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Evaluation of the geographic distribution of patients with hepatocellular carcinoma and treatments in Japan using data from the Japanese national database

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Abstract: The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), provided by the Ministry of Health, Labour and Welfare (MHLW), is an exhaustive repository that can be used to understand the nationwide epidemiology of hepatocellular carcinoma (HCC) in Japan. This study was conducted to clarify the geographic distribution of patients with HCC and treatments performed in each region of Japan using data from the NDB. A retrospective analysis was performed to determine the number of patients diagnosed, with HCC (International Classification of Diseases, 10th edition, code C22.0), who received treatment between 2016 and 2020. Number of incidences of HCC per 100,000 individuals in each Japanese region are 76 (Hokkaido), 63 (Tohoku), 55 (Kanto), 58 (Tokai), 74 (Hokuriku), 77 (Kinki), 93 (Chugoku), 101 (Shikoku), 93 (Kyushu), and 37 (Okinawa). Transarterial embolization/transarterial chemoembolization and curative treatments, including laparoscopic liver resection (LLR), open liver resection, and radiofrequency ablation, were the most frequently performed treatments in all regions, followed by systemic therapy. The proportion of patients receiving LLR was lowest in the Shikoku region (6.7%), which also had the lowest frequency of institutions certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) relative to the number of patients with HCC. Although the incidence of HCC varies across regions in Japan, the most frequently performed treatments remain consistent nationwide. This suggests that HCC treatment practices are largely standardized, regardless of geographic location. Certification by the JSHBPS appears to play a role in patient access to LLR.

***Keywords*:** hepatocellular carcinoma, geographic distribution, Japanese national database

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related mortality (*1*). In Japan, there are multiple nationwide registries, including the one maintained by the Japan Liver Cancer Association, which was previously referred to as the Liver Cancer Study Group of Japan (LCSGJ) (*2,3*). However, the nationwide follow-up survey conducted by the LCSGJ depended exclusively on data from approximately 500 specialized member institutions in Japan, and the presence of regional variations in treatment choices was not investigated in the study.

In addition, previous reports have demonstrated regional differences in the number of patients with hepatitis C virus (HCV) infection (*4*). Given that chronic HCV infection is a risk factor for HCC (*5,6*), the number of patients with HCC might vary across different regions of Japan. Therefore, investigating geographic distribution and treatment approaches in each region of Japan is crucial for investigating the real-world burden of HCC in Japan.

In 2011, the Ministry of Health, Labour and Welfare (MHLW) of Japan started providing access to the National Database of Health Insurance Claims

and Specific Health Checkups of Japan (NDB) for research use (*7*). The NDB is a comprehensive resource of health policy and research information and can be used for analyzing geographic distribution and clinical management of HCC across Japan.

In this study, we examined the NDB to provide an up-to-date view of the landscape of HCC incidence and treatment in Japan.

2. Materials and Methods

2.1. Data source

This study used data from the NDB, an extensive database that compiles electronic insurance claims data for all healthcare services and products covered by Japan's national health insurance system (*8*). Researchers may apply to the MHLW to obtain access to the smallest set of NDB data required for their research. The data supplied by the MHLW are anonymized. The NDB contains comprehensive information on patient demographics, health status, diagnoses, medical and dental procedures, prescription records, insurance claims, and health examination data from all hospitals and clinics across Japan.

For this study, we requested and acquired data associated with the International Classification of Diseases, 10th Revision (ICD-10) codes relevant to liver cancer, covering the period from April 2015 to September 2021. Our research team was granted access to 323 million medical records, 130 million Diagnosis Procedure Combination records, and 384,000 prescription records. The study protocol was approved by Ethics Committee of the National Center for Global Health and Medicine (approval number 004253-03).

2.2. Patient selection

The diagnostic data in the NDB are organized using ICD-10 codes. We classified patients with the code C22.0 (liver cell carcinoma) as having HCC. Individuals for whom this diagnosis code was the first assigned, with a lookback period of at least 12 months, were considered newly diagnosed cases of HCC. While no specific exclusion criteria were applied in this study, we did exclude patients who lacked treatment-related data from the analysis. The analysis was performed to determine the number of patients diagnosed with HCC and received treatments between 2016 and 2020, during which we had access to complete annual data.

2.3. Treatments

Interventions for HCC were defined as treatments administered within 180 days of diagnosis. Liver resection cases were classified as either open liver resection (OLR, procedure code K695) or laparoscopic liver resection (LLR, procedure code K695-2). A combined analysis was performed for transarterial embolization (TAE, procedure code K615) and transarterial chemoembolization (TACE, procedure code G003-3). Microwave and radiofrequency ablation (RFA) were grouped under RFA (K697-2, K697-3). TAE and TACE were examined together. Patients who were initially prescribed sorafenib (medication code 620006778), regorafenib (622225801), lenvatinib (622416001, 622416101), ramucirumab (622417901, 622418001), atezolizumab (622594601, 629900601), bevacizumab (620004872, 620004873), or cabozantinib (622796901, 622797001) were considered to have received systemic therapy (ST). Japan was divided into 10 regions based on its prefectures (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=112*).

2.4. Statistical analysis

Descriptive statistics were used to summarize incidence rates of HCC per 100,000 individuals and proportions of different therapeutic interventions, including TAE/TACE, LLR, OLR, RFA, and ST, across the 10 defined Japanese regions.

To examine regional differences, the chi-square test was applied to compare incidence of HCC and proportions of treatments among the regions. When a statistically significant chi-square result was obtained, pairwise comparisons with the Bonferroni correction were conducted between regions.

All statistical analyses were conducted using R statistical software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value of < 0.05 was considered statistically significant unless otherwise specified.

3. Results

TACE/TAE was performed most frequently (38.6%) in the total cohort, followed by OLR (24.1%), RFA (18.1%), LLR (12.6%), and ST (6.6%) (Figure 1).

Figure 2 shows that the number of incidences of HCC per 100,000 individuals in each Japanese region are 76 (Hokkaido), 63 (Tohoku), 55 (Kanto), 58 (Tokai), 74 (Hokuriku), 77 (Kinki), 93 (Chugoku), 101 (Shikoku), 93 (Kyushu), and 37 (Okinawa). The differences in the incidences between regions are statistically significant ($p < 0.0001$).

Types of treatments in each region are presented in Table 1 and Figure 3. Relative frequency at which a specific treatment was selected was significantly different between regions. This was further investigated using pairwise comparisons versus the region with the lowest proportion for each treatment (Table 2), which revealed that the proportion of patients receiving LLR was lowest in Shikoku (6.7%). The number of institutions certified

by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) is shown in Table 3. The ratio of patients per number of certified institutions was the highest in Shikoku. Furthermore, frequency of patients receiving TACE/TAE was higher in the Hokuriku and Tohoku regions. However, TAE/TACE and curative treatments, including LLR, OLR, and RFA, were the most frequently performed treatments in all regions.

4. Discussion

Our analysis of the NDB revealed that HCC treatment in Japan has been equalized to some extent. Specifically, although the incidence of HCC varied across each Japanese region, TAE/TACE and curative treatments (including LLR, OLR, and RFA) were the most frequently used regimens in all regions, which suggests standardization of HCC treatments.

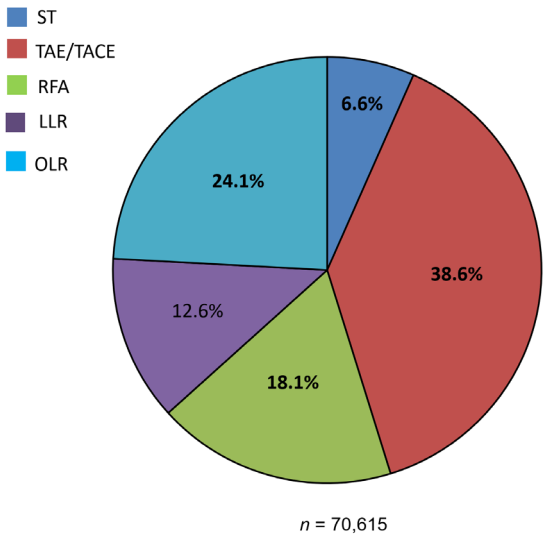

Figure 1. Nationwide proportions of HCC treatments. *Abbreviations*: TAE/TACE, transarterial embolization/transarterial chemoembolization; OLR, open liver resection; RFA, radiofrequency ablation; LLR, laparoscopic liver resection; ST, systemic therapy.

Although previous reports from the LCSGJ have documented the number of treated patients with HCC, the most recent data cover only the period from 2014 to 2015 and do not report geographic distribution (*3*). Therefore, analyzing more recent trends in HCC treatment, in the context of geographical distribution, is crucial. Moreover, past nationwide surveys have focused only on specialized centers for HCC treatment. As such, a more in-depth analysis of the NDB is essential for understanding current epidemiology of HCC and daily practice in each Japanese region.

Although treatment protocols appeared standardized across regions, a significant disparity was observed in number of patients relative to population size. This discrepancy may be attributed to the geographical distribution of the hepatitis virus across regions (*9*). However, the NDB does not provide comprehensive patient characteristics, such as chronic hepatitis virus infection. Therefore, this issue needs further investigation.

LLR requires specific skills and equipment and is increasingly performed for treatment of liver tumors, owing to its benefit of reducing pain and intraoperative blood loss, particularly for minor liver resections (*10*). The frequency at which LLR is performed is reflective of the relative access to minimally invasive surgery in each region. For instance, LLR was less frequently performed in Shikoku, which is consistent with the high ratio of patients per number of certified institutions in this region. We suggest that a certification system for education and training of highly skilled surgeons in Japan (*11*) would result in JSHBPS accreditation of more skilled hepatobiliary-pancreatic surgeons, which should ultimately help increase access to LLR in regions such as Shikoku. The board certification system by JSHBPS is established to nurture surgeons capable of performing safe and reliable advanced surgery in the hepato-pancreatic-biliary field. The certification

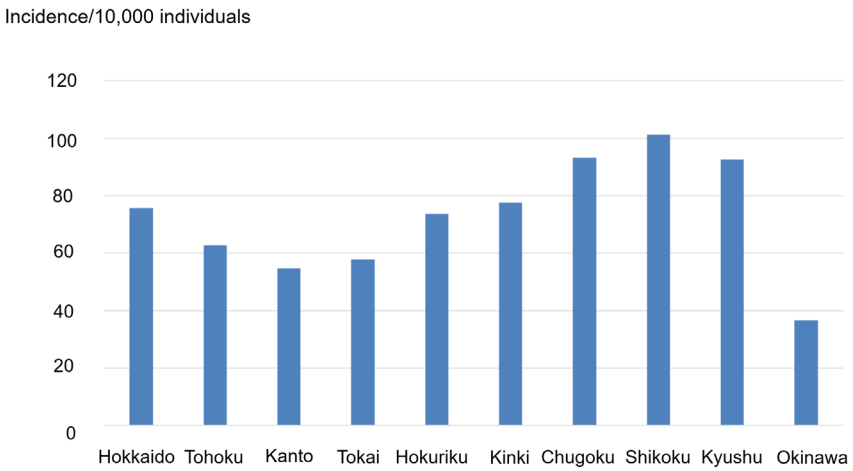

Figure 2. Distribution of HCC incidence per 10,000 individuals across regions from east to west Japan.

Table 1. Interregional differences in the frequency of HCC treatments in Japan

Treatment	Hokkaido (n = 3,850)	Tohoku (n = 6,541)	Kanto (n = 25,319)	Tokai (n = 8,487)	Hokuriku (n = 2,103)	Kinki (n = 15,687)	Chugoku (n = 6,582)	Shikoku (n = 3,618)	Kyushu (n = 11,621)	Okinawa (n = 539)	p value*
ST	319 (8.3)	386 (5.9)	1,387 (5.5)	585 (6.9)	130 (6.2)	749 (4.8)	367 (5.6)	**157 (4.3)**	542 (4.7)	36 (6.7)	< 0.001
OLR	969 (25.2)	1,157 (17.7)	5,429 (21.4)	1,727 (20.3)	**354 (16.8)**	2,864 (18.3)	1,531 (23.3)	641 (17.7)	2,237 (19.2)	143 (26.5)	< 0.001
LLR	368 (9.6)	478 (7.3)	2,331 (9.2)	752 (8.9)	219 (10.4)	2,187 (13.9)	829 (12.6)	**244 (6.7)**	1,392 (12.0)	64 (11.9)	< 0.001
RFA	597 (15.5)	766 (11.7)	4,750 (18.8)	1,176 (13.9)	305 (14.5)	2,532 (16.1)	**688 (10.5)**	491 (13.6)	1,402 (12.1)	64 (11.9)	< 0.001
TACE/TAE	**1,023 (26.6)**	2,471 (37.8)	8,039 (31.8)	2,782 (32.8)	795 (37.8)	4,805 (30.6)	1,938 (29.4)	977 (27.0)	4,249 (36.6)	191 (35.4)	< 0.001

*The chi-square test was used to compare regions. Data are expressed as numbers and (%) unless otherwise specified. The region with the lowest percentage is shown in bold. *Abbreviations*: ST, systemic therapy; OLR, open liver resection; LLR, laparoscopic liver resection; RFA, radiofrequency ablation; TACE/TAE, transarterial chemoembolization/transarterial embolization.

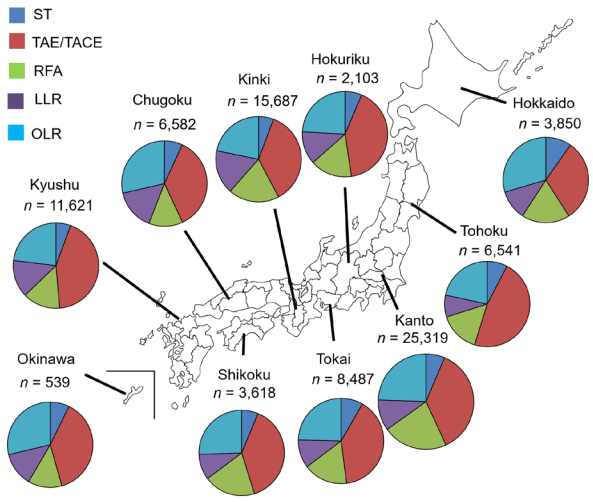

Figure 3. Treatments performed for hepatocellular carcinoma in each Japanese region. *Abbreviations*: TAE/TACE, transarterial embolization/transarterial chemoembolization; OLR, open liver resection; RFA, radiofrequency ablation; LLR, laparoscopic liver resection; ST, systemic therapy.

system is specific because, apart from annual volumes of advanced HPB surgeries, surgical records and videos are reviewed to guarantee quality of procedures. Studies have shown that LLR is performed more often at board-certified institutions than at non-certified institutions (*12*). In addition, limited geographical access may be a contributing factor to the low ratio. One previous study reported differences in the number of large medical centers and physician-to-bed ratio within each region of Japan, which might have also contributed to the discrepancy in frequency of LLR (*13,14*).

Sorafenib was the first approved ST for HCC (*15*). In Japan, most medications are typically covered by public health insurance shortly after their approval. Following approval of sorafenib, several other STs, such as lenvatinib, regorafenib, cabozantinib, and ramucirumab, became primary treatments for advanced HCC in Japan (*16,17*). However, ST accounted for the lowest proportion of patients (6.6%) in the national cohort (Figure 1), probably because more curative treatment options are currently preferentially used throughout Japan. The 180-day post-diagnosis duration might have been insufficient to accurately analyze the number of patients receiving ST.

Notably, the methodology employed in this study has certain limitations. First, data are analyzed retrospectively, and overlap with data of patients diagnosed with intrahepatic cholangiocarcinoma or mixed types is expected because differentiating these conditions without data from pathological examination is challenging. Second, information regarding specific patient characteristics, tumor stage, and prognosis is lacking. Third, sequential treatments are not correctly evaluated. Although we limited analysis to treatments administered within 180 days of diagnosis, sequential

Table 2. Region-based pairwise comparison of HCC treatment frequencies

Treatment	The lowest frequency	Proportion difference*[1] (adjusted *p* value*[2])								
	Shikoku	Hokkaido	Tokai	Okinawa	Hokuriku	Tohoku	Chugoku	Kanto	Kinki	Kyushu
ST	**4.3%**	+3.95% (< 0.001)	+2.55% (< 0.001)	+2.34% (0.144)	+1.84% (0.019)	+1.56% (0.007)	+1.24% (0.061)	+1.14% (0.039)	+0.44% (1.000)	+0.32% (1.000)
	Hokuriku	Okinawa	Hokkaido	Chugoku	Kanto	Tokai	Kyushu	Kinki	Shikoku	Tohoku
OLR	**16.8%**	+9.70% (< 0.001)	+8.34% (< 0.001)	+6.43% (< 0.001)	+4.61% (< 0.001)	+3.52% (0.003)	+2.41% (0.083)	+1.42% (1.000)	+0.88% (1.000)	+0.86% (1.000)
	Shikoku	Kinki	Chugoku	Kyushu	Okinawa	Hokuriku	Hokkaido	Kanto	Tokai	Tohoku
LLR	**6.7%**	+7.20% (< 0.001)	+5.85% (< 0.001)	+5.23% (< 0.001)	+5.13% (< 0.001)	+3.67% (< 0.001)	+2.81% (< 0.001)	+2.46% (< 0.001)	+2.12% (0.001)	+0.56% (1.000)
	Chugoku	Kanto	Kinki	Hokkaido	Hokuriku	Tokai	Shikoku	Kyushu	Okinawa	Tohoku
RFA	**10.5%**	+8.31% (< 0.001)	+5.69% (<0.001)	+5.05% (< 0.001)	+4.05% (< 0.001)	+3.40% (< 0.001)	+3.12% (< 0.001)	+1.61% (0.010)	+1.42% (1.000)	+1.26% (0.195)
	Hokkaido	Hokuriku	Tohoku	Kyushu	Okinawa	Tokai	Kanto	Kinki	Chugoku	Shikoku
TACE/TAE	**26.6%**	+11.23% (< 0.001)	+11.21% (< 0.001)	+9.99% (< 0.001)	+8.86% (< 0.001)	+6.21% (< 0.001)	+5.18% (< 0.001)	+4.06% (0.010)	+2.87% (0.015)	+0.43% (1.000)

*[1]The difference in treatment frequency between each region compared with the lowest frequency region was calculated. *[2]Adjusted *p* values for each pairwise comparison are shown. The Bonferroni method was used to adjust for multiplicity. *Abbreviations*: ST, systemic therapy; OLR, open liver resection; LLR, laparoscopic liver resection; RFA, radiofrequency ablation; TACE/TAE, transarterial chemoembolization/transarterial embolization.

Table 3. Number of institutions certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) in each Japanese region

Treatment	Hokkaido (*n* = 3,850)	Tohoku (*n* = 6,541)	Kanto (*n* = 25,319)	Tokai (*n* = 8,487)	Hokuriku (*n* = 2,103)	Kinki (*n* = 15,687)	Chugoku (*n* = 6,582)	Shikoku (*n* = 3,618)	Kyushu (*n* = 11,621)	Okinawa (*n* = 539)
Number of certified institutions	11	28	108	27	10	52	25	10	34	2
Number of patients	350	234	234	314	210	302	263	**362**	342	270

Data are expressed as numbers. The region with the highest number is shown in bold.

treatments such as neoadjuvant chemotherapy are categorized as chemotherapy instead of surgical treatment. This duration might have underestimated the number of patients receiving ST. Furthermore, analysis across individual medical facilities is not feasible, and data on certain rarely used medications are excluded to maintain confidentiality and anonymity of the NDB dataset.

In conclusion, although incidence of HCC differs in each Japanese region, most frequently performed treatments selected in each region remains consistent. This finding suggests that HCC treatments are mostly standardized across regions.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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