INTRODUCTION

Primary liver cancer, including hepatocellular carcinoma (HCC, 75–85% of cases), intrahepatic cholangiocarcinoma (10–15% of cases), and other rare types, is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide, as of 2018.1,2 Although the age-standardized rate (ASR) of liver cancer has decreased continuously annually since 1999, liver cancer is still the sixth most common cancer in Korea, with a crude rate of 30.1/100000 and ASR of 17.0/100000, which are relatively high, compared with rates seen in other countries.3 Moreover, liver cancer is the second most common...
cause of cancer-related mortality in Korea. The mortality rate for liver cancer is highest among individuals in their forties and fifties, the most economically active working-age population, which makes the economic burden of liver cancer highest among all cancers.4,5

Curative treatments for HCC, including hepatic resection, liver transplantation, and local ablative therapies, are recommended for early stage HCC and Barcelona Clinic Liver Cancer stage A HCC, with a reported median 5-year survival rate of 50% to 70% after curative treatments.6,8 Specifically, the 5-year disease-free survival rate is reportedly 23% to 56.3% after hepatic resection and 74% after liver transplantation.8,9 However, most patients with HCC are diagnosed at advanced stages, and curative treatments are occasionally unavailable based on tumor size, tumor location, and liver function.6,7,9-11 Therefore, early detection of HCC through cancer surveillance is crucial to implementing curative treatment and improving patient survival. As HCC almost exclusively develops in patients with well-known risk factors such as chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, liver cirrhosis, alcohol intake, and metabolic disease, HCC surveillance can be effective.12,13

South Korea launched the National Cancer Screening Program for liver cancer in 2003. HCC surveillance is recommended in high-risk individuals by several clinical practice guidelines; however, surveillance methods, including imaging modality and surveillance intervals, vary among the guidelines.14-16 In Korea, the National HCC surveillance program conducts serum alphafetoprotein tests and ultrasonography for high-risk people older than 40 years who had liver cirrhosis, tested positive for HBV antigen or anti-HCV antibody, or had chronic HBV or HCV liver disease. The International Classification of Diseases-10 codes (ICD-10) was used to identify patients who were diagnosed with HCC (ICD-10 code C22.0). Additionally, the NHIS Service code V193, which is applied to patients with pathological or radiological diagnosis of cancer who visited the hospital and underwent medical expense deduction, was used to select patients who visited health care institutions for HCC treatment.

A flow diagram of patient selection is shown in Fig. 1. Between January 2008 and December 2017, 3201852 patients were included in the national HCC surveillance program’s target population. Among them, 68448 patients visited the hospital for treatment of newly diagnosed HCC (both ICD-10 code C22.0 and NHIS code V193) between January 2011 and December 2018 and were retrospectively registered in this study. After excluding patients whose income or residential status were unidentifiable (n=3774), 64674 patients were included in the final study population, and the following demographic and medical information were evaluated: age, sex, income status, residential area, disability in the year of HCC diagnosis, liver cirrhosis, alcohol-related liver disease, HBV, HCV, and Charlson Comorbidity Index (CCI). For CCI, patient comorbidities detected during the 2 years prior to the diagnosis of HCC were analyzed.31

Surveillance intervals and curative therapy
We defined the date of HCC diagnosis (the date of the first visit to the medical institution with C22.0+V193 codes) as the index date and calculated surveillance intervals using the difference between the index date and the last surveillance date. Accordingly, surveillance intervals were classified into five groups: never screened, ≤6 months (6M), 7–12 months (1Y), 13–24 months (2Y), and 25–36 months (3Y).

In this study, we considered that curative therapy was administered when patients underwent hepatic resection, liver transplantation, or local ablative therapies, including percutaneous ethanol injection, radiofrequency ablation, cryoablation, and microwave ablation, within 1 year after the diagnosis of HCC.7,24

MATERIALS AND METHODS

Database
The National Health Insurance Service (NHIS) system is a health insurance program that covers the entire Korean population. In this study, the NHIS-National Health Information Database (NHIS-NHID) (NHIS-2020-1-539) was used to retrieve demographic and medical information of people who were eligible for inclusion in the national HCC surveillance program. This database contained not only demographic and socioeconomic data, but also healthcare information, including medical history, diagnoses, and prescription data. Additionally, we accessed the National Liver Cancer Surveillance Program database, which included laboratory and ultrasonography results. Furthermore, annual reports on the cause of death statistics issued by the Microdata Integrated Service of Statistics Korea were used to analyze all-cause mortality and its association with surveillance intervals.

Study population
The Institutional Review Board of National Health Insurance Service Ilsan Hospital approved this study (NHIMC 2020-06-008). The target population of the national HCC surveillance included high-risk people aged ≥40 years who had liver cirrhosis, tested positive for HBV antigen or anti-HCV antibody, or had chronic HBV or HCV liver disease. The International Classification of Diseases-10 codes (ICD-10) was used to identify patients who were diagnosed with HCC (ICD-10 code C22.0). Additionally, the NHIS Service code V193, which is applied to patients with pathological or radiological diagnosis of cancer who visited the hospital and underwent medical expense deduction, was used to select patients who visited health care institutions for HCC treatment.
All-cause mortality
Both NHIS data and the causes of death statistics provided by the Microdata Integrated Service of Statistics Korea were used to identify the deaths of study patients and to calculate all-cause mortality from the date of HCC diagnosis to the date of death or the end of 2018, whichever occurred first. Meanwhile, early diagnosis of cancer due to cancer surveillance can lead to an overestimation of prognosis and survival. To address lead-time bias, the Schwartz formula based on tumor volume doubling time and tumor diameter can be used. However, these necessary data were unavailable from the NHIS-NHID and national liver cancer surveillance program database that were used in this study. Therefore, we applied two different lead times (157 and 174 days) estimated by previous studies to adjust for lead-time bias.

Statistical analyses
The chi-square test was conducted to compare rates of receiving curative therapy and all-cause mortality between the different demographic and medical conditions. Odds ratios (ORs) computed by logistic regression were used to investigate the associations between the surveillance intervals and curative therapy. Additionally, Cox proportional hazards regression was performed to investigate the association between surveillance intervals and all-cause mortality. After univariable analyses of various demographic and clinical factors associated with curative treatments for HCC and all-cause mortality, multivariable analyses were performed using both logistic regression and Cox regression. All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA). A p value less than 0.05 was considered statistically significant.

RESULTS
Patient characteristics
Between January 2011 and December 2018, 64674 patients [sex: male, 49966 (77.3%); female, 14708 (22.7%); mean age: male, 60.9±10.0; female, 65.6±10.9] were diagnosed with HCC. The patient characteristics of the study cohort are summarized in Table 1. Among these patients, 63.4% (40983) of the patients had liver cirrhosis, and 53.8% (34823) and 11.1% (7203) had HBV and HCV infections, respectively. Patients underwent national HCC surveillance for ≤6 months (15587), 7–12 months (6569), 13–24 months (7383), and 25–36 months (3853) before the diagnosis of HCC. Patients who never underwent surveillance or received surveillance more than 36 months prior to the diagnosis were classified as never screened.

Association between HCC surveillance and curative therapy
In total, 41.6% (26885) of HCC patients received curative therapy. Patients in the 6M group (51.9%) received curative therapy more often than those in the other surveillance interval groups (1Y, 48.3%; 2Y, 43.8%; 3Y, 41.3%; and, never screened, 34.5%) (Table 2). As shown in Table 2, univariable analysis demonstrated a significant association between curative therapy and surveillance interval [1Y group: OR, 0.87; 95% confidence interval (CI), 0.82–0.92; 2Y group: OR, 0.72; 95% CI, 0.68–0.76; 3Y group: OR, 0.65; 95% CI, 0.61–0.70; never screened: OR, 0.49; 95% CI 0.47–0.51; p<0.001]. Likewise, age greater than 60 years, income status, living in rural areas, disability, liver cirrhosis, alcoholic liver disease, hepatitis infection, and CCI were significantly associated with curative therapy in univariable analysis.

After adjusting for covariates, surveillance interval was still found to be significantly associated with curative therapy. The adjusted OR for receiving curative therapy decreased as surveillance interval increased (Table 2). Compared to the 6M group, the adjusted ORs were 0.87 for the 1Y group (95% CI, 0.82–0.93; p<0.001), 0.76 for the 2Y group (95% CI, 0.72–0.81; p<0.001), 0.77 for the 3Y group (95% CI, 0.71–0.83; p<0.001), and 0.57 for the never screened group (95% CI, 0.54–0.59; p<0.001) (Table 2). Cirrhotic patients were more likely to receive curative therapy than non-cirrhotic patients (OR, 1.11; 95% CI, 1.07–1.15; p<0.001). Hepatitis infection was also independently associated with a
Greater likelihood of receiving curative therapy (hepatitis B: OR, 1.88; 95% CI, 1.81–1.96; hepatitis C: OR, 1.54; 95% CI, 1.46–1.64; co-infection: OR, 1.97; 95% CI, 1.80–2.15; p<0.001). The ORs of receiving curative therapy were 1.07 (95% CI, 1.02–1.13; p=0.007) for CCI 1, 0.67 (95% CI, 0.64–0.70; p<0.001) for CCI ≥2, 0.92 (95% CI, 0.87–0.98; p=0.004) for the 60–69 year age, 0.55 (95% CI, 0.52–0.59; p<0.001) for the ≥70 year age, and 1.13 (95% CI, 1.08–1.19; p=0.001) for disability. Compared to patients with low income, those with middle-high (OR, 1.20; 95% CI, 1.14–1.26; p<0.001) and high incomes (OR, 1.43; 95% CI, 1.36–1.50; p<0.001) were more likely to receive curative treatment, whereas those with medical aid (OR, 0.68; 95% CI, 0.63–0.73; p<0.001) were less likely to receive curative treatment (Table 2).

### Table 1. Patient Characteristics of the Study Cohort (n=64774)

| Parameter                  | Value (%) |
|----------------------------|-----------|
| Age (yr)                   |           |
| 40–49                      | 7453 (11.5) |
| 50–59                      | 21310 (33.0) |
| 60–69                      | 19591 (30.3) |
| ≥70                        | 16320 (25.2) |
| Sex                        |           |
| Male                       | 49896 (77.3) |
| Female                     | 14708 (22.7) |
| Income status              |           |
| Medical aid                | 4398 (6.8) |
| Low                        | 11280 (17.4) |
| Middle-low                 | 11777 (18.2) |
| Middle-high                | 15227 (23.5) |
| High                       | 21992 (34.0) |
| Residential area           |           |
| Capital area               | 24272 (37.5) |
| Metropolitan area          | 16562 (25.6) |
| Rural area                 | 23840 (36.9) |
| Disability                 |           |
| None                       | 54942 (85.0) |
| Disabled                   | 9732 (15.0) |
| Liver cirrhosis            |           |
| No                         | 23691 (36.6) |
| Yes                        | 40983 (63.4) |
| Alcoholic liver disease    |           |
| No                         | 56660 (87.6) |
| Yes                        | 8014 (12.4) |
| Hepatitis                  |           |
| None                       | 20308 (31.4) |
| Hepatitis B                | 34823 (53.8) |
| Hepatitis C                | 7203 (11.1) |
| Co-infection               | 2340 (3.6) |
| CCI                        |           |
| 0                          | 14178 (21.9) |
| 1                          | 11478 (17.8) |
| ≥2                         | 39018 (60.3) |
| Surveillance interval      |           |
| ≤6 months                  | 15587 (24.1) |
| 7–12 months                | 6569 (10.2) |
| 13–24 months               | 7385 (11.4) |
| 25–36 months               | 3853 (6.0) |
| Never screened             | 31282 (48.4) |

Table 1. Patient Characteristics of the Study Cohort (n=64774). Co-infection, hepatitis B and C infection; CCI, Charlson Comorbidity Index.

Association between HCC surveillance and all-cause mortality

In total, 43.7% (28279) of the patients died during the follow-up period. The cumulative mortalities of the 6M, 1Y, 2Y, 3Y, and never screened groups were 36.0%, 33.3%, 37.3%, 43.2%, and 51.4%, respectively (Table 3). Contrary to the rate of receiving curative therapy, the association between surveillance interval and all-cause mortality was not straightforward and varied. The hazard ratios (HR) for the 2Y group (adjusted HR, 1.07; 95% CI, 1.03–1.12; p=0.003), 3Y group (adjusted HR, 1.14; 95% CI, 1.08–1.21; p=0.001), and never screened groups (adjusted HR, 1.37; 95% CI, 1.33–1.42; p<0.001) were significantly greater than those of the 6M group (Table 3, Fig. 2). However, the HR of the 1Y group (adjusted HR, 0.96; 95% CI, 0.91–1.01; p=0.092) was not significantly different from that of the 6M group (Table 3). Even after adjusting for lead-time bias, the 1Y group surveillance interval was significantly associated with a lower risk of all-cause mortality than the 6M group surveillance interval (HRs with 157 days and 174 days of lead time, 0.91; p<0.001) (Table 4, Fig. 2). After correction of lead-time bias, the survival benefit of the 2Y group was not significantly different from that of the 6M group (HRs with 157 days and 174 days of lead time, 1.01; p=0.557 and p=0.721).

Patients who received potentially curative therapy were more likely to have survival benefits (adjusted HR, 0.26; 95% CI, 0.25–0.26; p<0.001) than those who did not receive curative therapy (Table 3, Fig. 3). The cumulative mortality of the patients who received curative therapy was 21.1%, whereas that of patients who did not receive curative therapy was 59.8%. A significant survival benefit was noted for patients with liver cirrhosis (adjusted HR, 0.96; 95% CI, 0.93–0.98; p<0.001) and those with hepatitis infection (hepatitis B: adjusted HR, 0.74; 95% CI, 0.72–0.76; hepatitis C: adjusted HR, 0.81; 95% CI, 0.78–0.84; co-infection: adjusted HR, 0.73; 95% CI, 0.68–0.78; all p<0.001) (Table 3). Significant associations with a survival benefit were also observed in the 50–59 years age (adjusted HR, 0.95; 95% CI, 0.91–0.99; p=0.018), 60–69 years age (adjusted HR, 0.92; 95% CI, 0.89–0.96; p<0.001), female (adjusted HR, 0.79; 95% CI, 0.77–0.81; p<0.001), middle-high income (adjusted HR, 0.94; 95% CI, 0.91–0.98; p=0.001), and high income (adjusted HR, 0.83; 95% CI, 0.80–0.86; p<0.001) (Table 3). On the other hand, an increased risk of mortality was associated with ages ≥70 (adjusted HR, 1.29; 95% CI, 1.23–1.34; p<0.001), living in metropolitan areas (adjusted HR, 1.24; 95% CI, 1.20–1.27; p<0.001), living in ru-
Table 2. Univariable and Multivariable Analyses of Variables Associated with Curative Therapy for Hepatocellular Carcinoma (HCC)

| Variables                         | Patients* (%) | Univariable analysis | Multivariable analysis |
|-----------------------------------|---------------|----------------------|------------------------|
|                                   |               | OR (95% CI)          | p value                | OR (95% CI)          | p value                |
| Total 26885/64674 (41.6)         |               | 1.00                 | 1.00                   |
| Surveillance interval             |               |                      |                        |
| ≤6 months                         | 8095/15587 (51.9) | 1.00 (0.82–0.92)     | <0.001                 | 0.87 (0.82–0.93)     | <0.001                 |
| 7–12 months                       | 3176/6569 (48.3) | 0.72 (0.68–0.76)     | <0.001                 | 0.76 (0.72–0.81)     | <0.001                 |
| 13–24 months                      | 3236/7383 (43.8) | 0.65 (0.61–0.70)     | <0.001                 | 0.77 (0.71–0.83)     | <0.001                 |
| 25–36 months                      | 1591/3853 (41.3) | 0.49 (0.47–0.51)     | <0.001                 | 0.57 (0.54–0.59)     | <0.001                 |
| Never screened                    | 10787/31282 (34.5) | 0.49 (0.47–0.51)     | <0.001                 | 0.57 (0.54–0.59)     | <0.001                 |
| Age (yr)                           |               |                      |                        |
| 40–49                             | 3574/7453 (48.0) | 1.00                 | 1.00                   |
| 50–59                             | 9974/21310 (46.8) | 0.96 (0.91–1.01)     | 0.087                  | 0.98 (0.93–1.04)     | 0.513                  |
| 60–69                             | 8598/19591 (43.9) | 0.85 (0.81–0.90)     | <0.001                 | 0.92 (0.87–0.98)     | 0.004                  |
| ≥70                               | 4739/13620 (29.0) | 0.44 (0.42–0.47)     | <0.001                 | 0.55 (0.52–0.59)     | <0.001                 |
| Sex                                |               |                      |                        |
| Male 20881/49966 (41.8)           | 1.00          | 1.00                 |
| Female 6004/14708 (40.8)          | 0.96 (0.93–1.00) | 0.036                | 1.02 (0.98–1.06)     | 0.336                  |
| Income status                      |               |                      |                        |
| Medical aid                       | 1271/4398 (28.9) | 0.63 (0.58–0.68)     | <0.001                 | 0.68 (0.63–0.73)     | <0.001                 |
| Low 4424/11280 (39.2)             | 1.00          | 1.00                 |
| Middle-low 4750/11777 (40.3)      | 1.05 (0.99–1.10) | 0.084                | 1.03 (0.97–1.09)     | 0.321                  |
| Middle-high 6571/15227 (43.2)     | 1.18 (1.12–1.24) | <0.001               | 1.20 (1.14–1.26)     | <0.001                 |
| High 9869/21992 (44.9)            | 1.26 (1.21–1.32) | <0.001               | 1.43 (1.36–1.50)     | <0.001                 |
| Residential area                   |               |                      |                        |
| Capital area 10274/24272 (42.3)   | 1.00          | 1.00                 |
| Metropolitan area 6952/16562 (42.0) | 0.99 (0.95–1.03) | 0.477                | 0.96 (0.93–1.01)     | 0.090                  |
| Rural area 9865/23840 (40.5)      | 0.93 (0.90–0.96) | <0.001               | 0.99 (0.95–1.03)     | 0.584                  |
| Disability                         |               |                      |                        |
| None 23015/54942 (41.9)           | 1.00          | 1.00                 |
| Disabled 3870/9732 (39.8)         | 0.92 (0.88–0.96) | <0.001               | 1.13 (1.08–1.19)     | <0.001                 |
| Liver cirrhosis                    |               |                      |                        |
| No 9091/23691 (38.4)              | 1.00          | 1.00                 |
| Yes 17794/40983 (43.4)            | 1.23 (1.19–1.27) | <0.001               | 1.11 (1.07–1.15)     | <0.001                 |
| Alcoholic liver disease            |               |                      |                        |
| No 23949/56660 (42.3)             | 1.00          | 1.00                 |
| Yes 2936/8014 (36.6)              | 0.79 (0.75–0.83) | <0.001               | 0.98 (0.93–1.03)     | 0.345                  |
| Hepatitis                          |               |                      |                        |
| None 5656/20308 (27.9)            | 1.00          | 1.00                 |
| Hepatitis B 17412/34823 (50.0)    | 2.59 (2.50–2.69) | <0.001               | 1.88 (1.81–1.96)     | <0.001                 |
| Hepatitis C 2695/7203 (37.4)      | 1.55 (1.46–1.64) | <0.001               | 1.54 (1.46–1.64)     | <0.001                 |
| Co-infection 1122/2340 (47.9)     | 2.39 (2.19–2.60) | <0.001               | 1.97 (1.80–2.15)     | <0.001                 |
| CCI                                |               |                      |                        |
| 0 7251/14178 (51.1)               | 1.00          | 1.00                 |
| 1 5829/11478 (50.8)               | 0.99 (0.94–1.04) | <0.001               | 1.07 (1.02–1.13)     | 0.007                  |
| ≥2 13865/39018 (35.4)             | 0.52 (0.50–0.54) | <0.001               | 0.67 (0.64–0.70)     | <0.001                 |

OR, odds ratio; CI, confidence interval; Co-infection, hepatitis B and C infection; CCI, Charlson Comorbidity Index.

*Data are presented as n1/n (%), where n1 refers to the number of patients who received curative therapy and n refers to the total number of patients in each subcategory.

DISCUSSION

Through this current study of nationwide cohort data, we analyzed the effectiveness of HCC surveillance and demonstrated...
# Table 3. Univariable and Multivariable Analyses of Variables Associated with All-Cause Mortality

| Variables                        | Patients* (%) | Univariable analysis | Multivariable analysis |
|----------------------------------|---------------|-----------------------|------------------------|
|                                  |               | HR (95% CI)           | p value               | HR (95% CI)           | p value   |
| Total                            | 28279/64674 (43.7) |                       |                        |                       |           |
| Surveillance interval            |               |                       |                        |                       |           |
| ≤6 months                        | 5608/15587 (36.0) | 1.00                  | 1.00                   |                       |           |
| 7–12 months                      | 2185/6569 (33.3) | 1.01 (0.96–1.06)      | 0.825                  | 0.96 (0.91–1.01)      | 0.092     |
| 13–24 months                     | 2751/7383 (37.3) | 1.18 (1.13–1.24)      | <0.001                 | 1.07 (1.03–1.12)      | 0.003     |
| 25–36 months                     | 1666/3853 (43.2) | 1.35 (1.28–1.43)      | <0.001                 | 1.14 (1.08–1.21)      | <0.001    |
| Never screened                   | 16069/31282 (51.4) | 1.69 (1.64–1.75)      | <0.001                 | 1.37 (1.33–1.42)      | <0.001    |
| Curative therapy                 |               |                       |                        |                       |           |
| No                               | 22595/37789 (59.8) | 1.00                  | 1.00                   |                       |           |
| Yes                              | 5684/26885 (21.1) | 0.22 (0.22–0.23)      | <0.001                 | 0.26 (0.25–0.26)      | <0.001    |
| Age (yr)                         |               |                       |                        |                       |           |
| 40–49                            | 2976/7453 (39.9) | 1.00                  | 1.00                   |                       |           |
| 50–59                            | 8443/21310 (39.6) | 0.99 (0.95–1.03)      | 0.493                  | 0.95 (0.91–0.99)      | 0.018     |
| 60–69                            | 7752/19591 (39.6) | 1.03 (0.99–1.07)      | 0.216                  | 0.92 (0.89–0.96)      | <0.001    |
| ≥70                              | 9108/16320 (55.8) | 1.74 (1.67–1.81)      | <0.001                 | 1.29 (1.23–1.34)      | <0.001    |
| Sex                              |               |                       |                        |                       |           |
| Male                             | 22389/49966 (44.8) | 1.00                  | 1.00                   |                       |           |
| Female                           | 5890/14708 (40.0) | 0.85 (0.82–0.87)      | <0.001                 | 0.79 (0.77–0.81)      | <0.001    |
| Income status                    |               |                       |                        |                       |           |
| Medical aid                      | 2493/4398 (56.7) | 1.22 (1.16–1.28)      | <0.001                 | 0.99 (0.94–1.04)      | 0.657     |
| Low                              | 5039/11280 (44.7) | 1.00                  | 1.00                   |                       |           |
| Middle-low                       | 5236/11777 (44.5) | 0.98 (0.94–1.02)      | 0.299                  | 0.99 (0.96–1.03)      | 0.706     |
| Middle-high                      | 6465/15227 (42.5) | 0.92 (0.88–0.95)      | <0.001                 | 0.94 (0.91–0.98)      | 0.001     |
| High                             | 9046/21992 (41.1) | 0.85 (0.82–0.88)      | <0.001                 | 0.83 (0.80–0.86)      | <0.001    |
| Residential area                 |               |                       |                        |                       |           |
| Capital area                     | 9741/24272 (40.1) | 1.00                  | 1.00                   |                       |           |
| Metropolitan area                | 7453/16562 (45.0) | 1.18 (1.15–1.22)      | <0.001                 | 1.24 (1.20–1.27)      | <0.001    |
| Rural area                       | 11085/23840 (46.5) | 1.24 (1.21–1.28)      | <0.001                 | 1.21 (1.18–1.24)      | <0.001    |
| Disability                       |               |                       |                        |                       |           |
| None                             | 23570/54942 (42.9) | 1.00                  | 1.00                   |                       |           |
| Disabled                         | 4709/9732 (48.4) | 1.16 (1.12–1.19)      | <0.001                 | 1.04 (1.00–1.07)      | 0.027     |
| Liver cirrhosis                  |               |                       |                        |                       |           |
| No                               | 10793/23811 (45.6) | 1.00                  | 1.00                   |                       |           |
| Yes                              | 17486/40983 (42.7) | 0.86 (0.84–0.88)      | <0.001                 | 0.96 (0.93–0.98)      | <0.001    |
| Alcoholic liver disease          |               |                       |                        |                       |           |
| No                               | 24188/56660 (42.7) | 1.00                  | 1.00                   |                       |           |
| Yes                              | 4091/8014 (51.1) | 1.23 (1.19–1.27)      | <0.001                 | 1.00 (0.97–1.04)      | 0.996     |
| Hepatitis                        |               |                       |                        |                       |           |
| None                             | 11444/20308 (56.4) | 1.00                  | 1.00                   |                       |           |
| Hepatitis B                      | 12428/34823 (35.7) | 0.49 (0.48–0.51)      | <0.001                 | 0.74 (0.72–0.76)      | <0.001    |
| Hepatitis C                      | 3495/7203 (48.5) | 0.73 (0.70–0.76)      | <0.001                 | 0.81 (0.78–0.84)      | <0.001    |
| Co-infection                     | 912/2340 (39.0) | 0.54 (0.51–0.58)      | <0.001                 | 0.73 (0.68–0.78)      | <0.001    |
| CCI                              |               |                       |                        |                       |           |
| 0                                | 4738/14178 (33.4) | 1.00                  | 1.00                   |                       |           |
| 1                                | 4157/11478 (36.2) | 1.08 (1.04–1.13)      | <0.001                 | 1.03 (0.99–1.07)      | 0.193     |
| ≥2                               | 19384/39018 (49.7) | 1.70 (1.64–1.75)      | <0.001                 | 1.23 (1.19–1.27)      | <0.001    |

HR, hazard ratio; CI, confidence interval; Co-infection, hepatitis B and C infection; CCI, Charlson Comorbidity Index.

*Data are presented as n1/n (%), where n1 refers to the number of deaths and n refers to the total number of patients in each subcategory.
that a longer surveillance interval was significantly associated with a decreased likelihood of receiving curative therapy. HCC surveillance programs have been proven to prolong the survival of patients with HCC by detecting HCC and increasing the application of curative therapies.22,26-32 One of the most important factors determining the effectiveness of a surveillance program is the selection of an optimal surveillance interval. In this study, a linear association was observed between surveillance interval and curative therapy, the most effective surveillance interval being 6 months. Similar to our study, Santi, et al.33 compared semiannual and annual surveillance and reported that semiannual surveillance was superior to annual surveillance in terms of early detection of HCC. In addition, Wu, et al.22 demonstrated that shorter surveillance intervals were associated with the probability of receiving curative therapy, although both 6-month and 12-month surveillance intervals showed a comparable chance of receiving curative therapy. However, reducing the surveillance interval to 3 months increased the detection of nonmalignant lesions and eventually led to a higher number of unnecessary procedures.34 Therefore, in accordance with our study, a surveillance interval of 6 months is considered to be effective in detecting HCC patients who may be candidates for curative therapy.

We considered hepatic resection, liver transplantation, and local ablative therapies performed within 1 year after the diagnosis of HCC as curative therapies. These curative therapies led to a significantly lower risk (adjusted HR, 0.26) of overall mortality, with a 38.7% reduction in the mortality rate in this study. This result was concordant with previous studies that reported 5-year survival rates of 23–80% after surgical interventions7,8,35,36 and 40–50% after local ablative therapies.36 Especially, the detection of small HCCs is important because tumor size, particularly less than 3 cm, is closely related to complete ablation of a tumor and, ultimately, a lower rate of local tumor recurrence.37,38

Notably, the 6M group and 1Y group showed comparable all-cause mortality after adjusting for lead-time bias with 157 days (B) and 174 days (C) of lead times, the survival benefit of the 7–12 months group became significantly higher than that of ≤6 months group. The difference between the ≤6 months and the 13–24 months groups became statistically insignificant.

Table 4. Association between Surveillance Intervals and All-Cause Mortality after Adjusting for Lead-Time Bias

| Surveillance interval | 157 days HR (95% CI) | p value | 174 days HR (95% CI) | p value |
|-----------------------|----------------------|---------|----------------------|---------|
| ≤6 months             | 1.00                 | 1.00    |
| 7–12 months           | 0.91 (0.87–0.96)     | <0.001  | 0.91 (0.86–0.95)     | <0.001  |
| 13–24 months          | 1.01 (0.97–1.06)     | 0.557   | 1.01 (0.96–1.06)     | 0.721   |
| 25–36 months          | 1.08 (1.02–1.14)     | 0.008   | 1.07 (1.01–1.13)     | 0.014   |
| Never screened        | 1.28 (1.24–1.32)     | <0.001  | 1.27 (1.23–1.31)     | <0.001  |

Fig. 3. Kaplan-Meier (KM) survival curves of patients with hepatocellular carcinoma (HCC) depending on curative therapy. The receipt of curative therapy was significantly associated with decreased overall survival among patients with HCC. Patients who did not receive curative therapy within 1 year from the diagnosis of HCC exhibited significantly lower overall survival than those who received curative therapy.
significant. This discrepancy might be due to various prognostic factors that can affect morbidity and mortality after curative therapies. Other than tumor size, another major prognostic factor is a patient’s liver function, which is known to influence treatment decisions and to be associated with late tumor recurrence after resection and all-cause mortality.\(^{23,39}\) Compared to patients with normal liver function who can achieve a 5-year survival rate of 70\%, those with portal hypertension show a lower 5-year survival rate of 50\%, which can be even lower in patients with impaired liver function.\(^{39}\) Liver cirrhosis, particularly decompensated liver cirrhosis, is associated with increased resection-related complications, postoperative liver failure, and mortality.\(^{7,13,39,42}\)

In Korea, the national HCC surveillance program does not exclude patients with severely impaired liver function, namely Child–Pugh class C, when designating the target population. The severity of liver function in the target population of the national HCC surveillance program is an important prognostic factor and may lead to results of all-cause mortality that are different from those of the chance to receive curative therapies in this study. Therefore, even though HCC surveillance with a 6-month surveillance interval can lead to higher rates of curative therapies, clinical factors, especially liver function, should be considered when evaluating prognosis and patient survival after treatment.

Unlike most previous observational studies, our study used a nationwide cohort, avoided selection bias, and tried to adjust for lead-time bias. Furthermore, through comprehensive health care information, various demographic and clinical factors, such as underlying liver disease and patient comorbidity, were investigated to correct possible confounding factors that might disturb the effect of HCC surveillance. Nevertheless, some limitations exist in this study. First, calculation of surveillance interval based on all surveillance results for the patients was not possible, because following the surveillance interval strictly is often difficult in the real world and the actual time interval between surveillance exams can vary. Moreover, we could not identify patients who personally underwent cancer screening at their own expense. Instead, we used the last surveillance date and the date of HCC diagnosis to define the surveillance interval. Second, pathological results and imaging data were not obtained to confirm the diagnosis of HCC. Future studies may include histopathological and imaging data of HCC to analyze all-cause mortality or liver-specific mortality because HCC prognosis can differ according to histopathologic variants. Although we tried to correct for lead-time bias, HCC surveillance might still detect indolent tumors, which would cause lead-time bias. Forth, since we followed up the patients and evaluated whether they were diagnosed with HCC or not until the end of 2018, patients with less than 3 years of follow-up may be included in the final study population, and inclusion of these patients may cause misclassification bias. Finally, since not all the necessary data were accessible, we could not evaluate accurate stages of HCC and consider liver function while evaluating all-cause mortality.

In conclusion, HCC surveillance, especially at a surveillance interval of 6 months, is independently associated with an increased chance of receiving curative therapy.

ACKNOWLEDGEMENTS

This work was supported by a National Health Insurance Service Ilsan Hospital grant (NHIMC 2019-20-022).

AUTHOR CONTRIBUTIONS

Conceptualization: Mi-Suk Park and Sumi Park. Data curation: Heejin Bae and Sang Ah Lee. Formal analysis: Sang Ah Lee. Funding acquisition: Sumi Park. Investigation: Heejin Bae and Mi-Suk Park. Methodology: Sang Ah Lee. Project administration: Sumi Park and Jong Won Choi. Resources: Sang Ah Lee and Shin Hye Hwang. Software: Heejin Bae and Sang Ah Lee. Supervision: Sumi Park and Mi-Suk Park. Validation: Sumi Park and Mi-Suk Park. Visualization: Heejin Bae. Writing—original draft: Heejin Bae. Writing—review & editing: Sang Ah Lee, Sumi Park, and Mi-Suk Park. Approval of final manuscript: all authors.

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