RESEARCH LETTER

Gastrointestinal Complications in Critically Ill Patients With and Without COVID-19

Coronavirus disease 2019 (COVID-19) appears to have significant extrapulmonary complications affecting multiple organ systems.[1-3] Critically ill patients with COVID-19 often develop gastrointestinal complications during their hospital stay, including bowel ischemia, transaminitis, gastrointestinal bleeding, pancreatitis, Ogilvie syndrome, and severe ileus.[3] Whether the high incidence of gastrointestinal complications is a manifestation of critical illness in general or is specific to COVID-19 remains unclear. We compared the incidence of gastrointestinal complications of critically ill patients with COVID-19–induced acute respiratory distress syndrome (ARDS) vs comparably ill patients with non–COVID-19 ARDS using propensity score analysis.

Methods | All patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on reverse transcriptase–polymerase chain reaction who were intubated and admitted to 1 of 13 (preexistent and surge) intensive care units (ICUs) of Massachusetts General Hospital between March 13, 2020, and May 7, 2020, were included, then matched to a cohort of patients admitted between 2018 and 2019 and meeting the Berlin criteria for ARDS.[4] No changes occurred in the ICU staffing models or protocols of care of ARDS during the study period. Propensity score matching

Table. Baseline Population Characteristics and Outcomes

Characteristic/outcome	No. (%)		*P* value
	Non-COVID-19 ARDS	COVID-19 ARDS	
Prematching characteristics			
No. of patients	244	242	
Age, median (IQR), y	62 (53-73.5)	60.5 (48-71)	.09
BMI, median (IQR)[a]	27.5 (23-32)	30 (27-35)	<.001
Sex			
Female	110 (45.1)	81 (33.5)	.009
Male	134 (54.9)	161 (66.5)	
Smoking	164 (67.2)	68 (28.1)	<.001
SOFA score, median (IQR)	7 (5-9)	6 (4-8)	<.001
Comorbidities			
Hypertension	144 (59.0)	128 (52.9)	.17
Chronic lung disease[b]	104 (42.6)	51 (21.1)	<.001
Diabetes	64 (26.2)	109 (45.0)	<.001
Congestive heart failure	56 (23.0)	19 (7.9)	<.001
Coronary artery disease	45 (18.4)	25 (10.3)	.01
Chronic kidney disease	42 (17.2)	38 (15.7)	.65
Postmatching characteristics			
No. of patients	92	92	
Age, median (IQR), y	64.5 (51.5-75.5)	62 (48.5-71.5)	.24
BMI, median (IQR)[a]	28 (25-33.5)	29 (25-32.5)	.55
Sex			
Female	40 (43)	38 (41)	.77
Male	52 (57)	54 (59)	
Smoking	39 (42)	36 (39)	.65
SOFA score, median (IQR)	7 (4-8.5)	7 (5-9)	.86
Comorbidities			
Hypertension	50 (54)	51 (55)	.88
Diabetes	35 (38)	34 (37)	.88
Chronic lung disease	29 (32)	27 (29)	.75
Chronic kidney disease	17 (18)	18 (20)	.85
Coronary artery disease	14 (15)	12 (13)	.67
Congestive heart failure	13 (14)	15 (16)	.68

(continued)

Table. Baseline Population Characteristics and Outcomes (continued)

Characteristic/outcome	No. (%) Non-COVID-19 ARDS	COVID-19 ARDS	*P* value
Outcomes			
No. of patients	92	92	
Pao_2:FIo_2 ratio[c]	168 (136-228)	191.5 (145.5-331)	.05
Any gastrointestinal complication	34 (37)	68 (74)	<.001
Transaminitis	25 (27)	51 (55)	<.001
Ileus	20 (22)	44 (48)	<.001
Ogilvie syndrome	1 (1)	2 (2)	.56
Mesenteric ischemia	0	4 (4)	.04
30-d Mortality	21 (23)	23 (25)	.73
Hospital LOS, median (IQR)	14 (9-24)	24 (13-36)	<.001
ICU LOS, median (IQR)	8.5 (4.5-15)	17 (8-25)	<.001
Days on opioid drip, median (IQR)	1 (0-4.5)	9 (4-15)	<.001
Days on ventilation, median (IQR)	6 (3-11)	13.5 (8.5-22.5)	<.001
Tracheostomy	11 (12)	28 (30)	.002
Emergency department readmission	10 (11)	10 (11)	.98
Other complications			
Venous thromboembolism	6 (7)	9 (10)	.42
Acute kidney injury	63 (68)	72 (78)	.13
Dialysis[d]	14 (22)	21 (29)	.36

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease 2019; FIo_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; Pao_2, partial pressure of arterial oxygen; SOFA, Sequential Organ Failure Assessment.

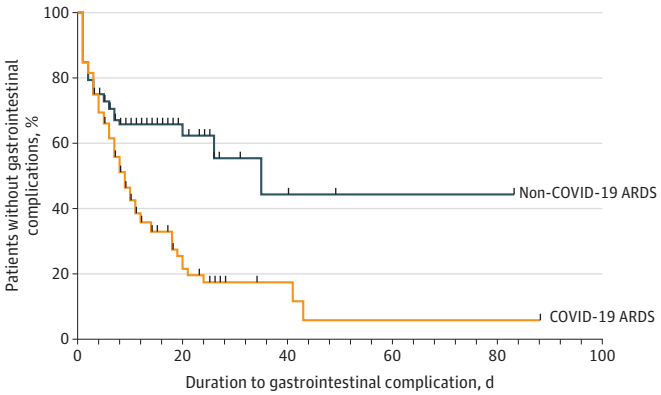
[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Includes asthma, chronic obstructive pulmonary disease, and interstitial lung disease.

[c] Pao_2:FIo_2 ratio on admission to the ICU.

[d] Percentage is of patients with acute kidney injury.

Figure. Kaplan-Meier Curves of Gastrointestinal Complications in Patients With Acute Respiratory Distress Syndrome (ARDS) With and Without Coronavirus Disease 19 (COVID-19)



No. at risk

Non-COVID-19 ARDS	92	46	19	6	4	1	1	1	1
COVID-19 ARDS	92	36	13	4	3	1	1	1	1

The 2 curves initially look similar but start separating around day 3 of the intensive care unit stay.

was performed adjusting for demographics (eg, age, sex, body mass index, smoking status), comorbidities (eg, chronic lung/kidney disease, congestive heart failure, coronary artery disease, hypertension, diabetes), and severity of illness on ICU admission (Sequential Organ Failure Assessment score). We examined in both groups the following gastrointestinal complications: transaminitis, ileus, Ogilvie syndrome, and mesenteric ischemia.

Wilcoxon rank sum, Pearson χ^2, and Fisher exact tests were used, as appropriate. To determine whether differences in the duration of illness between groups might contribute, incidence rate ratios and Kaplan-Meier curves looking at time to development of the complication from hospital admission were calculated. All tests were 2-tailed; statistical significance was defined as $P < .05$. Statistical analyses were performed on Stata version 15.0 (StataCorp LP). The Mass General Brigham Institutional Review Board ruled this study exempt including a waiver of informed consent.

Results | A total of 486 patients with ARDS met eligibility criteria, of which 244 had non-COVID-19 ARDS and 242 had COVID-19 ARDS. This report includes data from 141 patients with COVID-19 (58%) whose overall gastrointestinal complications have been previously described.[3] The median age of patients was 60.5 years (interquartile range, 48-71 years) and 62 years (interquartile range, 53-73.5) years for patients

with and without COVID-19, respectively, and the percentage of males was 66.5% and 54.9%, respectively.

Ninety-two patients with COVID-19 and ARDS were propensity score matched to 92 patients with non–COVID-19 ARDS (**Table**). The etiologies for ARDS among the non–COVID-19–matched cohort were bacterial pneumonia (60%), aspiration (27%), influenza (7%), respiratory syncytial virus infection (2%), and *Pneumocystis jiroveci* pneumonia (2%). Patients with COVID-19 were more likely to develop gastrointestinal complications compared with those without COVID-19 (74% vs 37%; $P < .001$; incidence rate ratio, 2.33 [95% CI, 1.52-3.63]). The difference in incidence was more evident after the third day of critical illness (**Figure**). Specifically, patients with COVID-19 developed more transaminitis (55% vs 27%; $P < .001$), severe ileus (48% vs 22%; $P < .001$), and bowel ischemia (4% vs 0%; $P = .04$). Three of the 4 patients with COVID-19 and bowel ischemia were taken to the operating room and had intraoperative findings consistent with COVID-19 bowel as previously described in different patients.[3] Pathology findings demonstrated fibrin thrombi in the microvasculature underlying areas of necrosis.

Discussion | This study found a higher rate of gastrointestinal complications, including mesenteric ischemia, in critically ill patients with COVID-19 compared with propensity score–matched patients without COVID-19, suggesting a distinct phenotype for COVID-19 compared with conventional ARDS. High expression of angiotensin-converting enzyme 2 receptors along the epithelial lining of the gut that act as host-cell receptors for SARS-CoV-2 could explain involvement of abdominal organs.[5] Higher opioid requirements and COVID-19–induced coagulopathy may also explain the disproportionately high rate of ileus and ischemic bowel disease.[2] Differences in duration of illness did not seem to explain the differences in gastrointestinal complications. Limitations of this study include the single center and the unavailability of inflammatory markers to use for matching. Further translational studies are warranted to examine the pathophysiology of these findings.

Mohamad El Moheb, MD
Leon Naar, MD
Mathias A. Christensen, BSc
Carolijn Kapoen, BSc
Lydia R. Maurer, MD
Maha Farhat, MD, MSc
Haytham M. A. Kaafarani, MD, MPH

Author Affiliations: Division of Trauma, Emergency Surgery, and Surgical Critical Care, Massachusetts General Hospital, Boston (El Moheb, Naar, Christensen, Kapoen, Maurer, Kaafarani); Division of Pulmonary and Critical Care, Massachusetts General Hospital, Boston (Farhat).

Corresponding Author: Haytham M. A. Kaafarani, MD, MPH, Harvard Medical School, Division of Trauma, Emergency Surgery, and Surgical Critical Care, 165 Cambridge St, Ste 810, Boston, MA 02114 (hkaafarani@mgh.harvard.edu).

Accepted for Publication: September 14, 2020.

Published Online: September 24, 2020. doi:10.1001/jama.2020.19400

Correction: This article was corrected on March 16, 2021, to fix the median (interquartile range) days on opioid drip reported in the Table for patients with acute respiratory distress syndrome with and without COVID-19.

Author Contributions: Dr Kaafarani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: El Moheb, Naar, Christensen, Maurer, Kaafarani.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: El Moheb, Farhat, Kaafarani.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: El Moheb, Naar, Christensen, Maurer, Farhat, Kaafarani.
Administrative, technical, or material support: Kaafarani.
Supervision: Maurer, Farhat, Kaafarani.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank George Velmahos, MD, PhD, Division of Trauma, Emergency Surgery, and Surgical Critical Care, Massachusetts General Hospital, Boston, for his clinical expertise and advice. Dr Velmahos was not compensated for his contributions.

1. Hirsch JS, Ng JH, Ross DW, et al; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98(1):209-218. doi:10.1016/j.kint.2020.05.006

2. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7(6):e438-e440. doi:10.1016/S2352-3026(20)30145-9

3. Kaafarani HMA, El Moheb M, Hwabejire JO, et al. Gastrointestinal complications in critically ill patients with COVID-19. *Ann Surg*. 2020;272(2):e61-e62. doi:10.1097/SLA.0000000000004004

4. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.

5. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun*. 2020;526(1):135-140. doi:10.1016/j.bbrc.2020.03.044

Preprint Servers' Policies, Submission Requirements, and Transparency in Reporting and Research Integrity Recommendations

Preprint servers are online platforms that enable free sharing of preprints, scholarly manuscripts that have not been peer reviewed or published in a traditional publishing venue (eg, journal, conference proceeding, book). They facilitate faster dissemination of research, soliciting of feedback or collaborations, and establishing of priority of discoveries and ideas.[1] However, they can also enable sharing of manuscripts that lack sufficient quality or methodological details necessary for research assessment, and can help spread unreliable and even fake information.[2] Since 2010, more than 30 new preprint servers have emerged, yet research on preprint servers is still scarce.[3] With the increase in the numbers of preprints and preprint servers, we explored servers' policies, submission requirements, and transparency in reporting and research integrity recommendations, as the latter are often perceived as mechanisms by which academic rigor and trustworthiness are fostered and preserved.[4]

Editorial page 1840

Related article page 1903

Supplemental content

Methods | We conducted a cross-sectional analysis of, to the best of our knowledge, all known preprint servers that do not limit posting of manuscripts to authors with specific institutional affiliations or study funding (eg, *Wellcome Open Research*) nor actively seek out peer reviewers (eg, *F1000*) (see the eAppendix in the Supplement for server