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.

JOURNAL OF HEPATOLOGY

SARS-CoV-2 massive testing: A window of opportunity to catch up with HCV elimination

To the Editor:

The 69th World Health Organization's assembly approved in 2016 a global strategy for eliminating viral hepatitis, as a threat to public health, by 2030.[1] Since then, great progress has been made in reducing the impact of viral hepatitis, particularly in relation to HCV.

The effects of achieving viral cure are countless, at both individual and population levels. In this regard, we read with great interest the work published by Calvaruso & Craxi,[2] explaining precisely the present, long-term and expected benefits induced by direct-acting antivirals (DAAs). Furthermore, as a consequence of the massive treatment with DAAs, Forns' group foresees a very optimistic scenario: cirrhosis related to HCV will be a marginal cause of hospital admissions in the near future.[3] Unfortunately, the pandemic caused by SARS-CoV-2 endangers these remarkable advances. In fact, the first wave of the COVID-19 pandemic overwhelmed healthcare systems around the world, with far-reaching consequences.[4] Along this line, Blach *et al.*[5] modeled the devastating consequences of delaying HCV elimination programs. This delay will be reflected in an increase of HCV-related mortality, both as consequence of cirrhosis complications and hepatocellular carcinoma (HCC) development. A single-year delay may result in an excess of 70,000 liver-related deaths and 44,000 excess HCC diagnoses.

The COVID-19 crisis has forced the diversion of the majority of healthcare resources towards the care of infected patients, impacting the management of those with other conditions. A clear example is patients infected with HCV.[6] Unfortunately, the closure of harm reduction centers, cancellation of elimination programs and medical consultations, as well as reduced access to healthcare centers, is decreasing the rate of HCV diagnoses. In fact, in a recent survey evaluating the impact of COVID-19 on viral hepatitis, up to 64% of participants reported it being impossible to access viral testing, with the closure of testing facilities being the main cause in the United States.[7] Consequently, this diagnostic delay will be translated into a delay in treatment initiation, whose consequences have been predicted by Blach *et al.*,[5] and have been seen in the past.[8]

Nowadays, asymptomatic carriers appear to be the most likely spreaders of the SARS-CoV-2. Thus, massive population-level testing is warranted, since home confinement – and re-confinement – cannot be long-lasting measures. Therefore, the vast majority of people should probably undergo SARS-CoV-2 testing. This provides a golden opportunity to catch up with HBV control and HCV elimination. Patients that must already attend healthcare facilities for SARS-CoV-2 testing, could also be screened for HCV and HBV, in a single visit. Integrating HCV detection programs[9] into SARS-CoV-2 testing will likely have a very small economic cost, with the potential to be hugely profitable down the line. Since COVID-19 may induce liver damage, albeit rarely, and the current viral armamentarium includes multiple potentially hepatotoxic drugs, HBV and HCV screening could be important in the management of patients with suspected SARS-CoV-2 infection. Furthermore, SARS-CoV-2 and hepatitis tests could be easily performed at the same time by means of point-of-care techniques, using saliva assays or dried blood spots, preventing further redundant analyses. Thus, establishing integrated diagnostic circuits may prevent unnecessary repeat sampling.

We are aware of the enormous resource burden caused by the pandemic. However, it is our duty to provide adequate care for non-COVID-19 patients. In fact, if their conditions remain undiagnosed as a consequence of the reintroduction of restrictive policies, their prognosis may be dismal. For this reason, and in agreement with adapting the cascade-of-care to the new coronavirus situation recommended by the EASL-ESCMID in their last position document,[10] we believe that mass and combined detection of SARS-CoV-2, HBV and HCV would allow us to respond simultaneously to several public health problems with minimal cost. As a matter of fact, this policy would keep us on track for viral elimination by 2030.

Therefore, in accordance with Wingrove *et al.*,[9] we consider that i) HCV and HBV status should be assessed in every patient undergoing SARS-CoV-2 testing; 2) HCV elimination programs should be restarted as soon as possible, especially in vulnerable populations, where the impact of the interruption of HCV elimination programs will be shocking. This way we will avoid the direct consequences of the paralysis of HCV elimination programs and, simultaneously, we send an optimistic message to people: public health programs can be maintained, even in these uncertain times.

Finally, we acknowledge that we are facing another SARS-CoV-2-related wave. However, the upcoming waves will be the consequences of the delayed diagnosis of other conditions resulting from the temporary suspension of many health programs. In the setting of liver diseases, this could be prevented by population-level anti-HCV and HBV testing in every patient undergoing SARS-CoV-2 testing.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interests

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

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

Keywords: HCV; COVID-19; SARS-CoV-2; Elimination; Massive test; Screening.
Received 29 August 2020; received in revised form 30 September 2020; accepted 1 October 2020; available online 9 October 2020
https://doi.org/10.1016/j.jhep.2020.10.001

Authors' contributions

All authors contributed equally.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.10.001.

References

Author names in bold designate shared co-first authorship

[1] WHO. Global Health Sector Strategy on Viral Hepatitis 2016-2021. Geneva: WHO; 2019.
[2] Calvaruso V, Craxì A. Hepatic benefits of HCV cure. J Hepatol 2020;73(6):1548–1556.
[3] Tajes SR, Pocurull A, Castillo J, Casanova G, Vega L, Lens S, et al. Hepatitis C-related cirrhosis will be a marginal cause of hospital admissions in the near future. J Hepatol 2020;73(6):1360–1367.
[4] Dinmohamed AG, Visser O, Verhoeven RHA, Louwman MWJ, van Nederveen FH, Willems SM, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. Lancet Oncol 2020;21(6):750–751.
[5] Blach S, Kondili LA, Aghemo A, Cai Z, Dugan E, Estes C, et al. Impact of COVID-19 on global hepatitis C elimination efforts. J Hepatol 2021;74(1):31–36.
[6] Karimi-Sari H, Rezaee-Zavareh MS. COVID-19 and viral hepatitis elimination programs: are we stepping backward? Liver Int 2020;40(8):2042.
[7] Wingrove C, Ferrier L, James C, Wang S. The impact of COVID-19 on hepatitis elimination. Lancet Gastroenterol Hepatol 2020;5:792–794.
[8] Lazarus JV, Picchio C, Dillon JF, Rockstroh JK, Weis N, Buti M. Too many people with viral hepatitis are diagnosed late — with dire consequences. Nat Rev Gastroenterol Hepatol 2019;16:451–452.
[9] Crespo J, Albillos A, Buti M, Calleja JL, García Samaniego J, Hernández Guerra M, et al. Elimination of hepatitis C. Positioning document of the Spanish Association for the Study of the Liver (AEEH). Rev Esp Enferm Dig 2019;111:862–873.
[10] **Boettler T, Marjot T,** Newsome PN, Mondelli MU, Maticic M, Cordero E, et al. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. JHEP Rep 2020;2:100169.

Javier Crespo[1,2,3]
Álvaro Díaz-González[1,2]
Paula Iruzubieta[1,2]
Susana Llerena[1,2]
Joaquín Cabezas[1,2,*]
[1]*Gastroenterology and Hepatology Department, Marqués de Valdecilla University Hospital, Santander, Spain*
[2]*Research Institute Valdecilla (*IDIVAL*), Santander, Spain*
[3]*School of Medicine, University of Cantabria, Santander, Spain*
[*]Corresponding author. Address: Gastroenterology and Hepatology Department, Marques de Valdecilla University Hospital, Research Institute Valdecilla (IDIVAL), Avda. de Valdecilla s/n. Santander, 39008 Cantabria, Spain. Tel.: +34 942 20 25 20; fax: +34 942 20 25 44.
E-mail address: joaquin.cabezas@scsalud.es (J. Cabezas)

Hepatic benefits of HCV cure: Don't forget coagulation!

To the Editor:

With great interest we have read the outstanding review by Calvaruso & Craxì, published recently in the *Journal of Hepatology*.[1] In their article, the authors elegantly review the hepatic benefits of sustained virological response (SVR; *i.e.* "HCV cure") in patients with chronic HCV infection treated with direct-acting antivirals (DAAs).

On one hand, in patients with mild to moderate fibrosis, the achievement of SVR prevents progression of liver fibrosis and improves survival, while on the other hand, in patients with cirrhosis (both compensated and decompensated), SVR is associated with reduced risks of decompensation, liver-related mortality, and hepatocellular carcinoma (HCC).[1]

In addition to the aforementioned hepatic benefits of HCV cure, a further positive effect of SVR in patients with cirrhosis treated with DAAs is the reversal of the hypercoagulable state.[2,3]

It is well known that patients with cirrhosis, particularly those who are decompensated, have complex coagulation changes that include reduced hepatic synthesis of both pro- and anticoagulant factors and increased levels of procoagulant factors synthetized outside the liver.[4] Current theory posits that these changes result in a rebalanced but precarious coagulation system which may easily tilt towards a hypercoagulable (prothrombotic) state.[5]

The clinical implications of cirrhotic coagulopathy have not yet been thoroughly understood. However, hypercoagulability may contribute to the occurrence of both macrovascular venous thrombosis, particularly portal vein thrombosis (PVT), and microvascular intra-hepatic (sinusoidal) thrombosis. On one hand, PVT has been correlated with increased risk of death in decompensated patients[6] and, when complete and extended to the superior mesenteric vein, with higher morbidity and mortality after liver transplantation.[7] On the other hand, sinusoidal micro-thrombosis could be implicated in parenchymal extinction and cirrhosis progression.[8] Therefore, by reverting the hypercoagulable state and preventing the development of such complications, one could potentially improve patient outcomes.

In a recent prospective study looking at the effect of DAAs on coagulopathy in patients with HCV-related cirrhosis, we demonstrated, by means of thrombomodulin-modified thrombin generation test, that SVR is associated with a profound reduction of *in vitro* hypercoagulability. This effect, which was likely the result of reduced systemic inflammation and improved hepatic synthesis of both pro- and anti-coagulant factors, was observed early after the end of antiviral therapy and persisted up to 1 year, when patients with cirrhosis demonstrated a thrombin generating capacity that became

Keywords: Cirrhosis; Portal vein thrombosis; Thrombin generation; SVR.
Received 1 September 2020; received in revised form 10 October 2020; accepted 28 October 2020; available online 16 December 2020
https://doi.org/10.1016/j.jhep.2020.10.031