Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Gastroenterology 2021;160:2585–2587

BRIEF COMMUNICATIONS

Association Between Collagenous and Lymphocytic Colitis and Risk of Severe Coronavirus Disease 2019

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Microscopic colitis (MC) is a chronic inflammatory disease of the large intestine that presents with watery diarrhea and primarily affects older adults. We and others have demonstrated that MC is associated with an increased risk of death from infectious causes.[1,2] Severe acute respiratory syndrome coronavirus 2 is a novel virus first discovered in China and is responsible for coronavirus disease 2019 (COVID-19). To date, no study has evaluated the association between MC, its subtypes of collagenous colitis (CC) and lymphocytic colitis (LC), and COVID-19. We therefore sought to examine the risk of severe COVID-19 in patients with MC as compared with the general population. We also compared the frequency of a risk variant from the 3p21.31 gene cluster associated with severe COVID-19[3] across MC subtypes.

Methods

Matched Cohort Study

Association Between MC and Matched General Population Control Subjects and Risk of Severe COVID-19

Study population. We identified all patients with MC diagnosed from January 1, 1990 to December 31, 2016 through a nationwide pathology cohort, the Epidemiology Strengthened by histoPathology Reports in Sweden (ESPRESSO) (see Supplementary Methods). We matched each patient with MC who was alive and living in Sweden as of February 1, 2020 with up to 5 population comparators according to a propensity score with a maximum caliper width of 0.2 of the pooled SD of the logit for each score. Propensity scores for likelihood of MC diagnosis were calculated from a list of demographics and comorbidities (see Supplementary Methods). Data on demographics, comorbidities, and medications were only available up to December 31, 2016 because of the Swedish government restrictions on updating non–COVID-19 related data in established cohorts during the time of the pandemic.

Outcome ascertainment. Our primary outcomes were (1) hospital admission with laboratory-confirmed COVID-19 as the primary diagnosis (International Classification of Diseases, 10th revision code U07.1) and (2) severe COVID-19, a composite outcome defined as COVID-19 intensive care admission or death due to COVID-19 or any death within 30 days of hospital admission with COVID-19.

Statistical analyses. Follow-up time was calculated from February 1, 2020 until death, severe COVID-19, or July 31, 2020, whichever came first. We used Cox proportional hazard modeling conditioned on propensity score to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Case-only Study

Frequency of Severe COVID-19 Risk Locus at 3p21.31 in MC Subtypes

Study population. We included data from 359 individuals diagnosed with CC (average age, 65.1 years; 85.2% women) and 172 patients with LC (average age, 64.7 years; 78.5% women) whose genotypes were available for the analysis of the 3p21.31 locus. Patients had been previously recruited at tertiary gastroenterology clinics from 3 municipalities in Sweden (see Supplementary Methods).

Genotyping and Analysis of COVID-19 Risk Locus 3p21.31. The 3p21.31 locus was studied using MC patients' single nucleotide polymorphism (SNP) rs13071258 genotypes, extracted from available Illumina Infinium Global Screening array data. Association was tested by comparing rs13071258 allele frequencies in CC and LC cases by using adjusted logistic regression and inverse-variance weighted fixed-effects meta-analysis (see Supplementary Methods).

[§]Authors share co-senior authorship.

Abbreviations used in this paper: CC, collagenous colitis; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; LC, lymphocytic colitis; MC, microscopic colitis.

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.02.029

Table 1. Risk of COVID-19 in Patients With MC and Matched Population Comparators

	No. of Cases		No. of Events (%)		Time at Risk (y)		Incidence Rate (95% CI) per 1000 Person-years		
Outcome	MC	Comparators	MC	Comparators	MC	Comparators	MC	Comparators	HR[a] (95% CI)
Overall									
Hospital admission	10,552	52,624	54 (0.51)	211 (0.40)	5182	25,859	10.4 (7.6–13.2)	8.2 (7.1–9.3)	1.25 (0.93–1.69)
Severe COVID-19	10,552	52,624	34 (0.32)	122 (0.23)	5191	25,894	6.5 (4.3–8.8)	4.7 (3.9–5.5)	1.39 (0.94–2.03)
CC									
Hospital admission	3237	16,138	25 (0.77)	36 (0.22)	1584	7935	15.8 (9.6–22.0)	4.5 (3.1–6.0)	3.40 (2.03–5.70)
Severe COVID-19	3237	16,138	15 (0.46)	29 (0.18)	1588	7940	9.4 (4.7–14.2)	3.7 (2.3–5.0)	2.48 (1.33-4.63)
LC									
Hospital admission	7315	36,486	29 (0.40)	175 (0.48)	3597	17,923	8.1 (5.1–11.0)	9.8 (8.3–11.2)	0.81 (0.55–1.20)
Severe COVID-19	7315	36,486	19 (0.26)	93 (0.25)	3602	17,954	5.3 (2.9–7.6)	5.2 (4.1–6.2)	1.03 (0.62–1.69)

[a]Conditioned on propensity score, which was derived from age, sex, county, education, Nordic country of birth, and medical comorbidities updated last on December 31, 2016 (cardiovascular disease, diabetes, chronic obstructive pulmonary disease, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidemia, obstructive sleep apnea, cancer, psychiatric disease).

Ethics

The cohort study was approved by the Stockholm Ethics Review Board (no.: 2014/1287-31/4, with a COVID-19 specific amendment: 2020-02307). Genetic analyses of Swedish MC patients were approved by the Stockholm Ethics Review Board (no.: 2016/271-31/1).

Results

We identified 10,563 individuals with a diagnosis of MC between 1990 and 2017 and propensity score matched 10,552 (3237 CC and 7315 LC) of them to 52,624 population comparators. The baseline characteristics of participants with MC and population comparators are presented in Supplementary Table 1.

In our primary analysis, we observed no increase in risk of hospital admission for COVID-19 or severe COVID-19 in patients with MC (Table 1). There was, however, a significantly increased risk of hospital admission for COVID-19 (HR, 3.40; 95% CI, 2.03–5.70) and severe COVID-19 (HR, 2.48; 95% CI, 1.33–4.63) in patients with CC compared with population comparators. There were no association between LC and risk of COVID-19 outcomes (Table 1). We also observed an increased risk of COVID-19 infections in patients with MC (HR, 1.27; 95% CI, 1.08–1.49) and CC (HR, 1.72; 95% CI, 1.29–2.28) but not LC (HR, 1.11; 95% CI, 0.91–1.36) as compared with population comparators. Additional adjustments for oral steroids (ie, budesonide and prednisone) and proton pump inhibitor use, which were ascertained before December of 2016, yielded similar estimates for the association between CC and hospital admission (HR, 3.20; 95% CI, 1.46–6.99) and severe COVID-19 (HR, 2.19; 95% CI, 0.92–5.12).

We explored the possibility that the observed association between CC and risk of COVID-19 outcomes may be at least in part related to genetic factors predisposing to severe COVID-19.[3] As shown in Supplementary Table 2, rs13071258 A variant, which represents the 3p21.31 risk locus for severe COVID-19, was significantly more common in CC compared with LC patients (respective allele frequencies 0.097 and 0.047; $P = .00464$ in the meta-analysis).

Discussion

In a nationwide cohort in Sweden, we found no association between MC and severe COVID-19 infection after accounting for comorbidities. Interestingly, compared with population comparators, the CC subtype was associated with a significant increase in risk of severe COVID-19 infection. In line with this observation, increased prevalence of a known severe COVID-19 risk variant was detected in patients with CC compared with LC in a pilot genetic study.

Although the exact biologic mechanism behind the observed association between CC and severe COVID-19 outcomes is unknown, it is possible that the increased risk may in part be related to genetic factors that modify immune response to viral pathogens. This is supported by previous genetic findings that showed an increased risk of CC (but not LC) with an extended HLA haplotype (8.1) encoding several molecules with a critical role in immune response to microbial and viral pathogens.[4–6] Additionally, we and others have demonstrated that patients with MC are at an increased risk of infectious disease.[1,2] Of interest and warranting further study in additional cohorts, we detected an increased prevalence of the rs13071258 A variant in CC compared with LC. The 3p21.31 locus, related to the rs13071258 A variant, harbors 6 genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*) that have functions relevant to MC. For example, *CCR9* is selectively expressed in intestinal homing T lymphocytes (intraepithelial lymphocytes)[7,8] that are expanded in MC.

The strengths of our study include nationwide coverage of both MC cases and COVID-19 hospitalizations, large sample size, and availability of genetic data in 3 independent cohorts. The limitations of our study include lack of data on individual lifestyle factors and medications and comorbidities around the time of COVID-19 diagnosis, which may have resulted in misclassification of a number of confounders.

In conclusion, in this population-based cohort study, we found that CC but not LC is associated with an increased risk of severe COVID-19 infections. Additional studies are needed to corroborate our findings; if replicated, they may suggest the existence of specific pathogenetic mechanisms shared between COVID-19 infection and severity and CC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2021.02.029.

References

1. Khalili H, et al. Clin Gastroenterol Hepatol 2020;18:2491–2499.e3.
2. Nyboe Andersen N, et al. Aliment Pharmacol Ther 2020;52:319–328.
3. Severe Covid-19 GWAS Group, et al. N Engl J Med 2020;383:1522–1534.
4. Stahl E, et al. Gastroenterology 2020;159:549–561.e8.
5. Westerlind H, et al. Gut 2017;66:421–428.
6. Westerlind H, et al. Am J Gastroenterol 2016;111:1211–1213.
7. Zabel BA, et al. J Exp Med 1999;190:1241–1256.
8. Kunkel EJ, et al. J Exp Med 2000;192:761–768.

Received October 26, 2020. Accepted February 9, 2021.

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Acknowledgments
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Data sharing statement: Not available from researchers according to Swedish law. Researchers can apply for the cohort study data through Swedish pathology departments, the Swedish National Board of Health and Welfare, and the government agency Statistics Sweden. For genetics data, please contact Dr Mauro D'Amato at mdamato@cicbiogune.es.

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Jonas F. Ludvigsson, MD, PhD (Conceptualization: Equal; Data curation: Lead; Funding acquisition: Equal; Writing – original draft: Equal).

Conflicts of interest
These authors disclose the following: Hamed Khalili has received consulting fees from Takeda and research funding from Takeda and Pfizer. Jonas F. Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG) that has received funding from Janssen Corporation. Jonas F. Ludvigsson and Hamed Khalili receive National Institutes of Health funding from the National Institute of Aging (R01 AG068390) to study the relationship between medications, the gut microbiome, and microscopic colitis.

Funding
This study was funded by Karolinska Institutet. Jonas F. Ludvigsson and Hamed Khalili receive National Institutes of Health funding from the National Institute of Aging (R01 AG068390) to study the relation ut microbiome, and microscopic colitis.

Supplementary Methods

Study Cohort and Identification of MC Cases

The ESPRESSO study contains biopsy data from Sweden's 28 pathology departments between 1965 and April 2017 (2.1 million unique individuals with a gastrointestinal biopsy report).[1] We identified patients with MC defined as having a colorectal biopsy (topography codes T67-68) with a SnoMed histopathology code of either M40600 or M47170. This method for ascertaining cases of MC has previously been validated and found to have a positive predictive value of 95% (95% CI, 91%–97%).[2] Importantly, this method identified symptomatic cases, with the most commonly reported symptoms of diarrhea (96% of patients), weight loss (24%), and abdominal pain (13%).[2] This study was approved by the Stockholm Ethics Review Board (no. 2014/1287-31/4, with a COVID-19 specific amendment: 2020-02307).

Ascertainment of Covariates

For the current study we retrieved data from the Swedish Patient Register (hospital-based inpatient and outpatient care) on the following comorbidities: cardiovascular disease (including thromboembolic disease, diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease), alcohol use disorders (including alcohol-related liver disease), obesity/dyslipidemia, obstructive sleep apnea, cancer, and psychiatric disease. The Patient Register began in 1964 and became nationwide in 1987.[3] Most medical diagnoses in the register have a positive predictive value of 85%–95%.[3] We also collected medication data from Swedish Prescribed Register. Medications included were steroids and use of proton pump inhibitors, which were selected based on their associations with risk of MC and/or COVID-19 outcomes. Steroid use was defined as any use of oral prednisone or budesonide before the matching date. Medication use was last updated on December 31, 2016. Propensity scores were derived from demographic data including age, sex, county, education, and Nordic country of birth, which were ascertained on February 1, 2020, and medical comorbidities including cardiovascular disease, diabetes, chronic obstructive pulmonary disease, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidemia, obstructive sleep apnea, cancer, and psychiatric disease, which were last updated on December 31, 2016.

Study Population for Genetic Studies in MC

Patients had been previously recruited at tertiary gastroenterology clinics from 3 municipalities in Sweden: Stockholm (Karolinska University Hospital, Sophiahemmet Hospital and Ersta Hospital), Malmo (Skåne University Hospital and Trelleborg Hospital), and Linköping (Linköping Hospital). Characteristics for most of these patients have been previously reported.[4,5] Diagnosis of MC and its subtypes was made according to consensus criteria based on the presence of chronic nonbloody diarrhea and histologic findings, including deposition of a subepithelial collagen layer of $\geq$10 μm and lymphocytic infiltration of the lamina propria, as previously described. Genetic analyses of Swedish MC patients were approved by the Stockholm Ethics Review Board (protocol 2016/271-31/1).

Genotyping and Analysis of COVID-19 Risk Locus 3p21.31

MC patients' genotypes were extracted for the locus 3p21.31 from available Illumina Infinium Global Screening array genome-wide data after standard quality control (excluding population outliers using the principal component analysis, related individuals, samples with phenotype–genotype discordant sex, call rate $>$ 98%, heterozygosity rate $>$ 3 SDs), and imputation (using the Haplotype Reference consortium panel and the Eagle haplotype phasing and Positional Burrows-Wheeler Transform software pipeline).[6] For the purpose of this study, we used genotype data available for the SNP marker rs13071258, which was imputed with high accuracy (information metric of imputation certainty, INFO = 0.898) and is a proxy in complete linkage disequilibrium (r^2 = 1) with the rs11385942 marker giving rise to the strongest association signal in the original severe COVID-19 Genome-wide Association Study.[7] The 3p21.31 locus was tested by comparing rs13071258 allele frequencies in CC and LC cases from the 3 municipalities using logistic regression under an additive genetic model implemented in PLINK 2.0 (www.cog-genomics.org/plink/2.0/),[8] adjusting for sex, age, and top 10 principal components. Meta-analysis was performed, based on fixed-effects and the inverse-variance weighted approach using the R package "meta".[9]

References

1. Ludvigsson JF, et al. Clin Epidemiol 2019;11:101–114.
2. Svensson M, et al. Scand J Gastroenterol 2018;53:1469–1475.
3. Ludvigsson JF, et al. BMC Public Health 2011;11:450.
4. Westerlind H, et al. Gut 2017;66:421–428.
5. Westerlind H, et al. Am J Gastroenterol 2016;111:1211–1213.
6. McCarthy S, et al. Nat Genet 2016;48:1279–1283.
7. Severe Covid-19 GWAS Group, et al. N Engl J Med 2020;383:1522–1534.
8. Chang CC, et al. Gigascience 2015;4:7.
9. Balduzzi S, et al. Evid Based Ment Health 2019;22:153–160.

Supplementary Table 1. Baseline Characteristics of Study Cohort After Propensity Score Matching[a]

Characteristic	CC (n = 3237)	Matched Comparators (n = 16,138)	LC (n = 7315)	Matched Comparators (n = 36,486)
Female gender	2564 (79.2)	12,795 (79.3)	5229 (71.5)	26,090 (71.5)
Male gender	673 (20.8)	3343 (20.7)	2086 (28.5)	10,396 (28.5)
Age at index date, y				
Mean (SD)	58.9 (13.9)	58.9 (13.9)	54.7 (16.6)	54.7 (16.6)
Median (IQR)	61.0 (50.6–68.8)	61.0 (50.7–68.8)	57.5 (43.8–67.0)	57.5 (43.8–67.1)
Range, min–max	4.2–92.7	3.5–92.7	1.2–95.1	0.8–95.9
Categories				
<18 y	15 (0.5)	72 (0.4)	125 (1.7)	623 (1.7)
18 to <40 y	323 (10.0)	1613 (10.0)	1370 (18.7)	6842 (18.8)
40 to <60 y	1196 (36.9)	5929 (36.7)	2598 (35.5)	12,990 (35.6)
≥60 y	1703 (52.6)	8524 (52.8)	3222 (44.0)	16,031 (43.9)
Age at start of follow-up, y				
Mean (SD)	69.2 (13.5)	69.2 (13.5)	64.8 (16.3)	64.8 (16.3)
Median (IQR)	71.9 (61.2–78.6)	71.9 (61.1–78.5)	68.1 (53.9–76.8)	68.2 (54.0–76.8)
Range, min–max	10.8–99.7	10.1–99.7	7.2–98.2	7.4–99.0
Categories				
<18 y	3 (0.1)	15 (0.1)	22 (0.3)	106 (0.3)
18 to <40 y	112 (3.5)	550 (3.4)	654 (8.9)	3260 (8.9)
40 to <60 y	636 (19.6)	3184 (19.7)	1837 (25.1)	9186 (25.2)
≥60 y	2486 (76.8)	12,389 (76.8)	4802 (65.6)	23,934 (65.6)
Country of birth				
Nordic country	3103 (95.9)	15,468 (95.8)	6762 (92.4)	33,874 (92.8)
Other	134 (4.1)	670 (4.2)	553 (7.6)	2612 (7.2)
Level of education				
≤9 y	743 (23.0)	3561 (22.1)	1324 (18.1)	6480 (17.8)
10–12 y	1441 (44.5)	7216 (44.7)	3140 (42.9)	15,666 (42.9)
>12 y	1049 (32.4)	5345 (33.1)	2826 (38.6)	14,246 (39.0)
Missing	4 (0.1)	16 (0.1)	25 (0.3)	94 (0.3)
Comorbidities[b]				
Any cardiovascular disease	1348 (41.6)	6779 (42.0)	2574 (35.2)	12,786 (35.0)
Diabetes	298 (9.2)	1268 (7.9)	574 (7.8)	2516 (6.9)
Chronic obstructive pulmonary disease	193 (6.0)	782 (4.8)	357 (4.9)	1512 (4.1)
End-stage renal disease	22 (0.7)	58 (0.4)	33 (0.5)	119 (0.3)
Alcohol liver disease	151 (4.7)	717 (4.4)	396 (5.4)	1853 (5.1)
Obesity/dyslipidemia	496 (15.3)	2301 (14.3)	986 (13.5)	4573 (12.5)
Obstructive sleep apnea	134 (4.1)	511 (3.2)	299 (4.1)	1130 (3.1)
Cancer	439 (13.6)	2210 (13.7)	844 (11.5)	4181 (11.5)
Psychiatric disease	739 (22.8)	3743 (23.2)	1817 (24.8)	9171 (25.1)
Medications[b]				
Oral steroids use[c]	2136 (66)	6455 (0.4)	4389 (60)	146 (0.4)
Proton pump inhibitors	1910 (59)	6455 (40)	3072 (42)	14,594 (40)
Follow-up to hospital admission, mo				
Mean (SD)	5.9 (0.5)	5.9 (0.4)	5.9 (0.4)	5.9 (0.5)
Median (IQR)	6.0 (6.0–6.0)	6.0 (6.0–6.0)	6.0 (6.0–6.0)	6.0 (6.0–6.0)
Range, min–max	0.2–6.0	0.0–6.0	0.1–6.0	0.0–6.0

Values are n (%) unless otherwise defined. IQR, interquartile range.
[a]Age, sex, county, education, Nordic country of birth, and medical comorbidities including cardiovascular disease, diabetes, chronic obstructive pulmonary disease, end-stage renal disease, alcohol liver disease/alcohol use disorder, obesity/dyslipidemia, obstructive sleep apnea, cancer, and psychiatric disease were included in the propensity score.
[b]Medication and comorbidities were last updated on December 31, 2016.
[c]Defined as oral budesonide or prednisone.

Supplementary Table 2. Distribution of Severe COVID-19 Risk Variant rs13071258 A in Patients With CC and LC

	No. of Cases		Allele Frequency				
	CC	LC	CC	LC	β^a	SE	*P*
Site							
Stockholm	113	63	0.082	0.035	0.891	0.636	.161
Malmo	133	48	0.130	0.098	0.399	0.433	.357
Linkoping	113	61	0.073	0.020	1.833	0.867	.346
Pooled analysis	359	172	0.097	0.047	0.741	0.331	.0251
Meta-analysis	359	172	0.097	0.047	0.886	0.313	.00464

[a]Estimates were derived from logistic regression under an additive genetic model adjusting for age, sex, and top 10 principal components.