Original Article
J Liver Cancer 2024;24(2):274-285
pISSN 2288-8128 • eISSN 2383-5001
https://doi.org/10.17998/jlc.2024.08.13

Evolving trends in treatment patterns for hepatocellular carcinoma in Korea from 2008 to 2022: a nationwide population-based study

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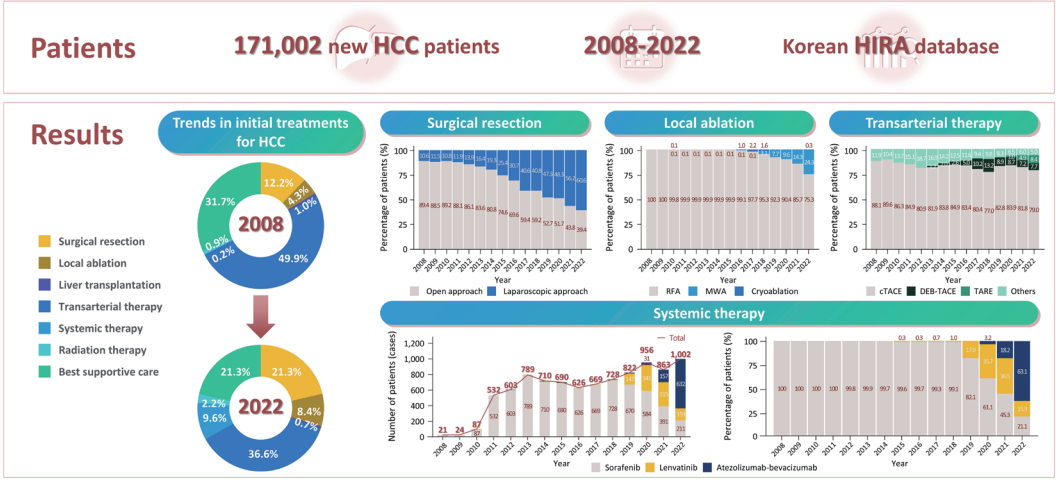

Received Jul. 24, 2024 • **Revised** Aug. 9, 2024 • **Accepted** Aug. 13, 2024

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Evolving trends in treatment patterns for hepatocellular carcinoma in Korea from 2008 to 2022: a nationwide population-based study

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Backgrounds/Aims: The treatment landscape for hepatocellular carcinoma (HCC) has significantly evolved over the past decade. We aimed to analyze trends in treatment patterns for HCC using a nationwide claims database from the Korean Health Insurance Review and Assessment Service.

Methods: This retrospective population-based cohort study analyzed 171,002 newly diagnosed HCC patients between 2008 and 2022. Etiologies and treatment modalities were categorized based on the ICD-10 codes and insurance data.

Results: The annual incidence decreased from 11,814 in 2008 to 10,443 in 2022. However, patients aged ≥70 increased noticeably, with those aged ≥80 rising from 3.8% in 2008 to 13.1% in 2022. From 2008 to 2022, the predominant cause of hepatitis B virus decreased from 68.9% to 59.7%, whereas nonalcoholic fatty liver disease increased from 8.9% to 15.8%. The initial treatment trends shifted: surgical resection and systemic therapy increased from 12.2% to 21.3% and from 0.2% to 9.6%, whereas transarterial therapy decreased from 49.9% to 36.6%. Best supportive care decreased from 31.7% to 21.3%. In the subgroup analysis, laparoscopic resection rate increased from 10.6% to 60.6% among the surgical resections. Sorafenib initially accounted for 100%, lenvatinib peaked at 36.5% in 2021, and atezolizumab-bevacizumab became the most widely used (63.1%) by 2022 among the systemic therapies.

Conclusions: This study demonstrates the temporal changes in the treatment patterns of Korean HCC patients. Surgical resection, particularly laparoscopic liver resection, and systemic therapy has increased significantly. These changes may have been influenced by reimbursement policies and advances in clinical research. **(J Liver Cancer 2024;24:274-285)**

Keywords: Hepatocellular carcinoma; Clinical practice patterns; Korea

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a significant health burden in Korea, as indicated by the high number of deaths attributed to this disease. In 2020, HCC was the second leading cause of cancer-related deaths in Korea, following lung cancer, with 10,565 deaths recorded.[1] The age-specific mortality rates further emphasize the severe impact of HCC, which is the leading cause of cancer-related deaths among individuals in their 40s and 50s in Korea.[1] Over the years, advancements in HCC treatment modalities have contributed to improved survival rates. Data from the Korean Primary Liver Cancer Registry 2012-2014 indicated that survival rates have steadily increased, with significant improvements in recent years.[2]

HCC treatment has shown substantial advancements over the years, marked by several key turning points from early to advanced-stage HCC.[3] First, liver resection has greatly reduced postoperative mortality from approximately 13.3% in the 1980s to approximately 1% in the 2010s,[4] and the 5-year survival rate has increased from 10.4% in the 1980s to 79% between 2008 and 2012.[5] Among various factors, improved selection criteria and the introduction of minimally invasive surgical techniques represent major milestones. Furthermore, there has been a rapid evolution in systemic treatment options for HCC. Since the introduction of sorafenib in 2007,[6] several new therapies have been approved, including lenvatinib,[7] atezolizumab-bevacizumab (AB),[8] and durvalumab-tremelimumab.[9] These advancements have expanded the role of systemic therapy. They are now integral to the treatment guidelines set forth by various professional societies, including the Korean Liver Cancer Association-National Cancer Center.[10,11]

The initial treatment patterns for HCC have also undergone significant changes. Data from the Korean National Health Insurance Service (NHIS) database (2008-2018) demonstrated a decline in the use of best supportive care alongside an increase in surgical resection and systemic therapies.[12] This shift underscores the importance of continuously updating treatment strategies and guidelines to reflect current practices and improve pa-

tient outcomes. Therefore, it is crucial to investigate the latest data regarding the current status of HCC treatment to achieve such advancements. In particular, it is important to examine data following the approval of AB in 2020 and its subsequent coverage by the Korean National Health Insurance in 2022. In this study, we analyzed the evolving treatment patterns of over 170,000 patients with HCC from 2008 to 2022 using the Korean Health Insurance Review and Assessment Service (HIRA) claims database.

METHODS

Study design and data source

This retrospective population-based cohort study used data extracted from the HIRA claims database. HIRA maintains a National Health Insurance (NHI) database that covers all medical claims in Korea and as they are generated in the process of reimbursing claims for healthcare services under the NHI system in Korea.[13] It contains healthcare information for almost the Korean population, including demographics, in-hospital treatment, disease diagnosis, prescription, and provider information.[14] The NHI system has covered almost all of Korea's total population, which numbered approximately 50 million as of 2014.[14] This study was conducted per the declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital with a waiver of informed consent (IRB number, X-2312-868-903).

Study population and clinical variables

This study aimed to investigate trends in treatment patterns for HCC in South Korea. Disease diagnosis was based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes, with data on procedures and prescriptions in the HIRA database. A total of 242,796 patients with HCC were enrolled from January 1, 2008 to December 31, 2022. In Korea, HCC was defined as ICD-10 code C22.0 with a cancer-specific deductible insurance code (V193). We excluded 71,794 patients for the following reasons: 1) history of prior treatment for HCC within 1 year before January 1, 2008 (washout period) (n=25,433), 2) diagnosis of other malignancies before HCC diagnosis (n=42,707), and 3) primary treatment for malignancies other than HCC in patients with multiple primary cancers (n=3,654). In the final analysis, 171,002 patients newly diagnosed with HCC were enrolled from January 1, 2008 to December 31, 2022 (Fig. 1).

The etiologies of HCC are categorized as hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and others (autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, Budd-Chiari syndrome, and cryptogenic). Cases in which HBV- or HCV-related diagnostic codes or the corresponding antiviral agents for HBV or HCV were used once during the study period were regarded as HBV- or HCV-related, respectively (Supplementary Table 1). Cases in which ALD diagnostic codes were present at least once were defined as ALD-related. NAFLD was determined based on diagnostic codes. We also defined NAFLD as cases with diagnostic codes for diabetes mellitus if the patients did not have any cause for the above-mentioned chronic liver diseases (Supplementary Table 1). When patients had more than two of the etiology of HCC, we classified them in the following order: HBV, HCV, others (Wilson's disease, autoimmune hepatitis, primary biliary cholangitis, and Budd-Chiari syndrome), ALD, NAFLD, and others (cryptogenic), which prioritizes causes based on the relative strength of their association with HCC.[15] For instance, we regarded HBV as the etiology of HCC if the patient has chronic hepatitis B and NAFLD in the present study. However, patients with autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, or Budd-Chiari syndrome were excluded from the NAFLD group and were considered as part of the other group.

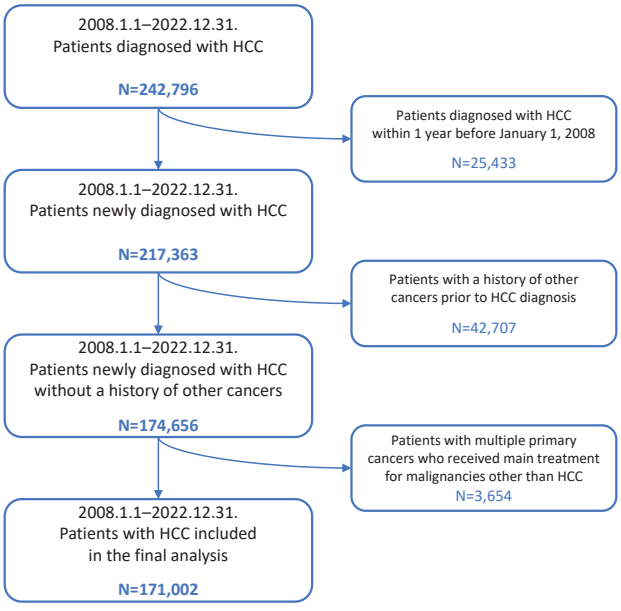

Figure 1. Study flow chart regarding initial treatments for HCC. HCC, hepatocellular carcinoma.

Treatment modalities for HCC were classified into surgical resection (including laparoscopic surgical resection), liver transplantation, local ablation therapy (radiofrequency ablation [RFA], microwave ablation [MWA], and cryoablation), transarterial therapy (conventional transarterial chemoembolization [cTACE], drug-eluting beads transarterial chemoembolization [DEB-TACE], transarterial radioembolization [TARE], or other transarterial therapy), radiation therapy, and systemic treatment (sorafenib, lenvatinib, and AB), and best supportive care. cTACE was defined as the use of lipiodol and the chemotherapeutic agents doxorubicin or cisplatin. DEB-TACE was defined as the use of DC beads or HepaSpheres (Supplementary Table 2). Cases in which either lipiodol or chemotherapeutic agents such as doxorubicin, cisplatin, or 5-fluorouracil alone were considered as other transarterial therapies. Best supportive care (BSC) was defined as the absence of treatment for HCC after its diagnosis. We excluded patients who received 1st line systemic treatment other than HCC (sorafenib for thyroid cancer and renal cell carcinoma, lenvatinib for thyroid cancer, atezolizumab for lung cancer, and bevacizumab for lung cancer, colorectal cancer, breast cancer, ovarian cancer, cervical cancer, and renal cell carcinoma).

Statistical analysis

The clinical outcomes in the present study were analyzed as follows. We investigated the annual and crude incidence rates of HCC. The annual incidence of HCC was determined based on the number of patients with HCC each year. The crude incidence rate was defined as cases per 100,000 persons, which was calculated using the mid-year resident registration population each year.[16] The annual incidence rate and the crude incidence rate of HCC were analyzed by etiology of HCC (HBV, HCV, alcohol, NAFLD, and others), and age group (<29, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥80 years). Second, the trend in initial treatment for HCC was investigated between 2008 and 2022. Initial treatments refers to the first therapeutic intervention after diagnosis, including surgery, transarterial therapy, or systemic therapy. First-line systemic therapy, on the other hand, refers to the first systemic therapy administered as an initial treatment or following other treatments. The treatment modalities were classified as surgical resection, local ablation therapy, liver transplantation, transarterial therapy, systemic treatment, radiation therapy, or BSC. We also analyzed the trend of initial treatment for HCC according to age group, HCC etiology (viral vs. non-viral), and place of residence (metropolitan [Seoul, Incheon, and Gyeonggi-do] vs. non-metropolitan areas). The index year of the initial treatment for HCC was determined based on the year of HCC diagnosis, excluding the analysis of first-line systemic therapy. First-line systemic therapy was calculated based on the date of the initial prescription of each systemic agent. Finally, detailed subgroup analyses were conducted on the initial HCC treatment according to each modality: surgical resection (open and laparoscopic approaches), local ablation therapy (RFA, MWA, and cryoablation), transarterial therapy (cTACE, DEB-TACE, TARE, and other transarterial therapies), and first-line systemic treatment (sorafenib, lenvatinib, and AB). Additionally, the annual number of treatments performed and the number of patients treated with each modality were investigated by year. R software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/) was used for the statistical analyses. GraphPad Prism (version 6.0; GraphPad Software, La Jolla, CA, USA) was used for the statistical analyses and graph generation.

RESULTS

Epidemiology

We first investigated whether the epidemiology of HCC in Korea changed during the study period, as it can affect treatment patterns. Regarding the annual incidence, there was a gradual decrease in the total number of newly diagnosed HCC cases from 2008 to 2022. In 2008, there were 11,814 cases, which slightly decreased to 10,443 cases by 2022 (Supplementary Fig. 1A). The male-to-female ratio is 3.56:1, showing a slight decrease from 3.62:1 in 2008 to 3.39:1 in 2022. In addition, the crude incidence rate (CR) per 100,000 people, calculated using the midyear resident registration population for each year, also showed a declining trend. In 2008, the CR was 23.9 cases per 100,000 people, which is reduced to 20.4 cases per 100,000 by 2022 (Supplementary Fig. 1A), indicating a slight overall decrease in the incidence of HCC over the observed period.

Next, we investigated the age-specific trends in the number of cases and CRs. The distribution of HCC cases across different age groups showed a significant concentration in older age groups. Specifically, the 70s and 80s or older age groups showed a marked increase in cases compared to previous years (Supplementary Fig. 1B). Furthermore, the CR increased from 61.1 to 67.4 per 100,000 people from 2008 to 2022 for the 80s or older age group. In contrast, other age groups showed a gradual decrease in CR (Supplementary Fig. 1B). Importantly, in 2008,

the 80s or older group accounted for 3.8% of HCC cases, which grew to 13.1% by 2022. Similarly, the proportion of 60s or more patients from 48.0% in 2008 to 67.0% in 2022 (Fig. 2A). Collectively, these data suggest a notable increase in the proportion of the elderly population with HCC.

In terms of the etiology of HCC, the distribution of HCC cases by etiology also revealed a shift over the years. HBV infection remains the predominant cause, accounting for the majority of cases. However, the number of cases attributed to ALD and NAFLD is expected to increase significantly by 2022 (Supplementary Fig. 1C). The percentage distribution reflected these changes. In 2008, HBV accounted for 68.9% of all HCC cases; however, this percentage will decrease to 59.7% by 2022. Meanwhile, the proportion of cases attributed to NAFLD increased from 7.5% in 2008 to 11.8% in 2022, and that of ALD increased from 8.9% to 15.8% during the same period (Fig. 2B, Supplementary Fig. 1C). These trends indicate a shifting landscape in the etiology of HCC, with a growing emphasis on non-viral etiologies, including ALD and NAFLD.

Initial treatment

Importantly, we analyzed the distribution of initial treatment modalities for HCC, which have evolved over the years (Fig. 3). In patients diagnosed with HCC in 2008, transarterial therapy was the predominant treatment, accounting for 5,890 cases (49.9%). However, by 2022, the proportion of transarterial therapy had decreased to 3,820 cases (36.6%). Surgical resection increased from 1,435 cases (12.2%) in 2008 to 2,221 cases (21.3%) in 2022. Only 21 cases (0.2%) of patients diagnosed with HCC in 2008 received systemic therapy, but this proportion increased to 1,002 cases (9.6%) by 2022. These trends highlight the increasing use of surgical resection and systemic therapy for HCC treatment, reflecting advancements in these treatments and their broader acceptance. The BSC decreased from 3,742 cases (31.7%) in 2008 to 2,226 cases (21.3%) in 2022, indicating a shift towards more active treatments.

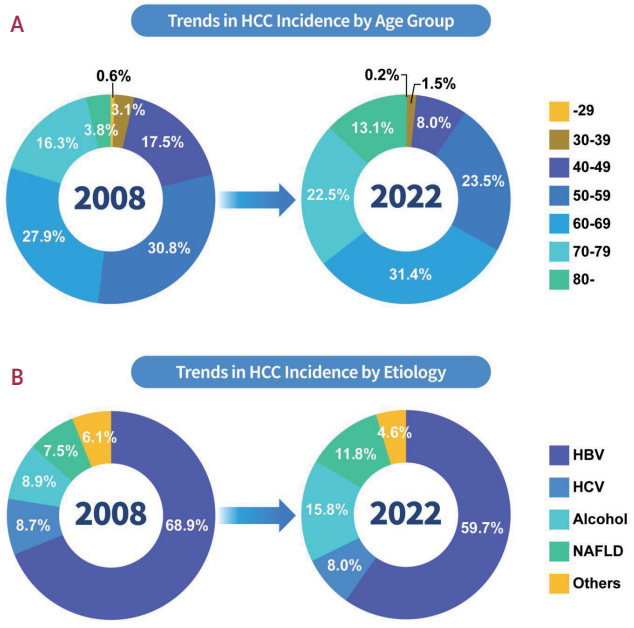

Figure 2. Comparison of the trends in incidence of HCC by age group and etiology between 2008 and 2022. (A) The percentage of HCC incidence by age group. (B) The percentage of HCC incidence by etiology. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

Subgroup analyses for the initial treatment

We then analyzed each treatment method by subdividing it into more specific categories. Surgical resection methods have seen significant changes between 2008 and 2022. The proportion of laparoscopic resections increased substantially from 10.6% in 2008 to 60.6% in 2022, indicating a shift towards minimally invasive surgical techniques (Fig. 4A). Local ablation techniques, including RFA, MWA, and cryoablation, have been introduced, and evolved over time. Although RFA remained dominant, accounting for 100% of the local ablations in 2008, its proportion decreased to 75.3% by 2022. MWA and cryoablation have been increasingly adopted, reaching 24.3% and 0.3% by 2022 (Fig. 4B). Transarterial therapy methods, such as cTACE, DEB-TACE, and TARE, have also evolved. cTACE, which accounted for 88.1% of transarterial therapies in 2008, decreased to 79.0% by 2022. DEB-TACE and TARE were introduced later, accounting for 7.7% and 8.4%, respectively, by 2022 (Fig. 4C).

The pattern of systemic therapy as the initial treatment for HCC has also changed markedly. Notably, the introduction of new systemic therapies, such as AB and lenvatinib, has significantly altered the treatment landscape. Lenvatinib accounted for 35.7% and 36.5% in 2020 and 2021, respectively; however, this proportion decreased to 15.9% by 2022. AB accounted for 18.2% of systemic therapy cases in 2021 following approval but rose to 63.1% by 2022 following the introduction of national health insurance reimbursement (Fig. 4D).

We also performed subgroup analyses of the initial treatment according to age, etiology, and place of residence. In the 30s, 40s, and 50s age groups, treatment patterns remained relatively stable; however, in the 70s and 80s age groups, surgical resection

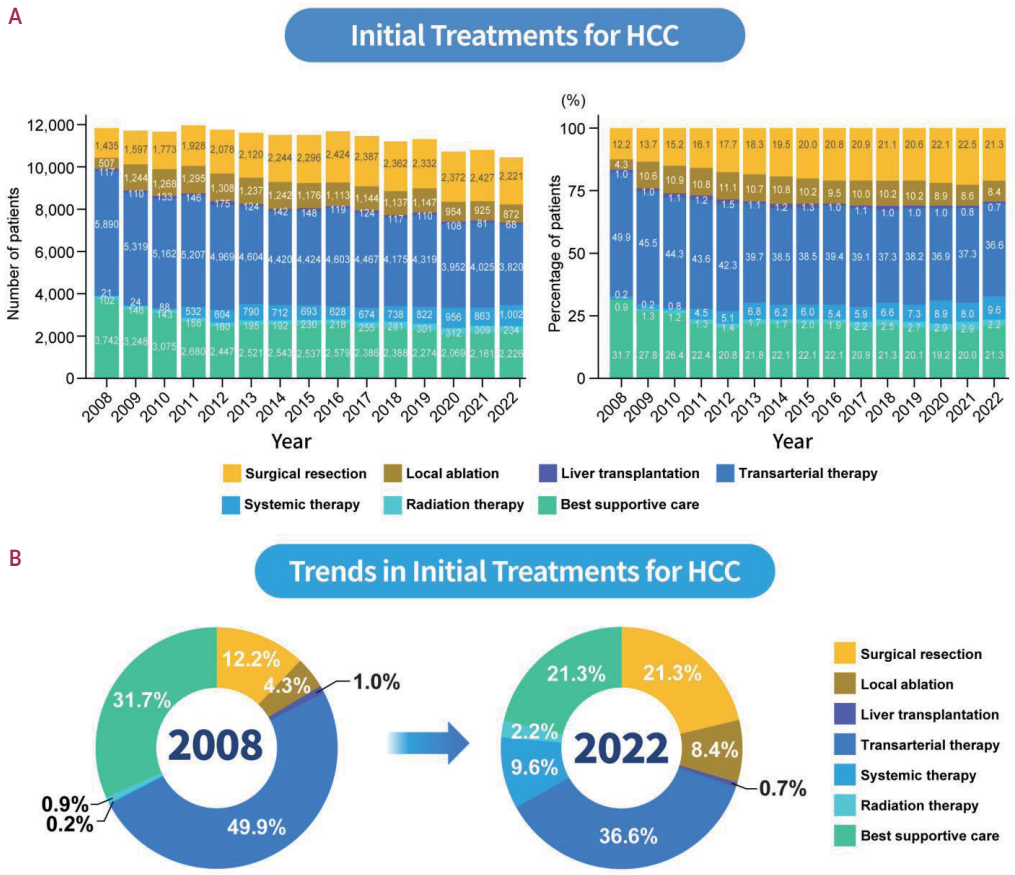

Figure 3. Initial treatments for HCC from 2008 to 2022. (A) Total cases and percentages of each treatment. (B) Comparison of initial treatment percentages between 2008 and 2022. HCC, hepatocellular carcinoma.

increased significantly (from 6.3% to 19.2% in the 70s and from 0.7% to 6.8% in the 80s or older). BSC was also significantly decreased in the 70s and 80s age groups (Supplementary Fig. 2A). For viral etiologies, the treatment pattern was similar to the overall trend, with minor variations. In non-viral etiologies, the proportion of BSC was higher. The proportions of other treatments, including surgical resection and systemic therapy, were generally lower than those in viral etiologies (Supplementary Fig. 2B). In addition, the differences in treatment patterns between the metropolitan and non-metropolitan areas were diminished (Supplementary Fig. 2C). Metropolitan areas showed an increase in surgical resection and a decrease in transarterial therapy. Nonmetropolitan areas also showed a slight decline in transarterial therapy and increased surgical resection and systemic therapy.

First-line systemic therapy

Next, we investigated the changes in the patterns of first-line systemic therapies, including sorafenib, lenvatinib, and AB, following their approval for national health insurance reimbursement, which is not restricted to the initial treatment for HCC at diagnosis. In 2008, nine patients with HCC were treated with first-line systemic therapy, which increased markedly to 3,249 by 2022 (Fig. 5A). Sorafenib was the sole therapy used until 2018, followed by lenvatinib in 2018 and AB in 2020. Following its approval and insurance coverage in 2020, AB soared to 1,954 cases by 2022, becoming the most frequently used first-line systemic therapy. Furthermore, a more granular analysis from 2019 to 2023 by quarter showed the significant impact of these new therapies on usage patterns (Fig. 5B). Sorafenib usage decreased consistently from 568 cases in Q1 2019 to 86 cases in Q1 2023. In contrast, lenvatinib usage peaked at 350 cases in Q4 2019 but decreased consistently to Q1 2023. AB showed a dramatic increase in post-approval and insurance coverage, becoming the dominant therapy, with 618 cases in Q1 2023. The proportion of each systemic therapy used as first-line treatment has shifted significantly. Sorafenib accounted for 100% of the cases in Q1

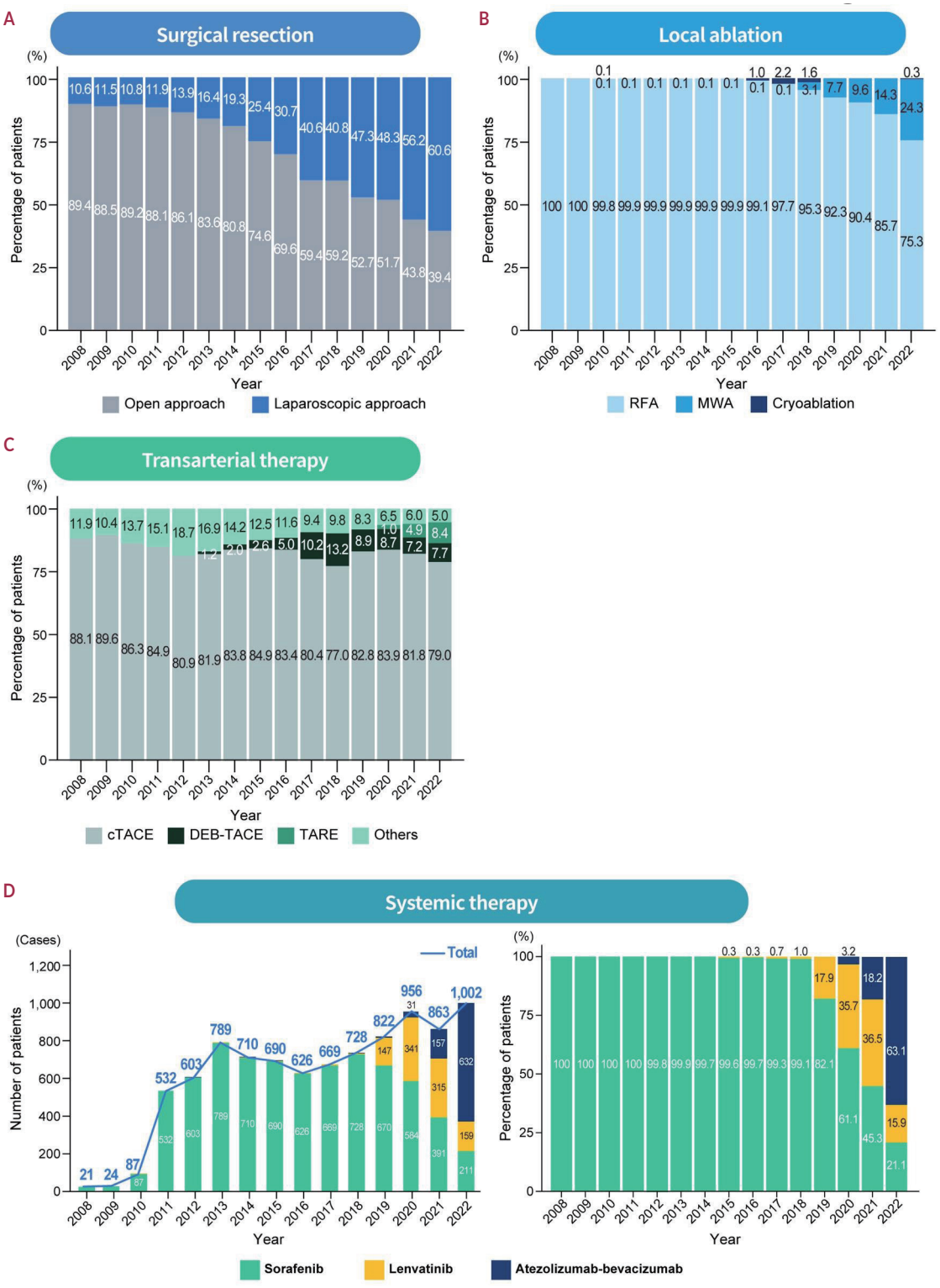

Figure 4. Subgroup analysis by each initial treatment modality. (A) Percentages of open and laparoscopic resections among surgical resections. (B) Percentages of RFA, MWA, and cryoablation among local ablation treatments. (C) Percentages of cTACE, DEB-TACE, TARE, and other treatments among transarterial therapies. (D) Number and percentage of patients who received sorafenib, lenvatinib, and atezolizumab-bevacizumab. RFA, radiofrequency ablation; MWA, microwave ablation; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; TARE, transarterial radioembolization.

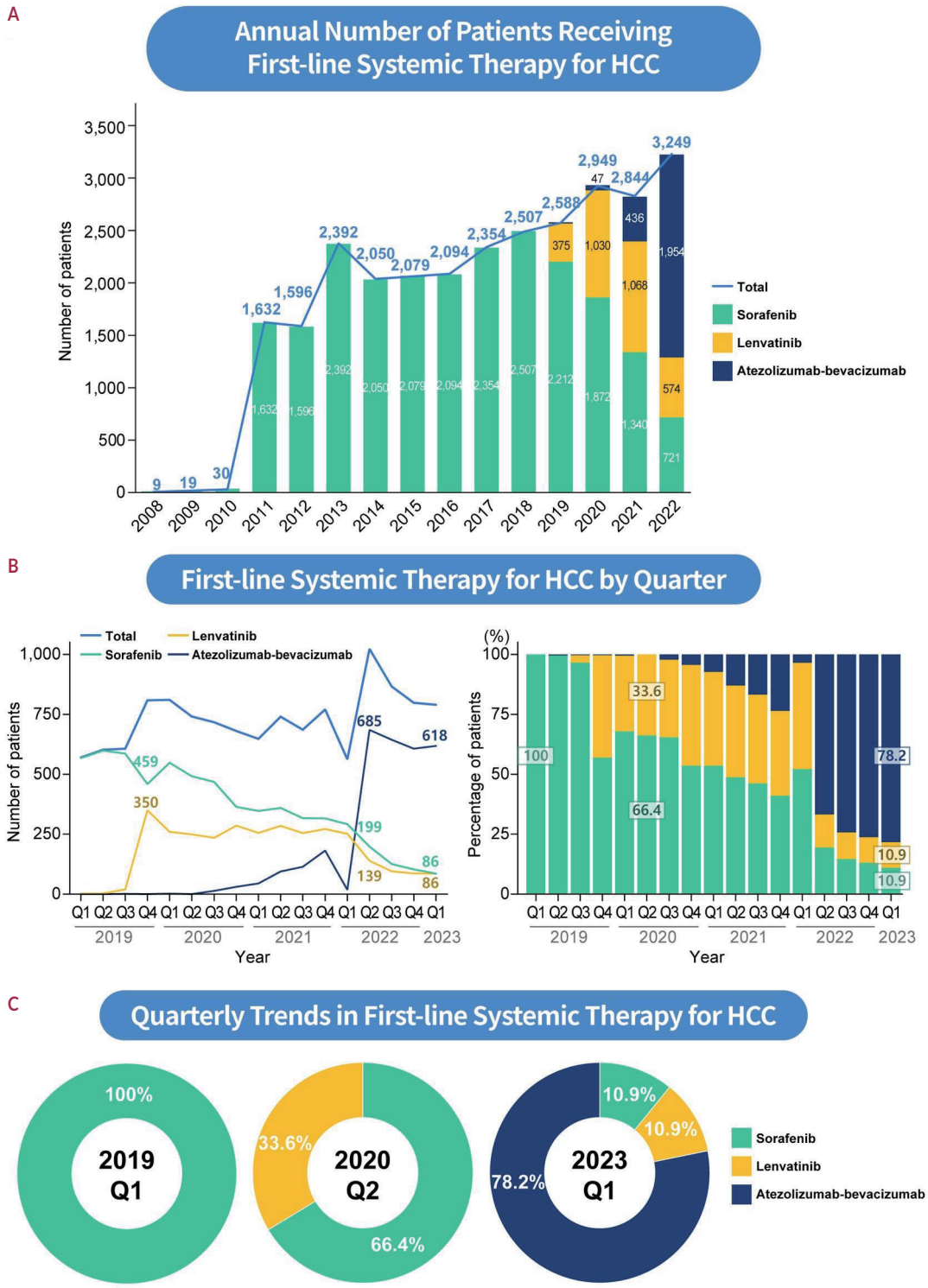

Figure 5. Status of first-line systemic therapy in patients with HCC regardless of prior loco-regional therapy. (A) Annual number of patients who received sorafenib, lenvatinib, and atezolizumab-bevacizumab from 2008 to 2022. (B) Number of patients and the percentages of each regimen by quarter, from the first quarter of 2019 to the first quarter of 2023. (C) Comparison of the percentages of each regimen between the first quarter of 2019, the second quarter of 2020, and the first quarter of 2023. HCC, hepatocellular carcinoma.

2019; sorafenib dominated with 66.4% in Q2 2020, with lenvatinib accounting for 33.6%; and AB increased to 78.2% in Q1 2023, with lenvatinib and sorafenib accounting for 10.9% each (Fig. 5C). These trends underscore the rapid evolution of first-line systemic therapies for HCC and highlight the increasing preference for newer therapies through the government's approval of national insurance coverage.

Total cases of each treatment

To investigate the total annual cases of each treatment, regardless of the initial or treatment line, we included patients diagnosed before 2008. A patient flowchart is presented in Supplementary Fig. 3. The number of procedures performed and the number of patients receiving therapy showed distinct patterns over time. Transarterial therapy remains the most commonly performed procedure, slightly decreasing from 26,895 in 2008 to 23,335 in 2022. Surgical resections have markedly increased from 1,724 in 2008 to 3,587 in 2022. In contrast, local ablation decreased from a peak of 4,032 in 2015 to 3,201 in 2022. Both systemic and radiation therapies resulted in significant increases. The number of systemic therapy cases increased sharply from 23 in 2008 to 4,501 in 2022, whereas the number of radiation therapy cases increased from 917 in 2008 to 4,126 in 2022 (Supplementary Fig. 4).

In the subgroup analyses (Supplementary Fig. 5), the number of laparoscopic resections increased significantly, peaking at 1,909 cases (53.2%) in 2022. Open approaches decreased in comparison with the initial treatment. RFA remained the dominant local ablation method, although its use has slightly decreased. MWA and cryoablation have been increasingly adopted, with MWA reaching 735 cases (23.0%) by 2022. cTACE remained the predominant transarterial therapy, although its use has decreased slightly. TARE showed a gradual increase in adoption, reaching 474 cases (2.0%) by 2022. Systemic therapy showed a pattern similar to that observed with first-line systemic therapy.

DISCUSSION

Investigating the latest data on the status of HCC treatment might be crucial for achieving continued advancements in clinical outcomes, as this is the starting point for clinical and basic research. This study aimed to analyze the treatment patterns of over 170,000 patients with HCC between 2008 and 2022 using the HIRA claims database. To the best of our knowledge, this is the first study to investigate HCC treatment patterns in a large nationwide cohort after the approval of AB as first-line systemic therapy. A key finding of our study was the significant shift in treatment modalities following the approval of AB in 2020 and its subsequent national insurance coverage in 2022. Another important observation was the increased adoption of minimally invasive surgical techniques during the study period. These changes have led to a general increase in the use of both surgical resection and systemic therapies. This shift from BSC towards more proactive interventions highlights the evolving strategy in HCC management to improve patient survival and quality of life.

We found that the epidemiology regarding HCC incidence, according to age group and etiology, has changed significantly over the years. We first found that the number of cases, percentage, and crude incidence among elderly patients over 70 had significantly increased in 2022 compared to 2008, which aligns with a former report using the NHIS database.[17] A previous report using a retrospective Korean HCC cohort showed that non-liver-related death was higher in patients aged 70 years and older. In contrast, overall survival (OS) was similar for those under 70.[18] Consequently, the treatment choice should be based on the HCC stage, liver function, and patient performance status rather than chronological age.[19] In fact, we showed that BSC has been decreasing, whereas surgical resection and systemic therapy have been increasing among all study patients and elderly patients. This finding may be linked to improved nonliver-related deaths over the years,[20] suggesting that this population's comorbidities and performance status have improved. In addition, effective treatments for HBV and HCV infections, which are still major causes of HCC in Korea, might also be associated with preserved liver function at diagnosis, leading to more assertive treatments.[20,21] Importantly, HCC monitoring via the national liver cancer screening program for patients with chronic viral hepatitis or liver cirrhosis also significantly contributed to the increased likelihood of early HCC detection, leading to more opportunities for curative treatment and ultimately improving OS.[22]

Additionally, we found an increase in the incidence of ALD and NAFLD as causes of HCC over time. Notably, the initial treatment patterns between viral and nonviral etiologies were significantly different, especially regarding surgical resection and BSC, although these differences have diminished over the years. A previous report showed that alcohol use and NAFLD etiology were factors related to inconsistent HCC surveillance and successful recognition of liver disease, respectively.[23] Therefore, HCC stage, performance status, or liver function at diag-

nosis might have caused these differences in initial treatment patterns, although this has to be proven in future studies. Furthermore, accurate epidemiological studies and effective screening strategies for at-risk patients are required to ensure that more patients in this population receive treatment.[24]

We showed that the overall number of surgical resection cases for HCC and its proportion as an initial treatment has been significantly increasing in Korea. This might be associated with effective HCC screening, as it can increase the opportunity to receive curative therapy owing to the diagnosis at an earlier stage.[22,25] In addition, the increase in laparoscopic resection and improvements in intraoperative and perioperative care have expanded the eligibility for surgical resection. In particular, laparoscopic resection is commonly used for minor resections in favorable locations, but major hepatectomies using this approach are gradually increasing, not only in high-volume centers.[26] Meta-analyses indicate that this approach reduces surgical blood loss, shortens hospital stay, and decreases 30-day morbidity compared to open resection. Recurrence-free survival and OS are similar between the techniques.[27,28] Consequently, laparoscopic resection may extend the resection criteria, allowing some patients with mild portal hypertension to safely undergo liver resection.

The field of systemic therapy for HCC showed limited progress until 2007; however, significant progress was made with the introduction of sorafenib and lenvatinib.[6,7] Despite initial setbacks, immune checkpoint inhibitors have shown promising results. AB outperformed sorafenib in the IMbrave150 trial, with a median survival of 19.2 months compared with 13.4 months for sorafenib.[8] AB became the preferred first-line regimen owing to its efficacy and manageable safety profile. Sorafenib, lenvatinib, and AB were approved by the Korean Ministry of Food and Drug Safety in 2008, 2018, and 2020, respectively, and will be reimbursed by the NHIS in 2011, 2019, and 2022. It is evident that not only advancements in systemic therapy but also insurance reimbursement status has markedly changed prescription patterns in Korea. The sharp increase in the number of systemic therapies following national insurance coverage for sorafenib (2011), lenvatinib (2019), and AB (2022) highlights this importance.

Transarterial therapy, local ablation, and radiation therapy play important roles in treating HCC. Transarterial therapy as an initial treatment for HCC has decreased slightly over the years; however, it remains the most commonly performed treatment, as evidenced by the annual number of procedures performed. Although the proportion of local ablation as an initial treatment is approximately 10%, the annual number of procedures is comparable to that of surgery, indicating its frequent use as subsequent therapy. Radiation therapy is seldom used as an initial treatment; however, it has become widely used, with nearly 4,000 patients receiving radiation therapy in 2022.

However, this study has some limitations. First, it is based on claims data, which restricts the analysis of non-reimbursed treatments. This study did not reflect on the use of MWA, cryoablation, DEB-TACE, TARE, or systemic therapy prior to reimbursement. As only regorafenib is reimbursed as a second-line systemic therapy, we did not analyze second-line systemic therapy patterns, which are equally important for understanding the full scope of HCC management and for improving patient outcomes. Second, some definitions in the analysis are indirect because of the nature of claims data. It should be noted that the classification of the etiology was not verified based on medical records or test results. Additionally, transarterial therapy (other than DEB-TACE or TARE) does not have a specific claims code. To address this issue, transarterial therapy has been defined as a combination of essential procedures and medications. Third, we did not stratify our analysis by subgroup, such as liver function and HCC stage, which can significantly influence treatment choices and effectiveness, because such information cannot be obtained from claims data. Moreover, survival data were not analyzed, which limited our ability to directly correlate treatment patterns with long-term patient outcomes.

In conclusion, the present study demonstrated the temporal changes in treatment patterns using nationwide data from over 170,000 patients with HCC in Korea between 2008 and 2022. Notably, while the best supportive care has decreased, surgical resection, particularly laparoscopic liver resection and systemic therapy, has significantly increased. The treatment landscape has shifted owing to the introduction of new treatment methods and drugs. This change appears to be influenced not only by clinical research outcomes, but also by government reimbursement policies. A glimpse into the current status of HCC treatment may provide a cornerstone for the appropriate allocation of healthcare resources and development of policies.

Acknowledgement

The authors thank the Korean Liver Cancer Association for providing the opportunity to conduct this research. We also thank the 25th board members of the Korean Liver Cancer Association for the review and valuable comments about this research.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethic Statement

This study was conducted per the declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital with a waiver of informed consent (IRB number, X-2312-868-903).

Funding Statement

None.

Data Availability

The data presented in this study are available upon reasonable request from the corresponding author.

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Supplementary Material

Supplementary data can be found with this article online https://doi.org/10.17998/jlc.2024.08.13.

REFERENCES

1. Kang MJ, Jung KW, Bang SH, Choi SH, Park EH, Yun EH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2020. Cancer Res Treat 2023;55:385-399.
2. Chon YE, Lee HA, Yoon JS, Park JY, Kim BH, Lee IJ, et al. Hepatocellular carcinoma in Korea between 2012 and 2014: an analysis of data from the Korean Nationwide Cancer Registry. J Liver Cancer 2020;20:135-147.
3. Singal AG, Kudo M, Bruix J. Breakthroughs in hepatocellular carcinoma therapies. Clin Gastroenterol Hepatol 2023;21:2135-2149.
4. Lee JS, Kim JM, Lee S, Choi JY, Cho W, Choi GS, et al. The prognosis in cases of hepatocellular carcinoma after hepatectomy: young patients versus older patients. Korean J Hepatobiliary Pancreat Surg 2015;19:154-160.
5. Park GC, Hwang S, Park YH, Choi JU; Korean Liver Cancer Study Group. Validation of prognostic impact of ADV score for resection of hepatocellular carcinoma: analysis using Korea Liver Cancer Registry database. Ann Surg Treat Res 2020;98:235-246.
6. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
7. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
8. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-873.
9. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1:EVIDoa2100070.
10. Korean Liver Cancer Association (KLCA), National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28:583-705.
11. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681-693.
12. Chon YE, Jeong SW, Jun DW. Hepatocellular carcinoma statistics in South Korea. Clin Mol Hepatol 2021;27:512-514.
13. Kyoung DS, Kim HS. Understanding and utilizing claim data from the Korean National Health Insurance Service (NHIS) and Health Insurance Review & Assessment (HIRA) database for research. J Lipid Atheroscler 2022;11:103-110.
14. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 2017;32:718-728.
15. Pinheiro PS, Jones PD, Medina H, Cranford HM, Koru-Sengul T, Bungum T, et al. Incidence of etiology-specific hepatocellular carcinoma: diverging trends and significant heterogeneity by race and ethnicity. Clin Gastroenterol Hepatol 2024;22:562-571.e8.
16. Park EH, Jung KW, Park NJ, Kang MJ, Yun EH, Kim HJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2021. Cancer Res Treat 2024;56:357-371.
17. Cho Y, Kim BH, Park JW. The emerging age-pattern changes of patients with hepatocellular carcinoma in Korea. Clin Mol Hepatol 2023;29:99-101.
18. Kim YJ, Jang BK, Kim ES, Chung WJ, Park KS, Cho KB, et al. Hepatocellular carcinoma in the elderly: clinical characteristics, treatment, survival analysis in Korean patients older than 70 years. J Korean Med Sci 2012;27:1147-1154.
19. Torimura T, Iwamoto H. Optimizing the management of intermediate-stage hepatocellular carcinoma: current trends and prospects. Clin Mol Hepatol 2021;27:236-245.
20. Hatanaka T, Kakizaki S, Hiraoka A, Kariyama K, Tsuji K, Ishikawa T, et al. The prognosis of elderly patients with hepatocellular carcinoma: a multicenter 19-year experience in Japan. Cancer Med 2023;12:345-357.
21. Kim BH, Lim YS, Kim EY, Kong HJ, Won YJ, Han S, et al. Temporal improvement in survival of patients with hepatocellular carcinoma in a hepatitis B virus-endemic population. J Gastroenterol Hepatol 2018;33:475-483.
22. Sohn W, Kang D, Kang M, Guallar E, Cho J, Paik YH. Impact of nation-

wide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. Clin Mol Hepatol 2022;28:851-863.
23. Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, et al. Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila) 2012;5:1124-1130.
24. Schneider CV, Schneider KM, Raptis A, Huang H, Trautwein C, Loomba R. Prevalence of at-risk MASH, MetALD and alcohol-associated steatotic liver disease in the general population. Aliment Pharmacol Ther 2024;59:1271-1281.
25. Bae H, Lee SA, Choi JW, Hwang SH, Park S, Park MS. Effectiveness of hepatocellular carcinoma surveillance and an optimal surveillance interval: nationwide cohort of Korea. Yonsei Med J 2021;62:758-766.
26. Chieh AKW, Chan A, Rotellar F, Kim KH. Laparoscopic major liver resections: current standards. Int J Surg 2020;82 Suppl:169-177.
27. Ciria R, Gomez-Luque I, Ocaña S, Cipriani F, Halls M, Briceño J, et al. A systematic review and meta-analysis comparing the short- and long-term outcomes for laparoscopic and open liver resections for hepatocellular carcinoma: updated results from the European guidelines meeting on laparoscopic liver surgery, Southampton, UK, 2017. Ann Surg Oncol 2019;26:252-263.
28. Witowski J, Rubinkiewicz M, Mizera M, Wysocki M, Gajewska N, Sitkowski M, et al. Meta-analysis of short- and long-term outcomes after pure laparoscopic versus open liver surgery in hepatocellular carcinoma patients. Surg Endosc 2019;33:1491-1507.