.7)	102,729 (19.7)	0.096	59,493 (23.6)	59,269 (23.5)	0.002
Acute kidney failure and chronic kidney disease	60,286 (23.6)	87,482 (16.8)	0.169	59,050 (26.6)	67,128 (26.6)	0.007
Overweight, obesity and other hyperalimentation	61,239 (23.9)	102,657 (19.7)	0.103	60,072 (23.8)	61,056 (24.2)	0.009
Chronic lower respiratory disease	57,972 (22.7)	85,917 (16.5)	0.156	56,433 (22.4)	56,302 (22.3)	0.001
Immunocompromised status	11,943 (4.7)	15,134 (2.9)	0.092	11,517 (4.6)	11,041 (4.4)	0.009
Rheumatoid arthritis	5579 (2.2)	7419 (1.4)	0.057	5389 (2.1)	5090 (2.0)	0.008
Human immunodeficiency virus disease	3215 (1.3)	4,87 (0.9)	0.031	3109 (1.2)	2749 (1.1)	0.013
Use of mechanical ventilation	4940 (1.9)	87,482 (1.2)	0.060	4747 (1.9)	4465 (1.8)	0.008

SD, standard deviation; Std diff, Standardized difference.

Table 2
Inflammatory profile of the study group with corticosteroid and control group without corticosteroid before and after matching.

	Study group		Control group		Standardized difference
	No of patients	Level	No of patients	Level	
Interleukin-6, pg/ml	3738	138.4 ± 537.2	698	94.3 ± 328.5	0.099
C-reactive protein, mg/L	51,585	49.0 ± 69.9	66,171	31.8 ± 57.5	0.268
Erythrocyte sedimentation rate, mm/h	39,807	36.0 ± 30.7	55,312	33.2 ± 29.5	0.093
Ferritin, ng/ml	55,851	542.1 ± 1544.3	76,009	390.3 ± 1179.1	0.110

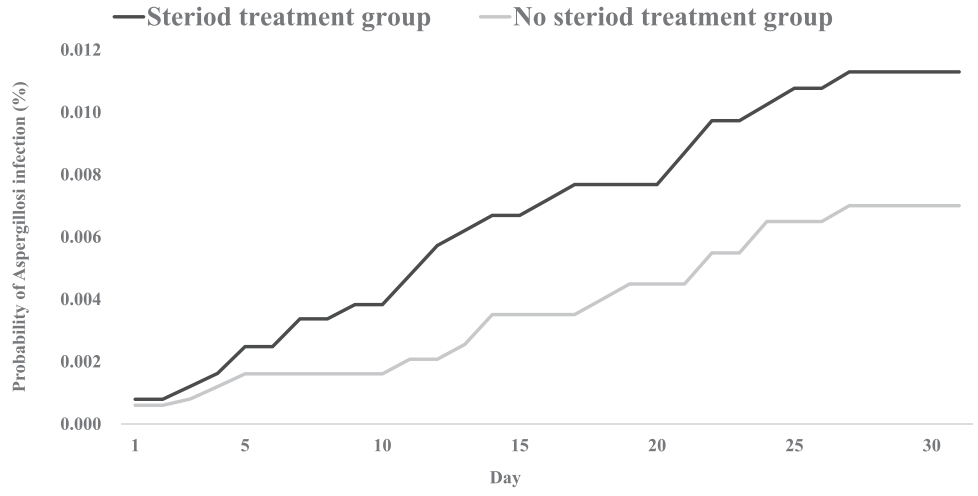

Fig. 1. The incidence of aspergillosis in COVID-19 patients with and without corticosteroid.

ter appropriate anti-fungal treatment to improve their clinical outcome.

The cause of our findings could be explained by the following two mechanisms. First, systemic corticosteroid could impair the immunity of the patients with COVID-19 and make them vulnerable to secondary infections, including aspergillosis. Second, the study group receiving corticosteroid had higher level of inflammatory profiles, such IL-6, CRP, ESR and ferritin than the control group. The hyperinflammatory status caused by dysregulated immune response may be associated with the increased risk of aspergillosis.

Despite this study had a large sample size and used a large database containing information on multiple nations, institutions, and races, which made our findings are generalizable, our study had several limitations. Because the dose and treatment duration of corticosteroid were not available, we cannot assess the dose-responsive relationship. In addition, although we performed propensity score matching to balance baseline characteristic between groups, residual confounding factors can remain.

In conclusion, our findings indicated that systemic corticosteroid could increase the risk of aspergillosis among hospitalized patients and suggested that physicians should be particularly cau-

tious about the potential risks of aspergillosis, particularly for those receiving corticosteroid.

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