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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
RESEARCH CORRESPONDENCE

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

Alessio Aghemo,*,‡ Daniele Piovani,†‡§ Tommaso Lorenzo Parigi,‡ Enrico Brunetta,‖ Nicola Pugliese,† Edoardo Vespa,‡ Paolo Dario Omodei,¶ Paoletta Pretoni,¶ Ana Lleo,*,‡ Alessandro Repici,‡,# Antonio Voza,‡ Maurizio Cecconi,‡,‡‡ Alberto Malesci,‡,¶ Stefanos Bonovas,†,§ and Silvio Danese,‡,§ for the Humanitas COVID-19 Task Forcea

*Division of Internal Medicine and Hepatology, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; †Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; ‡IBD Center, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; ¶Department of Internal Medicine, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; ‖Division of Gastroenterology, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; #Endoscopy Unit, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; **Emergency Department, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; and ‡‡Department of Anaesthesia and Intensive Care Medicine, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy

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. 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.

We analyzed a cohort of reverse-transcriptase polymerase chain reaction–confirmed COVID-19 patients 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

*© 2020 by the AGA Institute
1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.05.011

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
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.\(^1\)\(^2\)\(^3\)\(^4\) \(^5\) 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.

**References**

1. Zhou Z, Zhao N, Shu Y, et al. Journal pre-proof effect of gastrointestinal symptoms on patients infected with COVID-19. 2020. Available at: https://doi.org/10.1053/j.gastro.2020.03.020. Accessed April 6, 2020.
2. Zhang C, Shi L, Wang F. Liver injury in COVID-19: management and challenges. Lancet 2020;10:2019–2021. Available at: https://doi.org/10.1016/S2468-1253(20)30057-1. Accessed April 6, 2020.

3. Cecconi M, Piovani D, Brunetta E, et al. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for COVID-19 infection in Lombardy, Italy. J Clin Med 2020; 9:E1548.

4. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. Available at: http://www.ncbi.nlm.nih.gov/pubmed/32142773. Accessed April 6, 2020.

5. Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong Cohort and systematic review and meta-analysis. Gastroenterology 2020;pii:S0016-5085(20)30448-0.

6. Wang F, Wang H, Fan J, et al. Pancreatic injury patterns in patients with COVID-19 pneumonia. Gastroenterology. Available at: http://www.ncbi.nlm.nih.gov/pubmed/32247022. Accessed April 6, 2020.

7. Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–199.

8. Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int. https://doi.org/10.1111/liv.14435. Accessed April 6, 2020.

Reprint requests
Address requests for reprints to: Alessio Aghemo, MD, PhD, Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele 20090, Milan, Italy. e-mail: alessio.aghemo@hunimed.eu; fax: (+39) 0282242591.

Conflicts of interest
The authors disclose no conflicts.
**Supplementary Appendix. Humanitas Covid-19 Task Force**

| ACCORNERO         | STEFANO          |
|-------------------|------------------|
| AGHEMO            | ALESSIO          |
| ALI               | HUSSAM           |
| ANGELINI          | CLAUDIO          |
| ARCARI            | IVAN             |
| AROSIO            | PAOLA            |
| AZZOLINI          | ELENA            |
| BACCARIN          | ALESSANDRA       |
| BADALAMENTI       | SALVATORE        |
| BAGGIO            | SARA             |
| BARBAGALLO        | MICHELA          |
| BARBERI           | CATERINA         |
| BARBIC            | FRANCA           |
| BARBIERI          | VIVIANA          |
| BARBONE           | ALESSANDRO       |
| BASCIU            | ALESSIO          |
| BOCCIOLONE        | MONICA           |
| BOREA             | FEDERICA         |
| BORRONI           | MARIO            |
| BRESCIANI         | GIANLUIGI        |
| BRUNETTA          | ENRICO           |
| BULLETTI          | CINZIA           |
| CADONATI          | CRISTINA         |
| CALABRO'          | LORENZO          |
| CALATRONI         | MARTA            |
| CALVETTA          | ALBANIA ANTONIETTA |
| CANNATA           | FRANCESCO        |
| CANZIANI          | LORENZO          |
| CAPRETTI          | GIOVANNI LUIGI   |
| CARLANI           | ELISA            |
| CARRONE           | FLAMINIA         |
| CASANA            | MADDALENA        |
| CECCONI           | MAURIZIO         |
| CERIOTTI          | CARLO            |
| CICCARELLI        | MICHELE          |
| CIMINO            | MATTEO           |
| CIUFFINI          | LEONARDO         |
| COLAIuzzi         | CHIARA           |
| COLAPIETRO        | FRANCESCA        |
| COSTA             | GUIDO            |
| COZZI             | OTTAVIA          |
| CRAVIOTTO         | VINCENZO         |
| CRESPI            | CHIARA           |
| Crippa            | MASSIMO          |
| DA RIO            | LEONARDO         |
| DAL FARRA         | SARA             |
| D'ANTONIO         | FEDERICA         |
| DE AMBROGGI       | GUIDO            |
| DE DONATO         | MASSIMO          |
| DE LUCIA          | FRANCESCA        |
| DE SANTIS         | MARIA            |
| DELLE ROSE        | GIACOMO          |
| DI PILLA          | MARINA           |
| DIPAOLO           | FRANCA           |
| DIPASQUALE        | ANDREA           |
| DIPASQUALE        | ANGELO           |
| DROANDI           | GINEVERA         |
| FAZIO             | ROBERTA          |
| FERRANTE          | GIUSEPPE         |
| FERRARA           | ELISA CHIARA     |
| FERRARI           | MATTEO CARLO     |
| FERRI             | SEBASTIAN        |
| FOLCI             | MARCO            |
| FORESTI           | SARA             |
| FRANCHI           | ELOISA           |
| Supplementary Appendix. Continued | Supplementary Appendix. Continued |
|----------------------------------|----------------------------------|
| FRAOLINI ELIA                   | TESTONI LUCIA                   |
| FUGAZZA ALESSANDRO             | TORDATO FEDERICA               |
| FURFARO FEDERICA               | TRABUCCO ANGELA                |
| GALIMBERTI PAOLA               | ULIAN LUISA                    |
| GALTIERI ALESSIA PIERA         | VALENTINO ROSSELLA            |
| GAVAZZI FRANCESCA              | VALENTE ROSSELLA              |
| GENERALI ELENA                 | VENET WALTER                   |
| GOLETTI BENEDETTA              | VERLINGERI SIMONA              |
| GUIDELLI GIACOMO               | VESPAREDO ANTONIO              |
| JACOBS FLAVIA                  | ZANUSO VALENTINA              |
| KURIHARA HAYATO                | ZILLI ALESSANDRA              |
| LAGIOIA MICHELE                |                                |
| LIBRE' ANNA                    |                                |
| LOJAcono FERDINANDO            |                                |
| LUGHEZZANI GIOVANNI            |                                |
| MACCALLINI MARTA              |                                |
| MAIORINO ALFONSO FRANCESCO    |                                |
| MALESCI ALBERTO                |                                |
| MANTOVANI RICCARDO            |                                |
| MARCHETTINI DAVIDE            |                                |
| MARINELLO ARIANNA              |                                |
| MARKOPOULOS NIKOLAOS          |                                |
| MASETTI CHIARA                |                                |
| MILANI ANGELO                  |                                |
| MIRANI MARCO                   |                                |
| MORELLI PAOLA                  |                                |
| MOTTAP  FRANCESCA             |                                |
| MUNDULA VALERIA               |                                |
| NIGRO MATTIA                   |                                |
| OMODEI PAOLO                  |                                |
| ORMAS MONICA                  |                                |
| PAGLIARO ARIANNA              |                                |
| PALIOTTI ROBERTA              |                                |
| PARIGI TOMMASO LORENZO        |                                |
| PEDALE ROSA                   |                                |
| PEGORARO FRANCESCO            |                                |
| PELLEGATTA GAIA              |                                |
| PELLEGRINO MARTA              |                                |
| PETRIELLO GENNARO              |                                |
| PICCINI SARA                  |                                |
| POCATERRE DARTA               |                                |
| POLIANI LAURA                 |                                |
| PREATONI PAOLETTA             |                                |
| PROCIOPI FABIO                |                                |
| PUGGIONI FRANCESCA            |                                |
| PUGLIESE LUCA                 |                                |
| RACCA FRANCESCA               |                                |
| RANDAZZO MICHELE              |                                |
| REGAZZOLI LANCINI             |                                |
| REGGIANI FRANCESCO           |                                |
| RODOLFI STEFANO               |                                |
| RUONGO LIDIA                  |                                |
| SACCO CLARA                   |                                |
| SAVI MARZIA                   |                                |
| SCARFO ISIDE                  |                                |
| SHIFFER DANA                  |                                |
| SICOLI FEDERICO               |                                |
| SOLANO SIMONE                 |                                |
| SOLITANO VIRGINIA             |                                |
| STAINER ANNA                  |                                |
| STELLA MATTEO CARLO           |                                |
| STRANGI GIUSEPPE              |                                |
| TAORMINA ANTONIO              |                                |
## Supplementary Table 1. Association of Gastrointestinal Clinical and Laboratory Parameters With Clinical Deterioration Leading to ICU Transfer or Death in Hospitalized COVID-19 Patients

| Gastrointestinal characteristics at admission | Log-rank test | Cox proportional hazards analysis |
|-----------------------------------------------|--------------|----------------------------------|
|                                               | 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   | .055     | 0.84 0.46–1.51          | .615     |
| Alanine aminotransferase ($\geq 50 <$50 U/L) | 0.36 (1)    | .55      | 0.84 0.46–1.51   | .56      | 1.11 0.60–2.04          | .74      |
| Aspartate aminotransferase (per 10 U/L increase) | — —         | — —      | 1.03 0.99–1.08   | .12      | 1.04 0.99–1.08          | .065     |
| Aspartate aminotransferase ($\geq 50 <$50 U/L) | 1.22 (1)    | .27      | 1.30 0.81–2.08   | .28      | 1.30 0.81–2.08          | .28      |
| $\gamma$-Glutamyl transpeptidase (per 100 U/L increase) | — —         | — —      | 1.16 0.96–1.41   | .13      | 1.20 0.98–1.46          | .074     |
| $\gamma$-Glutamyl transpeptidase ($\geq 55 <$55 U/L) | 1.11 (1)    | .29      | 1.27 0.81–2.01   | .30      | 1.45 0.91–2.30          | .12      |
| Alkaline phosphatase (per 100 U/L increase)    | — —         | — —      | 1.14 1.06–1.23   | <.001    | 1.14 1.05–1.23          | .001     |
| Alkaline phosphatase ($\geq 150 <$150 U/L)    | 3.90 (1)    | .048     | 1.83 0.99–3.39   | .055     | 1.62 0.87–3.00          | .13      |
| Total bilirubin (per 1 mg/dL increase)         | — —         | — —      | 1.11 1.00–1.23   | .048     | 1.12 0.99–1.25          | .054     |
| Total bilirubin ($\geq 1.2 <$1.2 mg/dL)       | 3.26 (1)    | .071     | 1.70 0.94–3.08   | .079     | 1.39 0.76–2.56          | .29      |
| Direct bilirubin (per 1 mg/dL increase)        | — —         | — —      | 1.16 0.96–1.40   | .12      | 1.18 0.96–1.44          | .11      |
| Direct bilirubin ($\geq 0.3 <$0.3 mg/dL)      | 9.04 (1)    | .003     | 1.96 1.25–3.09   | .004     | 1.52 0.94–2.44          | .084     |
| Indirect bilirubin (per 1 mg/dL increase)      | — —         | — —      | 1.04 0.63–1.72   | .87      | 1.08 0.65–1.78          | .76      |
| Indirect bilirubin ($\geq 1.1 <$1.1 mg/dL)    | 0.02 (1)    | .88      | 1.07 0.43–2.65   | .89      | 1.28 0.51–3.20          | .60      |
| Amylase (per 10 U/L increase)                  | — —         | — —      | 1.04 0.98–1.10   | .23      | 1.04 0.98–1.11          | .17      |
| Amylase ($\geq 100 <$100 U/L)                  | 2.52 (1)    | .11      | 1.56 0.89–2.74   | .12      | 1.54 0.88–2.72          | .13      |
| Lipase (per 10 U/L increase)                   | — —         | — —      | 1.06 1.00–1.13   | .051     | 1.07 1.00–1.15          | .042     |
| Lipase ($\geq 68 <$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.