J Korean Med Sci. 2024 Jan 29;39(4):e22
https://doi.org/10.3346/jkms.2024.39.e22
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article

Public Health & Preventive Medicine

The Epidemiology of Hepatitis B Virus Infection in Korea: 15-Year Analysis

Log Young Kim [1*] **Jeong-Ju Yoo** [2*] **Young Chang** [3] **Hoongil Jo** [4] **Young Youn Cho** [5] **Sangheun Lee** [6] **Dong Hyeon Lee** [7] **Jae Young Jang** [3] **and the Korean Association for the Study of the Liver**

[1]Department of Big DATA Strategy, National Health Insurance Service, Wonju, Korea
[2]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea
[3]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, Wonkwang University School of Medicine and Wonkwang University Hospital, Iksan, Korea
[5]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea
[6]Department of Internal Medicine, Catholic Kwandong University College of Medicine, St. International Mary's Hospital, Incheon, Korea
[7]Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

Received: Sep 14, 2023
Accepted: Nov 27, 2023
Published online: Dec 20, 2023

Address for Correspondence:
Dong Hyeon Lee, MD, PhD
Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea.
Email: donghyeonlee83@gmail.com

Jae Young Jang, MD, PhD
Department of Internal Medicine, Institute for Digestive Research, Digestive Disease Center, Soonchunhyang University College of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea.
Email: jyjang@schmc.ac.kr

*Log young Kim and Jeong-Ju Yoo contributed equally to this work.

ORCID iDs
Log Young Kim
https://orcid.org/0000-0002-6160-8357
Jeong-Ju Yoo
https://orcid.org/0000-0002-7802-0381

ABSTRACT

Background: The purpose of this study is to investigate the epidemiological changes in chronic hepatitis B (CHB) and assess the impact of coronavirus disease 2019 (COVID-19) over the past 15 years in a region endemic to hepatitis B virus (HBV).
Methods: National Health Insurance Service claims data of hepatitis B patients spanning from 2007 to 2021 was utilized. To compare the characteristics of the hepatitis B group, a control group adjusted for age and gender through propensity score matching analysis was established.
Results: The number of patients with CHB has consistently increased over the past 15 years. The average age of the CHB patient group has shown a yearly rise, while the prevalence of male dominance has gradually diminished. The proportions of hepatocellular carcinoma, liver cirrhosis, and decompensation have exhibited a declining pattern, whereas the proportion of liver transplants has continuously risen. Patients with CHB have demonstrated significantly higher medical and medication costs compared to the control group. Moreover, patients with CHB have shown a higher prevalence of comorbidities along with a significantly higher rate of concomitant medication usage. During the COVID period, the HBV group experienced a substantial decrease in the number of outpatient visits and overall medical costs compared to the control group.
Conclusion: The epidemiology of CHB has undergone significant changes over the past 15 years, encompassing shifts in prevalence, severity, medical costs, and comorbidities. Furthermore, the impact of COVID-19 has been observed to decrease healthcare utilization among patients with CHB when compared to controls.

Keywords: HBV; Epidemiology; COVID-19 Infection

Young Chang
https://orcid.org/0000-0001-7752-7618
Hoongil Jo
https://orcid.org/0000-0002-0947-7185
Young Youn Cho
https://orcid.org/0000-0002-9384-5357
Sangheun Lee
https://orcid.org/0000-0002-7884-1622
Dong Hyeon Lee
https://orcid.org/0000-0003-2044-6854
Jae Young Jang
https://orcid.org/0000-0001-5335-752X

Funding
The study was supported by the Korean Association for the Study of the Liver (2003). This research was also partly supported by the Soonchunhyang University Research Fund (2003).

Disclosure
The authors have no potential conflicts of interest to disclose.

Data Availability Statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions
Conceptualization: Lee DH, Jang JY. Data curation: Chang Y, Jo H, Cho YY, Lee S. Formal analysis: Kim LY, Yoo JJ. Investigation: Kim LY, Yoo JJ, Chang Y, Jo H, Cho YY, Lee S, Lee DH, Jang JY. Writing - original draft: Kim LY, Yoo JJ.

INTRODUCTION

Effective antiviral agents have played a significant role in the management of chronic hepatitis B (CHB) infection.[1,2] Since the introduction of potent nucleos(t)ide analogs such as entecavir and tenofovir, the treatment landscape for CHB has undergone remarkable progress. These antiviral agents effectively suppress viral replication, alleviate liver inflammation, and impede disease progression, thereby significantly reducing the risk of complications such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[3-5] As a result, it can be anticipated that the epidemiology of hepatitis B has undergone significant changes compared to the past.[6,7] However, despite the gradual progress in combating hepatitis B, it remains a significant medical challenge in endemic regions and continues to be a major cause of HCC.[8,9]

The coronavirus disease 2019 (COVID-19) pandemic has had a significant impact on healthcare systems worldwide, affecting the delivery and accessibility of care for patients with chronic illnesses, including individuals with CHB.[10] As healthcare resources were redirected to manage the COVID-19 outbreak, the availability and timely administration of antiviral agents for patients with CHB may have been disrupted, potentially resulting in suboptimal treatment outcomes.[11] Furthermore, the COVID-19 pandemic has likely had multiple impacts on the epidemiology of CHB. Disruptions in routine immunization programs, diagnostic services, and treatment availability may have affected the prevalence and incidence of CHB. Moreover, changes in social determinants of health, including socioeconomic conditions, employment, and housing, may have influenced the risk factors associated with CHB infection and transmission.[12] The pandemic may have also impacted the adherence of CHB patients to their treatment regimens due to various factors, including limited access to healthcare providers, financial constraints, or concerns about visiting healthcare facilities and contracting the virus.[13]

Therefore, this study aims to analyze nationwide cross-sectional data in a hepatitis B virus (HBV) endemic area, providing a comprehensive overview of the epidemiological changes and patterns of hospital utilization among patients with CHB over the past 15 years, including the COVID-19 pandemic. Understanding these changes and their impacts is crucial for healthcare providers, policymakers, and researchers in developing evidence-based strategies to ensure the continuity of care and enhance outcomes for CHB patients during public health emergencies.

METHODS

Data source

We used the claim data of National Health Insurance Service (NHIS) in Korea. The Republic of Korea operates a universal health coverage system with mandatory social health insurance. This system covers approximately 98% of the total population, and the number of patients claiming health insurance each year amounts to around 46 million, accounting for approximately 90% of the registered resident population. To examine the overall pattern of CHB changes over a span of 15 years, data from the Korean NHIS were collected for the years 2007, 2011, 2015, 2019, 2020, and 2021. Due to limitations in the NHIS data retrieval system, data retrieval until 2019 followed a reverse chronological order rather than continuous retrieval over the full 12-year period. Starting from 2019, data were obtained for three

consecutive years to analyze the impact of COVID-19 on the treatment of patients with CHB, as the COVID-19 outbreak occurred towards the end of 2019.

The HBV group consisted of patients aged 18 years and above who had been diagnosed with CHB or any of its subcategories. The severity of liver disease was analyzed by subclassification into 1) cirrhosis, 2) decompensated cirrhosis, 3) HCC, and 4) liver transplantation. To compare the characteristics of CHB patients with the general population, the control group was defined as the general population without hepatitis B. The control group is not the concept of non-CHB patients who have visited a medical institution at least once, but rather the non-CHB population registered for health insurance eligibility. The control group of this study is the population with no CHB history in the current year among the population registered with health insurance in Korea. Therefore, even if populations who do not visit a medical facility can be included in the control group of this study. Propensity score matching (PSM) analysis was used to match the chronic HBV group with a 1:4 ratio to a control group with similar demographic characteristics. The adjusted variables used in PSM were age and sex. This analysis allowed for a comparison of medical costs, medication costs, number of hospital visits, comorbidities, and concomitant medications between the HBV group and the control group.

Definition

HBV was defined as a case with a diagnosis code of International Classification of Diseases 10th Revision (ICD-10) B18.0 or B18.1. Liver cirrhosis was defined by the presence of one of the following ICD-10 codes: K702, K703, K74, K766, or K767. Decompensated cirrhosis was defined as meeting two criteria: 1) having an ICD-10 code for cirrhosis, and 2) having one of the following: a procedure code (abdominal paracentesis [C8050], endoscopic treatment of esophageal or gastric varices sclerotherapy [Q7631], endoscopic treatment of esophageal or gastric varices ligation [Q7633]), a drug code (spironolactone [Anatomical Therapeutic Chemical {ATC} code: C03DA01], terlipressin [ATC code: H01BA04], other systemic hemostasis [ATC code: B02BX], somatostatin [ATC code: H01CB01], propranolol [ATC code: C07AA05]), or a diagnosis code (hepatorenal syndrome [K767], bacterial peritonitis [K658], hepatic failure [K729], esophageal varices with bleeding [I983], hepatic encephalopathy [K76.82]). HCC was defined by either the ICD-10 code C22.0 or the ICD-10 reimbursement benefit extension coverage code V193. Liver transplant was defined based on one of the following conditions: 1) cases with disease code Z944 and treatment code Q80, or 2) the ICD-10 reimbursement benefit extension coverage code V013. Additionally, we investigated whether antiviral treatment was administered, and the targeted drugs included tenofovir alafenamide, tenofovir disoproxil fumarate (DF), entecavir, besifovir, lamivudine, adefovir, telbivudine, clevudine, and peg-interferon alpha.

We assessed the presence of nine comorbidities based on ICD-10 codes, including cerebrovascular disease, coronary heart disease, diabetes, hyperlipidemia, hypertension, rheumatoid arthritis, osteoarthritis, fracture or osteoporosis, and chronic kidney disease. Additionally, comorbidity was evaluated using the Charlson Comorbidity Index. We also examined the use of 7 concomitant medications, which included anti-diabetic medication, dyslipidemia medication, anti-hypertension medication, osteoporosis medication, diuretics, systemic (oral or intravenous) corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs). Detailed definitions for each comorbidity and medication can be found in the **Supplementary Tables 1** and **2**.

https://doi.org/10.3346/jkms.2024.39.e22

Statistical analysis

Continuous variables were presented as means ± standard deviations, while categorical variables were expressed as proportions, unless otherwise specified. Differences between the groups were analyzed using Student's *t*-test for continuous variables and χ^2 test for categorical variables. PSM analysis was conducted to compare the hepatitis B group and the control group. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org). A two-sided *P* value < 0.05 was considered statistically significant.

Ethics statement

The study protocol was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (2023-03-004, date of registration: March 20, 2023), and it adhered to the ethical guidelines of the World Medical Association Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent from individual subjects was waived.

RESULTS

Trends in the prevalence of hepatitis B patients

Table 1 displays the prevalence and total number of hepatitis B patients categorized by year. The number of patients with CHB consistently increased from 252,977 in 2007 to 319,551 in 2011, further rising to 385,188 in 2015, and reaching 485,759 in 2019. Examining the gender ratio (**Table 1**, **Supplementary Fig. 1A**), the proportion of males was 62.6% in 2007. Nevertheless, the proportion of males has continuously declined over time, reaching 58.1% in 2021 (*P* for trend < 0.001). Concurrently, the average age of hepatitis B patients continued to rise (**Table 1**). In 2007, the average age was 47.0 ± 13.3 years, whereas in 2021, it was 55.6 ± 12.2 years, reflecting a consistent increase over the span of 15 years. Analyzing the age composition ratio (**Supplementary Fig. 1B**), it is evident that the patient groups aged 55–64 years and 65 years or older experienced significant growth, while the group aged younger than 35 years decreased significantly each year.

Subsequently, the characteristics of the patients in the antiviral drug group were examined (**Supplementary Table 3**). The proportion of patients taking antiviral drugs steadily increased from 31.5% in 2007 to 52.3% in 2021. However, similar to the overall hepatitis B patient population, the proportion of males decreased over time. Additionally, the proportion of

Table 1. Demographics and characteristics of patients

Characteristics	2007 (n = 252,977)	2011 (n = 319,551)	2015 (n = 385,188)	2019 (n = 485,759)	2020 (n = 484,294)	2021 (n = 503,370)	*P*
Prevalence of CHB[a]	0.65% (252,977/39,713,140)	0.77% (319,551/41,310,764)	0.89% (385,188/43,349,016)	1.08% (485,759/45,079,519)	1.07% (484,294/45,278,721)	1.11% (503,370/45,532,980)	< 0.001
Age, yr	47.0 ± 13.3	49.1 ± 12.8	51.8 ± 12.5	54.3 ± 12.3	55.1 ± 12.2	55.6 ± 12.2	< 0.001
Male	158,282 (62.6%)	196,939 (61.6%)	234,155 (60.8%)	284,746 (58.6%)	283,568 (58.6%)	292,388 (58.1%)	< 0.001
Annual medical cost, 10^3 KRW	1,579 ± 2,869	2,228 ± 3,110	2,574 ± 3,418	2,168 ± 4,068	2,392 ± 4,186	2,512 ± 4,174	< 0.001
Annual medical cost related with medication, 10^3 KRW	539 ± 1,430	897 ± 1,601	1,255 ± 1,848	904 ± 1,794	995 ± 1,826	1,017 ± 1,691	< 0.001
Visit of outpatient clinic, day	25.7 ± 5.3	27.0 ± 5.1	27.4 ± 4.7	25.3 ± 4.7	26.7 ± 4.6	26.9 ± 4.6	< 0.001
Hospital admission, day	6.7 ± 9.8	5.4 ± 8.5	4.6 ± 7.6	3.5 ± 6.8	3.6 ± 6.4	3.5 ± 6.1	< 0.001

CHB = chronic hepatitis B, KRW = South Korea won.
[a]Prevalence was calculated by dividing the number of chronic hepatitis B patients by the number of people registered with health insurance each year.

https://doi.org/10.3346/jkms.2024.39.e22

patients taking antiviral drugs increased among both men and women aged 55–64 years and those aged 65 years or older. Conversely, the proportion of patients taking antiviral drugs decreased in all patients under 35 years of age.

Medical expenditures and healthcare utilization in CHB

Compared to the control group, patients with CHB exhibited significantly higher medical costs (**Fig. 1A**, all $P < 0.001$). The annual per-person medical costs for CHB patients increased from 1,579 ± 2,869 (10^3 KRW) (equivalent to $1,179) in 2007 to 2,574 ± 3,418 (10^3 KRW) (equivalent to $1,923) in 2015. Subsequently, there was a decrease to 2,168 ± 4,068 (10^3 KRW) (equivalent to $1,620) in 2019. In 2021, medical costs began to rise again. Additionally, CHB

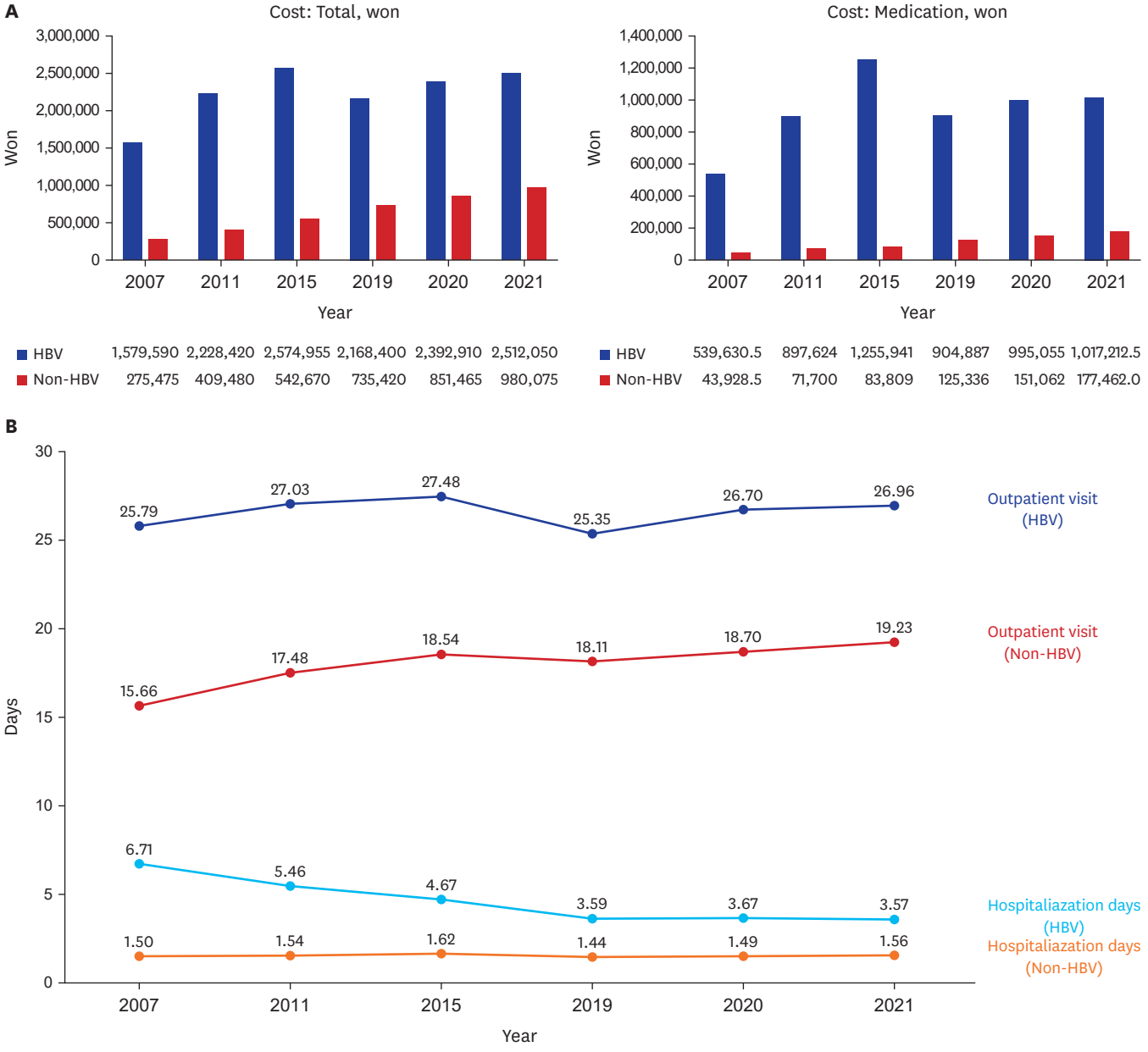

Fig. 1. Healthcare resource utilization: total medical costs (**A**) and number of visits to medical institutions (**B**).
HBV = hepatitis B virus.

https://doi.org/10.3346/jkms.2024.39.e22

patients experienced significantly higher medical costs related to medication compared to the control group (**Fig. 1B**, all $P < 0.001$). Similar to total medical costs, medication costs increased from 2007 to 2015, decreased in 2019, and increased in both 2020 and 2021.

The use of medical facilities was analyzed by categorizing the number of outpatient visits and hospitalization days. CHB patients had a significantly higher number of outpatient visits and hospitalization days compared to the control group (**Fig. 1B**, all $P < 0.001$). Throughout the 15-year observation period, the number of outpatient visits for CHB patients remained relatively stable at an average of 26 visits per year. Conversely, the number of hospitalization days displayed a continuous decreasing trend, declining from 6.7 days in 2007 to 3.57 days in 2021.

Geographical variations in healthcare utilization by residential areas

Subsequently, we conducted an analysis on the utilization patterns of medical institutions based on the patients' residential areas. The residential areas were classified into urban residents (Seoul, Gyeonggi-do, Incheon, Gwangju, Daegu, Daejeon, Busan, Ulsan), intermediate residents (Gyeongsangnam-do, Jeollabuk-do, Chungcheongnam-do), and rural residents (Gangwon-do, Gyeongsangbuk-do, Jeollanam-do, Jeju-do, Chungcheongbuk-do) based on the population distribution.

The majority of patients resided in metropolitan areas, followed by rural and intermediate areas (**Fig. 2A**). We then examined whether patients sought medical care within their residential area or opted for medical institutions outside their residential area (**Fig. 2B**). If the concentration factor exceeds 1, it indicates a preference for medical institutions within their residential area, while a factor below 1 suggests a tendency to seek healthcare outside their residence. Metropolitan residents demonstrated a higher likelihood of utilizing medical institutions within their residential area (concentration factor > 1), while intermediate or rural area residents tended to seek medical care outside their residential area (concentration factor < 1).

Subgroup analysis based on severity of liver disease: liver cirrhosis, decompensation, HCC, and liver transplantation

We conducted a subgroup analysis based on the severity of liver disease, including liver cirrhosis (all), decompensated cirrhosis, HCC, and liver transplant groups (**Table 2**). The number of patients in the liver cirrhosis, HCC, and liver transplant groups showed a continuous increase, while the number of decompensation patients began to decline from 2019 (**Fig. 3A**, P for trend < 0.001). Examining the proportions of each subgroup among all HBV patients, HCC, liver cirrhosis, and decompensation demonstrated a decreasing trend, whereas the proportion of liver transplants consistently increased (**Fig. 3B**). In terms of medical expenses and comorbidities, there was an increasing trend in medical costs following the order of liver cirrhosis, decompensation, HCC, and liver transplant. Additionally, the Charlson Comorbidity Index showed a significant increase.

Comorbidities and concurrent medications in patients with CHB

Comorbidities and concurrent medications of patients with CHB were analyzed in comparison to age- and sex-matched non-HBV controls (**Table 3**, **Supplementary Fig. 2**). In terms of comorbidities, the prevalence of cerebrovascular disease, coronary heart disease, diabetes, hyperlipidemia, hypertension, rheumatoid arthritis, osteoarthritis, osteoporosis or fracture, and chronic kidney disease was significantly higher in patients with CHB compared to the control group (all $P < 0.001$). Additionally, patients with CHB had a higher rate of taking concomitant medications, including antidiabetic, hypertension, osteoporosis,

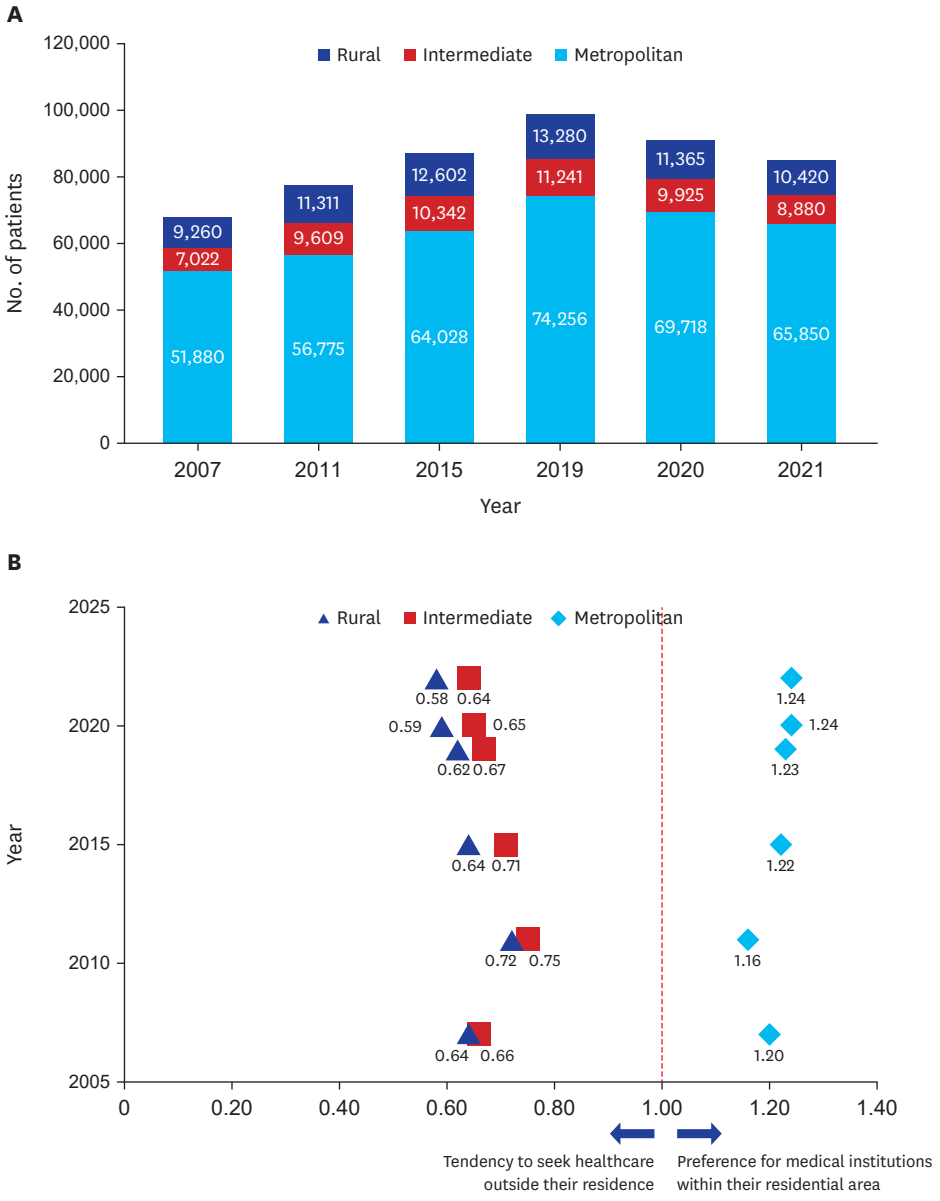

Fig. 2. Hepatitis B patient visits to medical institutions by residential area. (**A**) Number of patients by urban and rural areas, (**B**) concentration of medical care by region.

diuretics, systemic (intravenous or oral) corticosteroids, and NSAIDs, in comparison to the control group (all $P < 0.001$).

Comparison before and during COVID-19 pandemic

During COVID-19 pandemic, the number of CHB patients slightly decreased to 484,294 in 2020, coinciding with the onset of the COVID-19. Additionally, compared to 2019, the prevalence of CHB decreased from 1.08% to 1.07% in 2020. A decrease in medical facility utilization due to COVID has been observed since 2019, and the total medical cost (2,574,955 won to 2,168,400 won) and number of outpatient visit days (27.48 days to 23.35 days) decreased in the HBV group. Other than this decrease in medical facility utilization patterns, the severity of the disease or comorbidities did not show any significant changes before and after COVID-19.

https://doi.org/10.3346/jkms.2024.39.e22

Table 2. Characteristics and medical costs by severity of liver disease

Characteristics	2007 (n = 252,977)	2011 (n = 319,551)	2015 (n = 385,188)	2019 (n = 485,759)	2020 (n = 484,294)	2021 (n = 503,370)	*P*
Liver cirrhosis	63,542 (25.1)	79,241 (24.8)	106,326 (27.6)	117,497 (24.2)	117,296 (24.2)	118,054 (23.5)	< 0.001
Age, yr	52.2 ± 10.9	54.2 ± 10.5	56.0 ± 10.6	58.5 ± 10.6	59.2 ± 10.6	59.8 ± 10.6	< 0.001
Male	44,296 (69.7)	53,964 (68.1)	70,968 (66.7)	77,191 (65.7)	76,859 (65.5)	77,190 (65.1)	< 0.001
Annual medical cost, 10^3 KRW	5,128 ± 7,037	5,968 ± 8,181	6,100 ± 8,369	6,063 ± 8,962	6,956 ± 10,736	7,303 ± 11,287	< 0.001
Charlson Comorbidity Index	3.9 ± 3.0	3.4 ± 2.7	3.3 ± 2.5	3.3 ± 2.5	3.2 ± 2.5	3.2 ± 2.5	< 0.001
Decompensated cirrhosis	26,926 (10.6)	29,195 (9.1)	30,347 (7.9)	30,016 (6.2)	29,462 (6.1)	28,062 (5.6)	< 0.001
Age, yr	54.9 ± 10.4	56.5 ± 10.3	58.3 ± 10.4	60.5 ± 10.5	61.2 ± 10.5	61.7 ± 10.7	< 0.001
Male	18,587 (69.0)	19,943 (68.3)	20,403 (67.2)	19,837 (66.1)	19,421 (65.9)	19,152 (68.2)	< 0.001
Annual medical cost, 10^3 KRW	7,670 ± 8,678	9,018 ± 10,700	9,928 ± 11,762	10,570 ± 12,893	12,471 ± 15,739	13,170 ± 1,669	< 0.001
Charlson Comorbidity Index	5.7 ± 3.3	5.1 ± 3.1	5.2 ± 3.1	5.1 ± 3.0	5.0 ± 3.1	5.0 ± 3.1	< 0.001
Hepatocellular carcinoma	45,838 (18.1)	76,137 (23.8)	113,019 (29.3)	134,720 (27.7)	135,564 (28.0)	137,199 (27.3)	< 0.001
Age, yr	53.0 ± 11.9	54.1 ± 11.7	55.5 ± 11.8	58.0 ± 11.7	58.7 ± 11.7	59.4 ± 11.7	< 0.001
Male	31,380 (68.5)	49,969 (65.6)	73,070 (64.7)	85,005 (63.1)	83,394 (61.5)	85,905 (62.6)	< 0.001
Annual medical cost, 10^3 KRW	6,553 ± 8,078	6,852 ± 8,925	6,831 ± 9,136	7,455 ± 10,840	8,729 ± 12,893	9,290 ± 13,661	< 0.001
Charlson Comorbidity Index	5.1 ± 3.3	4.1 ± 2.9	3.9 ± 2.7	3.9 ± 2.7	3.9 ± 2.7	3.9 ± 2.6	< 0.001
Liver transplant	2,771 (1.1)	4,210 (1.3)	6,622 (1.7)	8,269 (1.7)	8,509 (1.8)	8,681 (1.7)	< 0.001
Age, yr	51.8 ± 8.3	54.0 ± 8.0	56.8 ± 8.4	59.3 ± 8.7	60.1 ± 8.7	60.7 ± 8.8	< 0.001
Male	2,134 (77.0)	3,274 (77.8)	5,122 (77.3)	6,406 (77.5)	6,578 (77.3)	6,706 (77.2)	< 0.001
Annual medical cost, 10^3 KRW	20,900 ± 17,960	22,827 ± 21,011	19,735 ± 18,940	16,075 ± 16,286	18,774 ± 20,958	19,179 ± 21,370	< 0.001
Charlson Comorbidity Index	4.7 ± 3.0	4.3 ± 2.6	4.1 ± 2.5	4.1 ± 2.4	4.0 ± 2.4	4.0 ± 2.4	< 0.001

Values are presented as number (%).
KRW = South Korea won.

DISCUSSION

Through our study, we have gained insights into the changing trends in the prevalence, severity, medical costs, and comorbidities of CHB over a 15-year period in South Korea, which is considered an endemic region for HBV. Additionally, we have obtained valuable information on how the healthcare utilization by CHB patients has evolved during the COVID-19 pandemic.

The initial finding of our study challenges the common perception that CHB is gradually being overcome. Instead, we have observed a consistent increase in the number of CHB patients each year. It might be related with an increase in health checkups. To find out whether the increase in the number of hepatitis B patients was due to an increase in detection due to an increase in health checkups, we additionally investigated the number of people tested for hepatitis B surface antigen (**Supplementary Table 4**). From 2007 to 2021, the number of people tested for hepatitis B surface antigen was confirmed to increase overall. The second hypothesis is cohort effects. In the case of hepatitis B, a cure is rare, and cohort effects accumulate over several decades, contributing to the ongoing rise in the number of patients.[14,15] In other words, individuals born before 1992, when the hepatitis B vaccine was actively recommended, continue to exhibit a high prevalence of the disease due to the cohort effect. It was not until 2002 that the South Korean government initiated medical support for the hepatitis B vaccine, specifically targeting newborns.[16-18] Given that the positive rate of hepatitis B surface antigen remains notably high among individuals in their 30s to 60s (30s: 3.0%; 40s: 3.3%; 50s: 5.0%; 60s: 4.4%), we anticipate that this cohort effect will persist for at least another 30 years into the future.[6] Furthermore, the rise in hepatitis B prevalence could be attributed to the increasing number of North Korean defectors and foreign workers (such as those from China and Mongolia) who have a higher prevalence of hepatitis B compared to South Koreans.[19,20] Therefore, despite the declining HBsAg positivity rate, it is imperative to maintain ongoing public health concerns and research pertaining to hepatitis B.[21]

https://doi.org/10.3346/jkms.2024.39.e22

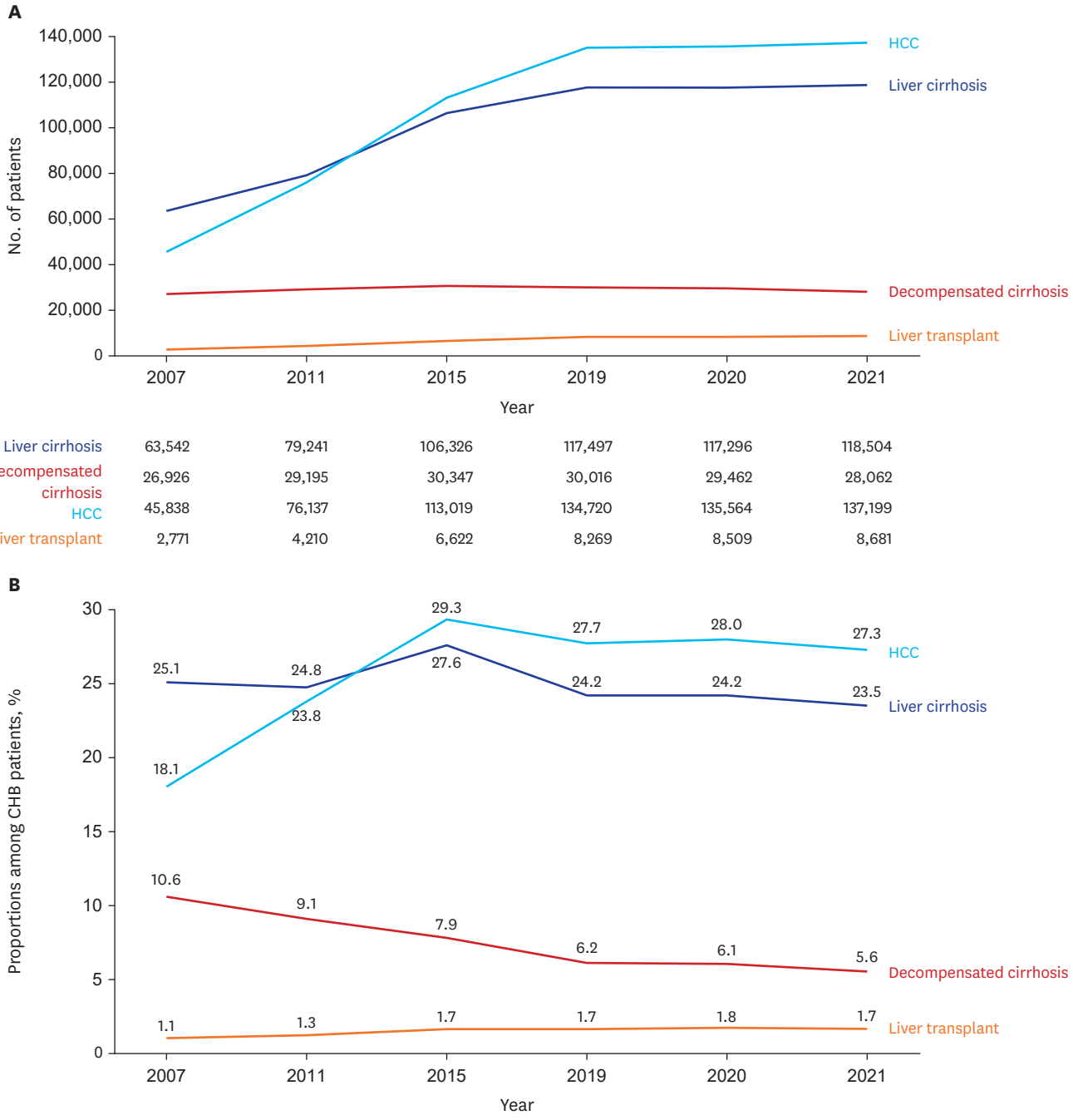

Fig. 3. Subgroup analysis: total number (**A**) and proportion of patients (**B**) by liver disease severity.
HCC = hepatocellular carcinoma, CHB = chronic hepatitis B.

The second significant finding of our study is the changing global characteristics of hepatitis B patients. Historically, a substantial proportion of patients with CHB were middle-aged men in their 50s and 60s. However, we have observed a declining trend in male dominance, and similar to hepatitis C, there has been a rapid increase in the number of patients aged 65 years or older. This shift indicates a shift in the demographics of hepatitis B patients. The observed increase in the average age of hepatitis B patients can be interpreted as a collective decrease in the severity of liver disease. This can be attributed to the availability of effective antiviral

https://doi.org/10.3346/jkms.2024.39.e22

JKMS

Table 3. Comparison of comorbidities and concurrent medication between the HBV group and the control group

Characteristics	2007		2011		2015		2019		2020		2021	
	HBV (n = 253,002)	Control (n = 1,011,908)	HBV (n = 319,551)	Control (n = 1,278,204)	HBV (n = 385,188)	Control (n = 1,540,752)	HBV (n = 485,759)	Control (n = 1,943,036)	HBV (n = 484,294)	Control (n = 1,937,176)	HBV (n = 503,370)	Control (n = 2,013,480)
Comorbidities												
Cerebrovascular disease	10,610 (4.2)	30,590 (3.0)	12,225 (3.8)	42,549 (3.3)	16,208 (4.2)	59,092 (3.8)	28,505 (5.9)	107,422 (5.5)	28,226 (5.8)	106,633 (5.5)	30,102 (6.0)	116,185 (5.8)
Coronary heart disease	17,695 (7.0)	39,611 (3.9)	19,863 (6.2)	55,405 (4.3)	23,951 (6.2)	76,822 (5.0)	33,670 (6.9)	115,259 (5.9)	34,352 (7.1)	115,977 (6.0)	37,053 (7.4)	128,202 (6.4)
Diabetes	45,292 (17.9)	74,681 (7.4)	66,569 (20.8)	143,677 (11.2)	89,093 (23.1)	218,555 (14.2)	128,874 (26.5)	354,598 (18.2)	132,400 (27.3)	370,117 (19.1)	143,615 (28.5)	417,344 (20.7)
Dyslipidemia	68,495 (27.1)	113,996 (11.3)	108,414 (33.9)	228,259 (17.9)	176,237 (45.8)	394,273 (25.6)	272,084 (56.0)	678,875 (34.9)	278,516 (57.5)	706,965 (36.5)	284,416 (56.5)	751,815 (37.3)
Hypertension	66,846 (26.4)	184,123 (18.2)	80,942 (25.3)	254,768 (19.9)	107,436 (27.9)	350,393 (222.7)	170,088 (35.0)	584,287 (30.1)	176,824 (36.5)	606,529 (31.3)	188,745 (37.5)	661,640 (32.9)
Rheumatoid arthritis	7,073 (2.8)	17,652 (1.7)	7,939 (2.5)	21,571 (1.7)	11,269 (2.9)	30,985 (2.0)	16,688 (3.4)	45,712 (2.4)	16,669 (3.4)	44,332 (2.3)	17,983 (3.6)	49,488 (2.5)
Osteoarthritis	35,511 (14.0)	115,772 (11.4)	53,030 (16.6)	185,244 (14.5)	79,307 (20.6)	279,728 (18.2)	119,809 (24.7)	434,300 (22.4)	115,286 (23.8)	419,280 (21.6)	125,629 (25.0)	460,868 (22.9)
Fracture/ osteoporosis	18,881 (7.5)	54,404 (5.4)	32,331 (10.1)	101,427 (7.9)	45,073 (11.7)	137,380 (8.9)	73,861 (15.2)	218,312 (11.2)	74,162 (15.3)	218,855 (11.3)	81,567 (16.2)	241,564 (12.0)
Chronic kidney disease	3,093 (4.9)	2,911 (0.3)	5,608 (1.8)	6,295 (0.5)	8,317 (2.2)	11,623 (0.8)	13,531 (2.8)	22,493 (1.2)	14,200 (2.9)	23,866 (1.2)	15,226 (3.0)	26,857 (1.3)
Concomitant medication												
Diabetes	24,810 (9.8)	58,009 (5.7)	35,689 (11.2)	94,877 (7.4)	47,911 (12.4)	140,747 (9.1)	76,356 (15.7)	231,988 (11.9)	79,641 (16.4)	245,294 (12.7)	84,075 (16.7)	271,240 (13.5)
Dyslipidemia	23,910 (9.5)	71,617 (7.1)	38,611 (12.1)	149,807 (11.7)	63,242 (16.4)	262,886 (17.1)	114,548 (23.6)	474,879 (24.4)	128,788 (26.6)	524,619 (27.1)	145,744 (29.0)	601,332 (29.9)
Hypertension	54,307 (21.5)	164,723 (16.3)	78,084 (24.4)	259,229 (20.3)	102,331 (26.6)	352,098 (22.9)	151,744 (31.2)	527,704 (27.2)	158,124 (32.7)	548,733 (28.3)	168,760 (33.5)	596,830 (29.6)
Diuretics	35,939 (14.2)	63,548 (6.3)	36,552 (11.4)	67,773 (5.3)	34,459 (8.9)	70,740 (4.6)	45,200 (9.3)	104,614 (5.4)	44,718 (9.2)	103,606 (5.3)	45,567 (9.1)	110,806 (5.5)
Osteoporosis	16,611 (6.6)	46,740 (4.6)	25,391 (7.9)	76,966 (6.0)	32,902 (8.5)	103,940 (6.7)	93,474 (19.2)	274,508 (14.1)	95,019 (19.6)	279,265 (14.4)	100,716 (20.0)	304,594 (15.1)
NSAIDs	166,016 (65.6)	599,483 (59.2)	228,698 (71.6)	839,530 (65.7)	282,988 (73.5)	1,052,686 (68.3)	385,234 (79.3)	1,434,140 (73.8)	352,543 (72.8)	1,305,658 (67.4)	357,628 (71.0)	1,331,877 (66.1)
Corticosteroid	68,290 (27.0)	254,264 (25.1)	98,013 (30.7)	372,868 (29.2)	128,771 (33.4)	495,368 (32.2)	247,548 (51.0)	901,866 (46.4)	223,185 (46.1)	798,637 (41.2)	227,552 (45.2)	817,606 (40.6)

Values are presented as number (%).
HBV = hepatitis B virus, NSAID = nonsteroidal anti-inflammatory drug.

drugs and an improvement in the prognosis of individuals with hepatitis B. These factors might have contributed to an overall improvement in the management and outcomes of hepatitis B patients.[22,23] With the increasing number of elderly patients and improving prognosis of HBV, clinicians need to prioritize the aspects of quality of life. It is crucial for clinicians to be prepared to address the needs of elderly patients with CHB who often have comorbidities and require multiple concomitant medications. Specifically, given the higher prevalence of renal dysfunction and osteoporosis among CHB patients compared to the control group, careful consideration is necessary when selecting antiviral treatments.[24] Another notable change in patients with CHB is the declining the proportion of decompensated cirrhosis, and this might be related with effectiveness of antiviral therapies.[25,26] This can be inferred from the decreasing proportion of decompensation patients, as well as the rates of liver cirrhosis and hospitalization days.[27] However, it is essential to note the increasing incidence of HCC and liver transplantation. We think that there are some putative reasons to explain the increasing number of HCC among CHB since the effective antiviral therapy was introduced. Age is well-known risk factor of HCC. If more patients with CHB could survive longer, more patients could have a chance to have HCC. Also, the early diagnosis and more sophisticated treatment for HCC might lead to longer survival of HCC patients, which might attribute the increase or maintenance of the number of HCC forward.

The third significant finding of our study pertains to the medical costs associated CHB patients. Notably, a considerable portion of the medical expenses incurred were attributed to the costs of antiviral drugs. In contrast to the control group, the overall medical costs for the CHB group showed a decline between 2015 and 2019. This reduction can be attributed to the introduction of generic drugs like tenofovir DF or entecavir after the expiration of the patent period, leading to a decrease in the overall drug prices. Although patients with CHB exhibited higher medical costs compared to the control group, the majority of these costs demonstrated a significant surge following the development of decompensated cirrhosis or HCC.[28] Given the recent surge in the use of costly antiviral medications, which often require long-term administration, there is a potential for further escalation in medication costs. However, considering the significant reduction in the incidence of HCC and complications related to cirrhosis

https://doi.org/10.3346/jkms.2024.39.e22

due to the use of these drugs, it can be concluded that the active use of antiviral medications is cost-effective when considering the overall disease progression.[29]

Lastly, the present study showed the potential impact of the COVID-19 pandemic on changes in healthcare utilization patterns among CHB patients. Among them, both the number of outpatient visits and overall medical costs significantly decreased during the COVID-19 pandemic compared to the control group. Several factors may explain this finding. First, South Korea, with its relatively small land area and a national medical insurance system that is affordable and accessible, had limited adoption of telemedicine and remote care compared to Western countries during the COVID-19 pandemic. Second, healthcare systems had to prioritize essential services during the pandemic, resulting in the postponement or cancellation of non-urgent medical procedures and consultations.[30] This likely caused delays in routine liver monitoring, imaging, and other elective procedures for CHB patients. To ensure that CHB patients receive appropriate care and support throughout future endemic situations, it is crucial for healthcare providers to monitor and adapt to these changes effectively.

In conclusion, the number of CHB patients in South Korea continues to increase annually. The patient population is aging, and the dominance of males among CHB patients is gradually declining. CHB patients experience higher medical costs, medication costs, outpatient visits, and longer hospitalization days compared to the control group, particularly as the disease progresses to cirrhosis and HCC. Furthermore, the CHB group exhibits a higher prevalence of comorbidities and greater medication use compared to the control group. Fortunately, effective antiviral treatment has led to a gradual reduction in the severity of liver disease among CHB patients. During the COVID-19 pandemic, the CHB patient group experienced a significant decrease in the number of visits to medical institutions, but there were indications of a slow recovery. Future research should focus on understanding the long-term implications of these changes on disease progression, management strategies, and health outcomes for CHB patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Comorbidity

Supplementary Table 2
Concomitant medication

Supplementary Table 3
Distribution of patients prescribed with antiviral drugs by age

Supplementary Table 4
Number of people tested for HBsAg by year

Supplementary Fig. 1
Total number of patients with chronic hepatitis B (**A**) and composition by age (**B**).

Supplementary Fig. 2
Comparison of (**A**) comorbidities and (**B**) medications taken across the chronic hepatitis B and control groups.

https://doi.org/10.3346/jkms.2024.39.e22

REFERENCES

1. Chien RN, Liaw YF. Current trend in antiviral therapy for chronic hepatitis B. *Viruses* 2022;14(2):434. PUBMED | CROSSREF
2. Broquetas T, Carrión JA. Current perspectives on nucleos(t)ide analogue therapy for the long-term treatment of hepatitis B virus. *Hepat Med* 2022;14:87-100. PUBMED | CROSSREF
3. Les I, García-Martínez R, Córdoba J, Quintana M, Esteban R, Buti M. Current trends in chronic hepatitis B management: results of a questionnaire. *Eur J Gastroenterol Hepatol* 2009;21(10):1177-83. PUBMED | CROSSREF
4. Perrillo RP, Marcellin P. Effect of newer oral antiviral agents on future therapy of chronic hepatitis B. *Antivir Ther* 2010;15(1):13-22. PUBMED | CROSSREF
5. Liu LZ, Sun J, Hou J, Chan HL. Improvements in the management of chronic hepatitis B virus infection. *Expert Rev Gastroenterol Hepatol* 2018;12(11):1153-66. PUBMED | CROSSREF
6. Yim SY, Kim JH. The epidemiology of hepatitis B virus infection in Korea. *Korean J Intern Med* 2019;34(5):945-53. PUBMED | CROSSREF
7. Sinn DH. Natural history and treatment indications of chronic hepatitis B. *Korean J Gastroenterol* 2019;74(5):245-50. PUBMED | CROSSREF
8. Korean Liver Cancer Association (KLCA); National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. *J Liver Cancer* 2023;23(1):1-120. PUBMED | CROSSREF
9. Choi S, Kim BK, Yon DK, Lee SW, Lee HG, Chang HH, et al. Global burden of primary liver cancer and its association with underlying aetiologies, sociodemographic status, and sex differences from 1990-2019: a DALY-based analysis of the Global Burden of Disease 2019 study. *Clin Mol Hepatol* 2023;29(2):433-52. PUBMED | CROSSREF
10. Pley CM, McNaughton AL, Matthews PC, Lourenco J. The global impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of hepatitis B virus (HBV) infection. *BMJ Glob Health* 2021;6(1):e004275. PUBMED | CROSSREF
11. Kim Y, Gordon A, Rowerdink K, Herrera Scott L, Chi W. The impact of the COVID-19 pandemic on health care utilization among insured individuals with common chronic conditions. *Med Care* 2022;60(9):673-9. PUBMED | CROSSREF
12. Kondili LA, Buti M, Riveiro-Barciela M, Maticic M, Negro F, Berg T, et al. Impact of the COVID-19 pandemic on hepatitis B and C elimination: an EASL survey. *JHEP Rep* 2022;4(9):100531. PUBMED | CROSSREF
13. Xiridou M, Adam P, Meiberg A, Visser M, Matser A, de Wit J, et al. The impact of the COVID-19 pandemic on hepatitis B virus vaccination and transmission among men who have sex with men: a mathematical modelling study. *Vaccine* 2022;40(33):4889-96. PUBMED | CROSSREF
14. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021;7(1):6. PUBMED | CROSSREF
15. Halegoua-De Marzio D, Hann HW. Then and now: the progress in hepatitis B treatment over the past 20 years. *World J Gastroenterol* 2014;20(2):401-13. PUBMED | CROSSREF
16. Kim DY. History and future of hepatitis B virus control in South Korea. *Clin Mol Hepatol* 2021;27(4):620-2. PUBMED | CROSSREF
17. Song BG, Sinn DH, Kang W, Gwak GY, Paik YH, Choi MS, et al. Changes in the prevalence of hepatitis B and metabolic abnormalities among young men in Korea. *Korean J Intern Med* 2022;37(5):1082-7. PUBMED | CROSSREF
18. Lee YS, Lee HS, Kim JH, Chang SW, Hyun MH, Bak H, et al. Role of tenofovir disoproxil fumarate in prevention of perinatal transmission of hepatitis B virus from mother to child: a systematic review and meta-analysis. *Korean J Intern Med* 2021;36(1):76-85. PUBMED | CROSSREF
19. Cho EJ, Kim SE, Suk KT, An J, Jeong SW, Chung WJ, et al. Current status and strategies for hepatitis B control in Korea. *Clin Mol Hepatol* 2017;23(3):205-11. PUBMED | CROSSREF
20. Choi HR, Kim BS, Won CW, Ahn HC. HBsAg and anti-HBs prevalence in North Korean defectors. *J Korean Acad Fam Med* 1999;20(12):1778-83.
21. Yoo SH, Kim SS, Kim SG, Kwon JH, Lee HA, Seo YS, et al. Current status of ultrasonography in national cancer surveillance program for hepatocellular carcinoma in South Korea: a large-scale multicenter study. *J Liver Cancer* 2023;23(1):189-201. PUBMED | CROSSREF
22. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67(4):1560-99. PUBMED | CROSSREF

23. GBD 2019 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol* 2022;7(9):796-829. PUBMED | CROSSREF

24. Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. *Clin Mol Hepatol* 2019;25(2):93-159. PUBMED | CROSSREF

25. Kim DS, Park SY, Kim BK, Park JY, Kim DY, Han KH, et al. Revised Korean antiviral guideline reduces the hepatitis B-related hepatocellular carcinoma risk in cirrhotic patients. *J Korean Med Sci* 2021;36(16):e105. PUBMED | CROSSREF

26. Lee HW. Long term efficacy of antiviral therapy: mortality and incidence of hepatocellular carcinoma. *Korean J Gastroenterol* 2019;74(5):251-7. PUBMED | CROSSREF

27. Jang WY, Chung WJ, Jang BK, Hwang JS, Lee HJ, Hwang MJ, et al. Changes in characteristics of patients with liver cirrhosis visiting a tertiary hospital over 15 years: a retrospective multi-center study in Korea. *J Korean Med Sci* 2020;35(29):e233. PUBMED | CROSSREF

28. Jang W, Lee HW, Lee JS, Kim BK, Kim SU, Park JY, et al. Clinical characteristics and prognosis of Korean patients with hepatocellular carcinoma with respect to etiology. *J Liver Cancer* 2022;22(2):158-66. PUBMED | CROSSREF

29. Lee H, Kim BK, Jang S, Ahn SH. Cost-effectiveness analysis of antiviral therapy for untreated minimally active chronic hepatitis B to prevent liver disease progression. *Clin Transl Gastroenterol* 2021;12(2):e00299. PUBMED | CROSSREF

30. Webb E, Hernández-Quevedo C, Williams G, Scarpetti G, Reed S, Panteli D. Providing health services effectively during the first wave of COVID-19: a cross-country comparison on planning services, managing cases, and maintaining essential services. *Health Policy* 2022;126(5):382-90. PUBMED | CROSSREF