



## Hepatocellular Carcinoma in Korea between 2012 and 2014: an Analysis of Data from the Korean Nationwide Cancer Registry

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**Background/Aims:** Considering the high prevalence and mortality of hepatocellular carcinoma (HCC) in Korea, accurate statistics for HCC are important. We evaluated the characteristics of Korean patients with newly diagnosed HCC.

**Methods:** We retrospectively evaluated data from the Korean Primary Liver Cancer Registry (KPLCR). The baseline characteristics, treatment modalities, and overall survival (OS) of 4,572 patients with HCC registered in the KPLCR between 2012 and 2014 were investigated.

**Results:** At the time of HCC diagnosis, the median age was 60.0 years, with male predominance (79.6%). Hepatitis B virus infection was the most common etiology (59.1%). The rates of Barcelona Clinic Liver Cancer (BCLC) stages 0, A, B, C, and D at diagnosis were 3.9%, 36.9%, 12.5%, 39.4%, and 7.3%, respectively. The proportion of very early or early stage HCC at diagnosis (BCLC stage 0 or A) in the 2012-2014 cohort was significantly lower than that in the 2008-2011 cohort (40.8% vs. 48.3%,  $P < 0.001$ ). Transarterial therapy (37.5%) was the most commonly performed initial treatment, followed by surgical resection (19.8%), best supportive care (19.1%), and local ablation (10.6%). The median OS was 2.9 years, and the 1-, 3-, and 5-year OS rates were 67.7%, 49.3% and 41.9%, respectively. The OS rate of the 2012-2014 cohort was significantly higher than that of the 2008-2011 cohort (log-rank,  $P < 0.001$ ).

**Conclusions:** The OS of HCC patients registered in the KPLCR between 2012 and 2014 significantly improved. Nevertheless, as about half of the HCC patients were diagnosed at an advanced stage, vigorous and optimized HCC screening strategies should be implemented. (J Liver Cancer 2020;20:135-147)

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## INTRODUCTION

Liver cancer is the second most common cause of cancer-related deaths worldwide, with almost 800,000 deaths annually.<sup>1</sup> Hepatocellular carcinoma (HCC) accounts for more than 80% of all liver cancers, representing a major global health problem.<sup>2</sup> In South Korea, liver cancer is the sixth most common cancer and the second leading cause of cancer-related deaths.<sup>3</sup> Hepatitis B virus (HBV) infection is the major etiology of HCC attributable to 62-75% of total cases.<sup>4</sup> In an effort to reduce HBV infection, a nationwide vaccination project has been successfully implemented to enhance HBV prevention, and antiviral treatment has been widely spread to control viral replications.<sup>5</sup> Owing to this effort, the prevalence of chronic hepatitis B and liver disease related mortality has been significantly reduced, and the age-standardized incidence rate of HCC has shown a gradually decreasing trend since 2000.<sup>3</sup> Nonetheless, as the life expectancy and the likelihood of developing HCC increase in patients with HBV, the socioeconomic burden of HCC is expected to increase.<sup>6</sup>

HCC screening in high risk patients is known to improve the prognosis of HCC through the early detection of tumor and application of curative treatments.<sup>7</sup> A national HCC surveillance program with ultrasonography and serum alpha-fetoprotein (AFP) test at 6-month intervals for patients at high risk for HCC has been established in Korea since 2003.<sup>8</sup> The participation rate for this surveillance program has increased annually from 2003 to 2012.<sup>9</sup> One of the most important issues worth studying might be whether patient survival has increased in correlation with the implementation of the national HCC surveillance program.

Regarding HCC treatment, various modalities and multidisciplinary approaches have been introduced.<sup>10,11</sup> Sorafenib, a multi-kinase inhibitor was first introduced in Korea as a systemic treatment for unresectable HCC in 2008, and its prescriptions have increased over time with the gradual expansion of insurance coverage.<sup>12</sup> Radiation therapy has also been recognized as a treatment for HCC since the early 2000s, and is performed solely or in combination with transarterial therapy or systemic treatment nowadays.<sup>13</sup> Therefore,

the prognosis and survival of HCC patients may have changed with changes in HCC characteristics and treatments over time.

The Korean Primary Liver Cancer Registry (KPLCR) is a nationwide population-based cancer registry, and the samples registered here are guaranteed to be representative of HCC in Korea. Based on these data, we have published a paper on HCC statistics in Korea previously.<sup>14</sup> In the present study, we investigated the characteristics (clinical and tumor characteristics, treatment modalities, and survival) of Korean patients with newly diagnosed HCC between 2012 and 2014.

## METHODS

### 1. Patients

Patients were selected from the KPLCR between January 2012 and December 2014. Details of the KPLCR have been described in our previous article.<sup>14</sup> Briefly, the KPLCR is a random sample consisting of 15% of newly diagnosed HCC patients in Korea, which represents the characteristics of HCC of Korea. HCC was diagnosed based on histological evidence or via dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) findings (nodule >1 cm with arterial hypervascularity and portal-/delayed-phase washout).<sup>10,11</sup>

Between 2012 and 2014, 4,593 patients were registered in the KPLCR. Of these, 21 patients were histologically diagnosed with other malignancies and initially excluded from the study. Among the remaining 4,572 patients with HCC, we excluded 1) patients who received their initial treatment more than 120 days from the date of diagnosis (n=72) and 2) patients lacking information on treatment modalities (n=4). Finally, a total of 4,496 HCC patients was selected as the treatment group. The treatment group consisted of patients who received active treatment (n=3,639) and those who received best supportive care (n=857). Supplementary Fig. 1 shows a flow chart of patient selection in the present study. Seventy-two patients who received an initial treatment more than 120 days after the first HCC diagnosis were initially excluded from the treatment group and subsequent survival

analyses because they were likely to receive the treatment at a more advanced tumor stage than their initial tumor stage.<sup>15</sup> The need for institutional review board approval and written informed consent were waived because the KPLCR data were collected as part of the Korean Central Cancer Registry (KCCR) in accordance with the Cancer Control Act.

## 2. Data collection and definitions

Patient information was obtained from the medical records of each hospital where the HCC diagnosis was made. Well-trained KCCR registry record personnel at each hospital investigated the medical records. Data were extracted using a standardized case record form and validated by statisticians at the KCCR and KPLCR. The data included baseline characteristics such as demographic, laboratory, and tumor variables, and treatment factors, including treatment modalities and overall survival (OS) of the patients. All tumor characteristics were assessed by diagnostic imaging such as dynamic CT or MRI scans. The modified Union for International Cancer Control (mUICC)<sup>16</sup> and Barcelona Clinic Liver Cancer (BCLC) staging systems<sup>17</sup> were adapted for HCC staging. The OS was measured from the date of HCC diagnosis until death from any cause. Death certificate information was obtained from national statistical data collected by the Korean Ministry of Government Administration and Home Affairs. Individual patients' vital statistics data were identified using 13-digit unique resident registration numbers issued to all Koreans. The data cutoff date was December 31, 2017. For comparative analyses with the previous period, data of the 2008-2011 cohort (n=5,974) were extracted from the KPLCR.<sup>14</sup> Data of the 2003-2005 cohort (n=4,520) were extracted from the nationwide HCC cohort of the Korean Liver Cancer Study Group which was founded in 1999 by a group of leading liver specialists in Korea.<sup>18</sup>

## 3. Statistical analysis

The data are presented as numbers (percentages) or medians (interquartile ranges [IQRs]), as appropriate. The significance of differences among continuous and categorical vari-

ables was examined using the student *t*-test (or Mann-Whitney *U* test) and chi-squared test (or Fisher's exact test), respectively. The OS of patients was evaluated using the Kaplan-Meier method, and the survival differences were compared by using the log-rank test. A Cox regression analysis was performed to assess the association between OS and the variables, and to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.5.2 (The R Project for Statistical Computing, Vienna, Austria). Two-sided *P*-values <0.05 were considered to indicate statistical significance.

## RESULTS

### 1. Baseline characteristics

The baseline characteristics of the study population (2012-2014; n=4,572) are summarized in Table 1. The median age was 60 years (IQR, 53-70 years) with male predominance (79.6%). HBV was the most common etiology (59.1%), followed by alcohol (13.5%), hepatitis C virus (10.8%), and others (16.8%). With regard to liver function, 72.9%, 22.4%, and 4.7% of patients were classified into Child-Turcotte-Pugh (CTP) classes A, B, and C, respectively, and the median Model for End stage Liver Disease (MELD) score was 8.0. The median AFP level was 30.7 ng/mL (IQR, 5.8-679.7 ng/mL). According to the mUICC staging system, stage II (36.6%) was most common, followed by stage III (25.7%), stage I (15.0%), stage IV-A (11.8%), and stage IV-B (10.1%). According to the BCLC staging system, stage C (39.4%) was most common, followed by stage A (36.9%), stage B (12.5%), stage D (8.6%), and stage 0 (3.9%). Solitary tumors were observed among 60.0% of the patients, and the median maximum tumor diameter was 3.4 cm (IQR, 2.0-6.8 cm). Macroscopic portal vein and hepatic vein invasions were detected in 23.3% and 5.7% of patients, respectively. Bile duct invasion was noticed in 2.2% of patients. Lymph node metastasis and distant metastasis were observed in 7.3% and 10.1% of patients, respectively.

We compared the baseline characteristics of the study

**Table 1.** Baseline characteristics of the study population (2012-2014; n=4,572) and comparison with the data from 2008-2011 (n=6,028)

| Variable                             | 2012-2014                | 2008-2011                | P-value |
|--------------------------------------|--------------------------|--------------------------|---------|
| Demographic variable                 |                          |                          |         |
| Age (years)                          | 60.0 (53.0-76.0)         | 59.0 (51.0-68.0)         | <0.001  |
| Sex (male)                           | 3,638 (79.6)             | 4,790 (78.7)             | 0.310   |
| Diabetes                             | 1,197 (26.4)             | 1,401 (23.0)             | 0.001   |
| Hypertension                         | 1,648 (36.4)             | 1,808 (29.7)             | <0.001  |
| Body mass index (kg/m <sup>2</sup> ) | 23.7 (21.5-25.9)         | 23.7 (21.7-25.8)         | 0.800   |
| Smoking                              | 2,069 (45.7)             | 2,657 (43.7)             | 0.240   |
| Etiology                             | (n=4,572, missing=0)     | (n=5,291, missing=792)   | <0.001  |
| HBV <sup>†</sup>                     | 2,700 (59.1)             | 3,810 (72.0)             |         |
| HCV                                  | 490 (10.7)               | 636 (12.0)               |         |
| Alcohol                              | 616 (13.5)               | 711 (13.4)               |         |
| Others                               | 766 (16.8)               | 134 (2.5)                |         |
| Performance status <sup>*</sup>      | (n=3,114, missing=1,458) | (n=4,162, missing=1,921) | <0.001  |
| 0                                    | 2,224 (71.4)             | 3,231 (77.6)             |         |
| 1                                    | 665 (21.4)               | 641 (15.4)               |         |
| 2                                    | 141 (4.5)                | 159 (3.8)                |         |
| 3                                    | 62 (2.0)                 | 74 (1.8)                 |         |
| 4                                    | 22 (0.7)                 | 57 (1.4)                 |         |
| Ascites                              | (n=4,566, missing=6)     | (n=6,006, missing=77)    | 0.610   |
| Absent                               | 3,462 (75.8)             | 4,509 (75.1)             |         |
| Mild                                 | 701 (15.4)               | 964 (16.1)               |         |
| Moderate to severe                   | 403 (8.8)                | 533 (8.9)                |         |
| Encephalopathy                       | (n=4,567, missing=5)     | (n=6,045, missing=38)    | 0.270   |
| None                                 | 4,468 (97.8)             | 5,894 (97.5)             |         |
| Mild to moderate (grade 1 or 2)      | 84 (1.8)                 | 119 (2.0)                |         |
| Severe (grade 3 or 4)                | 15 (0.3)                 | 32 (0.5)                 |         |
| Laboratory variable                  |                          |                          |         |
| Total bilirubin (mg/dL)              | 0.9 (0.6-1.5)            | 1.0 (0.70-1.60)          | <0.001  |
| Serum albumin (g/dL)                 | 3.8 (3.3-4.3)            | 3.8 (3.2-4.2)            | <0.001  |
| Alanine aminotransferase (IU/L)      | 35.0 (23.0-57.5)         | 38.0 (24.0-61.0)         | <0.001  |
| Platelet count (10 <sup>9</sup> /L)  | 144.0 (100.0-196.0)      | 139.0 (95.0-199.0)       | 0.151   |
| Prothrombin time (INR)               | 1.10 (1.03-1.21)         | 1.11 (1.04-1.22)         | 0.020   |
| Creatinine (mg/dL)                   | 0.88 (0.73-1.02)         | 0.90 (0.74-1.00)         | 0.305   |
| Sodium (mmol/L)                      | 139.0 (136.0-141.0)      | 139.0 (136.0-141.0)      | 0.482   |
| Glucose (mg/dL)                      | 110.0 (95.0-142.0)       | 109.0 (94.0-139.0)       | 0.200   |
| Total cholesterol (mg/dL)            | 156.0 (131.0-183.0)      | 155.0 (130.0-182.0)      | 0.252   |
| Child-Turcotte-Pugh class            | (n=4,425, missing=147)   | (n=5,719, missing=364)   | <0.001  |
| A                                    | 3,226 (72.9)             | 4,063 (71.0)             |         |
| B                                    | 991 (22.4)               | 1,362 (23.8)             |         |
| C                                    | 208 (4.7)                | 294 (5.1)                |         |
| MELD score                           | 8.0 (7.0-1.0)            | 8.6 (7.3-11.1)           | <0.001  |
| MELD-Na score                        | 10.0 (8.0-13.0)          | 10.1 (8.0-13.8)          | 0.003   |

**Table 1.** Continued

| Variable                    | 2012-2014              | 2008-2011              | P-value |
|-----------------------------|------------------------|------------------------|---------|
| Tumor variable              |                        |                        |         |
| Alpha-fetoprotein (ng/mL)   | 30.7 (5.8-679.7)       | 47.4 (7.3-785.0)       | <0.001  |
| PIVKA-II (mAU/mL)           | 125.0 (27.0-2,228.0)   | 144.5 (30.0-1,373.0)   | 0.008   |
| Numbers of tumors           | (n=4,552, missing=20)  | (n=6,161, missing=22)  | 0.624   |
| 1                           | 2,729 (60.0)           | 3,725 (61.5)           |         |
| 2                           | 646 (14.2)             | 826 (13.6)             |         |
| 3                           | 186 (4.1)              | 247 (4.1)              |         |
| 4                           | 74 (1.6)               | 95 (1.6)               |         |
| ≥5                          | 917 (20.1)             | 1,168 (19.3)           |         |
| Maximum tumor diameter (cm) | 3.4 (2.0-6.8)          | 3.0 (2.0-5.4)          | <0.001  |
| Portal vein invasion        | 1,061 (23.3)           | 1,477 (24.3)           | 0.242   |
| Hepatic vein invasion       | 261 (5.7)              | 339 (5.6)              | 0.498   |
| Bile duct invasion          | 100 (2.2)              | 159 (2.6)              | 0.191   |
| Lymph node metastasis       | 331 (7.3)              | 431 (7.1)              | 0.492   |
| Distant metastasis          | 460 (10.1)             | 602 (9.9)              | 0.490   |
| Modified UICC Stage         | (n=4,534, missing=38)  | (n=6,045, missing=38)  | 0.643   |
| Stage I                     | 685 (15.0)             | 854 (14.1)             |         |
| Stage II                    | 1,674 (36.6)           | 2,267 (37.5)           |         |
| Stage III                   | 1,174 (25.7)           | 1,577 (26.1)           |         |
| Stage IV-A                  | 541 (11.8)             | 746 (12.3)             |         |
| Stage IV-B                  | 460 (10.1)             | 601 (9.9)              |         |
| BCLC stage                  | (n=3,727, missing=845) | (n=5,697, missing=386) | <0.001  |
| 0                           | 145 (3.9)              | 489 (8.6)              |         |
| A                           | 1,376 (36.9)           | 2,260 (39.7)           |         |
| B                           | 465 (12.5)             | 658 (11.5)             |         |
| C                           | 1,470 (39.4)           | 1,923 (33.8)           |         |
| D                           | 271 (7.3)              | 391 (6.9)              |         |

The values are presented as the median (interquartile range) or number (%).

HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End stage Liver Disease; PIVKA-II, protein induced by vitamin K absence-II; UICC, Union for International Cancer Control; BCLC, Barcelona Clinic Liver Cancer.

\*Performance status was classified as follows: 0, fully active without symptoms; 1, ambulatory with symptoms; 2, bedridden <50% of the time; 3, bedridden >50% of the time but capable of self-care; 4, bedridden 100% of the time and incapable of self-care; †Patients co-infected with HBV and HCV (n=87) were also included.

populations of 2012-2014 vs. 2008-2011. Patients in the 2012-2014 study population were significantly older (60 years vs. 59 years), and had lower proportion of HBV etiology (59.1% vs. 72.0%), CTP class B or C (27.1% vs. 28.9%), MELD score (8.0 vs. 8.6), and AFP level (30.7 ng/mL vs. 47.4 ng/mL). However, patients in the 2012-2014 cohort had a higher proportion of poor performance status (≥1: 28.6% vs. 22.4%), advanced stage (BCLC stage C or D: 46.7% vs. 40.7%), and had larger maximal diameter (3.4 cm vs. 3.0 cm)

(all  $P<0.05$ ).

## 2. Initial treatment modality

Table 2 presents the distribution of initial treatment modalities in the treatment group (n=4,496). The most common treatment modality was transarterial therapy (37.5%), followed by surgical resection (19.8%), best supportive care (19.1%), and local ablation therapy (10.6%). A majority of

**Table 2.** Distribution of initial treatment modalities among patients in the treatment groups in 2012-2014 (n=4,496) and 2008-2011 (n=5,974)

| Treatment modality              | 2012-2014    | 2008-2011    |
|---------------------------------|--------------|--------------|
| Surgical resection              | 890 (19.8)   | 998 (16.7)   |
| Liver transplantation           | 51 (1.1)     | 55 (0.9)     |
| Local ablation therapy          | 476 (10.6)   | 636 (10.6)   |
| RFA                             | 440          | 594          |
| PEI                             | 35           | 37           |
| Other local ablation            | 1            | 5            |
| Transarterial therapy           | 1,685 (37.5) | 2,493 (41.7) |
| Conventional TACE               | 1,527        | 2,407        |
| TACE with drug-eluting beads    | 99           | 64           |
| Radioembolization               | 21           | 7            |
| HAIC                            | 38           | 82           |
| Combination therapy*            | 113 (2.5)    | 108 (1.8)    |
| Systemic therapy                | 228 (5.1)    | 224 (3.7)    |
| Sorafenib                       | 205          | 175          |
| Other systemic agents           | 23           | 77           |
| External beam radiation therapy | 66 (1.5)     | 61 (1.0)     |
| Best supportive care            | 857 (19.1)   | 1,295 (21.7) |
| Miscellaneous therapies†        | 130 (2.9)    | 104 (1.7)    |

The values are presented as number (%) unless otherwise indicated.

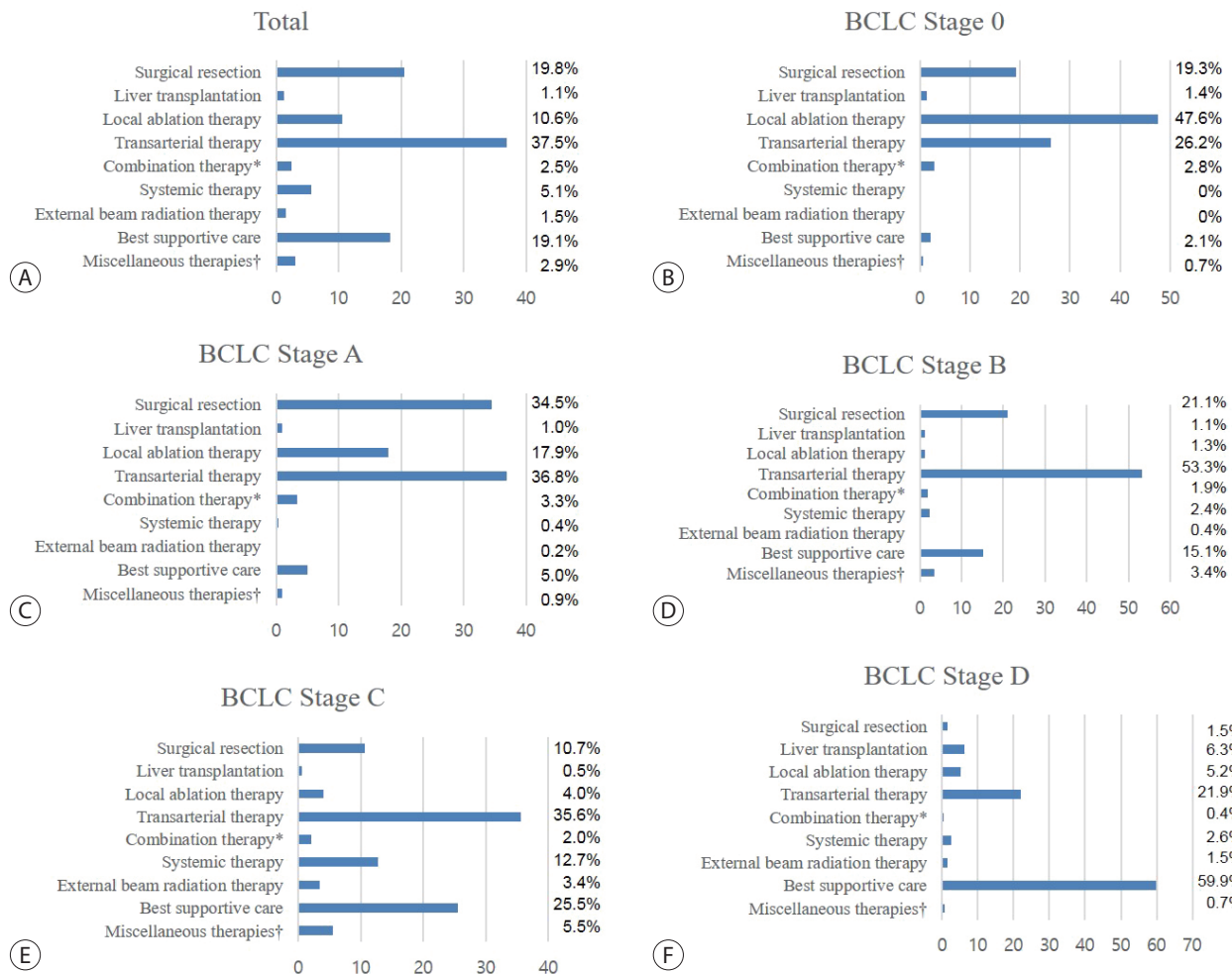
RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

\*Combination therapy was defined as combined treatment with local ablation therapy and transarterial therapy; †Miscellaneous therapies were defined as unclassifiable treatment modalities (i.e., combination therapies other than transarterial therapy and local ablation therapy).

patients who underwent local ablation therapy received radiofrequency ablation (440 of 476, 92.4%). Among patients who underwent transarterial therapies, conventional transarterial chemoembolization was the most frequently performed procedure (1,527 of 1,685, 96.6%). Sorafenib was the most common systemic therapeutic agent (175 of 224, 78.1%). There were significant differences in the trends of initial treatment modality between the patients of the 2012-2014 and 2008-2011 cohorts ( $P<0.001$ ). Compared to the 2008-2011 cohort, the proportion of patients treated with transarterial therapy in the 2012-2014 cohort decreased (from 41.7% to 37.5%), and the proportion of patients who underwent surgical resection (from 16.7% to 19.8%) or liver transplantation (from 0.9% to 1.1%) increased. The proportion of patients who underwent systemic therapy (from 3.7% to 5.1%) or external beam radiation therapy (from 1.0% to 1.5%) also increased (all  $P<0.05$ ).

The distribution of treatment modalities, according to the BCLC stage, is shown in Fig. 1. Among patients with BCLC stage 0, local ablation therapy was most widely performed (47.6%). For HCC of BCLC stages A, B, and C, transarterial therapy was the most common mode of treatment at each stage (36.8% in BCLC A, 53.3% in BCLC B, and 35.6% in BCLC C). Most patients with BCLC stage D, received best supportive care (59.9%). When we investigated the adherence rate of the real-world HCC treatment practice in comparison with the BCLC treatment guideline, the overall adherence rate of the total study population was 38.2%. The rates of adherence to the BCLC treatment guideline according to each BCLC stage are depicted in Supplementary Table 1. For patients with BCLC stage C, although systemic treatment (i.e., sorafenib) is the recommended method of treatment, the adherence rate was merely 11.7%.





**Figure 1.** Initial treatment modalities of the study population (A) and subgroups according to the Barcelona Clinic Liver Cancer (BCLC) stage (B), stage A (C), stage B (D), stage C (E), and stage D (F). \*Combination therapy was defined as combined treatment with local ablation transarterial therapy; †Miscellaneous therapies were defined as unclassifiable treatment modalities (i.e., combination therapies other than transarterial therapy and local ablation therapy).

### 3. Survival analyses

Table 3 presents the median OS and annual OS rates of the entire study population, and the OS rates according to the baseline characteristics. The median OS was 2.90 years (IQR, 2.64-3.11 years), and the 1-, 3-, and 5-year OS rates were 67.7%, 49.3%, and 41.9%, respectively. The OS rate of the 2012-2014 cohort was significantly higher than that of the 2008-2011 cohort as well as the 2003-2005 cohort (both log-rank tests,  $P < 0.001$ ) (Fig. 2). The unadjusted HR of death was 0.64 (95% CI, 0.61-0.68;  $P < 0.001$ ) in the 2012-2014 cohort compared with the 2003-2005 cohort. The unadjusted

HR of death was 0.75 (95% CI, 0.72-0.79,  $P < 0.001$ ) in the 2008-2011 cohort compared with the 2003-2005 cohort. All of the survival curves according to CTP class (Fig. 3A), mUICC stage (Fig. 3B), BCLC stage (Fig. 3C), and AFP level (Fig. 3D) showed significant differences in survival (all log-rank tests,  $P < 0.001$ ). We also performed *post hoc* analyses for multiple comparisons between each survival curve and found significant survival differences between all CTP classes, between all HCC stages, and between all AFP levels (all pairwise comparisons using log-rank tests,  $P < 0.001$ ).

**Table 3.** Overall survival rates (%) of the study population according to baseline characteristics and initial treatment modalities

| Variable   | Value        | Median OS<br>(years, 95% CI) | Year |      |      |      |      |
|--|--------------|------------------------------|------|------|------|------|------|
|  |              |                              | 1    | 2    | 3    | 4    | 5    |
| All patients   | 4,572 (100)  | 2.90 (2.64-3.11)             | 67.7 | 56.6 | 49.3 | 44.6 | 41.9 |
| Age (years; n=4,572, missing values=0)                           |              |                              |      |      |      |      |      |
| <40  | 136 (3.0)    | 2.70 (1.26-5.48)             | 61.8 | 53.7 | 47.1 | 44.1 | 42.3 |
| 40-49  | 557 (12.2)   | 2.99 (2.27-4.25)             | 65.2 | 56   | 49.9 | 46.1 | 43.9 |
| 50-59  | 1,486 (32.5) | 4.18 (3.50-5.94)             | 69.9 | 61   | 54.8 | 50.8 | 48   |
| 60-69  | 1,209 (26.4) | 4.19 (3.54-5.37)             | 72.9 | 62.5 | 54.7 | 50.7 | 47.7 |
| ≥70  | 1,184 (25.9) | 1.65 (1.50-1.87)             | 61.7 | 45.8 | 37   | 29.8 | 27.4 |
| Sex (n=4,572, missing values=0)                                  |              |                              |      |      |      |      |      |
| Male   | 3,638 (79.6) | 2.67 (2.43-2.92)             | 66.6 | 55.2 | 47.7 | 43.3 | 40.5 |
| Female   | 934 (20.4)   | 3.92 (3.22-5.47)             | 72.1 | 62.2 | 55.6 | 49.6 | 47.3 |
| Etiology (n=4,572, missing values=0)                             |              |                              |      |      |      |      |      |
| HBV*   | 2,700 (59.1) | 3.64 (3.12-4.34)             | 68.2 | 58.9 | 52.4 | 49.0 | 46.5 |
| HCV  | 490 (10.7)   | 2.56 (2.15-3.06)             | 72.4 | 55.7 | 46.7 | 38.0 | 34.5 |
| Alcohol  | 616 (13.5)   | 2.46 (2.04-2.88)             | 68.0 | 54.5 | 45.0 | 39.4 | 36.4 |
| Others   | 766 (16.8)   | 2.04 (1.68-2.44)             | 62.1 | 50.3 | 43.0 | 37.1 | 35.0 |
| Child-Turcotte-Pugh classification (n=4,425, missing values=147) |              |                              |      |      |      |      |      |
| A  | 3,226 (72.9) | NR (5.24-NR)                 | 79.7 | 68.4 | 60.6 | 55.5 | 52.1 |
| B  | 991 (22.4)   | 0.57 (0.49-0.68)             | 39.1 | 27.9 | 21.6 | 17.6 | 16.6 |
| C  | 208 (4.7)    | 0.25 (0.20-0.33)             | 26.4 | 19.2 | 13.9 | 12.5 | 11.1 |
| Alpha-fetoprotein (ng/mL; n=4,197, missing values=375)           |              |                              |      |      |      |      |      |
| <11.45   | 1,599 (38.1) | NR (NR-NR)                   | 85.2 | 74.5 | 66.4 | 61.3 | 58.2 |
| 11.45-19.99  | 314 (7.5)    | 4.36 (3.61-5.15)             | 77.1 | 66.6 | 59.6 | 52.2 | 46.4 |
| 20.00-99.99  | 653 (15.6)   | 3.48 (2.99-4.31)             | 75.0 | 62.6 | 53.4 | 47.6 | 44.6 |
| 100.00-199.99  | 217 (5.2)    | 3.24 (2.28-4.77)             | 71.4 | 60.4 | 52.5 | 45.2 | 42.2 |
| 200.00-399.99  | 226 (5.4)    | 2.17 (1.34-2.68)             | 62.4 | 51.8 | 42.0 | 36.7 | 33.7 |
| ≥400.00  | 1,188 (28.3) | 0.61 (0.55-0.68)             | 39.0 | 28.3 | 23.7 | 21.5 | 20.4 |
| Modified UICC stage (n=4,534, missing values=38)                 |              |                              |      |      |      |      |      |
| Stage I  | 685 (15.0)   | NR (NR-NR)                   | 93.9 | 87.9 | 81.8 | 76.6 | 74.0 |
| Stage II   | 1,674 (36.6) | NR (NR-NR)                   | 87.0 | 76.9 | 68.7 | 62.7 | 59.1 |
| Stage III  | 1,174 (25.7) | 1.85 (1.63-2.07)             | 64.4 | 48.0 | 37.9 | 32.7 | 29.5 |
| Stage IV-A   | 541 (11.8)   | 0.44 (0.39-0.50)             | 29.8 | 16.6 | 13.1 | 10.7 | 9.3  |
| Stage IV-B   | 460 (10.1)   | 0.27 (0.25-0.31)             | 13.5 | 6.1  | 3.7  | 2.0  | 2.0  |
| BCLC stage (n=3,727, missing values=845)                         |              |                              |      |      |      |      |      |
| 0  | 145 (3.9)    | NR (NR-NR)                   | 97.2 | 93.8 | 91.0 | 86.2 | 83.4 |
| A  | 1,376 (36.9) | NR (NR-NR)                   | 92.7 | 83.6 | 76.3 | 71.0 | 66.8 |
| B  | 465 (12.5)   | 2.81 (2.39-3.29)             | 75.7 | 59.8 | 48.4 | 40.9 | 36.7 |
| C  | 1,470 (39.4) | 0.75 (0.67-0.87)             | 44.6 | 31.6 | 24.9 | 21.3 | 19.7 |
| D  | 271 (7.3)    | 0.25 (0.21-0.32)             | 24.7 | 18.1 | 13.3 | 11.1 | 10.1 |



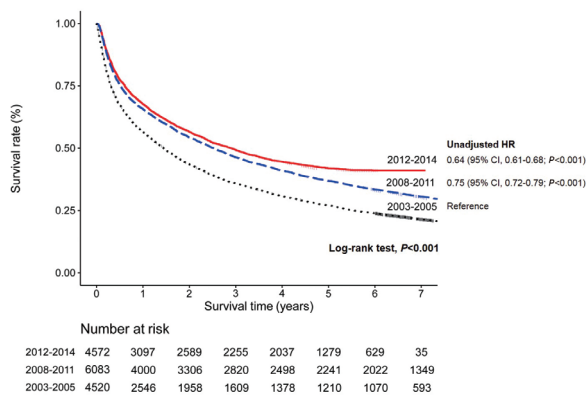
**Table 3.** Continued

| Variable  | Value        | Median OS<br>(years, 95% CI) | Year |      |      |      |      |
|---|--------------|------------------------------|------|------|------|------|------|
|   |              |                              | 1    | 2    | 3    | 4    | 5    |
| Initial treatment modalities (n=4,496, missing values=76) |              |                              |      |      |      |      |      |
| Surgical resection  | 888 (19.8)   | NR (NR-NR)                   | 93.9 | 88.2 | 82.7 | 79.5 | 77.5 |
| Liver transplantation                                     | 51 (1.1)     | NR (NR-NR)                   | 90.2 | 78.4 | 68.6 | 64.7 | 62.2 |
| Local ablation therapy                                    | 464 (10.3)   | NR (NR-NR)                   | 94.8 | 89.4 | 83.0 | 77.2 | 74.2 |
| Transarterial therapy                                     | 1,675 (37.3) | 2.53 (2.38-2.86)             | 73.8 | 57.1 | 46.3 | 39.8 | 35.5 |
| Combination therapy <sup>†</sup>                          | 113 (2.5)    | 3.60 (2.85-NR)               | 69.9 | 61.9 | 57.5 | 47.8 | 45.0 |
| Systemic therapy  | 211 (4.7)    | 0.35 (0.32-0.40)             | 18.0 | 8.1  | 6.6  | 4.7  | 4.7  |
| External beam radiation therapy                           | 60 (1.3)     | 0.59 (0.50-0.80)             | 26.7 | 16.7 | 10.0 | 10.0 | 10.0 |
| Best supportive care                                      | 857 (19.1)   | 0.31 (0.28-0.34)             | 28.1 | 20.4 | 16.1 | 13.2 | 12.0 |
| Miscellaneous therapies <sup>‡</sup>                      | 177 (3.9)    | 1.38 (0.98-1.86)             | 55.4 | 40.1 | 34.5 | 31.6 | 30.4 |

The values are expressed as the median (interquartile range) or number (%).

OS, overall survival; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reached; UICC, Union for International Cancer Control; BCLC, Barcelona Clinic Liver Cancer.

<sup>†</sup>Patients co-infected with HBV and HCV (n=87) were also included; <sup>†</sup>Combination therapy was defined as a combined treatment with local ablation therapy and transarterial therapy; <sup>‡</sup>Miscellaneous therapies were defined as unclassifiable treatment modalities (i.e., combination therapies other than transarterial therapy and local ablation therapy).



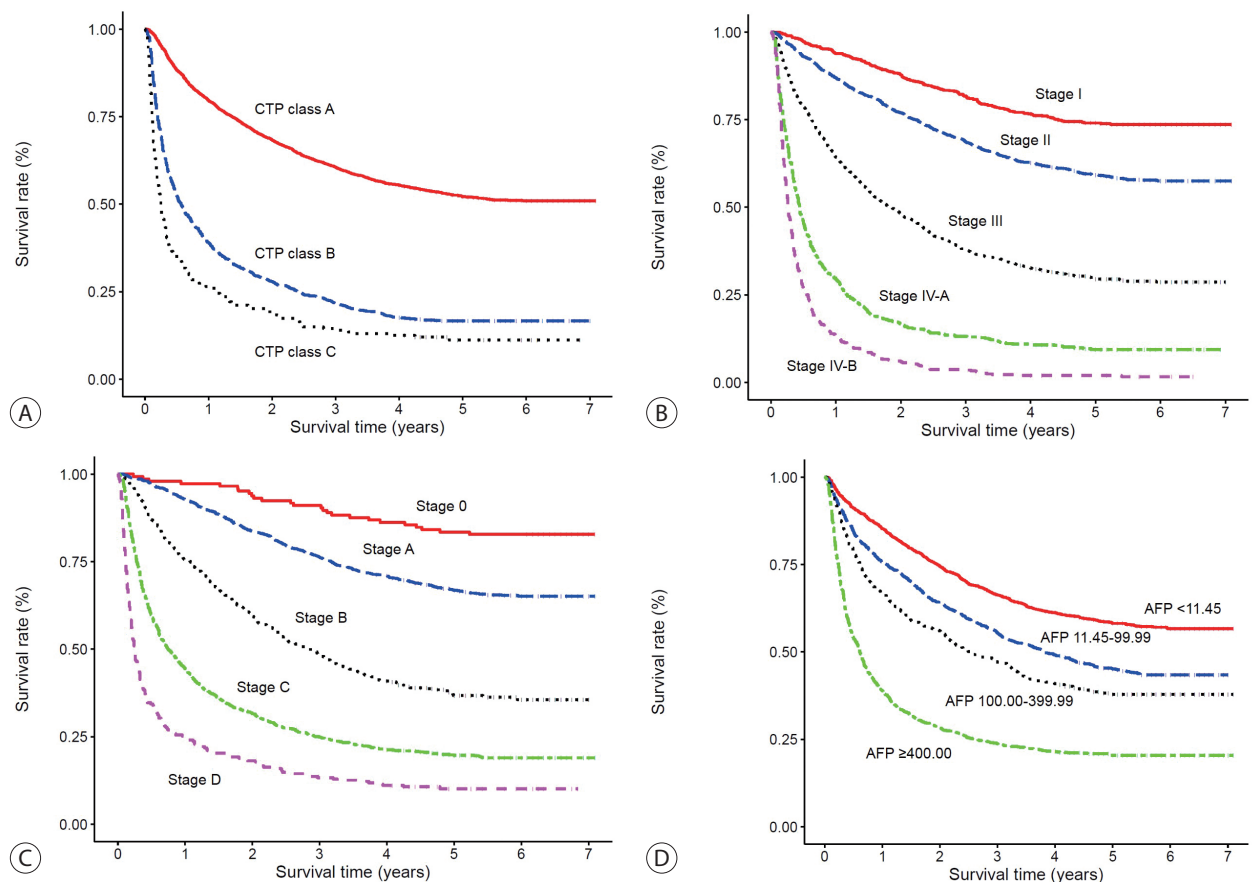
**Figure 2.** Overall survival curves for Korean patients with hepatocellular carcinoma in 2012-2014, 2008-2011, and 2003-2005. HR, hazard ratio; CI, confidence interval.

## DISCUSSION

We have presented representative HCC data of Koreans regarding clinical and tumor characteristics, initial treatment modalities, and OS between 2012 and 2014. As the present study was conducted using KPLCR data as part of a continuous study that serially collected Korean HCC data, comparative analyses between the data of 2012-2014 and 2008-2011

were possible. Although about 40% of the HCC patients were diagnosed at very early or early stage (BCLC stage 0 or A), another half of the HCC patients (46.7%) were diagnosed at advanced stages (BCLC stage C or D). The proportion of patients who underwent transarterial therapy as an initial treatment reduced overtime, but it was still the most commonly performed initial treatment for HCC. Compared to the previous periods (2008-2011 cohort or 2003-2005 cohort), the OS of the 2012-2014 cohort had improved significantly, with a 5-year OS rate of 42%.

The most prominent change in HCC etiology was that the prevalence of HBV-related HCC significantly decreased compared to 2008-2011. This may have occurred in conjunction with the increase in HCC patients according to different etiologies other than viral hepatitis or alcohol. HCC originating from non-alcoholic fatty liver disease (NAFLD) has shown an increasing trend worldwide. NAFLD is a disease spectrum that starts from simple steatosis, progresses to non-alcoholic steatohepatitis, and to cirrhosis, which has a high chance of developing HCC. Moreover, a recent study has shown that dysregulation of lipid metabolism in NAFLD causing a selective loss of intrahepatic CD4<sup>+</sup> T lymphocytes



**Figure 3.** Overall survival curves for the subgroups divided by the Child-Turcotte-Pugh classes (A), modified Union for International Cancer Control stages (B), Barcelona Clinic Liver Cancer stages (C), and the serum levels of alpha-fetoprotein (D). CTP, Child-Turcotte-Pugh; AFP, alpha-fetoprotein.

can directly contribute to HCC initiation and progression.<sup>19</sup> Research on the prevalence of NAFLD in the general population in Korea is limited; however, the prevalence of NAFLD diagnosed by ultrasound from health check-ups is known to be 16-33%.<sup>20-22</sup> NAFLD is known to accompany other metabolic diseases such as obesity and diabetes, both of which are showing steadily increasing prevalence rates (obesity,<sup>23</sup> 29.7% in 2009 to 32.4% in 2015; diabetes,<sup>24</sup> 10.1% in 2010 to 14.4% in 2016).

Compared to HCC patients in the 2008-2011 cohort, those in the 2012-2014 cohort had better liver function, with more patients having CTP class A and low MELD scores. This phenomenon may also be due to the generalization of antiviral treatment with the expanded reimbursement of drugs. By inhibiting viral replication, antiviral drugs reduce liver inflammation and fibrosis, leading to preserved liver function and

decreased cirrhosis-related complications. However, the maximum tumor diameter increased significantly compared to the previous period. As previously mentioned, the proportion of patients with HCC of other etiologies (e.g., NAFLD) increased. Patients with HCC of other etiologies do not tend to undergo regular HCC surveillance and tend to be diagnosed later with large size HCC. In a study conducted by Marrero et al.,<sup>25</sup> patients with cryptogenic HCC presented larger maximum tumor diameters than those with viral or alcohol-related HCC. Despite the national HCC surveillance program, the proportion of patients with advanced stage HCC (BCLC stage C or D, 46.7%), who might not be candidates for potentially curative treatment, increased compared to the previous period (2008-2011). Therefore, further efforts should be made to improve the scale and quality of the HCC surveillance program for early detection of HCC. Serum AFP

tests and ultrasound, which are currently being performed as part of the national cancer screening project, should be thoroughly integrated and monitored. Specifically, careful attention and optimized surveillance strategies should be implemented among patients who are prone to surveillance failure (such as those with advanced liver fibrosis, high AFP levels, or diabetes mellitus).<sup>7</sup> Another reason for the increased proportion of patients with advanced stage HCC may be partly related to the poorer performance status accompanied by older age in the 2012-2014 cohort.

Of note, transarterial therapy was the most commonly used modality as initial treatment. In addition to patients with HCC of BCLC stage B who are indicated according to the international guidelines, transarterial therapy is the most widely used treatment modality among patients with HCC of BCLC stage A or C. In patients with BCLC stage A who are not subject to surgery or patients with BCLC stage C with minimal vessel invasion and relatively preserved liver function, transarterial therapy is still considered to be an effective treatment if technically accessible. However, compared to the 2008-2011 cohort, the proportion of patients receiving transarterial therapy has decreased. In contrast, the proportion of patients receiving potentially curative treatments such as surgical resection or liver transplantation has significantly increased. The proportions of patients receiving systemic therapy and radiation therapy have also increased. In short, although the overall rate of adherence to the treatment guideline is relatively low, the rates of adherence to the BCLC treatment guidelines among both patients with early and advanced stage diseases have increased (Supplementary Table 1). Considering the trend toward increasing proportion of radiation and combination therapy in this cohort, and the recent introduction of new systemic therapeutic agents (e.g., lenvatinib, nivolumab, regorafenib, and atezolizumab plus bevacizumab) in real-world practice, it is expected that HCC treatment will be more diversified and improved in the future.

It is very encouraging to witness an increasing OS of HCC patients over the study period (compared to either the 2003-2005 or 2008-2011 cohort). This may be partly due to the decreased rate of best supportive care and improved HCC

treatment result. For instance, surgery as a curative treatment was performed increasingly even among patients with BCLC stages B and C. In a previous study, hepatic resection was well tolerated with low mortality and survival benefit, necessitating the stratification of patients and optimization of treatment among patients with HCC of BCLC stage B and C who are highly heterogeneous.<sup>26</sup> The presence and level of vascular invasion and malignant portal vein thrombosis is an important determinant for surgery. In addition to these tumor factors, preserved liver function is another important factor, and in our cohort of patients with HCC of BCLC stages B and C, more than 90% of patients undergoing surgical resection were confirmed to have CTP class A. Therefore, the increased proportion of HCC patients with preserved liver function (CTP class A) in the 2012-2014 cohort may be associated with increased survival. In the subgroup analyses, the OS of HCC patients significantly differed according to the baseline serum AFP level (Fig. 3D). In our previous study, not only the AFP level at HCC diagnosis but also a high AFP level at baseline or 6 months before diagnosis was predictive of first HCC detection at advanced stage.<sup>7</sup> Collectively, AFP is a valuable baseline predictor of HCC, and thus, serial testing and monitoring are warranted in patients with a high risk for HCC.

The present study had several limitations. First, this cohort does not represent all Korean HCC patients because those included in this cohort are patients who received care and treatment at the hospital. However, data regarding patients who received in-hospital care are the most representative information regarding HCC treatment statuses nationwide. Second, there were significant levels of missing data of critical variables such as performance status or BCLC stage. Nevertheless, there were no significant differences in terms of demographic variables and HCC stages among those with available performance status data and those without. Lastly, important data regarding second-line treatment or antiviral treatment in patients with viral hepatitis were not collected. These factors related to the prognosis of HCC patients have been subsequently investigated in the KPLCR and, therefore, will be incorporated in future research.

In conclusion, the OS of HCC patients registered in the

KPLCR between 2012 and 2014 significantly improved compared to the previous period. Nevertheless, as about half of the patients were still diagnosed with HCC at an advanced stage, vigorous and optimized HCC screening strategies should be implemented. Although transarterial therapy is the most widely used, various attempts at treatment diversification should be made.

## AUTHORSHIP STATEMENT

1) Jeong-Hoon Lee and Young Eun Chon take responsibility for the integrity of the work as a whole, from inception to published article.

2) Specific author contributions: Conception: Young Eun Chon, Han Ah Lee, Jun Sik Yoon and Jeong-Hoon Lee; study design: Young Eun Chon, Han Ah Lee, Jun Sik Yoon and Jeong-Hoon Lee; participation in patient management and data collection: Jun Sik Yoon, Han Ah Lee, Jun Yong Park, Bo Hyun Kim, In Joon Lee, Suk Kyun Hong, Dong Hyeon Lee, Hyun-Joo Kong, Young-Joo Won, Eunyung Kim, Young Eun Chon, and Jeong-Hoon Lee; contribution to the data acquisition, responsibility for writing the paper, and statistical analysis: Young Eun Chon, Han Ah Lee, Jun Sik Yoon, and Jeong-Hoon Lee.

3) All authors have reviewed the paper and approved the final version.

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## SUPPLEMENTARY MATERIAL

Supplementary data can be found with this article online <http://www.e-jlc.org/html/https://doi.org/10.17998/jlc.20.2.135>.

## Conflicts of Interest

The authors have no conflicts to disclose.

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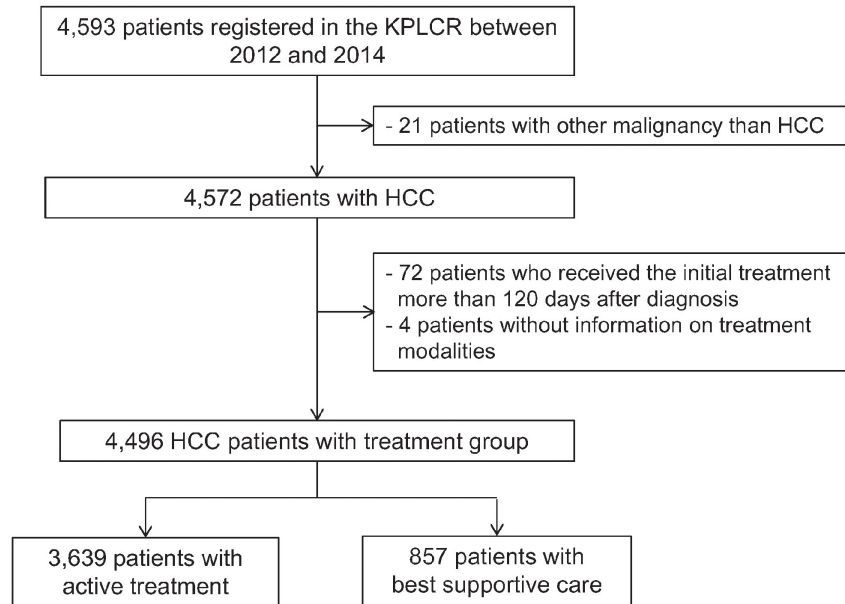
**Supplementary Table 1.** Rates of adherence to the BCLC treatment guideline in each BCLC stage and the total study population

| BCLC stage | Value (2012-2014)  |
|------------|--------------------|
| 0 or A     | 817/1,491 (54.8)   |
| B          | 253/459 (55.1)     |
| C          | 170/1,451 (11.7)   |
| D          | 161/264 (61.0)     |
| Total      | 1,401/3,665 (38.2) |

| BCLC stage | Value (2008-2011)  |
|------------|--------------------|
| 0 or A     | 1,277/2,695 (47.4) |
| B          | 407/648 (62.8)     |
| C          | 180/1,899 (9.5)    |
| D          | 258/381 (67.7)     |
| Total      | 2,122/5,623 (37.7) |

The data are presented as number (%).

BCLC, Barcelona Clinic Liver Cancer.



**Supplementary Figure 1.** Flow chart of patient selection in the present study. KPLCR, Korean Primary Liver Cancer Registry; HCC, hepatocellular carcinoma.