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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Focusing on Gastrointestinal Symptoms in COVID-19 Is Far From Enough

Dear Editors:

We had great interest in the article by Yael et al.[1] It confirmed that the gastrointestinal symptoms (especially for diarrhea) were common in patients with coronavirus disease-2019 (COVID-19). In comparison with the other reports on this topic,[2,3] this case-control study can provide more significance and credibility owing to the correction of baseline status for gastrointestinal symptoms in non– patients with COVID-19. However, we do have some concerns about it.

First, the setting of the control group was arbitrary. The distribution and detail of various diseases were unclear (lung diseases or others). It may decrease the reliability benefited from case-control study. Second, the evaluation of gastrointestinal symptoms mainly depended on the subjective judgement of patients, which might be inaccurate and misunderstood. It was imperfect that no objective evidence from laboratory or imaging examination confirmed the final conclusion.

Third, huge heterogeneity existed among the nonsevere, severe, and critical groups classified by the COVID-19 guidance.[4] The subgroup analysis was performed on the basis of the ward where the patients with COVID-19 stayed (hospital or intensive care admission). It was a lack of accuracy and rigor for differentiating the condition status in patients with COVID-19. It may neutralize the differences relating to various degrees of COVID-19.

In response to the shortcomings above, our clinical data can provide additional evidence to refine this topic on COVID-19. For balancing the baseline status in control groups, 122 non–COVID-19 pneumonia, 99 lung tumors, and 248 healthy patients participating medical examination, who were definitely determined to not have COVID-19, were randomly recruited for comparative analysis at the corresponding period. In Renmin Hospital of Wuhan University (January to March, 2020), 148 patients with COVID-19 with their information about gastrointestinal symptoms and fecal examination were recruited. Informed consent was waived for this minimal risk study approved by the ethics committee. For adding the objective evidence, the gastrointestinal symptoms and fecal examination results were simultaneously collected and analyzed. It was observed that the incidence of diarrhea in the COVID-19 pneumonia group was significantly higher than that of non–COVID-19 pneumonia and lung tumor groups (both $P < .01$). In a comparative analysis of fecal examination results, the change of fecal property with accordance to diarrhea was confirmed in the COVID-19 group (all $P < .001$). The erythrocyte, leukocyte and occult blood (OB) in feces can be used as indirect predictors for gastrointestinal damage. After excluding the critical cases from COVID-19 group, the detection rates of erythrocyte, leukocyte, and OB in feces were not higher than those of the control groups (non–COVID-19 pneumonia, lung tumor, and healthy participants).

For a rigorous analysis, the patients in COVID-19 group was divided into 3 subgroups (76 not severe, 55 severe, and 17 critical cases). No significant difference was found (all $P > .05$) in the subgroup analysis (severe vs nonsevere, critical vs noncritical, and survivor vs nonsurvivor) of gastrointestinal symptoms, except for anorexia between survivors and nonsurvivors ($P = .009$). In the subgroup analysis of fecal examination results, the detection rates of leukocytes and OB in feces were only significant different between critical and noncritical group (both $P < .001$). In the survival analysis, the abnormal results of leukocyte and OB in feces were obviously associated with higher mortality risk (log-rank test, $P < .001$). Detailed data are provided in Supplementary Table 1.

More than 80% of patients with COVID-19 are noncritical cases.[5] The risk for abnormal fecal examination (erythrocyte, leukocyte, and/or OB) results in noncritical COVID-19 may be similar to the baseline status of others

lung diseases, but the risk in critical COVID-19 was increased. The appearance of erythrocytes, leukocytes, and OB in feces represented the gastrointestinal damage, and indicated an increased risk of death in case of the exclusion of underlying diseases in the gastrointestinal tract. It is known that gastrointestinal ulcer and bleeding is common in critical patients, especially in those with respiratory failure.[6,7] High possibility of multiple organ dysfunction syndrome in critical COVID-19 cases can increase the risk of secondary damage in gastrointestinal tract, resulting in the occurrence of abnormal fecal examination. Meanwhile, the occurrence of gastrointestinal damage can prompt gastrointestinal dysfunction which accelerate the process from multiple organ dysfunction syndrome to death. Consequently, the abnormal fecal examination results may be used as risk factors of mortality in patients with COVID-19, especially for critical cases.

Among the gastrointestinal symptoms relative to COVID-19, diarrhea is confirmed as the most common one. However, it is not sufficient to simply focus on these gastrointestinal symptoms. For gastrointestinal evaluation, a fecal examination is a simple and economic test that may provide valuable information about gastrointestinal damage and prognostic risk.

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.2020.05.043.

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Reply. We thank Drs Liu, Xiang, and Deng for their correspondence regarding our recent manuscript "Gastrointestinal Symptoms and COVID-19: Case-Control Study from the United States."[1] In their letter titled "Focusing on Gastrointestinal Symptoms in COVID-19 Is Far from Enough," the authors suggest that in patients with coronavirus disease-2019 (COVID-19), stool-based testing for leukocytes and erythrocytes/occult blood, rather than patient-reported gastrointestinal symptoms, should be considered. We reviewed their data with interest but remain unconvinced that stool-based testing adds value to the clinical diagnosis of diarrhea among patients with known or suspected COVID-19.

In our study, conducted among outpatients with respiratory symptoms being evaluated for COVID-19 during the height of the pandemic, the presence of gastrointestinal symptoms (diarrhea or nausea/vomiting) was associated with a 70% increased risk of testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The authors note that control patients in our study—patients who tested negative for COVID-19—were not limited to a specific disease state. This is correct. The primary value of our study is that it demonstrates that the clinical presence of gastrointestinal symptoms can substantially alter the pretest probability of COVID-19 among patients who have not yet been tested and therefore not yet diagnosed with COVID-19 or with other conditions. Multiple other studies have confirmed that gastrointestinal symptoms, either in combination with respiratory disease or alone, are a hallmark of presentation for many patients with COVID-19,[2–4] and widespread awareness of these symptoms now informs decisions regarding whom to test.

We see major barriers to implementing stool-based testing among patients with suspected COVID-19. First, handling these otherwise unnecessary biospecimens might increase risk for spreading of SARS-CoV-2. Second, the stool-based testing described by Liu et al—fecal leukocytes, erythrocytes, and occult blood—is notoriously inaccurate.[5–7] Even within their own data, it is unclear whether such stool markers indicate critical illness from any cause or COVID-19 specifically. Although it seems possible that fecal leukocytes and/or occult blood might help to classify disease severity once COVID-19 is diagnosed, there are already well-

Supplementary Table 1. Clinical Characteristics and Fecal Examinations

	COVID-19 Pneumonia							COVID-19	Non–COVID-19 Pneumonia[e]	Lung Tumor[a]	Healthy Subject[f,g]	*P* Value[h]
	Survivor	Nonsurvivor	*P* Value[m]	Nonsevere	Severe[b]	Critical[c]	*P* value[d]					
Age	56.5 ±15.2	72.8 ± 14.1	<.001	52.9 ± 14.9	60.3 ± 14.6[i]	71.4 ± 13.5[j]	<.001	57.8 ± 15.7	56.9 ± 15.7	56.9 ± 10.9	44.6 ± 12.1[j]	<.001
Sex												
Male	59	8	.12	32	24	11	.237	67	67[i]	43	102	.010
Female	77	4		44	31	6		81	45	56	146	
Discharge status												
Survivor	136	-	NA	76	55	5	<.001	136	-	-	-	NA
Nonsurvivor	-	12		0	0	12		12	-	-	-	
Nausea												
None	133	12	.999	75	53	17	.704	145	110	99	-	.456
Yes	3	0		1	2	0		3	2	0	-	
Emesis												
None	135	12	.999	76	54	17	.486	147	112	99	-	.999
Yes	1	0		0	1	0		1	-	0	-	
Anorexia												
None	115	6	.009	61	49	11	.067	121	87	99[j]	-	<.001
Yes	21	6		15	6	6		27	25	0	-	
Jaundice												
None	135	12	.999	75	55	17	.999	147	112	99	-	.999
Yes	1	0		1	0	0		1	-	0	-	
Abdominal pain												
None	135	11	.156	76	54	16	.098	146	112	99	-	.341
Yes	1	1		0	1	1		2	-	0	-	
Abdominal distension												
None	136	11	.081	76	55	16	.115	147	111	99	-	.999
Yes	0	1		0	0	1		1	1	0	-	
Diarrhea												
None	120	10	.641	68	47	15	.822	130	109[i]	99[j]	-	<.001
Yes	16	2		8	8	2		18	3	0	-	
Gastrointestinal symptoms												
None	101	5	.039	55	41	10	.445	106	84	99[j]	-	<.001
Yes	35	7		21	14	7		42	28	0	-	
Stool color												
Yellow	133	7	<.001	74	54	12[j]	.001	140	110	97	137	.468
Brown	3	2		2	1	2		5	2	2	1	
Dark green	0	1		0	0	1		1	0	0	0	
Dark red	0	2		0	0	2		2	0	0	0	

Supplementary Table 1. Continued

	COVID-19 Pneumonia							COVID-19	Non–COVID-19 Pneumonia[e]	Lung Tumor[a]	Healthy Subject[f,g]	*P* Value[h]
	Survivor	Nonsurvivor	*P* Value[m]	Nonsevere	Severe[b]	Critical[c]	*P* value[d]					
Stool property												
Soft	124	5	<.001	69	51	9[j]	.001	129	84[j]	82[j]	116[j]	<.001
Half loose	0	0		0	0	0		-	20	13	21	
Loose	9	4		5	4	4		13	8	4	1	
Watery	0	2		0	0	2		2	0	0	0	
Mushy	2	1		2	0	1		3	0	0	0	
Mucoid	1	0		0	0	1		1	0	0	0	
Leukocyte												
None	134	9	.004	75	55	13[j]	.001	143	111	98	138	.096
Yes	2	3		1	0	4		5	1	1	0	
Erythrocyte												
None	136	11	.081	76	55	16	.115	147	112	98	138	.574
Yes	0	1		0	0	1		1	0	1	0	
Lipid droplet												
None	136	12	NA	76	55	17	NA	148	110	93[i]	127[j]	<.001
Yes	-	-		-	-	-		0	2	6	11	
Yeast-like fungi												
None	136	12	NA	76	55	17	NA	148	105[i]	98	137	.001
Yes	-	-		-	-	-		0	7	1	1	
Stool OB[k]												
None	112	4	<.001	61	48	7[j]	<.001	116	92[l]	83	188	.033
Weakly positive	3	0		2	0	1		3	12	8	9	
Positive	1	5		0	1	5		6	7	8	13	
Strongly positive	0	3		0	0	3		3	0	0	0	

COVID-19, coronavirus disease-2019.
[a]Statistical comparison between COVID-19 group and lung tumor group.
[b]Statistical comparison between the nonsevere and severe cases in COVID-19 group.
[c]Statistical comparison between the critical subgroup and noncritical subgroup (mild and severe cases) in patients with COVID-19.
[d]Statistical comparison among the mild, severe, and critical cases in COVID-19 group.
[e]Statistical comparison between COVID-19 group and non–COVID-19 pneumonia group.
[f]There were 248 healthy subjects who received 210 fecal OB tests and 138 stool tests.
[g]Statistical comparison between COVID-19 group and healthy subjects.
[h]Statistical comparison among COVID-19, non–COVID-19 pneumonia, lung tumor and healthy subjects.
[i]$P < .01$.
[j]$P < .001$.
[k]Twenty patients with COVID-19 and 1 non–COVID-19 pneumonia patients did not have stool OB test.
[l]$P < .05$.
[m]Statistical comparison between survivor group and nonsurvivor group.