PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA
DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

REVIEW ARTICLE

Scientific evidence on hepatitis B and SARS-CoV-2 infection: An integrative review

Evidências científicas sobre hepatite B e infecção por SARS-CoV-2: revisão integrativa

Evidencias científicas sobre la hepatitis B y la infección por SARS-CoV-2: revisión integradora

https://doi.org/10.17058/reci.v13i4.18618

Received: *18/06/2023*
Accepted: *21/08/2023*
Available online: *04/12/2023*

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ABSTRACT

Background and Objective: Hepatitis B is an infectious disease caused by a virus from the *hepadnaviridae* family, with worldwide distribution, and represents a serious global health problem. The pathology may have been affected by the COVID-19 pandemic, caused by the SARS-CoV-2 virus, making it possible for serious outcomes to occur when overlapping viral types. This study sought to describe the levels of scientific evidence of research carried out on the topic, establishing a relationship between hepatitis B virus infection and SARS-CoV-2 infection. **Content:** integrative literature review, with searches performed in the databases of the Medical Literature Analysis and Retrieval System Online, and Scientific Electronic Library Online, with analysis centered on the description of the methodological design, and on the classification of the level of evidence. **Conclusion**: the scientific production on hepatitis B associated with SARS-CoV-2 infection corresponds mostly to studies with a low level of evidence. The selected publications presented limitations such as the occurrence of studies with a small number of samples, lack of subsidiary data of patients in treatment, and occurrence of non-randomized selection. The results suggest the need for further investigations for the purpose of technological improvement, identification of risk factors, therapeutic intervention, and advanced clinical investigation, in order to encourage evidence-based healthcare practices.

Keywords*: Hepatitis B. SARS-CoV-2. COVID-19.*

RESUMO

Justificativa e Objetivos: a hepatite B é uma doença infectocontagiosa provocada por um vírus da família *hepadnaviridae*, com distribuição mundial, e representa um grave problema de saúde global. A patologia pode ter sido afetada pela pandemia de COVID-19, provocada pelo vírus SARS-CoV-2, sendo possível a ocorrência de desfechos graves na sobreposição entre os dos tipos virais. Este estudo buscou descrever os níveis de evidências científicas de pesquisas realizadas sobre o tema, estabelecendo relação entre a infecção por vírus da hepatite B e a infecção

por SARS-CoV-2. **Conteúdo:** revisão integrativa da literatura, com buscas realizadas nas bases de dados do *Medical Literature Analysis and Retrieval System Online* e *Scientific Electronic Library Online*, com análise centrada na descrição do delineamento metodológico e na classificação do nível de evidência. **Conclusão:** a produção científica sobre hepatite B associada a infecção por SARS-CoV-2 corresponde majoritariamente a pesquisas com baixo nível de evidência. As publicações selecionadas apresentaram limitações, como a ocorrência de estudos com número reduzido de amostras, falta de dados subsidiários de pacientes em tratamento e ocorrência de seleção não randomizada. Os resultados sugerem a necessidade de novas investigações para fins de incrementos tecnológicos, identificação de fatores de risco, intervenção terapêutica e investigação clínica avançada, de forma a fomentar práticas assistenciais em saúde baseadas em evidências.

Descritores: *Hepatite B. SARS-CoV-2. COVID-19.*

RESUMEN

Justificación y Objetivo: la hepatitis B es una enfermedad infecciosa contagiosa causada por un virus de la familia *hepadnaviridae*, de distribución mundial, y representa un grave problema de salud mundial. Su patología puede haberse visto afectada por la pandemia de COVID-19, provocada por el virus SARS-CoV-2, y son posibles desenlaces graves cuando se superponen tipos virales. Este estudio buscó describir los niveles de evidencia científica de las investigaciones realizadas sobre el tema, estableciendo una relación entre la infección por el virus de la hepatitis B y la infección por el SARS-CoV-2. **Contenido:** revisión integradora de la literatura, con búsquedas realizadas en las bases de datos *Medical Literature Analysis and Retrieval System Online* y *Scientific Electronic Library Online*, con un análisis centrado en la descripción del diseño metodológico y en la clasificación del nivel de evidencia. **Conclusión:** la producción científica sobre la hepatitis B asociada a la infección por SARS-CoV-2 corresponde, en su mayoría, a investigaciones con bajo nivel de evidencia. Las publicaciones seleccionadas presentaron limitaciones como la ocurrencia de estudios con un número reducido de muestras, la falta de datos subsidiarios de los pacientes en tratamiento y la ocurrencia de selección no aleatoria. Los resultados sugieren la necesidad de seguir investigando para mejorar la tecnología, identificar los factores de riesgo, intervenir terapéuticamente y realizar investigación clínica avanzada, con el fin de promover prácticas sanitarias basadas en la evidencia.

Palabras llave: *Hepatitis B. SARS-CoV-2. COVID-19.*

INTRODUCTION

Hepatitis B is an infectious disease caused by a virus belonging to the hepadnaviridae family, described as the hepatitis B virus (HBV). This virus has tropism for human liver cells.[1] It is a globally distributed infection, with estimates pointing to a worldwide occurrence of around 300 million chronically infected people, with indicators of 1.5 million new cases per year.[2]

Hepatitis B is transmitted parenterally, percutaneously (by sharing needles and syringes and other contaminated sharps); invasive procedures that do not follow biosafety rules; sharing materials and personal objects with a solution that can come into contact with the infected individual's blood (toothbrushes, razors); sexually; and vertically, which can occur during childbirth or during the perinatal period in the mother-child relationship.[3-5]

The infection can develop into acute and chronic forms, both of which, in most cases, are asymptomatic or mildly symptomatic.[3,1] Progression to the chronic form of the disease, in addition to requiring ongoing health care, increases the risk of developing conditions such as cirrhosis of the liver and hepatocellular carcinoma.[1]

The hepatitis B virus has a direct relationship with physiological complications, including immunological ones, which makes those affected vulnerable to worsening liver conditions, among other alterations in the body.[1] Thus, in the context of the pandemic caused by the SARS-CoV-2 virus, which causes the coronavirus-19 (COVID-19) disease, generating a risk of harmful interaction,[6] the study of co-infections gains prominence, given the need for specific monitoring of SARS-CoV-2 cases in HBV patients.

SARS-CoV-2 is a ribonucleic acid (RNA) virus belonging to the Nidovirales family of viruses. SARS-CoV-2 has proteins called receptor binding-domain (RBD) that bind to angiotensin-converting enzyme 2 (ACE2) receptors, affecting cells in the respiratory system. The virus is transmitted through contact with respiratory droplets present in symptomatic or asymptomatic infected individuals. The main symptoms of COVID-19 are fever, cough, headache, loss of taste or smell, diarrhea, chest pain and severe dyspnea, with an incubation period ranging from 2 to 14 days.[6,7]

Epidemiological data show that the world has recorded around 760 million confirmed cases of COVID-19, with 6.8 million confirmed deaths from the infection. In Brazil, there have been 37 million cases and around 700,000 deaths from COVID-19.[8] Overall figures make the overlap between the SARS-CoV-2 and HBV viruses inevitable, in epidemiological terms.

The global emergency scenario caused by the SARS-CoV-2 pandemic and the occurrence of COVID-19, associated with other diseases, may be related to the in-

Please cite this article as: *de Oliveira MS, Pinheiro da Costa E, Pinho da Silva JA. Evidências científicas sobre hepatite B e infecção por SARS-CoV-2: revisão integrativa. Rev Epidemiol Control Infect [Internet]. 12º de dezembro de 2023 [citado 16º de janeiro de 2024];13(4). Disponível em: https://online.unisc.br/seer/index.php/epidemiologia/article/view/18618*

creased risk of serious outcomes, especially for patients with chronic hepatitis B, due to the factors mentioned above. In this sense, surveying scientific studies and mapping levels of evidence is an important measure for updating clinical management and healthcare practices. That said, the present study sought to describe the levels of scientific evidence from research carried out on the subject, establishing a relationship between hepatitis B virus infection and SARS-CoV-2.

METHOD

This is an integrative review on the subject of the level of scientific evidence on hepatitis B and SARS-COV-2 infection. The integrative review is one of the methods of evidence-based healthcare practice, and consists of gathering and synthesizing scientific production on a given topic in a systematic way in order to deepen knowledge on the subject.[9]

The research was carried out from May to November 2022, following six methodological stages, established according to the literature,[9-11] as shown in figure 1.

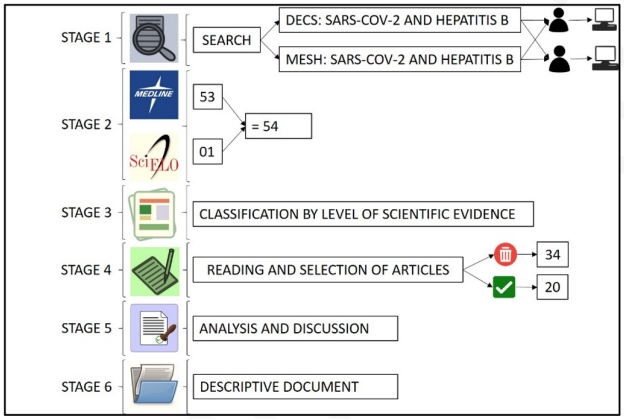

Figure 1. Flowchart of the research's methodological stages.

In the first stage, the guiding question was formulated: "What levels of scientific evidence are available in the studies produced on the relationship between chronic hepatitis B and SARS-CoV-2 infection?" This was an important question for selecting and analyzing the studies included in the research. The following keywords were then listed as primary inclusion criteria: Hepatitis B and SARS-CoV-2, according to the health sciences descriptors (DECS), and hepatitis B and SARS-CoV-2, according to the medical subject headings (Mesh).

In the second stage, the databases for the search and the eligibility criteria for the inclusion and exclusion of studies were defined, considering the analysis of the method and the observation of content pertinent to the relationship between hepatitis B and SARS-CoV-2 infection. The search was carried out in pairs using Boolean operators. Scientific articles found based on the descriptors defined in the first stage, published in English, Spanish and Portuguese, without restriction of territory, with a focus on hepatitis B and SARS-CoV-2 infection (COVID-19), with an abstract available in the databases: Medical Literature Analysis and Retrieval System Online (Medline) and Scientific Electronic Library Online (SciElo), published between 2020 and 2022, were considered eligible. At the time of the search, 53 articles were found in the Medline database and 1 article in SciElo, totaling 54 publications, with no exclusions, as all the studies found in the search strategy met the research eligibility criteria.

For the third stage, Table 1 proposed by Oliveira et al[11] was used to organize and present the results found, characterizing the studies according to the classification of levels of scientific evidence, according to the Melnyk and Fineout-Overholt model.[12] The classification being:

1. Evidence from a systematic review or meta-analysis of all relevant randomized controlled clinical trials or from clinical guidelines based on systematic reviews of randomized controlled clinical trials;
2. Evidence derived from at least one well-designed randomized controlled clinical trial;
3. Evidence obtained from well-designed clinical trials without randomization;
4. Evidence from well-designed cohort and case--control studies;
5. Evidence from systematic reviews of descriptive and qualitative studies;
6. Evidence derived from a single descriptive or qualitative study;
7. Evidence derived from the opinion of authorities and/or expert committee reports.

The fourth stage involved reading the abstracts of the scientific articles found and applying the eligibility criteria, as shown in Figure 1, as well as critically analyzing the articles found and applying and classifying the level of evidence of the studies. After reading the abstracts, 26 Medline articles were excluded because they did not fit the proposed theme, leaving a total of 28 articles. In the critical analysis of the articles found, 8 more articles were excluded as they also did not fit the proposed theme, resulting in 20 selected studies.

In the fifth stage, which corresponds to the interpretation of the results achieved, we discussed the data obtained from the results.

The sixth stage involved preparing the descriptive document for the study and presenting this review.

Regarding ethical aspects, the study does not involve human beings directly or indirectly, only published data, and there is no obligation to submit it to a research ethics committee. However, the authors declare that they have followed the ethical precepts described in Resolution No. 466 of 2012, as well as other guarantees of right.

RESULTS

The selected studies are listed in chart 1, considering information such as the titles of the papers, authors, journal of publication, thematic considerations, and the classification of the level of evidence.

Chart 1. Characterization of publications on the relationship between hepatitis B and SARS-CoV-2 infection, according to reference, thematic considerations, type of study, and level of evidence.

Reference	Thematic considerations	Type of study	Level of evidence
Jiménez-Mendoza J, Rivera-López F, González-Lara M, Valdez-Echeverría R, Castro-Narro G, Tore A, et al. Seroprevalence of hepatitis B and C viruses in moderate and severe COVID-19 inpatients: A cross-sectional study at a referral center in Mexico. Ann Hepatol. May 2022;27(3):100684.	Investigates the seroprevalence of hepatitis B and C viruses in patients hospitalized with COVID-19 in Mexico.[13]	Cross-sectional (retrospective) study	VI
Choe JW, Jung YK, Yim HJ, Seo GH. Clinical Effect of Hepatitis B Virus on COVID-19 Infected Patients: A Nationwide Population-Based Study Using the Health Insurance Review & Assessment Service Database. J Korean Med Sci. 2022;37(4):e 29.	Evaluates the effects of the hepatitis B virus on the body of patients infected with COVID-19.[14]	Cohort	IV
Librero Jiménez M, López Garrido MÁ, Fernández Cano MC. Letter to the editor: Reactivation of HBV triggered by SARS-CoV-2 in a patient with cirrhosis. Hepatology. March 2022;75(3):765–6.	Investigates possible reactivation of HBV triggered by SARS-CoV-2 infection.[15]	Case report	VI
Sagnelli C, Pisaturo M, Curatolo C, Codella AV, Coppola N, Sagnelli E. Hepatitis B virus/hepatitis D virus epidemiology: Changes over time and possible future influence of the SARS-CoV-2 pandemic. World J Gastroenterol. November 14, 2021;27(42):7271–84.	Describes the epidemiology of hepatitis B and D, and possible changes resulting from the SARS-CoV-2 pandemic.[16]	Literature review	V
Gómez Camarero J, Badia Aranda E, Quiñones Castro R, Saiz Chumillas RM, Alcoba Vega L, Díez Ruiz S, et al. Hepatitis B and C screening in hospitalized patients with SARS-CoV-2 infection. Gastroenterol Hepatol. April 2022;45(4):256–64. Doi: 10.1016/j.gastrohep.2021.09.002	Evaluates the results of a screening program for hepatitis B and C in hospitalized patients with COVID-19.[17]	Cross-sectional (prospective)	VI
Kazmi SK, Khan FMA, Natoli V, Hunain R, Islam Z, Costa AC dos S, et al. Viral hepatitis amidst COVID-19 in Africa: Implications and recommendations. J Med Virol. January 2022;94(1):7–10.	Scenario of viral hepatitis in the COVID-19 pandemic in Africa, consequences and recommendations.18	Literature review	V
Jindal A. Letter to the Editor: Outcomes in chronic hepatitis B infection and COVID-19 Not always benign! Hepatology. January 2022;75(1):230–230.	The author's opinion on the outcomes of hepatitis B and COVID-19 infections.[19]	Letter to the editor	VII
Lv X, Yang J, Deng K. Letter to the Editor: Unanswered questions about hepatitis B virus infection in patients with COVID-19. Hepatology. January 2022;75(1):229–229.	The author's opinion on unanswered questions regarding hepatitis B patients infected with COVID-19.[20]	Letter to the editor	VII
Alqahtani SA, Buti M. COVID-19 and Hepatitis B Infection. Antivir Ther. November 2020;25(8):389–97.	Presents the clinical relationship of patients with hepatitis B infected with COVID-19.[21]	Literature review	V
Pley CM, McNaughton AL, Matthews PC, Lourenço J. The global impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of hepatitis B virus (HBV) infection. BMJ Glob Health. January 2021;6(1):e004275.	Provides an overview of the impact of the COVID-19 pandemic on the progress of hepatitis B virus programs around the world with a focus on the possible consequences for prevention, diagnosis, and treatment.[22]	Literature review	V
Liu R, Zhao L, Cheng X, Han H, Li C, Li D, et al. Clinical characteristics of COVID-19 patients with hepatitis B virus infection — a retrospective study. Liver Int. April 2021;41(4):720–30.	Study of the impact of co-infection with SARS-CoV-2 and chronic hepatitis B.[23]	Cohort study	IV
Ding Z yang, Li G xun, Chen L, Shu C, Song J, Wang W, et al. Association of liver abnormalities with in-hospital mortality in patients with COVID-19. J Hepatol. June 2021;74(6):1295–302.	Study of the association between liver abnormalities and hospital mortality in COVID-19 patients.[24]	Retrospective cohort study	IV
Yu R, Tan S, Dan Y, Lu Y, Zhang J, Tan Z, et al. Effect of SARS-CoV-2 coinfection was not apparent on the dynamics of chronic hepatitis B infection. Virology. January 2021;553:131–4.	Claims that the effects of SARS-CoV-2 co-infection were not apparent in the dynamics of chronic Hepatitis B infection.[25]	Cohort study	IV

Ali E, Ziglam H, Kohla S, Ahmed M, Yassin M. A Case of Fulminant Liver Failure in a 24-Year-Old Man with Coinfection with Hepatitis B Virus and SARS-CoV-2. Am J Case Rep. September 3, 2020.	Presents the case of fulminant liver failure in a 24-year-old man with co-infection with hepatitis B virus and SARS-CoV-2.[26]	Case report	VI
Rodríguez Tajes S, Miralpeix A, Costa J, López Suñé E, Laguno M, Pocurull A, et al. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. J Viral Hepat. January 2021;28(1):89–94.	Analyzes the risk of HBV reactivation in patients with severe COVID-19 and resolved HBV infection under immunosuppressive therapy.[27]	Prospective cohort study	IV
Wu J, Yu J, Shi X, Li W, Song S, Zhao L, et al. Epidemiological and clinical characteristics of 70 cases of coronavirus disease and concomitant hepatitis B virus infection: A multicentre descriptive study. J Viral Hepat. January 2021;28(1):80–8.	Analysis of 70 cases of co-infection by SARS-CoV-2 and hepatitis B to determine epidemiological, clinical, treatment, and outcome characteristics.[28]	Multicenter descriptive study	VI
Lv XH, Yang JL, Deng K. Clinical Outcomes of COVID-19 Patients with Chronic Hepatitis B Virus Infection Still Need to Be Explored. Clin Gastroenterol Hepatol. December 2020;18(13):3055–6.	Presents the authors' analysis of the results of a cohort study, determining that the clinical outcomes of COVID-19 patients with chronic hepatitis B virus infection still need to be explored.[29]	Letter to the editor	VII
Zhang B, Huang W, Zhang S. Clinical Features and Outcomes of Coronavirus Disease 2019 (COVID-19) Patients with Chronic Hepatitis B Virus Infection. Clin Gastroenterol Hepatol. October 2020;18(11):2633–7.	Reports the clinical evolution of COVID-19 patients with chronic hepatitis B virus infection and provides a reference for the clinical management of patients.[30]	Descriptive study/ Letter to the editor	VI
Anugwom CM, Aby ES, Debes JD. Inverse Association Between Chronic Hepatitis B Infection and Coronavirus Disease 2019 (COVID-19): Immune Exhaustion or Coincidence? Clin Infect Dis. June 5, 2020;ciaa592.	Authors' analysis of a study that showed an inverse association between chronic hepatitis B infection and coronavirus 2019 disease (COVID-19).[31]	Letter to the editor	VII
Lv XH, Yang JL, Deng K. COVID-19 Patients with Hepatitis B Virus Infection. Am J Gastroenterol. June 2021;116(6):1357–8.	Author's response to an article published on COVID-19 patients with hepatitis B virus infection.[32]	Letter to the editor	VII

The publications selected took place between 2020 and 2022. The studies were published in seven categories of journals: 30% in the field of hepatology, 15% in the field of gastroenterology and hepatology, 15% in the field of medical sciences, 15% in the field of virology, 10% in the field of gastroenterology, 10% in the field of viral hepatitis and 5% in the field of clinical infectious diseases. In terms of research design, most of the studies were observational, followed by literature reviews and expert opinions.

Regarding classification of the level of evidence according to the method adopted: 30% are level VI studies, those derived from a single descriptive or qualitative study; 25% level IV studies, i.e. evidence from well-designed cohort and case-control studies; 25% level VII, evidence derived from the opinion of authorities and/or expert committee reports; 20% level V studies, evidence originating from a systematic review of descriptive and qualitative studies.

DISCUSSION

The result of this integrative review outlines the scientific production on the relationship between hepatitis B and SARS-CoV-2 infection, from 2020 to 2022, the period corresponding to the duration of the pandemic by the new coronavirus. Although hepatitis B is a disease with important liver complications, such as cirrhosis and hepatocellular carcinoma, and which presents a global distribution and high morbidity and mortality,[2,1] the scientific production selected on the relationship between HBV infection and SARS-CoV-2 infection was discreet.

Of the studies found in this review, 30% corresponded to evidence level VI, i.e. evidence derived from a descriptive or qualitative study, considered to be of a low level.[9] When it comes to evidence-based health practices, descriptive studies and the personal experience of professionals are important, but the production of research considered to be of high scientific evidence, as in the case of a review with meta-analysis and randomized clinical trials, provides a better basis for making clinical and care decisions.[33]

Based on the research design, the results showed a significant number of letters to the editor (25%). The articles that were answered, despite fitting the theme proposed by this study, were not found at the time of the peer review, possibly due to the incompatibility of descriptors[34] or because they addressed subjects that indirectly raised questions about the relationship between HBV and SARS-CoV-2.

Among the findings of relevance, it was observed

that some studies indicate that there are two main routes of liver damage caused by SARS-CoV-2, the first can be explained by the binding of the virus to ACE2 receptors, which is found in abundance in the respiratory tract, but can also be found in liver cells, involved in functions related to the immune system.[21,28] The second route is related to drug-induced liver damage through the use of potentially hepatotoxic drugs used in the treatment of SARS-CoV-2 infection, especially the prolonged use of immunosuppressants.[21,28]

It was also observed that patients co-infected with HBV and SARS-CoV-2 showed a higher frequency of gastrointestinal symptoms. The laboratory abnormalities are similar to other studies found in this review, which indicate high levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as levels of white blood cells, lymphocytes and platelet counts below normal. According to the authors, there were no differences between length of stay and poor prognosis in the two groups.[21,24,27,28]

One of the studies found in this review presents a case report of fulminant liver failure in a patient with HBV co-infected with SARS-CoV-2. In this case, the patient presented a rapid evolution of the condition, suggestive of the result of co-infection by SARS-CoV-2, in view of the mechanism known as the "cytokine storm" caused by the virus.[26] The finding of this report corroborates the hypothesis that SARS-CoV-2 can affect the host's immune response and increase HBV viral replication or its pathophysiological damage, both in acute and chronic infections.

It is important to note that studies suggest that HBV can cause a phenomenon known as "immune exhaustion", resulting from a reduction in the reactivity of T lymphocytes, disabling the production of cytokines and response to HBV and other viruses. In this sense, publications indicate that this phenomenon may reduce the cytokine storm common in patients with the COVID-19 condition.[21,31]

One of the cohorts included in this review points out in its results that in the group of patients co-infected with HBV and SARS-CoV-2, a series of systemic deregulations occurred, such as a decrease in immune cells, mainly lymphocytes; increased levels of TCD8 cells; thrombocytopenia; disorganized lipid metabolism; and elevated creatine kinase levels. This could be indicative of a worsening of the disease in this group of patients. Even so, the results of the study showed no significant differences in severity between cases of co-infection with SARS-CoV-2 and those with HBV monoinfection.[23]

When studying the clinical effect of hepatitis B in patients infected with COVID-19, another cohort study pointed out in its results that among HBV-infected patients the mortality rate was 13.5%, while among uninfected patients the rate was 8.2%. However, it should be noted that those affected by HBV also had other types of comorbidities. Furthermore, when adjusting for age, gender, cirrhosis, and comorbidities, no significant differences were observed between the two groups in terms of clinical outcomes. The results of this study indicate that HBV infection itself did not seem to affect the outcome of SARS-CoV-2 infection in these patients, nor did the antiviral therapy used for HBV reduce mortality, suggesting that there is no direct relationship of severity between hepatitis B and SARS-CoV-2 infection.[14]

A published case report presents the case of a patient infected with SARS-CoV-2, who presented HBV reactivation. According to the authors, the reason for the reactivation and multiplication of HBV may be due to co-infection with SARS-CoV-2, given that other causes were ruled out.[15] However, studies suggest that factors associated with the treatment of COVID-19 can trigger consequences in HBV infection.

Regarding the treatment of choice for SARS-CoV-2 infection, the immunosuppressants and corticosteroids used to treat the infection are considered to be at high risk of HBV reactivation, which highlights the importance of screening for the disease at the time of hospitalization of patients infected with SARS-CoV-2.[13] A study carried out in Spain points out that screening for hepatitis B in patients hospitalized with COVID-19 was necessary, given the risk of drug reactivation. The results of this cross-sectional study showed HBV reactivation in 14.2% of patients who did not use entecavir prophylaxis during treatment with immunosuppressants.[17]

A prospective cohort, with the aim of establishing the risk of hepatitis B virus reactivation in COVID-19 patients, showed in its results that 87% of co-infected patients had high ALT levels. Most of the patients who required immunomodulatory therapy, tocilizumab being the main medication, received prophylaxis with entecavir. Among the sample, none of the patients who received prophylaxis showed HBV seroconversion. Two patients who did not receive prophylaxis had a quantifiable viral load (HBV-DNA), but at low levels. Therefore, the data from this study indicate that immunomodulatory therapy over a short period of time may not be directly related to HBV reactivation in patients infected with SARS-CoV-2.[27]

A retrospective cohort study carried out in three centers of a hospital designated for the treatment of COVID-19 in Wuhan, China, highlights that there were no significant differences in the chemical levels of liver function between the groups of HBV patients co-infected with SARS-CoV-2 and those monoinfected with SARS-CoV-2. The mortality rate was 6% in the co-infected group, which also showed no difference between the groups.[24] The findings of another publication corroborate these results, stating that there were no significant changes in clinical characteristics or in liver function and enzyme tests. Another important finding was that co-infection with SARS--CoV-2 did not trigger seroconversion of chronic hepatitis B. Co-infection also did not cause changes in COVID-19 severity or an increase in length of hospital stay.[25]

However, a Chinese study found predictive evidence that a large proportion of HBV carriers, when infected with SARS-CoV-2, will not have severe disease outcomes. According to the authors' study, 26% of patients presented dysfunctions in liver function tests on admission, of which 19% progressed to severe disease, but this finding

was not related to the HBV infection status. In view of this, the authors recommend that liver function be constantly evaluated in COVID-19 patients who are hospitalized.[30]

A large part of the outpatient care sectors for viral hepatitis has been discontinued during the pandemic, corresponding to around 90%. In Italy, 26% of the beds made available for liver conditions have been converted into COVID-19 beds. Reduced access to these health services, including testing and screening programs, equipment, and human resources, may be a determining factor in the reduction of early detection of HBV, and the continuity of treatment of chronic carriers of the infection.[16,18,22]

Although HBV can be prevented through immunization, vaccination coverage has dropped significantly in the pandemic period. Global HBV vaccination levels have increased since the 1990s, but in 2020, the year the COVID-19 pandemic began, vaccination rates fell to the same levels as in 1990. In the first year of the pandemic, SARS-CoV-2 infection drastically impacted 25 years of progress in global hepatitis B vaccination, and this reduction in vaccination coverage may increase the incidence of HBV infection in early childhood and consequently increase the risk of chronic hepatitis B.[22,16] The effects of the COVID-19 pandemic on HBV vaccination and control may even outweigh the number of direct deaths from SARS-CoV-2 infection in the long term.[22]

The data reveal observational estimates whose parameters are often linked to government indicators or scientific opinions, and are subject to variations resulting from delays in feeding the systems, underreporting, and estimation errors. In addition, the scarcity of epidemiological data on the association between HBV infections and SARS-CoV-2 imposes limitations on the analyses, requiring studies which can test the various hypotheses raised through descriptive data, especially on a clinical basis.

The circulation and contact restrictions imposed worldwide to control COVID-19 may have interfered with the HBV transmission chain. The compulsory rules of controlled circulation may have impacted the disease through other risk factors, such as alcohol and drug use, unprotected sex, and an increase in home births without adequate prophylaxis.[22,16] The synergy between pre-existing risk factors and the SARS-CoV-2 pandemic suggests a critical scenario, negatively affecting the WHO strategy to eliminate hepatitis B as a public health threat by 2030.[2]

Mapping levels of evidence for the purposes of health care practices is an important measure, but integrative review studies have limitations in terms of their use in day-to-day health actions, since they produce an extract, i.e. a snapshot of the health situation investigated in a given time and space, requiring the production of studies with a higher level of evidence, such as meta-analyses or randomized clinical trials.

However, by describing the levels of scientific evidence of research associating SARS-CoV-2 infection with chronic HBV infection, this study has produced a critical description of the real potential of the studies listed, showing a high number of observational studies, which add little to care practices, and consequently highlighting and indicating the need for new research on the subject, with higher levels of evidence.

CONCLUSION

In view of the above, it can be concluded that the scientific production on hepatitis B associated with SARS-CoV-2 infection corresponds mostly to research with a low level of evidence, revealing incipient findings that may guide clinical and healthcare practices.

The publications selected for this review had some limitations which may impact on the validation of the results observed and described. In general, there were studies with small sample sizes, a lack of subsidiary data on patients undergoing treatment and non-randomized selection. In addition, the research method for integrative reviews produces a thematic snapshot, according to the position of the researchers at the time of the research, a reality that can change over time, especially considering a topic with recent facts, thus requiring a subsidiary analysis of other studies with methodological variety and checking for updates on the problem studied.

However, although the relationship between SARS-CoV-2 infection and HBV has not been fully clarified, it is clear that the pandemic caused by the SARS-CoV-2 virus had a negative impact on the process of prevention, diagnosis and management of hepatitis B in the world, the impacts of which need time, technological improvements, and new research focused on the evaluation of pharmacological therapies, the identification of risk factors, and advanced clinical research to promote innovations in public policies and evidence-based care practices.

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Elissandra Pinheiro da Costa contributed to all stages of the research, including: project design, bibliographic research, scientific writing, data collection, data analysis, and preparation of the scientific manuscript.

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Marcelo Siqueira de Oliveira contributed to and guided all stages of the research, including: drawing up the project, indicating and implementing the method, searching the literature, scientific writing, supervising data collection, analyzing the data collected, and preparing the scientific manuscript.

All the authors have approved the final version to be published and are responsible for all aspects of the study, including ensuring its accuracy and integrity.