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Patients with eosinophilic gastrointestinal disorders have lower in-hospital mortality rates related to COVID-19

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Clinical Implication

Compared to non-EGID COVID-19 positive patients, EGID COVID-19 positive individuals stayed longer in the hospital, yet had a lower hazard of in-patient mortality. This analysis suggests that EGID may provide a protective effect against severe COVID-19 outcomes.

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In the United States, the COVID-19 pandemic was the third leading cause of death in 2020.¹ Peripheral eosinophilia is hypothesized to play a protective role in COVID-19.² Yet, little is known about eosinophilic gastrointestinal disease (EGID) and COVID-19 outcomes. The mucosal responses of EGID patients may protect against severe effects of COVID-19 by reducing viral entry into cells.^{3,4} We hypothesized that EGID would be protective against severe outcomes in COVID-19 infections. We reviewed administrative data from an extensive central medical system in the United States to identify all COVID-19 cases and compared hospitalization rates, ventilator dependence, and death between patients with and without EGID.

Data were used from the *Cerner COVID-19 De-Identified Data Cohort*. This cohort contains patient encounter-level information and is a subset of the larger *Cerner Real-World Data* cohort. Our primary cohort of COVID-19 positive patients identified those having either a diagnosis code of COVID-19 infection or a recent positive SARS-CoV-2 lab result by nucleic acid amplification (NAA) with probe detection. For comparison to a larger sample of patients, a secondary cohort used records of patients identified as having a diagnosis code of possible exposure or infection of COVID-19 or a recent positive lab result for possible COVID-19-related testing. Patients with COVID-19 indications spanning from December 2019 to September 2020 were included. Tables E1 and E2 on their demographic and clinical characteristics are provided.

The outcomes of interest included the categorical hospitalization, the non-parametric continuous maximum length of stay (LOS), and survival times to invasive ventilator dependence (IVD) and in-hospital mortality. The primary predictor of interest was a history of EGID. Demographic predictors of interest were age, sex, race and ethnicity, insurance, and US geographical region. Clinical predictors included EGID-related symptoms and procedures,

associated atopic diseases, conditions related to adverse COVID-19 outcomes, and EGID medications.

A nearest neighbor “greedy” matching method was used to obtain matched controls. Demographically/clinically similar patients were matched by EGID diagnosis status in a 4:1 ratio on age, gender, race and ethnicity, insurance, geographical region, atopic conditions, and comorbidities known to be associated with worse COVID-19 outcomes. Unadjusted outcomes, between EGID and matched non-EGID patients, were compared with Chi-Squared tests and Wilcoxon Rank-sum tests for hospitalization and maximum LOS, respectively. Survival curves of time to IVD and in-hospital mortality, by EGID status, were compared with log-Rank Chi-Squared tests. For adjusted associations of EGID status with the outcomes of interest, regression models were employed. Hospitalization was fit with a Poisson model, maximum LOS with an exponential model, and time to IVD and in-hospital mortality with a Cox-Proportional hazards model. All models were adjusted for EGID symptoms, procedures, and medications. From the Cox models, adjusted survival curves were plotted for the time to event outcomes, with different lines for EGID and non-EGID patients. For comparison, all previous analyses were repeated on the larger COVID-19 exposed and positive cohort.

Analyses were conducted on the primary cohort of COVID-19 positive patients (Table I). EGID patients, compared to matched non-EGID patients, had higher percentages of hospitalization (53.6% vs. 44.6%, $P=0.09$), and stayed longer in the hospital (median maximum LOS: 1.5 vs. 0.3, $P=0.062$). Non-EGID were intubated faster and died relatively faster, although these findings were not statistically significant in the unadjusted analysis. When adjusting for confounding variables, EGID patients did exhibit again higher hospitalization and maximum

LOS, yet a lower hazard of IVD (aHR: 0.95, 95% CI=0.50-1.79) and in-hospital mortality (aHR: 0.38, 95% CI=0.11-1.39). Again, these results were not significant.

Analyses were repeated on the larger COVID-19 exposed and positive cohort (Table I). EGID patients, compared to non-EGID patients, had higher hospitalization, significantly higher maximum LOS (median maximum LOS: 1.3 vs. 0.9, $P=0.02$), intubated slower and died relatively slower (mean survival time: 260 vs. 225, $P=0.01$). EGID patients had a significantly lower hazard of IVD (aHR: 0.61, 95% CI=0.38-0.99) and in-hospital mortality (aHR: 0.28, 95% CI=0.09-0.85) than non-EGID patients. Adjusted curves are provided in Figure 1.

This study examined the largest cohort of EGID patients with COVID-19 infection to date. Even after controlling for COVID-19 related comorbidities, patients with EGID were still found to have similar infection course and lower IVD and in-hospital mortality than non-EGID patients. These results imply that there is some mechanistic feature of EGID that leads to a less severe COVID-19 course.

An observational Italian study on EGID patients found no reports of COVID-19 diagnosis among the 130/145 patients contacted.⁵ In a similar analysis of 1,526 cases of COVID-19, asthma and inhaled corticosteroids (ICS) was not associated with increased risk for severe outcomes.⁶ Thus, atopy and EGID may offer a protective immune response.

In support of our findings, a worldwide registry of EGID patients found COVID-19 infections to appear mild to moderate.⁷ One possible explanation for milder infection is that due to upregulated IL-13 in EGID, there might be a decrease in expression of ACE2 and TMPRSS2 on epithelial cells in EGID patients, which are critical for SARS-CoV-2 infection.⁸ Low tissue ACE2/TMPRSS2 levels have been demonstrated in esophageal tissue of EoE.⁴

Eosinophils also play a fundamental role in antiviral responses. Eosinophil-derived neurotoxin is a ribonuclease with antiviral activity, and peripheral eosinophilia is associated with more favorable outcomes in COVID-19.⁹

Limitations of this study include the lack of availability of serum AEC prior and at the time of COVID-19 infection, duration of EGID, and not knowing if the eosinophilia in the GI tract is primary or secondary. Also, a quarter of patients in this study were non-adults and we know that COVID-19 outcomes are better in children than adults. All of these confounders could have influenced the results of this study. Nonetheless, a major strength of this study is that the size of the *Cerner COVID-19 De-Identified Data Cohort* made it possible to study COVID-19 outcomes in EGID patients on a large scale, despite the fact that it is a rare disease.

In conclusion, our analysis supports previous findings that EGID may provide a protective effect against severe COVID-19 outcomes. Though no specific conclusions can be made about mechanisms driving these observations, it is plausible that the reduced expression of ACE2/TMPRSS2 and the eosinophilic disease itself may play a protective role in COVID-19 mortality, and this should be assessed in future studies.

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Table I. Associations of EGID (and matched¹ non-EGID) with COVID-19 outcomes among COVID-19 positive patients (EGID: 125; Matched Controls: 500) and COVID-19 exposed and positive patients (EGID: 432; Matched Controls: 1,728)

Variables	Hospitalization	Maximum LOS (Days)	Time to Invasive Ventilator Dependence (Days)	Time to In-Hospital Mortality (Days)
COVID-19 positive				
Unadjusted²	n (%³)	Median [Q1-Q3]	Mean⁴ (95% CI)	Mean⁴ (95% CI)
No EGID	223 (44.6)	0.3 (0.1, 4.8)	111 (102, 120)	162 (111, 213)
EGID	67 (53.6)	1.5 (0.1, 6.1)	142 (122, 162)	167 (156, 178)
Adjusted⁵	aIRR⁶ (95% CI)	e^{β7} (95% CI)	aHR⁸ (95% CI)	aHR⁸ (95% CI)
No EGID	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
EGID	1.21 (0.98, 1.49)	1.31 (0.83, 2.06)	0.95 (0.50, 1.79)	0.38 (0.11, 1.39)
COVID-19 exposed and positive				
Unadjusted⁹	n (%)	Median [Q1-Q3]	Mean (95% CI)	Mean (95% CI)
No EGID	846 (49.0)	0.9 (0.1, 4.0)	191 (171, 211)	225 (207, 243)
EGID	229 (53.0)	1.3 (0.2, 4.2)	222 (199, 245)	260 (250, 270)
Adjusted	aIRR (95% CI)	e^β (95% CI)	aHR (95% CI)	aHR (95% CI)
No EGID	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
EGID	1.02 (0.91, 1.14)	1.08 (0.85, 1.36)	0.61 (0.38, 0.99)	0.28 (0.09, 0.85)

¹ Matched on age, gender, race/ethnicity, insurance, region, atopic conditions, comorbidities known to be associated with worse COVID-19 outcomes;

² Hospitalization compared with Chi-square test, maximum LOS compared with Wilcoxon Rank-sum test, time to event survival curves compared with log-rank test (hospitalization P: 0.09, maximum LOS P: 0.062, time to IVD P: 0.62, time to in-hospital mortality P: 0.067);

³ Column %'s;

⁴ Mean survival times (Wald 95% CI's) restricted to the highest survival time per EGID group (median not used because survival probability did not drop below 50%);

⁵ Adjusted for symptoms, procedures, and EGID medications;

⁶ Adjusted incidence risk ratio;

⁷ Adjusted exponentiated coefficient;

⁸ Adjusted hazard ratio;

⁹ Hospitalization compared with Chi-square test, maximum LOS compared with Wilcoxon Rank-sum test, time to event survival curves compared with log-rank test (hospitalization P: 0.15, maximum LOS P: 0.02, time to IVD P: 0.11, time to in-hospital mortality P: 0.01);

Figure 1. Adjusted curves of survival from in-hospital mortality among COVID-19 exposed and positive patients by EGID status.

