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 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 of Pathology 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 for each 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 across MC subtypes.

**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).

**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.

\(^1\) Clinical and Translational Epidemiology Unit and Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts; \(^2\) The Broad Institute of MIT and Harvard, Cambridge, Massachusetts; \(^3\) Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; \(^4\) Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; \(^5\) School of Biological Sciences, Monash University, Clayton, Victoria, Australia; \(^6\) Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm Sweden; \(^7\) Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; \(^8\) Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; \(^9\) Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom; and \(^10\) Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York

© 2021 by the AGA Institute

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

| Outcome                  | No. of Cases | No. of Events (%) | Time at Risk (y) | Incidence Rate (95% CI) per 1000 Person-years |
|--------------------------|--------------|-------------------|------------------|-----------------------------------------------|
|                          | MC           | Comparators       | MC              | Comparators                                  |
| 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) |

for CC compared with 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. 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. Additionally, we and others have demonstrated that patients with MC are at an increased risk of infectious disease. 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, ZLTFL1, CCR9, FYCO1, CXCR6, and XCR1) that have functions relevant to MC. For example, CCR9 is selectively expressed in intestinal homing T lymphocytes (intraepithelial lymphocytes) 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 pathogenic 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. Westerlund H, et al. Gut 2017;66:421–428.
6. Westerlund 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.

Correspondence

Address correspondence to: Mauro D’Amato, PhD, Gastrointestinal Genetics Lab, CIC bioGUNE, Basque Research and Technology Alliance, Parque Tecnológico de Bizkaia, 48160 Derio, Spain. e-mail: mdamato@cibigune.es; or Jonas F. Ludvigsson, MD, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden. e-mail: jonasludvigsson@yahoo.com.

Acknowledgments

COVID-19 and microscopic colitis collaborators are as follows: Andreas Munch,1 Klas Sjöberg,2 Sven Almer,3 Lina Vigné,4 Izabela Janczewska,5 Bodil Ohlsson,6 Francesca Bresso,7 Maire-Rose Mellander,4 Ola Olén,8–10 Bjorn Roelstraete,11 Andre Franke,12 and Tracey G. Simon.13 Affiliations are as follows: 1Department of Gastroenterology, Department of Biomedical and Clinical Sciences (BKV), Faculty of Health Sciences, Linköping University, Linköping, Sweden; 2Department of Clinical Sciences, Lund University, Department of Gastroenterology, Skane University Hospital, Malmo, Sweden; 3Division of Gastroenterology, Department of Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden; 4Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; 5Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; 6Department of Gastroenterology, Skane University Hospital, Malmo, Sweden; 7Clinical Epidemiology Unit and Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts.

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 genetic data, please contact Dr Mauro D’Amato at mdamato@cibigune.es.

CRediT Authorship Contributions

Hamed Khalili, MD (Conceptualization: Equal; Methodology: Equal; Writing – original draft: Equal); Tenghao Zheng, PhD (Formal analysis: Supporting; Writing – review & editing: Supporting); Jonas Söderling, PhD (Formal analysis: Lead; Writing – review & editing: Supporting); Emma Larsson, PhD (Methodology: Supporting; Writing – review & editing: Supporting); Mauro D’Amato, PhD (Data curation: Equal; Funding acquisition: Equal; Methodology: Equal; Writing – review & editing: Supporting); 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 relationship 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 method identified symptomatic cases, with the most commonly reported symptoms of diarrhea (96% of patients), weight loss (24%), and abdominal pain (13%). This method identified symptomatic cases, with the most commonly reported symptoms of diarrhea (96% of patients), weight loss (24%), and abdominal pain (13%).

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%.4 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 ≥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 (r² = 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. Westerlund H, et al. Gut 2017;66:421–428.
5. Westerlund 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. Baiduzzi S, et al. Evid Based Ment Health 2019;22:153–160.
## Supplementary Table 1. Baseline Characteristics of Study Cohort After Propensity Score Matching

| 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 (50.6–88.8) | 61.0 (50.7–88.8) | 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 |               |                                  |              |                                  |
| 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   |               |                                  |              |                                  |
| Oral steroids use | 2136 (66) | 6455 (40.4)                      | 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.

aAge, 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.

bMedication and comorbidities were last updated on December 31, 2016.

cDefined as oral budesonide or prednisone.
## Supplementary Table 2: Distribution of Severe COVID-19 Risk Variant rs13071258 A in Patients With CC and LC

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

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