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.

Authors' contributions

MM and MK contributed equally to formulating the reply.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.06.023.

References

[1] Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73:1063–1071.

[2] El Kassas M, Elbaz T, Elsharkawy A, Omar H, Esmat G. HCV in Egypt, prevention, treatment and key barriers to elimination. Expert Rev Anti Infect Ther 2018;16(4):345–350.

[3] Bonanada C, García-Blasa S, Tarazona-Santabalbinac F, Sanchisa J, Bertomeu-Gonzálezd V, Fácilaf L, et al. The effect of age on mortality in patients with Covid-19: a metanalysis with 611,583 subjects. J Am Med Dir Assoc 2020;21(7):915–918.

[4] Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver Int 2012;32(9):1407–1414.

[5] Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Rep 2020;2:100113.

[6] Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology 2020;72(1):287–304.

Mohammed A. Medhat[1]
Mohamed El Kassas[2,*]
[1]*Tropical Medicine and Gastroenterology Department, Faculty of Medicine, Assiut University, Cairo, Egypt*
[2]*Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt*
[*]Corresponding author. Address: Endemic Medicine Department, Faculty of Medicine, Helwan University, Ain Helwan, Postal code: 11795, Cairo, Egypt. Tel.: +201114455552.
E-mail address: m_elkassas@hq.helwan.edu.eg (M. El Kassas)

Reply to: Correspondence on "High rates of 30-day mortality in patients with cirrhosis and COVID-19"

To the Editor:

We read with interest the letters by Gao *et al.* and Medhat *et al.* on our recently published paper reporting data on the impact of COVID-19 on cirrhotic patients in an Italian multicentre cohort.[1]

Both letters pointed out the limited sample size of our study, which had already been acknowledged as a possible limitation in the discussion section of our paper. So far, no studies have been able to enrol significantly larger cohorts of SARS-CoV-2-infected patients with cirrhosis, although data are warranted to better characterize the natural history of COVID-19 in this setting. However, 2 recent studies seem to confirm our findings. In fact, a single study conducted in North America enrolling 37 patients has confirmed the high mortality rates of patients with cirrhosis and COVID-19, whilst an ongoing international registry has shown a mortality risk similar to ours in 103 patients with cirrhosis.[2,3]

Gao *et al.* raised some concerns regarding the statistical analysis used to predict mortality and suggested that we perform a logistic regression analysis. The logistic regression analysis confirmed that CLIF-OF (odds ratio 1.77; 95% CI 1.24–2.54; $p = 0.002$) and moderate to severe lung failure (odds ratio 1.86; 95% 1.00–3.44; $p = 0.048$) were the only 2 independent predictors of mortality.

Gao and colleagues also suggested that MELD, Child-Pugh and CLIF-OF scores might have been influenced by thromboprophylaxis. However, in our study, these scores were calculated at COVID-19 diagnosis, *i.e.* before thromboprophylaxis was started. As low molecular weight heparin was used in most cases, we do not foresee any significant impact of this treatment on international normalized ratio values.

Regarding the comments by Medhat *et al.*, we acknowledge that patients with cirrhosis and COVID-19 were significantly older than those with cirrhosis without COVID-19. However, at multivariate analysis including both patients with cirrhosis and COVID-19 and those with cirrhosis only, COVID-19 (hazard ratio 3.594; 95% CI 1.465–8.819; $p = 0.005$) and CLIF-OF (hazard ratio 1.369; 95% CI 1.219–1.539, $p \leq 0.0001$) but neither age nor comorbidities, independently predicted mortality. Moreover, at multivariate analysis, the presence of comorbidities did not independently predict mortality in the 50 patients with cirrhosis and COVID-19.

Finally, we agree that acute-on-chronic liver failure (ACLF) was not the cause of death in most of our patients, as respiratory failure accounted for 71% of deaths. However, we demonstrated that the mortality rates were significantly higher in our cohort of patients with cirrhosis than in a control-group of non-cirrhotic patients with COVID-19. Moreover, ACLF at COVID-19 was diagnosed in 14 (28%) patients and both the CLIF-OF and CLIF-C scores independently predicted mortality in our cohort.

These findings suggest that SARS-CoV-2 infection had a precipitating role in causing deterioration in MELD and Child-Pugh scores. Resulting liver failure has been shown to be (in addition to respiratory failure) associated with mortality in these patients.[1] This is not a surprising, given the well-known effects of infections as drivers of liver disease worsening and death in the setting of cirrhosis.

While the real role of interaction between SARS-CoV-2 and ACE-2 receptors in liver cells is yet to be elucidated, we agree that the long-term effects of SARS-CoV-2 on cirrhosis might deserve attention. As suggested by EASL recommendations on

Keywords: Liver transplantation; Hepatocellular carcinoma; SARS-CoV-2; Hepatitis; HBV; HCV.
Received 24 July 2020; accepted 28 July 2020; available online 7 August 2020
https://doi.org/10.1016/j.jhep.2020.08.001

the management of patients with cirrhosis during the SARS-CoV-2 pandemic, we still need to implement systems that enable remote management of patients, to reduce their exposure to risk, as we have already suggested for the management of patients with hepatocellular carcinoma.[4,5]

Conflict of interest

Massimo Iavarone: Speaking/Teaching, consultant and advisory board for Bayer, Gilead Sciences, BMS, Janssen, Ipsen, MSD, BTG-Boston Scientific, AbbVie, Guerbet, EISAI; Roberta D'Ambrosio: teaching and speaking for AbbVie, Gilead, MSD; Advisory Board for AbbVie, MSD, Research Grant from Gilead; Pietro Lampertico: Advisory Board/Speaker Bureau for BMS, Roche, Gilead, GSK, AbbVie, MSD, Arrowhead, Alnylam, Janssen, Spring Bank, MYR, Eiger.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Statistical analysis: Massimo Iavarone, Pietro Lampertico; writing of the article: Massimo Iavarone, Roberta D'Ambrosio and Pietro Lampertico.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.08.001.

References

Author names in bold designate shared co-first authorship

[1] Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73:1063–1071.
[2] Bajaj JS, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared to cirrhosis alone and COVID-19 alone: a multi-center matched cohort. Gut 2020. https://doi.org/10.1136/gutjnl-2020-322118.
[3] **Moon AM**, **Webb GJ**, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry. J Hepatol 2020;73(3):705–708.
[4] Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Rep 2020;2:100113.
[5] Iavarone M, Sangiovanni A, Carrafiello G, Rossi G, Lampertico P. Management of hepatocellular carcinoma in the time of COVID-19. Ann Oncol 2020;31(8):1084–1085.

Massimo Iavarone[1,*]
Roberta D'Ambrosio[1]
Pietro Lampertico[1,2]
On behalf of CirCoV study group[†]
[1]*Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Milan, Italy*
[2]*Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*
[*]Corresponding author. Address: Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F. Sforza 28, 20122 Milan, Italy. Tel.: 39-0255035432, fax: 39-0250320410.
E-mail address: massimo.iavarone@gmail.com (M. Iavarone)

[†] CirCoV study group: M. Iavarone, R. D'Ambrosio, A. Rimondi, P. Lampertico (Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Milan, Italy); A. Soria, P. Bonfanti (Division of Infectious Diseases, San Gerardo Hospital, ASST Monza, University of Milano - Bicocca School of Medicine, Monza, Italy); M. Triolo, S. Fagiuoli (Gastroenterology 1 - Hepatology & Transplantology, ASST Papa Giovanni XXIII, Bergamo, Italy); N. Pugliese, A. Aghemo (Division of Internal Medicine and Hepatology, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano (MI), Italy); P. Del Poggio (Division of Gastroenterology. Policlinico S. Marco, Zingonia – Bergamo, Italy); G. Perricone, L.S. Belli (Hepatology and Gastroenterology Unit, Niguarda Hospital, Milan, Italy); S. Massironi, M. Lucà, P. Invernizzi (Division of Gastroenterology and Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy); A. Spinetti, C. Carriero (Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili General Hospital, Brescia, Italy); E. Buscarini, M. Pedaci (Division of Gastroenterology and Endoscopy, ASST Ospedale Maggiore, Crema, Italy); M. Viganò, M.G. Rumi (Division of Hepatology, Ospedale San Giuseppe, Italy).

Validation of Baveno VI and expanded Baveno VI criteria to identify high-risk varices in patients with MAFLD-related compensated cirrhosis

To the Editor:

Metabolic dysfunction-associated fatty liver disease (MAFLD), as a new entity, is a highly prevalent disease affecting more than one-quarter of the world's population, and is the leading cause of chronic liver disease in the United States and Europe.[1,2] We read with interest the recent article by Eslam and Newsome *et al.*,[1] in which they proposed a new definition for MAFLD-related cirrhosis. MAFLD-related cirrhosis is the result of multiple etiological factors and complex interactions between metabolic dysfunction, poor lifestyle habits and diet, imbalanced microbiota and genetic predisposition.[3–5] MAFLD-related cirrhosis patients with concomitant and disease-modifying etiologies (*e.g.* hepatitis B or C viral infection and alcohol consumption) are likely to have different natural history and response to management compared to those with a single etiology.[6] Due to limited investigations, protocols for screening gastroesophageal varices among patients with MAFLD-related compensated

Received 7 June 2020; received in revised form 19 June 2020; accepted 24 June 2020; available online 21 September 2020
https://doi.org/10.1016/j.jhep.2020.06.042