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.

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Gastrointestinal and Hepatic Manifestations of 2019 Novel Coronavirus Disease in a Large Cohort of Infected Patients From New York: Clinical Implications

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Recent reports suggest that prevalence of gastrointestinal (GI) and hepatic manifestations in COVID-19 are higher than initially reported, particularly in Western populations. New York City has arguably been the epicenter of the COVID-19 pandemic in the United States, creating a unique opportunity to further the understanding of this disease. Our objectives were to investigate the prevalence of GI and hepatic manifestations of patients with COVID-19, and explore their effect on the clinical outcomes in these patients.

Methods

This is a retrospective review of consecutive adult patients (age ≥18) with a positive real-time reverse-transcription polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 recorded between March 4 and April 9, 2020, at 1 of our 2 hospitals in Manhattan (an academic tertiary referral center and a smaller community hospital). The history, laboratory data, and outcome measures were extracted from patients' medical records, using an structured abstraction tool. All vital signs and laboratory data were collected at presentation. "GI manifestation" was defined as presence of nausea, vomiting, diarrhea, or abdominal pain. Patients were considered to have indication of liver injury at presentation if they had elevated alanine aminotransferase, aspartate aminotransferase, total bilirubin, or alkaline phosphatase. The primary clinical outcome for admitted patients was defined as a composite of intensive care unit (ICU) admission or death (details of methods are available in the supplementary material).

Results

A total of 1059 patients diagnosed with COVID-19 with a mean age of 61 (SD 18) years (58% male) were included in the study (Table 1). At presentation, 22% of patients had diarrhea, 7% had abdominal pain, and 16% and 9% had nausea and vomiting, respectively; 33% of patients had at least 1 GI manifestation. At presentation, patients had a mean alanine aminotransferase of 50 (65), mean aspartate aminotransferase of 60 (79) U/L, mean total bilirubin 0.7 (0.6) mg/dL, and mean alkaline phosphatase of 88 (74) U/L; 62% of the patients had biochemical evidence of liver injury with at least 1 of their liver enzymes elevated.

In multivariable analysis of the effect of gender, age, preexisting immunosuppression, inflammatory bowel disease, or chronic liver disease on presence of GI manifestation or liver injury, female patients (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.01–1.69, $P = .048$), and patients with chronic liver disease (OR 2.18, 95% CI 1.08–4.44, $P = .031$) were more likely to present with GI symptoms; however, age, immunosuppression, and inflammatory bowel disease were not associated with GI symptoms at presentation. Only older age was significantly associated with higher rate of liver test abnormalities at presentation (OR 1.01, 95% CI 1.00–1,02, $P = .031$).

Both GI manifestations (78% vs 70% for patients without GI symptoms, $P = .007$) and liver injury (87% vs 76% for patients without liver injury, $P < .001$) on presentation were associated with higher admission rate. Those with GI symptoms had lower rates of death (8.5% vs 16.5% in patients without GI symptoms, $P = .003$), and lower risk of the composite of death and ICU admission (28% versus 38% in patients without GI symptoms, $P = .006$) in univariable analysis.

In multivariable analysis, liver injury at presentation (OR 2.53, $P < .001$), as well as older age (OR 1.03, $P < .001$), number of comorbidities (OR 1.19, $P = .021$), tachypnea (OR 1.73, $P = .008$) and severe hypoxia (OR 1.47, $P = .047$) remained independent predictors of the composite outcome of death or ICU admissions in patients admitted with COVID-19, but GI manifestations did not have any significant effect on the outcome (Supplementary Table 1).

The independent predictors of the composite outcome of death or ICU admission from the multivariable model were then analyzed to find an optimal decision tree for splitting patients into low- and high-risk categories and predicting the composite outcome (Figure 1). The first node of the decision tree was hypoxia as the most informative predictor, followed by presence of liver injury as the second most informative predictor (second node) in patients with severe hypoxia.

Abbreviations used in this paper: **CI, confidence interval; COVID-19, coronavirus disease 2019; GI, gastrointestinal; ICU, intensive care unit; OR, odds ratio.**

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Table 1. Demographic, Laboratory, and Cinical Findings of Patients With COVID-19 at Presentation

Variable	Total, n = 1059	Outpatient, n = 291	Inpatient, n = 768	*P*
Age, *y*	61.1 (18.3)	51.6 (17.8)	64.7 (17.1)	.000
Diagnostic delay, *d*[a]	7.4 (6.1)	7.2 (8.2)	7.5 (5.3)	.526
Body mass index, kg/m^2	28.8 (8.3)	28.2 (8.2)	29 (8.3)	.368
Male	611 (57.7)	145 (49.8)	466 (60.7)	.001
Race/ethnicity				.119
White/Caucasian	352 (45)	106 (46)	246 (44)	
Black/African American	136 (17)	48 (21)	88 (15)	
Asian	106 (13)	28 (12)	78 (14)	
Other	198 (25)	47 (21)	151 (27)	
Preexisting comorbidities				
Hypertension	506 (47.8)	90 (30.9)	416 (54.2)	.000
Diabetes	274 (25.9)	43 (14.8)	231 (30.1)	.000
Chronic kidney disease	131 (12.4)	21 (7.2)	110 (14.3)	.002
Cardio-vascular disease	193 (18.2)	32 (11)	161 (21)	.000
COPD/Asthma	123 (11.6)	27 (9.3)	96 (12.5)	.146
Obstructive sleep apnea	46 (4.3)	6 (2.1)	40 (5.2)	.031
VTE	68 (6.4)	8 (2.7)	60 (7.8)	.004
Cancer	120 (11.3)	24 (8.2)	96 (12.5)	.053
IBD	17 (1.6)	2 (0.7)	15 (2)	.162
Chronic liver disease	32 (3)	8 (2.7)	24 (3.1)	.750
Solid organ transplantation	26 (2.5)	2 (0.7)	24 (3.1)	.037
Vital signs				
fever	253 (26.8)	58 (26.7)	195 (26.8)	.987
Respiratory rate	20.6 (5.4)	18.7 (4.1)	21.1 (5.6)	.000
Heart rate	94.2 (18.9)	93.9 (17.1)	94.3 (19.5)	.762
Mean arterial pressure, mm Hg	93.5 (14.4)	95.1 (15)	93 (14.2)	.062
Hypoxia on presentation				.000
No	150 (71)	250 (35)		
Moderate	48 (23)	236 (33)		
Severe	14 (7)	230 (32)		
Symptoms				
Fever	717 (67.7)	187 (64.3)	530 (69)	.140
Cough	682 (64.4)	179 (61.5)	503 (65.5)	.227
Shortness of breath	625 (59)	119 (40.9)	506 (65.9)	.000
Myalgia/fatigue	300 (28.3)	89 (30.6)	211 (27.5)	.316
Anorexia	240 (22.7)	50 (17.2)	190 (24.7)	.009
Altered mental status	135 (12.7)	21 (7.2)	114 (14.8)	.001
Nausea	168 (15.9)	45 (15.5)	123 (16)	.826
Vomiting	91 (8.6)	24 (8.2)	67 (8.7)	.805
Diarrhea	234 (22.1)	47 (16.2)	187 (24.3)	.004
Abdominal pain	72 (6.8)	16 (5.5)	56 (7.3)	.302
Anosmia	51 (4.8)	21 (7.2)	30 (3.9)	.027
Dysgeusia	57 (5.4)	20 (6.9)	37 (4.8)	.188
Anticoagulant	168 (15.9)	22 (7.6)	146 (19)	.000
Aspirin	124 (11.7)	17 (5.8)	107 (13.9)	.000
NSAIDs	119 (11.2)	22 (7.6)	97 (12.6)	.021
Chronic steroids	41 (3.9)	3 (1)	38 (4.9)	.008
Immunosuppressant	34 (3.2)	4 (1.4)	30 (3.9)	.046
statin	307 (29)	46 (15.8)	261 (34)	.000
Laboratory findings				
White blood cell count, $\times 10^3$	7.6 (6.1)	6.1 (2.5)	8 (6.6)	.000
Absolute lymphocyte count, $\times 10^3$	1.3 (2.8)	1.6 (3.9)	1.3 (2.5)	.163
Absolute neutrophil count, $\times 10^3$	7.9 (12.7)	6.6 (11.9)	8.2 (12.8)	.141
Platelet count, $\times 10^3$	214.5 (100.2)	201.9 (89.9)	217.4 (102.2)	.074
Procalcitonin, ng/mL	1 (5.5)	0.4 (1.5)	1.1 (5.9)	.219
D-dimer, ng/mL	1800.2 (5046.7)	926.6 (2277.1)	1901.4 (5266.7)	.201
C-reactive protein, mg/dL	14.8 (13.5)	8.2 (9.4)	15.8 (13.8)	.000
Erythrocyte sedimentation rate, mm/hr	69.7 (33.6)	50.8 (31.4)	72.2 (33.2)	.000
Lactate dehydrogenase, U/L	497.2 (939.6)	357.6 (179.1)	518.9 (1006)	.139
Ferritin, ng/mL	1259.6 (2081.9)	841.9 (1495.2)	1314.9 (2142.7)	.088
Troponin I, ng/mL	0.9 (17.4)	0.1 (0.2)	1 (18.7)	.658

Table 1. Continued

Variable	Total, n = 1059	Outpatient, n = 291	Inpatient, n = 768	*P*
Creatine kinase, U/L	355.4 (739.4)	216.2 (274.3)	369.8 (770.5)	.211
IL-6, pg/mL	81 (151.9)	6 (1.7)	83.9 (154.2)	.387
Albumin, g/dL	3.3 (0.6)	3.6 (0.7)	3.2 (0.6)	.000
Total bilirubin, mg/dL	0.7 (0.6)	0.6 (0.3)	0.7 (0.6)	.017
ALT, U/L	49.5 (64.9)	42.2 (48.3)	51 (67.7)	.142
AST, U/L	59.5 (78.5)	46.4 (56.2)	62.1 (82.1)	.030
Alkaline phosphatase, U/L	88.1 (74.1)	82.7 (49.6)	89.2 (78.2)	.342
INR	1.3 (0.8)	1.4 (1.3)	1.3 (0.7)	.286
aPTT, *s*	30.5 (14.8)	28.4 (10.5)	30.8 (15.3)	.182

NOTE. Data are mean (SD), n (%), or n/N (%). *P* values were calculated using Student *t* and χ^2 tests.
ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; IL, interleukin; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; VTE, venous thromboembolism.
[a]Diagnostic delay defined as time between first symptom and performing the first COVID-19 polymerase chain reaction test.

Discussion

This analysis reveals a high prevalence of GI manifestations and liver injury (based on elevated liver enzymes) at presentation in COVID-19. Although both GI and hepatic manifestations were associated with increased admission rates, only liver injury at presentation was an independent predictor of ICU admission and death and ICU admission.

Our results indicate that almost one-third of patients reported digestive issues, most commonly diarrhea. One potential explanation for the high rate of diarrhea seen may be related to the high affinity of severe acute respiratory syndrome coronavirus 2 for angiotensin-converting enzyme 2 receptor, and the abundant angiotensin-converting enzyme 2 expression on colonic and ileal epithelial cells.[1] Prior studies suggest that the presence and severity of digestive symptoms on initial presentation was correlated with worsening disease severity.[2] In contrast, we observed a trend for the presence of GI symptoms on initial presentation to be associated with less severe disease in univariable analysis (Supplementary Table 1), and no significant effect in multivariable analysis. This might be due to higher admission rates in patients with relatively mild respiratory involvement but significant GI symptoms.

In our cohort, 62% presented with at least 1 elevated liver enzyme, similar to the available literature.[3] We did not find the elevation of either total bilirubin or alkaline

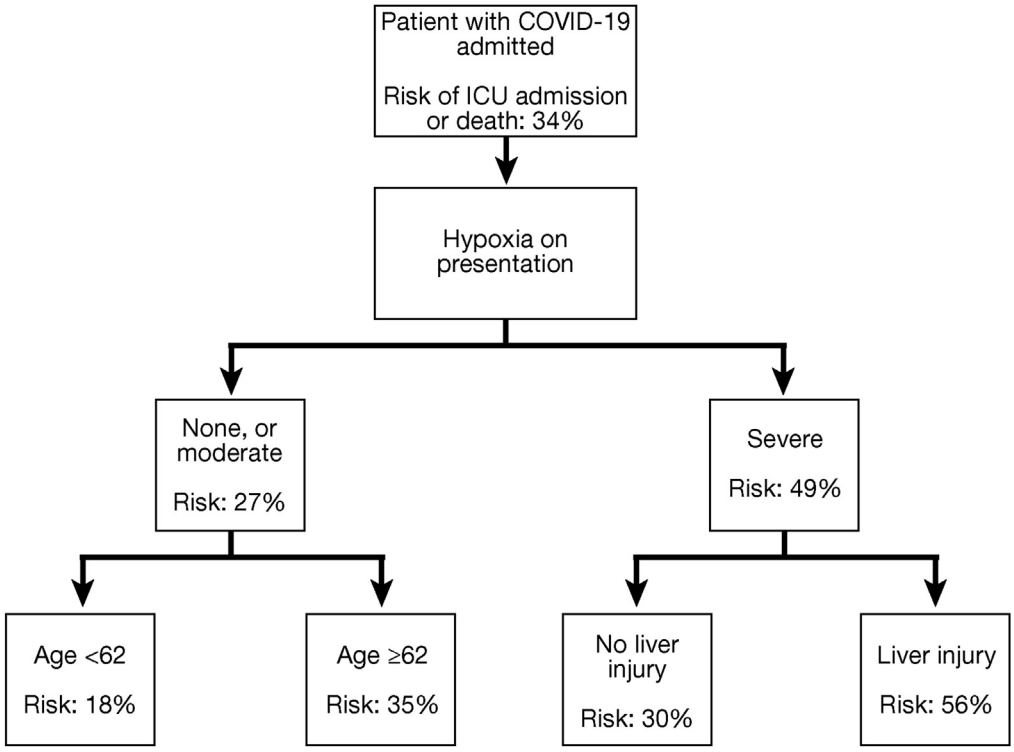

Figure 1. Optimal decision tree for categorizing patients admitted for COVID-19 based on the predictors of the composite outcome of death or ICU admission.

phosphatase to be common, and did not observe any cases of clinically significant acute liver injury or acute liver failure as a complication of COVID-19. The presence of liver injury on presentation, however, was associated with a significantly higher risk of ICU admission and death. High prevalence of liver injury in COVID-19 may be due to direct viral infection of liver cells[4]; however, the pathology of hepatic injury in COVID-19 is likely multifactorial, and may include an indirect reflection of the systemic inflammatory response resulting in compromised vascular hemodynamics and immune hyperactivity and cytokine activation.[5–7]

In summary, we found that patients with COVID-19 commonly exhibit GI manifestations. Liver injury was also commonly seen on initial presentation, and was independently associated with poor clinical outcomes. These results provide clarification of the diagnosis of patients with COVID-19, and can be considered in risk stratification.

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.2020.05.010.

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Conflict of interest
The authors disclose no conflicts.

Supplementary Material

Methods

Patients and exposure variables. This is a retrospective review of all adult patients (age ≥18) with a positive real-time reverse-transcription polymerase chain reaction (RT-PCR) test from a respiratory sample (naso- or oropharyngeal, or bronchial/sputum samples) for severe acute respiratory syndrome coronavirus 2 recorded between March 4 and April 9, 2020, at 1 of our 2 hospitals in Manhattan (an academic tertiary referral center and a smaller community hospital). The study was reviewed and approved by the institutional review board at our medical center (IRB 1804019146).

The epidemiological history, demographics data, clinical characteristics, laboratory data, treatment programs, and outcome measures were obtained from patients' medical records. Clinical outcomes were followed up to April 16, 2020. Presence of comorbidities (cancer, chronic kidney disease, chronic obstructive pulmonary disease, asthma, cardiovascular disease, history of venous thromboembolism, diabetes, hypertension, inflammatory bowel disease, or chronic liver disease or solid organ transplantation) was extracted. A list of medications of interest, including anticoagulants, steroids, statins, nonsteroidal anti-inflammatory drugs, and nonsteroidal immunosuppressive medications was extracted for each patient at the time of the COVID-19 diagnosis. Laboratory and imaging data and outcome measures were obtained from patients' medical records.

For each patient, the time of presentation was defined as the time when the PCR test for COVID-19 was performed. Patients' date of first symptoms and date of positive PCR for COVID-19, as well as their initial vital signs (with fever defined as temperature ≥37.8°C) and general symptoms at presentation (subjective fever, cough, shortness of breath, anorexia, altered mental status, myalgia, and fatigue) were recorded. For each patient, the presence or absence at presentation of a list of GI manifestations of interest (nausea, vomiting, diarrhea, and abdominal pain) was confirmed using the medical records.

A comprehensive set of laboratory studies was also extracted for patients at presentation. These studies included liver enzyme tests, including alkaline phosphatase, total bilirubin, aspartate aminotransferase and alanine aminotransferase, as well as biomarkers linked to disease severity and outcomes in COVID-19 based on the available evidence.

Patients' admission status was divided into "outpatient," including temporary observation (defined as admission to emergency department and discharge within 24 hours), and "inpatient" (admission to hospital for 24 hours or more). Patients degree of hypoxemia on presentation was categorized as (1) not hypoxic defined as an oxygen saturation of ≥95% on room air, (2) moderate hypoxia defined as maintaining an oxygen saturation of 90% to 95% on room air or ≥90% with 4 L or less supplemental oxygen through a nasal cannula, and (3) severe hypoxia defined as needing more than 4 L of supplemental oxygen, non-rebreather mask, or noninvasive (eg, bilevel positive airway pressure) or invasive ventilation to maintain an oxygen saturation of ≥90%, or failure to maintain an oxygen saturation of ≥90%. Patients were considered to have GI manifestations at presentation if they complained of any of the symptoms of nausea, vomiting, diarrhea, or abdominal pain. Patients were considered to have indication of liver injury at presentation if they had alanine aminotransferase or aspartate aminotransferase >40 U/L, total bilirubin>1.2 mg/dL, or alkaline phosphatase >50 U/L (upper limit of normal at our laboratory).

COVID-19 treatment and clinical outcomes. For admitted patients, data were extracted regarding their clinical course including need for supplementary oxygen, noninvasive positive pressure ventilation, or invasive ventilatory support with mechanical ventilation, ICU admission, and death.

The main outcome of this study was defined as the prevalence of GI symptoms or laboratory evidence of liver or biliary dysfunction/injury at presentation with COVID-19 as defined previously ("GI manifestation" and "liver injury", respectively). The secondary outcome was the effect of GI manifestation and liver injury at presentation on admission rate and death and ICU admission for inpatients. The primary clinical outcome for admitted patients was defined as a composite of ICU admission (with or without invasive mechanical ventilation) or death.

Statistical analysis. Descriptive statistics were reported as means (standard deviation, SD), or counts and proportions. Variables were compared using Student t and χ^2 tests in unadjusted analysis. Logistic regressions were used for univariable and multivariable analysis. Chi-square automatic interaction detection with adjusted significance testing (Bonferroni method) with no limitation on the number of branches was used to find the optimal decision tree structure for predicting the risk of the composite outcome of death or ICU admission and splitting the patients into low- and high-risk groups, based on a set of independent variables. All analyses were based on nonmissing data, and missing data were not imputed. Sensitivity analysis was performed to investigate the liver enzyme tests with the highest discrimination for prediction of the composite outcome of death or ICU admission using the receiver operating characteristic curve analysis. Area under the curve and its 95% confidence intervals are reported. The optimal cutoff point for each liver enzyme was defined as the point nearest to the perfect sensitivity and specificity on the receiver operating characteristic curve. All tests were 2-tailed with a significance level of alpha = 0.05, except when adjusted for multiple comparisons as described previously. All analyses were performed with Stata 13.0 for Windows, StataCorp LP (College Station, TX).

Supplementary Table 1. Risk Factors for the Composite Outcome of Death or ICU Admission in Patients Admitted With COVID-19

	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Risk factors				
Age	**1.027 (1.017–1.037)**	**.000**	**1.029 (1.013–1.044)**	**.000**
Male gender	**1.442 (1.046–1.988)**	**.026**	1.264 (0.818–1.954)	.291
BMI	1.011 (0.99–1.033)	.315		
Race/ethnicity				
White/Caucasian	**Reference**			
Black/African-American	**0.545 (0.304–0.973)**	**.040**	0.569 (0.285–1.138)	.111
Asian	**1.629 (0.966–2.749)**	**.067**	1.542 (0.835–2.845)	.166
Other	**0.704 (0.449–1.106)**	**.128**	0.962 (0.563–1.646)	.888
GI manifestation at presentation	**0.629 (0.453–0.873)**	**.006**	0.766 (0.487–1.204)	.248
Liver injury at presentation	**2.2 (1.549–3.124)**	**.000**	**2.533 (1.591–4.032)**	**.000**
Preexisting comorbidities				
Number of preexisting comorbidities	**1.194 (1.076–1.324)**	**.001**	**1.192 (1.026–1.384)**	**.021**
IBD	0.473 (0.132–1.694)	.250		
Chronic liver disease	0.784 (0.321–1.917)	.594		
Solid organ transplantation	1.024 (0.428–2.45)	.957		
Hypertension	**1.629 (1.188–2.233)**	**.002**		
Diabetes	1.375 (0.991–1.908)	.057		
Chronic kidney disease	1.174 (0.767–1.797)	.460		
Cardiovascular disease	**1.919 (1.339–2.75)**	**.000**		
COPD/Asthma	1.224 (0.782–1.915)	.376		
Obstructive sleep apnea	**2.354 (1.23–4.506)**	**.010**		
VTE	1.523 (0.891–2.601)	.124		
Cancer	0.92 (0.581–1.456)	.721		
Vital signs at presentation				
Fever	1.316 (0.93–1.86)	.121		
Respiratory rate[a]	**2.612 (1.933–3.532)**	**.000**	**1.733 (1.152–2.607)**	**.008**
Heart rate[a]	**1.119 (1.033–1.212)**	**.006**	1.108 (0.989–1.242)	.077
Mean arterial pressure, mm Hg[a]	0.941 (0.843–1.05)	.273		
Hypoxia on presentation				
No	**Reference**			
Moderate	**1.224 (0.817–1.832)**	**.327**	0.901 (0.528–1.538)	.704
Severe	**2.847 (1.928–4.206)**	**.000**	**1.678 (0.984–2.861)**	**.047**
Laboratory findings				
White blood cell count, $\times 10^3$	**1.039 (1.004–1.076)**	**.031**		
Absolute lymphocyte count, $\times 10^3$	1.033 (0.97–1.1)	.314		
Absolute neutrophil count, $\times 10^3$	**1.031 (1.014–1.049)**	**.000**		
Platelet count, $\times 10^3$	0.999 (0.998–1.001)	.309		
ALT, U/L[a]	1.007 (0.984–1.03)	.550		
AST, U/L[a]	1.034 (1.007–1.062)	.015		
Alkaline phosphatase, U/L[a]	1 (0.981–1.021)	.962		
Total bilirubin, mg/dL	**1.411 (1.044–1.907)**	**.025**		
Albumin, g/dL	**0.744 (0.577–0.96)**	**.023**		
Procalcitonin, ng/mL[a]	1.084 (0.828–1.419)	.557		
D-dimer, ng/mL[b]	**1.006 (1.002–1.011)**	**.005**		
C reactive protein, mg/dL	**1.018 (1.005–1.031)**	**.008**		
Lactate dehydrogenase, U/L[b]	**1.293 (1.182–1.414)**	**.000**		
Ferritin, ng/mL[b]	**1.015 (1.003–1.026)**	**.015**		
Troponin I, ng/mL	0.995 (0.977–1.014)	.605		
Creatine kinase, U/L[b]	1.029 (0.999–1.061)	.059		
IL-6, pg/mL	1.003 (0.998–1.007)	.233		

NOTE. Values in bold indicate significance.
ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; IL, interleukin; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; VTE, venous thromboembolism.
[a]The OR is for 10 units change in the risk factor.
[b]The OR is for 100 units change in the risk factor.