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.

remained increased (Fig. 1A), on June 11, 2020, the patient began therapy with ursodeoxycholic acid (UDCA; 10 mg/kg). At the last blood exams on September 16, 2020, after 3 months of treatment, GGT and AP were reduced to 144 U/L (normal 1–38) and 155 U/L (normal 38–126), respectively. Transaminases fluctuated during the follow-up period between normal and only slightly increased values.

The supposition of a possible overlap syndrome between PBC and autoimmune hepatitis, advanced during the acute phase, was thereafter excluded based on EASL's revised criteria.[4] On the basis of these results, we hypothesize that SARS-CoV-2 infection could have triggered the expression of PBC and GBS in a genetically predisposed individual already suffering from autoimmune thyroiditis. This hypothesis is further supported by the fact that SARS-CoV-2 is an RNA virus capable of inducing a profound activation of the immune system and also by the previous finding that infection by a human RNA beta-retrovirus, related to the mouse mammary tumor virus, was suggested as a possible trigger for PBC development.[5]

To the best of our knowledge this is the first reported case of PBC developing during or soon after COVID-19. We conclude that the search for anti-mitochondrial autoantibodies should be performed in individuals with elevated GGT and/or AP during SARS-CoV-2 infection, particularly in those with a pre-existing autoimmune disease.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions
Dr Bartoli and Dr Gitto share the co-authorship, they retrieved and analysed the literature and wrote the major part of the case report, Dr Cursaro revised the manuscript, Dr Sighinolfi provided histology data and microscope images and Prof Andreone revised the entire work, largely contributing with the conclusions.

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Alessandra Bartoli[1,2,†]
Stefano Gitto[3,†]
Pamela Sighinolfi[4]
Carmela Cursaro[1]
Pietro Andreone[1,5,*]
[1]*Division of Internal Medicine, Department of Medical and Surgical Sciences, Maternal-Infantile and Adult, University of Modena and Reggio Emilia, Modena, Italy*
[2]*Postgraduate school of Allergy and Clinical Immunology, University of Modena and Reggio Emilia, Italy*
[3]*Division of Internal Medicine, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*
[4]*Division of Pathology, Department of Medical and Surgical Sciences, Maternal-Infantile and Adult, University of Modena and Reggio Emilia, Modena, Italy*
[5]*Chief of Postgraduate School of Allergy and Clinical Immunology, University of Modena and Reggio Emilia, Italy*
[*]Corresponding author: Prof Pietro Andreone, Medicina Interna Metabolico-Nutrizionale, Ospedale Clinicizzato di Baggiovara, Via Pietro Giardini 1355, 41126 Modena, Italy.
E-mail address: pietro.andreone@unimore.it (P. Andreone)

[†] Dr. Alessandra Bartoli and Dr. Stefano Gitto shared co-first authorship.

Impact of the COVID-19 pandemic on HCV elimination in Spain

To the Editor:

We read with great interest the article by Sarah Blach and co-workers[1] investigating the impact of COVID-19 on global hepatitis C elimination efforts. The authors show that over the next 10 years a *1-year delay* scenario related to COVID-19 would result in 44,800 excess hepatocellular carcinoma (HCC) cases globally and 72,300 excess liver-related deaths, relative to a *no delay* scenario. The excess HCC cases and deaths would be among high-income countries.[1]

Spain is one of the 45 high-income countries on the right track to reach HCV elimination by 2030 if the current screening

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and therapy rates are maintained.[2] However, COVID-19 strongly hit the country in March 2020 and continues to date. The first wave from March to June prompted a country-wide lockdown and the second wave has been ongoing since September. During this overall period, there has been a drop in HCV testing, linkage to care, harm reduction programs, and microelimination programs.[3] We aimed to assess the impact of COVID-19 on hepatitis C elimination in Spain.

A previously validated Markov model[4] was adapted to simulate the effect of pandemic-related delays in HCV diagnosis and treatment on future advanced liver-related disease and deaths in the next 10 years. We used the data obtained to evaluate repercussions on the WHO goals by 2030 and to calculate the economic impact regarding healthcare costs (€, 2020).

A cohort of 15,859 patients was analysed comparing two scenarios: the *non-COVID-19* scenario, where all patients would be diagnosed and treated in the first year, 2020, and the *COVID-19* scenario where there would be an 18-month delay from the beginning of 2020 to the end of June 2021 with a view to the expected vaccine availability in mid-2021. The simulation used clinical data from patients with HCV treated with direct-acting antivirals in Spain (January 2019 to August 2020).[5] In the COVID-19 scenario, the number of monthly HCV treatments decreased by between 19% and 84%[5] from early 2020 to June 2021. In addition, it was assumed that patients would be treated in the following year and a half (50% from July 2021 and 50% during 2022), based on the 2019 distribution of patients. Patients with a delay in diagnosis and treatment progressed according to the natural course of the disease. Cohort baseline characteristics (average age and fibrosis) and sustained virological response were taken from published real-world data in Spain.[5]

Fig. 1 shows the results for both scenarios by 2030. An 18-month delay in HCV diagnosis and treatment due to the COVID pandemic in a cohort of 15,859 patients would increase the number of liver-related deaths, HCC, and HCV-related decompensated cirrhosis by 117, 73, and 118 cases, respectively. In economic terms this would translate into a 1.0 M€ cost increase due to decompensated cirrhosis and a 1.3 M€ increase due to HCC. Furthermore, a high number of patients (34 *vs.* 48) would need a liver transplant due to decompensated cirrhosis or HCC. The cost associated with liver transplantation would increase by 2.5 M€ (5.8 *vs.* 8.3) for the total cohort during this period.

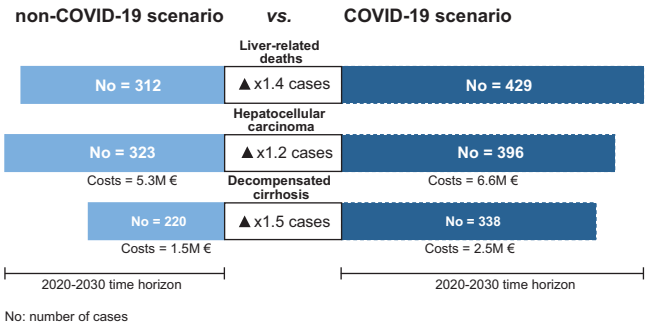

Fig. 1. Impact of the COVID-19-related diagnostic and treatment delay on HCV burden (clinical and economic) over the next 10 years.

The data derived here are based on a simulation with 15,859 patients, but it is estimated that 76,839 people still have active HCV infection in Spain.[6] Thus, if a larger number of patients is affected by the COVID-19 pandemic, the actual clinical and economic impact would be greater.

The data we report were estimated with a different methodology than that used by Blach[1] in her study on the global impact of COVID-19 on hepatitis C elimination. Nonetheless, the findings are similar: delaying HCV elimination programs will be associated with an increase in HCV-related morbidity and mortality in the next 10 years.

Spain was on track for HCV elimination, but the COVID-19 pandemic has hindered efforts to maintain the cascade of care for HCV and many microelimination programs.[7] The excess morbidity and mortality caused by this delay calls for the reinforcement of screening programs, particularly in vulnerable populations and those with more difficult access to primary care physicians.[8] This will be possible if the EASL guidelines for hepatitis C are applied.[9] In summary, hepatitis C elimination must continue to be a political goal and a priority of our health system. The implementation of telehealth, home-delivery services for drugs or HCV screening when COVID tests are performed could minimize the impact of the COVID pandemic on HCV patients and HCV elimination.

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Conflicts of Interest

MB: Advisory Board participant for Gilead and Abbvie. RDH and MAC are employees of Pharmacoeconomics & Outcomes Research Iberia, a consultancy firm specialising in the economic evaluation of healthcare interventions that has received unconditional funding from Gilead Sciences.

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Authors' contributions

All authors contributed equally to the concept and design, to the preparation of the manuscript and read and approved the final manuscript. RDH performed the modelling analyses.

Supplementary data

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Maria Buti[1,*]
Raquel Domínguez-Hernández[2]
Miguel Angel Casado[2]
[1]Liver Unit, Hospital Vall d'Hebron, Barcelona, Spain
[2]Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid, Spain
[*]Corresponding author. Address: Liver Unit, Hospital Vall d`Hebron, Barcelona, Spain.
E-mail address: mbuti@vhebron.net (M. Buti)

NNMT aggravates hepatic steatosis, but alleviates liver injury in alcoholic liver disease

To the Editor:

We congratulate Song *et al.* for their pioneering work in which they revealed a novel pathophysiological role of nicotinamide N-methyltransferase (NNMT) in the development of alcoholic liver disease.[1] Song *et al.* reported that chronic alcohol consumption enhanced hepatic NNMT expression by activating the PERK-ATF4 pathway, 1 of 3 canonical pathways activated in response to endoplasmic reticulum stress. Furthermore, the study showed that upregulated NNMT expression was concomitant with incremental hepatic 1-methylnicotinamide (1-MNA) content (a product of NNMT-catalyzed reaction), indicative of enhanced enzymatic activity. Importantly, their data demonstrated that NNMT knockdown inhibited hepatic *de novo* lipogenesis and ameliorated alcohol-induced hepatic steatosis.[1] Although it has been documented that NNMT activation is associated with fatty liver development in high-fat diet (HFD)-fed mice[2] and genetic knockdown of *NNMT* improved hepatic steatosis in HFD-induced obese mice,[3] this is the first study which links hepatic NNMT overactivation to the pathogenesis of alcoholic fatty liver development. In support of their results, we observed that NNMT overexpression exacerbated liver triglyceride (TG) deposition in an alcohol-fed global NNMT overexpression mouse model, which was generated by microinjection of linearized transgene into C57BL/6J fertilized eggs (Fig. 1A-B).

In mechanistic investigations, Song *et al.* found that, although NNMT knockdown blunted the alcohol-induced reduction of hepatic NAD^+ content, the inhibitory effect of NNMT knockdown on *de novo* lipogenesis was NAD^+-independent. This observation is different to those from the HFD-feeding model.[2] Although the authors implied that increased hepatic 1-MNA derived from NNMT activation may contribute to hepatic fat deposition,[1] they did not provide further evidence to support this. To complement their data, we conducted 1-MNA supplementation experiments in alcohol-fed mice and found that 1-MNA intervention significantly enhanced hepatic lipid accumulation (Fig. 1C). Similarly, in cultured AML-12 hepatocytes, 1-MNA aggravated oleic acid-induced hepatic TG accumulation (Fig. 1D). Unexpectedly, we observed that, contrary to its adverse effect on TG accumulation, 1-MNA supplementation alleviated liver injury induced by chronic alcohol feeding (Fig. 1E-G). These data prompted us to speculate that NNMT activation may differentially regulate liver TG accumulation and hepatotoxicity. To test our hypothesis, we conducted more measurements in NNMT-overexpressing mice exposed to an alcohol-containing diet and observed that NNMT overexpression alleviated liver injury (Fig. 1H-J). Similarly, transgenic NNMT overexpression weakly reduced plasma alanine aminotransferase levels in HFD-fed mice with nicotinamide supplementation.[2] This evidence collectively implies that NNMT upregulation aggravates hepatic steatosis but alleviates liver injury.

The reason for the differential regulation of NNMT on hepatic lipid metabolism and injury is unclear; however, it is unequivocal that increasing TG synthesis is protective against non-esterified free fatty acid-induced lipotoxicity.[4] Genetically silencing diacylglycerol acyltransferase 2, an essential enzyme catalyzing the final step in hepatocyte triglyceride biosynthesis, strongly alleviated hepatic steatosis, but exacerbates liver damage and fibrosis.[5] Similar results were observed in methionine choline-deficient diet-fed mice with interleukin-6 signaling blockade and CD18 mutations.[6,7] To further confirm this notion, we established a stable NNMT-overexpressing hepatocyte model by transfecting human NNMT into HepG2 cells; we observed that NNMT overexpression reversed palmitate-induced cell death (Fig. 1K). In support of our findings, overexpressing NNMT prevented, while knocking-down NNMT aggravated, palmitate-induced lipotoxicity in renal cells.[8]

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