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# RESEARCH CORRESPONDENCE

## COVID-19 Digestive System Involvement and Clinical Outcomes in a Large Academic Hospital in Milan, Italy

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Since February 2020, the COVID-19 pandemic has spread to Italy affecting more than 100,000 people. Several studies have reported a high prevalence of gastrointestinal (GI) symptoms, and investigated their potential association with clinical outcomes.[1] The timing, clinical significance, and possible impact on viral spread of GI symptoms presentation have not been fully elucidated. Elevation of liver function tests and other laboratory values has also been reported; however, their prognostic significance has not been clearly established.[2]

We analyzed a cohort of reverse-transcriptase polymerase chain reaction–confirmed COVID-19 patients[3] consecutively admitted to Humanitas Hospital, Milan, Italy, to describe the prevalence of GI symptoms and GI/liver tests abnormalities, and their association with clinical outcomes.

### Methods

Clinical and laboratory data were extracted from electronic medical records. Presence of vomit and diarrhea (defined as passing of 3 or more loose stools per day) as reported at admission or during the week preceding admission were recorded as per electronic medical records. To explore the associations between GI clinical and laboratory parameters with clinical deterioration we used survival model for censored observations. The composite study end point was clinical deterioration defined as intensive care unit (ICU) transfer or death within 20 days of hospital admission. Time to event was defined as the time from hospital admission until the date of event or censoring. We used log-rank tests and Cox regression analysis. Missing data were not imputed. We presented hazard ratios with 95% confidence intervals (CI).

### Results

From February 22 to March 30, 2020, 325 reverse-transcriptase polymerase chain reaction–confirmed COVID-19 patients had been admitted to the Humanitas Research Hospital. The analysis was restricted to 292 patients, after excluding those who were transferred to the ICU, or died, within the first day. Patients were predominantly males (68.2%) with a mean age of 65.0 ± 14.1 years. Diarrhea (27.1%) was the most frequent GI symptom. Patients' characteristics are summarized in Table 1.

As of March 30, 129 patients (44.2%) had been discharged, and 107 (36.6%) were still hospitalized. Clinical deterioration occurred in 82 patients (28.1%), including 27 (9.2%) patients who were transferred to ICU, and 56 (19.2%) who died.

Among admission parameters, the presence of any GI symptom (ie, diarrhea or vomit), and alkaline phosphatase, total bilirubin, direct bilirubin, and lipase levels were significantly associated with ICU transfer or death in the univariable analyses (Supplementary Table 1). Of these, the occurrence of any GI symptom (adjusted hazard ratio [aHR], 0.47; 95% CI, 0.23–0.97; $P = .041$), alkaline phosphatase levels (aHR, 1.14; 95% CI, 1.05–1.23, per 100 U/L increase; $P = .001$) and high lipase

[a]A list of investigators in the Humanitas COVID-19 Task Force is provided in the Supplementary Appendix

*Abbreviations used in this paper:* aHR, adjusted hazard ratio; CI, confidence interval; GI, gastrointestinal; ICU, intensive care unit.

Most current article


1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.05.011

**Table 1.** Association Between Clinical and Laboratory Gastrointestinal Parameters of Hospitalized COVID-19 Patients (n = 292) and Clinical Deterioration Leading to ICU Transfer or Death Adjusted by Age and Gender

| | | Cox proportional hazards analysis | | |
|---|---|---|---|---|
| | Mean ± SD or n (%) | Adjusted[a] HR | 95% CI | *P* value |
| Demographic characteristics | | | | |
| Age, *y* | 65.0 ± 14.1 | — | — | — |
| ≥65 | 161/292 (55.1) | | | |
| <65 | 131/292 (44.9) | | | |
| Gender | | — | — | — |
| Female | 93/292 (31.8) | | | |
| Male | 199/292 (68.2) | | | |
| Gastrointestinal symptoms | | | | |
| Diarrhea | 69/255 (27.1) | 0.79 | 0.42–1.46 | .45 |
| Vomit | 11/274 (4.0) | — | — | — |
| Any gastrointestinal symptom (ie, diarrhea or vomit) | 69/245 (28.2) | 0.47 | 0.23–0.97 | **.041** |
| Blood biochemistry | | | | |
| Alanine aminotransferase ≥50 *U/L* | 54/292 (18.5) | 1.11 | 0.60–2.04 | .74 |
| Aspartate aminotransferase ≥50 *U/L* | 78/292 (26.7) | 1.30 | 0.81–2.08 | .28 |
| γ-Glutamyl transpeptidase ≥55 *U/L* | 102/282 (36.2) | 1.45 | 0.91–2.30 | .12 |
| Alkaline phosphatase ≥150 *U/L* | 27/280 (9.6) | 1.62 | 0.87–3.00 | .13 |
| Total bilirubin ≥1.2 *mg/dL* | 31/292 (10.6) | 1.39 | 0.76–2.56 | .29 |
| Direct bilirubin ≥0.3 *mg/dL* | 70/283 (24.7) | 1.52 | 0.94–2.44 | .084 |
| Indirect bilirubin ≥1.1 *mg/dL* | 16/269 (6.0) | 1.28 | 0.51–3.20 | .60 |
| Amylase ≥100 *U/L* | 43/288 (14.9) | 1.54 | 0.88–2.72 | .13 |
| Lipase ≥68 *U/L* | 28/249 (11.2) | 2.02 | 1.08–3.80 | **.028** |

NOTE. Boldface indicates statistically significant P values.
CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; SD, standard deviation.
[a]Adjusted for age and gender.

levels (aHR, 2.02; 95% CI, 1.08–3.80; $P = .028$) remained significant after adjustment for age and sex (Supplementary Table 1). Importantly, the presence of GI symptoms was inversely associated with the risk of clinical deterioration, whereas higher levels of alkaline phosphatase and lipase predicted a poor prognosis.

## Discussion

In a cohort of COVID-19 admitted patients, we found a high prevalence of GI symptoms. Interestingly, the presence of diarrhea or vomit was associated with a better prognosis, independently of patient age and sex. It is worth noting that we excluded patients admitted in critical conditions in whom a detailed medical history about GI symptoms was not adequately assessed. Our findings could be explained by a prevalent GI viral localization rather than respiratory. GI tropism of SARS-CoV2 has been demonstrated in a recent study that detected SARS-CoV2 more frequently in the stools of patients presenting with diarrhea.[4,5]

We also found that elevated lipase and alkaline phosphatase levels were associated with poor prognosis; whether this reflects a greater systemic inflammatory response or an early sign of multiorgan failure needs to be ascertained.[6] Because angiotensin-converting enzyme-2 receptors are highly expressed by pancreatic islets, a possible direct cytopathic injury seems likely.[6] The action of Sars-CoV on the pancreas through these receptors can induce acute hyperglycemia and transient type-2-diabetes,[7] possibly leading to further complications and poor prognosis. The correlation we observed with alkaline phosphatase is intriguing because angiotensin-converting enzyme-2 receptors are also abundantly expressed on endothelial liver cells, which makes liver a potential target for SARS-CoV.[8] However, liver biopsies of patients with COVID-19 have not shown signs of biliary tract damage or cholestasis, thus we cannot exclude that high alkaline phosphatase reflects bone diseases and systemic frailty.

In conclusion, we observed that biochemical elevations of liver and GI tests and GI symptoms are common at presentation in hospitalized patients with COVID-19, with high lipase and alkaline phosphatase levels and the absence of vomit/diarrhea predicting poor clinical outcomes.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.05.011.

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**Conflicts of interest**
The authors disclose no conflicts.

**Supplementary Appendix.** Humanitas Covid-19 Task Force

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**Supplementary Table 1.** Association of Gastrointestinal Clinical and Laboratory Parameters With Clinical Deterioration Leading to ICU Transfer or Death in Hospitalized COVID-19 Patients

| | Log-rank test | | Cox proportional hazards analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| Gastrointestinal characteristics at admission | Chi-square (d.f.) | *P* value | Crude HR | (95% CI) | *P* value | Adjusted[a] HR | (95% CI) | *P* value |
| Gastrointestinal symptoms | | | | | | | | |
| Diarrhea | 2.88 (1) | .089 | 0.60 | 0.33–1.10 | .097 | 0.79 | 0.42–1.46 | .45 |
| Vomit | 3.62 (1) | .057 | — | — | — | — | — | — |
| Any gastrointestinal symptom (ie, diarrhea or vomit) | 8.53 (1) | **.004** | 0.37 | 0.18–0.75 | **.006** | 0.47 | 0.23–0.97 | **.041** |
| Blood biochemistry | | | | | | | | |
| Alanine aminotransferase (per 10 *U/L* increase) | — | — | 1.01 | 0.95–1.07 | .87 | 1.03 | 0.98–1.08 | .19 |
| Alanine aminotransferase (≥50 vs <50 *U/L*) | 0.36 (1) | .55 | 0.84 | 0.46–1.51 | .56 | 1.11 | 0.60–2.04 | .74 |
| Aspartate aminotransferase (per 10 *U/L* increase) | — | — | 1.03 | 0.99–1.08 | .12 | 1.04 | 0.997–1.09 | .065 |
| Aspartate aminotransferase (≥50 vs <50 *U/L*) | 1.22 (1) | .27 | 1.30 | 0.81–2.08 | .28 | 1.30 | 0.81–2.08 | .28 |
| γ-Glutamyl transpeptidase (per 100 *U/L* increase) | — | — | 1.16 | 0.96–1.41 | .13 | 1.20 | 0.98–1.46 | .074 |
| γ-Glutamyl transpeptidase (≥55 vs <55 *U/L*) | 1.11 (1) | .29 | 1.27 | 0.81–2.01 | .30 | 1.45 | 0.91–2.30 | .12 |
| Alkaline phosphatase (per 100 *U/L* increase) | — | — | 1.14 | 1.06–1.23 | **< .001** | 1.14 | 1.05–1.23 | **.001** |
| Alkaline phosphatase (≥150 vs <150 *U/L*) | 3.90 (1) | **.048** | 1.83 | 0.99–3.39 | .055 | 1.62 | 0.87–3.00 | .13 |
| Total bilirubin (per 1 *mg/dL* increase) | — | — | 1.11 | 1.00–1.23 | **.048** | 1.12 | 0.998–1.25 | .054 |
| Total bilirubin (≥1.2 vs <1.2 *mg/dL*) | 3.26 (1) | .071 | 1.70 | 0.94–3.08 | .079 | 1.39 | 0.76–2.56 | .29 |
| Direct bilirubin (per 1 *mg/dL* increase) | — | — | 1.16 | 0.96–1.40 | .12 | 1.18 | 0.96–1.44 | .11 |
| Direct bilirubin (≥0.3 vs <0.3 *mg/dL*) | 9.04 (1) | **.003** | 1.96 | 1.25–3.09 | **.004** | 1.52 | 0.94–2.44 | .084 |
| Indirect bilirubin (per 1 *mg/dL* increase) | — | — | 1.04 | 0.63–1.72 | .87 | 1.08 | 0.65–1.78 | .76 |
| Indirect bilirubin (≥1.1 vs <1.1 *mg/dL*) | 0.02 (1) | .88 | 1.07 | 0.43–2.65 | .89 | 1.28 | 0.51–3.20 | .60 |
| Amylase (per 10 *U/L* increase) | — | — | 1.04 | 0.98–1.10 | .23 | 1.04 | 0.98–1.11 | .17 |
| Amylase (≥100 vs <100 *U/L*) | 2.52 (1) | .11 | 1.56 | 0.89–2.74 | .12 | 1.54 | 0.88–2.72 | .13 |
| Lipase (per 10 *U/L* increase) | — | — | 1.06 | 1.00–1.13 | .051 | 1.07 | 1.002–1.15 | **.042** |
| Lipase (≥68 vs <68 *U/L*) | 4.89 (1) | **.027** | 1.98 | 1.06–3.71 | **.033** | 2.02 | 1.08–3.80 | **.028** |

NOTE. Boldface indicates statistically significant *P* values.
CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; SD, standard deviation.
[a]Adjusted for age and gender.