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JOURNAL OF HEPATOLOGY

Impact of the COVID-19 pandemic on hepatitis C diagnosis in Brazil: Is the global hepatitis C elimination strategy at risk?

To the Editor:

We have read with interest the article by Blach *et al.* evaluating the impact of COVID-19 on global hepatitis C elimination efforts. A delay in elimination programs will be associated with an increase in global morbidity and mortality related to hepatitis C over the next 10 years.[1] The emergence of the new coronavirus responsible for COVID-19, at the end of 2019, placed great pressure on healthcare systems worldwide. In Brazil, the first case of COVID-19 was registered on February 26, 2020;[2] since then, the country has been one of the main pandemic epicenters, ranking third in number of cases and second in number of deaths worldwide.[3]

Due to the pandemic, the actions of surveillance and control programs for infectious diseases in Brazil have been severely affected, leading to the regression of achievements made in recent years.[4] These include the viral hepatitis control program, which, in accordance with the World Health Organization, in 2018, launched a plan to eliminate hepatitis C by 2030. Some countries have already indicated significant impacts on diagnosis of new cases of hepatitis as a result of the COVID-19 pandemic.[5,6] Our objective, therefore, was to analyze the impact of the COVID-19 pandemic on the incidence and number of cases of hepatitis C in Brazil.

We conducted a time series study, involving all confirmed cases of hepatitis C registered in Brazil between January 2015 and December 2020. The period from 2015 to 2019 was used to calculate the expected number of cases of hepatitis C for the year 2020. Data were extracted from the Department of Chronic Conditions and Sexually Transmitted Infections of the Brazilian Ministry of Health,[7] and data on COVID-19 were extracted from the CoVida network.[8]

For analysis, an adaptation of the P score was applied,[9] considering the following equation:

$$P-Score = \frac{No.\ of\ HCV\ cases\ in\ 2020\ (pandemic\ year) - Expected\ HCV\ case\ numbers\ in\ 2020}{Expected\ HCV\ case\ numbers\ in\ 2020} x100$$

where:

The expected value of the event is calculated considering the average of the past 5 years, prior to the occurrence of the COVID-19 pandemic (2015 to 2019), as recommended.[9] The results are expressed as percentages, where positive values indicate excess, and negative values indicate a decrease in the number of cases.

Between 2015 and 2020, 129,499 new cases of hepatitis C were diagnosed in Brazil, 56.4% of which were in males (n = 73,068). In 2020, 24,043 new cases were expected (incidence of 13.2/100,000 inhabitants). However, only 9,286 (5.2/100,000) were diagnosed. This represents a 61.4% decrease in the number of diagnoses and a 62.0% decrease in the incidence rate. A total of 14,700 individuals were not diagnosed in 2020. Females showed the greatest drop in the number of new diagnosed cases (number of cases: −63.5%; incidence rate: −64.0%) (Fig. 1A,B).

In relation to regions of Brazil, impacts were greatest in the Southeast Region (number of cases: −68.4%; incidence rate: −69.1%). In females, there was a 70.8% decrease in the number of cases diagnosed and a 71.5% decrease in the incidence rate. These results indicate that approximately 4,600 men and 3,900 women with hepatitis C in the Southeast Region went undiagnosed (Fig. 1C)

On the municipal level, a decrease in the number of diagnoses was observed in 3,211 municipalities, accounting for 85.5% of the notifying municipalities, *i.e.*, excluding those that did not report any cases during the period from 2015 to 2020 (n = 1,808; 32.5%). The 545 municipalities with an increased number of diagnoses have small populations and accounted for only 2.6% (n = 3,332) of cases during the entire period (Fig. 1D).

Due to the pandemic, health services have had to reallocate professionals and suspend outpatient care and surgeries in order to meet the growing demand stemming from severe acute respiratory syndrome. Moreover, due to fears of contracting COVID-19 at health services, patients have delayed seeking medical care when symptoms appear or when they have been exposed to risk factors. As a result of these changes, there have been negative impacts on surveillance programs and detection of new cases of several diseases.[4,10]

If the challenges to eliminating hepatitis C were momentous before the pandemic, this plan has now become even more challenging. The COVID-19 pandemic has jeopardized the Brazilian plan for eliminating hepatitis C by 2030. Thus, it is crucial, along with advances in COVID-19 vaccination in Brazil, to concentrate efforts on controlling hepatitis C throughout the country, focusing on diagnosis and treatment of new cases.

Keywords: coronavirus; COVID-19; elimination; HCV; viral hepatitis.
Received 26 July 2021; accepted 4 August 2021; available online 24 August 2021
https://doi.org/10.1016/j.jhep.2021.08.005

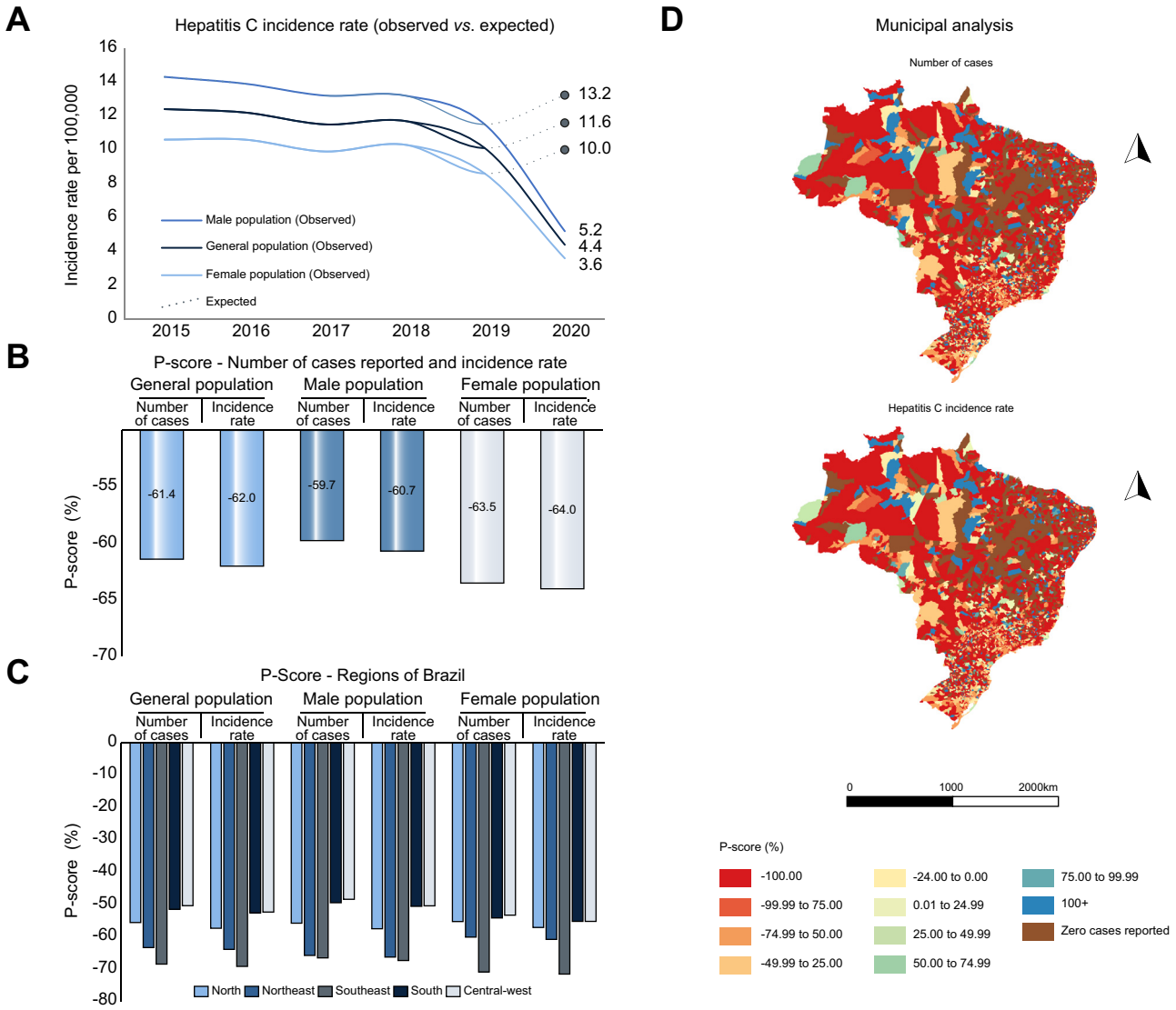

Fig. 1. Impact of the COVID-19 pandemic on diagnosis of hepatitis C in Brazil. (A) Hepatitis C incidence rate; (B) P-score for number of cases and incidence rate of HCV in the Brazilian population; (C) P-score for number of cases and incidence rate of HCV by region; (D) P-score for number of cases and incidence rate of HCV by Brazilian municipality. (This figure appears in color on the web.)

Financial support
The authors received no financial support to produce this manuscript.

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

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

Authors' contributions
R.F.C and C.D.F.S conceived the study, carried out the analysis and drafted the manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.08.005.

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G-CSF in acute-on-chronic liver failure – Art of 'patient selection' is paramount!

To the Editor:

The study by Engelmann *et al.* failed to show a significant beneficial effect of granulocyte-colony stimulating factor (G-CSF) in treating patients with acute-on-chronic liver failure (ACLF).[1] The use of G-CSF neither improved 3- and 12-month transplant-free survival nor led to an improvement in model for end-stage liver disease (MELD) score or new infections. This was independent of the nature of the precipitating event, severity of ACLF or type of organ failure. We believe the negative results in this study are mainly due to limitations in patient selection, as these cohorts did not match with the pathophysiological basis of the mechanisms of action of the growth factor used, G-CSF. Several important issues need further consideration. First, previous studies have shown that G-CSF reduces MELD scores and infections and improves survival in carefully selected patients with ACLF resulting from severe alcoholic hepatitis and reactivation of hepatitis B.[2,3] In both these disease states, intense inflammation and early immunoparesis have been documented.[4] The use of G-CSF ameliorated intrahepatic injury via recruitment of plasmacytoid dendritic cells and reduced interferon gamma production. In addition, it helped recruit neutrophils and monocytes from the bone marrow.[5] Additionally, G-CSF mobilized bone marrow and hepatic progenitor cells.[6] In these studies, G-CSF was used in early stages of ACLF before the onset of sepsis and extrahepatic organ failures. The role of G-CSF in augmenting liver regeneration in sick ACLF patients with sepsis and organ failure is debatable. In the Engelmann study, almost 40% of patients had bacterial infection at enrollment (was reported to be 54% in the data presented at AASLD, 2019). Moreover, almost two-thirds received G-CSF when they already had hepatorenal syndrome and/or cardiorespiratory failure. This is indeed too late for any growth factor to reverse the clinical state. Further, G-CSF is helpful to prevent the development of sepsis but not to treat sepsis. One should select patients without organ failures and sepsis to test the potential benefits of G-CSF. Second, the authors tried, but failed to analyze their data based on ACLF as defined by Asian Pacific Association for the Study of Liver (APASL) criteria. APASL ACLF criteria do not include patients with extrahepatic insults. However, 50% of patients shown as belonging to the APASL ACLF cohort in the GRAFT study had bacterial infection or variceal bleed as a precipitating factor. Third, exogenous GCSF therapy enhances the production, mobilization, and function of neutrophils that will increase the host response to infection in ACLF.[7] It was difficult to explain the higher incidence of spontaneous bacterial peritonitis (17 *vs.* 8) and lower incidence of pneumonia (9 *vs.* 15) in the G-CSF group compared to the control group. Fourth, the role of G-CSF in decompensated cirrhosis is limited due to the exhausted state of the bone-marrow niche.[8] In late stages of ACLF, the potential regenerative capacity of bone marrow is limited and must be evaluated before using G-CSF. A bone-marrow aspiration or biopsy should be done before starting G-CSF therapy. It is also not clear why the study was aborted when the two arms were showing comparable results. This is all the more important, as only 33% of the patients received the full 12 doses as per protocol. Importantly, in the presence of severe systemic inflammatory response syndrome and organ failures in ACLF, it is also important to rule out secondary hemophagocytic lymphohistiocytosis as in these situations, administration of G-CSF would be detrimental.[5,9]

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

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

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

Authors' contributions

A.J - Manuscript prepration ; S.k.S- Manuscript revision.

Keywords: ACLF; G-CSF; Cirrhosis.
Received 23 August 2021; accepted 25 August 2021; available online 1 September 2021
https://doi.org/10.1016/j.jhep.2021.08.022