Original Article
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Current status of ultrasonography in national cancer surveillance program for hepatocellular carcinoma in South Korea: a large-scale multicenter study

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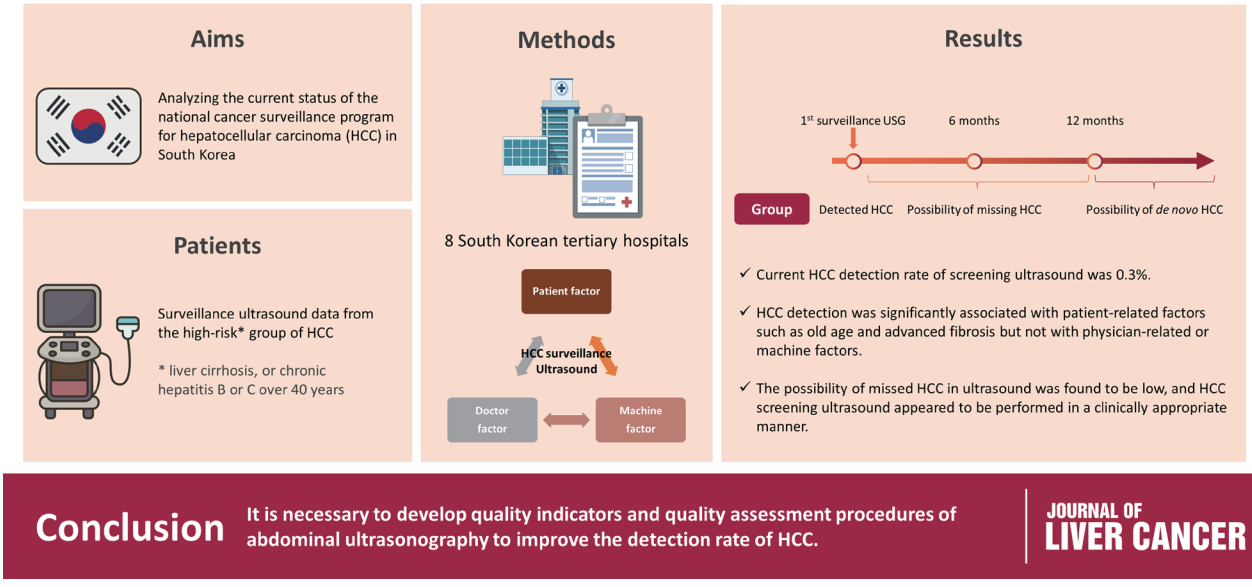

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Background/Aim: Abdominal ultrasonography (USG) is recommended as a surveillance test for high-risk groups for hepatocellular carcinoma (HCC). This study aimed to analyze the current status of the national cancer surveillance program for HCC in South Korea and investigate the effects of patient-, physician-, and machine-related factors on HCC detection sensitivity.

Methods: This multicenter retrospective cohort study collected surveillance USG data from the high-risk group for HCC (liver cirrhosis or chronic hepatitis B or C >40 years of age) at eight South Korean tertiary hospitals in 2017.

Results: In 2017, 45 experienced hepatologists or radiologists performed 8,512 USG examinations. The physicians had a mean 15.0±8.3 years of experience; more hepatologists (61.4%) than radiologists (38.6%) participated. Each USG scan took a mean 12.2±3.4 minutes. The HCC detection rate by surveillance USG was 0.3% (n=23). Over 27 months of follow-up, an additional 135 patients (0.7%) developed new HCC. The patients were classified into three groups based on timing of HCC diagnosis since the 1st surveillance USG, and no significant intergroup difference in HCC characteristics was noted. HCC detection was significantly associated with patient-related factors, such as old age and advanced fibrosis, but not with physician- or machine-related factors.

Conclusions: This is the first study of the current status of USG as a surveillance method for HCC at tertiary hospitals in South Korea. It is necessary to develop quality indicators and quality assessment procedures for USG to improve the detection rate of HCC. **(J Liver Cancer 2023;23:189-201)**

Keywords: Ultrasonography; Surveillance; Carcinoma, hepatocellular

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INTRODUCTION

Unlike other cancers, hepatocellular carcinoma (HCC) is frequently found in high-risk groups, for which surveillance tests are recommended.[1] Surveillance tests can reduce cancer-related deaths by enabling the detection of HCC at an earlier stage and increasing the chances of cure through interventions.[2] The currently most commonly recommended surveillance tests are abdominal ultrasonography (USG) and/or alpha-fetoprotein (AFP) determination.[3]

In South Korea, the national cancer screening project is well established, and individuals at a higher risk of HCC undergo USG tests every 6 months.[4] Additionally, since 2018, the benefits of upper USG have been made available to the general public, with 80% of the cost covered by the national healthcare system. However, the results of USG tests are more subject to interpretation than those of computed tomography (CT) and magnetic resonance imaging (MRI) and may vary depending on the patient's condition or examiner's expertise.[5] However, the quality indicators for USG examinations have not yet been established. It is worth noting that several quality indicators for colonoscopy have been developed, including adenoma detection rate, withdrawal time, and bowel preparation quality.[6] In the case of USG examinations, there is no known unique quality indicator to assess factors such as appropriate patient selection, examiner experience, or examination duration. The development of quality indicators is crucial for the effective use of USG as a surveillance test for HCC detection. Patient-, physician-, and machine-related factors can play important roles in the USG-based diagnosis of HCC. Physician- and machine-related factors are modifiable and can easily be incorporated as quality indicators.

The primary purpose of the present study was to analyze the current status of the national cancer surveillance program for HCC and its HCC detection rate. The secondary purpose

was to investigate the effects of patient-, physician-, and machine-related factors on HCC detection sensitivity.

METHODS

1. Data source

In South Korea, the national cancer surveillance program for HCC is available for individuals who have been identified as being at high risk. The high-risk group for HCC was defined as individuals >40 years of age with chronic hepatitis B or C or those with liver cirrhosis regardless of age. For individuals in the high-risk group, regular surveillance tests, consisting of USG and AFP, were performed every 6 months. The present study investigated patients who underwent HCC surveillance tests at eight tertiary institutions in the Seoul and Gyeongin metropolitan areas in South Korea from January 1, 2017 to December 31, 2017. The results of all surveillance tests were included from tests performed at health screening centers located in tertiary hospitals, radiology departments, and gastroenterology departments. Since one purpose of this study was to verify the HCC diagnosis rate through surveillance USG, patients with a history of undergoing a CT or MRI scan within 6 months prior to the USG were excluded because of the possibility of an altered USG sensitivity rate. Patients with a history of HCC were also excluded. The final analyses were based on data obtained from 7,989 subjects.

The study protocol was approved by the Institutional Review Board (IRB) of each hospital (SCHBC 2019-09-009-001; date of registration: December 26, 2019) and conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. Each IRB waived the requirement for informed consent owing to the retrospective nature of the study. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines were followed (Supplementary Table 1).

2. Data collection and classification of HCC

Three aspects of the surveillance test were investigated: patient-related (age, sex, body mass index, etiology, liver cirrhosis, fatty liver, ascites, poor sonic window, liver function, and other laboratory tests), physician-related (department, experience, duration of the examination), and machine-related (manufacturer, model) factors (Fig. 1). Skin-to-liver thickness was defined as the shortest distance from the skin

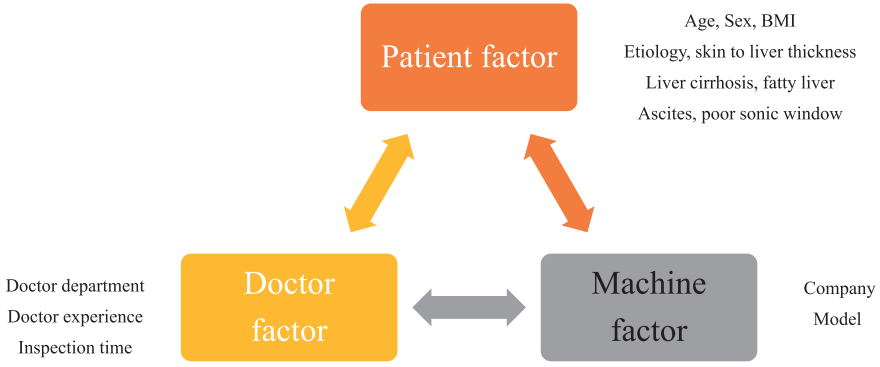

Figure 1. Three aspects of the surveillance test. BMI, body mass index.

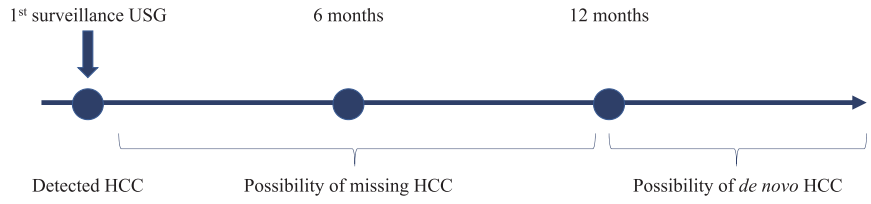

Figure 2. Brief schematic of hepatocellular carcinoma classification. USG, ultrasound; HCC, hepatocellular carcinoma.

Table 1. Baseline characteristics of the study subjects

Variable	Total (n=7,989)
Patient factor	
Sex	
Male	4,531 (56.7)
Female	3,458 (43.3)
Age (years)	53.6±11.0
Etiology	
HBV	5,992 (75.0)
HCV	899 (11.3)
Alcohol	362 (4.5)
Others	736 (9.2)
Body mass index (kg/m^2)	24.1±3.3
Antiviral therapy (HBV, HCV patients only)	4,637 (69.7)
Presence of encephalopathy	28 (0.4)
Platelet (×10^3)	188.1±75.8
AST (U/L)	31.9±35.9
ALT (U/L)	31.0±50.6
Total bilirubin (mg/dL)	1.0±3.4
Albumin (mg/dL)	4.4±0.4
PT INR	1.1±0.8
Serum creatinine (mEq/dL)	1.1±4.3
HBeAg positive, only in HBV	1,363 (22.7)
HBV DNA, only in HBV (×10^7 IU/mL)	1.807±12.426
FIB-4 score	2.2±2.8
<1.0	1,383 (23.8)
1.0–2.5	3,176 (54.6)
>2.5	1,259 (21.6)
APRI	0.6±1.0
Presence of fatty liver	2,338 (29.3)
Presence of liver cirrhosis	2,299 (28.8)
Presence of ascites	93 (1.2)
Child Pugh score (liver cirrhosis only)	5.5±1.3
Child Pugh class (liver cirrhosis only)	
Class A	1,685 (73.3)
Class B	576 (25.1)
Class C	38 (1.6)
MELD score	9.4±4.6
Transient elastography (kPa)	8.8±10.5
Poor sonic window	
No	7,479 (93.6)
Yes	510 (6.4)
Skin to liver thickness (cm)	1.8±0.5
Doctor factor	
Doctor department	
Gastroenterology	4,919 (61.6)
Radiology	3,070 (38.4)
Doctor experience (years)	15.1±8.3
<15	4,310 (53.9)
≥15	3,679 (46.1)
Sonographic examination length (minutes)	12.2±3.4
Machine factor, company	
GE Healthcare	3,140 (39.3)
PHILIPS	691 (8.6)
TOSHIBA	3,625 (45.4)
HITACHI	237 (3.0)
SIEMENS	296 (3.7)

Values are presented as number (%) or mean±standard deviation.
FIB-4, fibrosis-4 score; APRI, AST to platelet ratio index; MELD: model for end-stage liver disease.

to the liver capsule of the right lobe in the intercostal view.

Considering the doubling time for HCC tumor volume, HCC was classified as follows based on the timing of HCC detection since the 1st surveillance USG: 1) detected HCC, HCCs found on the 1st surveillance test; 2) possibility of missing HCC found within 12 months after the 1st surveillance USG; and 3) possibility of *de novo* HCC found 12 months after the 1st surveillance USG. Fig. 2 shows a brief schematic of this classification. HCC was defined as a case in which suspicious lesions were found through USG and subsequent imaging tests, such as CT or MRI, confirmed the findings according to the Korean Liver Cancer Association-National Cancer Center practice guidelines.[7]

3. Statistical analysis

Frequencies and percentages were used for descriptive statistics. Significant intergroup differences were investigated using the chi-squared test for categorical variables and Student's *t*-test for continuous variables. A logistic regression analysis was performed to assess the relationship between in-hospital mortality and other factors. Only the factors signifi-

Table 2. Baseline characteristics by the time of HCC diagnosis

Variable	Total (n=7,989)	HCC (-) (n=7,831)	HCC (+) in the 1st surveillance USG (n=23)	HCC (+) within 12 months since the 1st surveillance USG (n=23)	HCC (+) after 12 months since the 1st surveillance USG (n=112)	*P*-value
Patient factor						
Sex						0.040
Male	4,531 (56.7)	4,427 (56.5)	17 (73.9)	18 (78.3)	69 (61.6)	
Female	3,458 (43.3)	3,404 (43.5)	6 (26.1)	5 (21.7)	43 (38.4)	
Age (years)	53.6±11.0	53.4±11.0	64.3±11.3	58.0±10.1	61.5±10.3	<0.001
Etiology						0.351
HBV	5,992 (75.0)	5,886 (75.2)	17 (73.9)	13 (56.5)	76 (67.9)	
HCV	899 (11.3)	878 (11.2)	3 (13.0)	4 (17.4)	14 (12.5)	
Alcohol	362 (4.5)	350 (4.5)	1 (4.3)	3 (13.0)	8 (7.1)	
Others	736 (9.2)	717 (9.2)	2 (8.7)	3 (13.0)	14 (12.5)	
Body mass index (kg/m^2)	24.1±3.3	24.1±3.3	24.7±4.2	24.4±4.1	24.8±3.4	0.173
Antiviral therapy	4,637 (69.7)	4,538 (69.5)	13 (65.0)	15 (88.2)	71 (79.8)	0.061
Encephalopathy	28 (0.4)	24 (0.3)	1 (4.3)	1 (4.3)	2 (1.8)	<0.001
Platelet (×10^3)	188.1±75.8	189.3±75.6	154.6±62.1	118.8±56.0	131.6±63.0	<0.001
AST (U/L)	31.9±35.9	31.7±36.0	39.0±27.4	37.4±17.4	39.5±33.2	0.083
ALT (U/L)	31.0±50.6	30.9±51.0	33.2±21.0	29.6±17.2	31.9±22.9	0.992
Total bilirubin (mg/dL)	1.0±3.4	1.0±3.4	1.1±0.6	1.6±1.5	1.1±0.6	0.831
Albumin (mg/dL)	4.4±0.4	4.4±0.4	4.0±0.5	3.9±0.6	4.2±0.5	<0.001
PT INR	1.1±0.8	1.1±0.8	1.1±0.1	1.2±0.2	1.2±1.4	0.215
Serum creatinine (mEq/dL)	1.1±4.3	1.1±4.3	1.2±1.1	1.0±0.2	0.9±0.5	0.980
HBeAg positive, only in chronic hepatitis B	1,363 (28.0)	1,345 (28.1)	4 (28.6)	3 (30.0)	11 (17.2)	0.286
HBV DNA, only in HBV (×10^7 IU/mL)	1.807±12.426	1.836±12.529	0.134±0.428	3.9±13.6	0.193±1.441	0.660
FIB-4 score	2.2±2.8	2.1±2.8	3.1±2.3	5.3±5.3	4.1±3.3	<0.001
<1.0	1,383 (23.8)	1,376 (24.1)	2 (14.3)	1 (5.3)	4 (5.8)	
1.0–2.5	3,176 (54.6)	3,144 (55.0)	4 (28.6)	5 (26.3)	23 (33.3)	
>2.5	1,259 (21.6)	1,196 (20.9)	8 (57.1)	13 (68.4)	42 (60.9)	
APRI	0.6±1.0	0.5±1.0	0.8±0.6	1.1±1.2	1.0±1.0	<0.001
Presence of fatty liver	2,338 (29.3)	2,328 (29.7)	3 (13.0)	0 (0.0)	7 (6.2)	<0.001
Presence of liver cirrhosis	2,299 (28.8)	2,181 (27.9)	12 (52.2)	18 (78.3)	88 (78.6)	<0.001
Presence of ascites	93 (1.2)	87 (1.1)	0 (0.0)	2 (8.7)	4 (3.6)	0.001
Child Pugh score	5.5±1.3	5.5±1.3	5.6±1.4	6.0±1.6	5.7±1.3	0.303
Child Pugh class						0.098
Class A	3,986 (86.7)	3,867 (86.7)	18 (90.0)	16 (76.2)	85 (84.2)	
Class B	576 (12.5)	556 (12.5)	1 (5.0)	4 (19.0)	15 (14.9)	
Class C	38 (0.8)	35 (0.8)	1 (5.0)	1 (4.8)	1 (1.0)	
MELD score	9.4±4.6	9.4±4.6	9.7±3.4	11.0±5.2	9.9±5.0	0.268

Table 2. Continued

Variable	Total (n=7,989)	HCC (-) (n=7,831)	HCC (+) in the 1st surveillance USG (n=23)	HCC (+) within 12 months since the 1st surveillance USG (n=23)	HCC (+) after 12 months since the 1st surveillance USG (n=112)	*P*-value
Transient elastography (kPa)	8.8±10.5	8.7±10.2	7.2±0.7	18.6±14.4	20.7±18.9	<0.001
Poor sonic window						0.096
No	7,479 (93.6)	7,331 (93.6)	21 (91.3)	19 (82.6)	108 (96.4)	
Yes	510 (6.4)	500 (6.4)	2 (8.7)	4 (17.4)	4 (3.6)	
Skin to liver thickness (cm)	1.8±0.5	1.8±0.5	1.9±0.5	1.8±0.4	1.8±0.5	0.219
Doctor factor						
Doctor department						0.273
Gastroenterology	4,919 (61.6)	4,827 (61.6)	14 (60.9)	17 (73.9)	61 (54.5)	
Radiology	3,070 (38.4)	3,004 (38.4)	9 (39.1)	6 (26.1)	51 (45.5)	
Doctor experience (years)	15.1±8.3	15.2±8.3	14.5±4.2	18.4±6.2	13.6±7.4	0.051
<15	4,310 (53.9)	4,217 (53.9)	11 (47.8)	6 (26.1)	76 (67.9)	
≥15	3,679 (46.1)	3,614 (46.1)	12 (52.2)	17 (73.9)	36 (32.1)	
Sonographic examination length (minutes)	12.2±3.4	12.2±3.4	13.4±3.0	13.8±3.7	12.2±2.8	0.055
Machine factor, company						0.051
GE Healthcare	3,140 (39.3)	3,086 (39.4)	9 (39.1)	15 (65.2)	30 (26.8)	
PHILIPS	691 (8.6)	674 (8.6)	2 (8.7)	0 (0.0)	15 (13.4)	
TOSHIBA	3,625 (45.4)	3,552 (45.4)	9 (39.1)	6 (26.1)	58 (51.8)	
HITACHI	237 (3.0)	230 (2.9)	1 (4.3)	2 (8.7)	4 (3.6)	
SIEMENS	296 (3.7)	289 (3.7)	2 (8.7)	0 (0.0)	5 (4.5)	

Values are presented as number (%) or mean±standard deviation.
HCC, hepatocellular carcinoma; USG, ultrasound.

cant in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using R version 4.3.1 (The R Foundation for Statistical Computing; Vienna, Austria). Statistical significance was set at $P<0.05$.

RESULTS

1. Baseline characteristics of HCC surveillance subjects

In 2017, 7,989 patients underwent USG at eight tertiary hospitals for HCC surveillance. The subjects' baseline characteristics are presented in Table 1. There were 4,531 males (56.7%), and the mean age was 53.6±11.0 years. The most common underlying disease was hepatitis B virus (HBV) (75.0%), followed by hepatitis C virus (HCV) (11.3%), others (9.2%), and alcohol (4.5%). Of the 6,891 patients with viral hepatitis (HBV or HCV), 4,637 (69.7%) received antiviral therapy.

The average fibrosis-4 (FIB-4) and aminotransferase to platelet ratio index (APRI) scores were 2.2 and 0.6, respectively. Among the participants, 28.8% had cirrhosis. Of these cirrhotic patients, 614 (26.7%) had Child-Pugh class B or C. A total of 93 patients (1.2%) had ascites, while 28 (0.4%) had any grade of hepatic encephalopathy. On the USG screen, the average skin to liver thickness of the patients was 1.8±0.5 cm; 510 subjects (6.4%) had a poor sonic window.

Table 3. Comparison between HCC and non-HCC groups

Variable	Total (n=7,989)	HCC (-) (n=7,831)	HCC (+) (n=158)	*P*-value
Patient factor				
Sex				0.024
Male	4,531 (56.7)	4,427 (56.5)	104 (65.8)	
Female	3,458 (43.3)	3,404 (43.5)	54 (34.2)	
Age (years)	53.6±11.0	53.4±11.0	61.4±10.5	<0.001
Etiology				0.083
HBV	5,992 (75.0)	5,886 (75.2)	106 (67.1)	
HCV	899 (11.3)	878 (11.2)	21 (13.3)	
Alcohol	362 (4.5)	350 (4.5)	12 (7.6)	
Others	736 (9.2)	717 (9.2)	19 (12.0)	
Body mass index (kg/m^2)	24.1±3.3	24.1±3.3	24.8±3.6	0.028
Antiviral therapy	4,637 (69.7)	4,538 (69.5)	99 (78.6)	0.036
Encephalopathy	28 (0.4)	24 (0.3)	4 (2.5)	<0.001
Platelet (×10^3)	188.1±75.8	189.3±75.6	133.0±62.3	<0.001
AST (U/L)	31.9±35.9	31.7±36.0	39.1±30.4	0.003
ALT (U/L)	31.0±50.6	30.9±51.0	31.7±21.8	0.669
Total bilirubin (mg/dL)	1.0±3.4	1.0±3.4	1.2±0.8	0.009
Albumin (mg/dL)	4.4±0.4	4.4±0.4	4.1±0.5	<0.001
PT INR	1.1±0.8	1.1±0.8	1.2±1.2	0.172
Serum creatinine (mEq/dL)	1.1±4.3	1.1 ± 4.3	1.0 ± 0.6	0.091
HBeAg positive, only in chronic hepatitis B	1,363 (28.0)	1,345 (28.1)	18 (20.5)	0.141
HBV DNA, only in HBV (×10^7 IU/mL)	1.807±12.426	1.836±12.529	0.158±1.231	<0.001
FIB-4 score	2.2±2.8	2.1±2.8	4.2±3.7	<0.001
<1.0	1,383 (23.8)	1,376 (24.1)	7 (6.9)	
1.0–2.5	3,176 (54.6)	3,144 (55.0)	32 (31.4)	
>2.5	1,259 (21.6)	1,196 (20.9)	63 (61.8)	
APRI	0.6±1.0	0.5±1.0	1.0±1.0	<0.001
Presence of fatty liver	2,338 (29.3)	2,328 (29.7)	10 (6.3)	<0.001
Presence of liver cirrhosis	2,299 (28.8)	2,181 (27.9)	118 (74.7)	<0.001
Presence of ascites	93 (1.2)	87 (1.1)	6 (3.8)	0.006
Child Pugh score	5.5±1.3	5.5±1.3	5.7±1.3	0.132
Child Pugh class				0.186
Class A	3,986 (86.7)	3,867 (86.7)	119 (83.8)	
Class B	576 (12.5)	556 (12.5)	20 (14.1)	
Class C	38 (0.8)	35 (0.8)	3 (2.1)	
MELD score	9.4±4.6	9.4±4.6	10.0±4.8	0.102
Transient elastography (kPa)	8.8±10.5	8.7±10.2	19.7±17.7	<0.001
Poor sonic window				1.000
No	7,479 (93.6)	7,331 (93.6)	148 (93.7)	
Yes	510 (6.4)	500 (6.4)	10 (6.3)	

Table 3. Continued

Variable	Total (n=7,989)	HCC (-) (n=7,831)	HCC (+) (n=158)	*P*-value
Skin to liver thickness (cm)	1.8±0.5	1.8±0.5	1.9±0.5	0.043
Doctor factor				
Doctor department				0.429
Gastroenterology	4,919 (61.6)	4,827 (61.6)	92 (58.2)	
Radiology	3,070 (38.4)	3,004 (38.4)	66 (41.8)	
Doctor experience (years)	15.1±8.3	15.2±8.3	14.4±7.0	0.186
<15	4,310 (53.9)	4,217 (53.9)	93 (58.9)	0.242
≥15	3,679 (46.1)	3,614 (46.1)	65 (41.1)	
Sonographic examination length (minutes)	12.2±3.4	12.2±3.4	12.6±3.0	0.104
Machine factor, company				0.505
GE Healthcare	3,140 (39.3)	3,086 (39.4)	54 (34.2)	
PHILIPS	691 (8.6)	674 (8.6)	17 (10.8)	
TOSHIBA	3,625 (45.4)	3,552 (45.4)	73 (46.2)	
HITACHI	237 (3.0)	230 (2.9)	7 (4.4)	
SIEMENS	296 (3.7)	289 (3.7)	7 (4.4)	

Values are presented as number (%) or mean±standard deviation.
HCC, hepatocellular carcinoma; USG, ultrasound.

Regarding physician-related factors, HCC surveillance tests were performed by expert gastroenterologists in 4,919 subjects (61.6%) and expert radiologists in 3,070 subjects (38.4%). The average physician USG experience was 15.1±8.3 years. The mean USG duration was 12.2±3.4 minutes. Regarding machine-related factors, the most commonly used abdominal USG machines were manufactured by TOSHIBA (45.4%), followed by GE Healthcare (39.3%) and PHILIPS (8.6%).

2. HCC detection rate through surveillance USG test

The total number of patients diagnosed with HCC through the 1st USG surveillance test was 23 (0.3% of all subjects). Among the 23 patients (0.3%), HCC was not found on the 1st surveillance USG test but was found within 12 months after the 1st surveillance USG. Additionally, HCC was not found in the 1st surveillance USG test but was found more than 12 months after the 1st surveillance USG test in 112 patients (1.4%). In summary, the HCC diagnosis rate in the 1st surveillance USG test was 0.3%, and an additional 135 patients (1.7%) were diagnosed with HCC over the next 27 months.

We classified all subjects into four groups: a group without HCC, a group with HCC detected through the 1st surveillance USG test, a group with HCC detected within 12 months of the 1st surveillance USG test, and a group with HCC detected 12 months after the 1st surveillance USG test. The characteristics of the study groups are presented in Table 2. The subjects in the HCC detection group (those with HCC detected through the 1st surveillance USG test) were significantly older than those in the other groups ($P<0.001$). However, no significant difference in liver function or fibrosis burden was noted between the detection group and the later diagnosed groups (those with HCC detected within or after 12 months of the 1st surveillance USG test). Additionally, there was no significant difference between the detection and the later diagnosis groups in terms of examiner experience, USG duration, or USG machine manufacturer.

3. Characteristics of patients with HCC

During the mean observation period of 27.2±9.7 months,

Table 4. Characteristics of hepatocellular carcinoma by the time of diagnosis

Variable	Total (n=158)	HCC (+) in the 1st surveillance USG (n=23)	HCC (+) within 12 months since the 1st surveillance USG (n=23)	HCC (+) after 12 months since the 1st surveillance USG (n=112)	*P*-value
Tumor location					0.915
Right	49 (62.8)	14 (60.9)	14 (66.7)	21 (61.8)	
Left	21 (26.9)	6 (26.1)	6 (28.6)	9 (26.5)	
Both	8 (10.3)	3 (13.0)	1 (4.8)	4 (11.8)	
Tumor size (cm)	2.4±2.0	3.0±3.6	2.2±1.7	2.4±1.6	0.373
Tumor echogenicity					0.844
Hypoechoic	94 (75.8)	17 (73.9)	19 (86.4)	58 (73.4)	
Isoechoic	12 (9.7)	2 (8.7)	2 (9.1)	8 (10.1)	
Hyperechoic	17 (13.7)	4 (17.4)	1 (4.5)	12 (15.2)	
Non-visualization	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.3)	
Tumor type					0.531
Nodular	154 (98.1)	23 (100.0)	23 (100.0)	108 (97.3)	
Infiltrative	3 (1.9)	0 (0.0)	0 (0.0)	3 (2.7)	
BCLC stage					0.147
A	134 (87.0)	18 (78.3)	20 (87.0)	96 (88.9)	
B	11 (7.1)	2 (8.7)	1 (4.3)	8 (7.4)	
C	8 (5.2)	3 (13.0)	1 (4.3)	4 (3.7)	
D	1 (0.6)	0 (0.0)	1 (4.3)	0 (0.0)	
T stage					0.178
T1	92 (59.7)	10 (43.5)	18 (78.3)	64 (59.3)	
T2	49 (31.8)	10 (43.5)	3 (13.0)	36 (33.3)	
T3	10 (6.5)	3 (13.0)	1 (4.3)	6 (5.6)	
T4	3 (1.9)	0 (0.0)	1 (4.3)	2 (1.9)	
N stage					0.057
N0	153 (99.4)	23 (100.0)	22 (95.7)	108 (100.0)	
N1	1 (0.6)	0 (0.0)	1 (4.3)	0 (0.0)	
M stage					0.561
M0	151 (98.1)	22 (95.7)	23 (100.0)	106 (98.1)	
M1	3 (1.9)	1 (4.3)	0 (0.0)	2 (1.9)	

Values are presented as number (%) or mean±standard deviation.
HCC, hepatocellular carcinoma; USG, ultrasound; BCLC, Barcelona Clinic Liver Cancer.

158 patients (2.0%) developed HCC. The characteristics of the groups with versus without HCC are compared in Table 3. The proportion of males in the HCC group (65.8%) was higher than that in the non-HCC group (56.5%; P=0.024), and the subjects in the HCC group were significantly older (mean, 61.4 years) than those in the non-HCC group (mean, 53.4 years; P<0.001). Additionally, a higher proportion of patients was taking antiviral drugs in the HCC versus non-HCC group. However, there was no significant difference in the incidence of HCC according to etiology (P=0.083).

The fibrosis burden was higher in the HCC versus non-HCC group when evaluated using FIB-4 score, APRI score, or transient elastography. In addition, subjects in the HCC group were significantly more likely to have liver cirrhosis (74.7%) than those in the non-HCC group (27.9%; $P<0.001$). Meanwhile, a significantly lower proportion of subjects had fatty liver disease in the HCC (6.3%) versus non-HCC group (29.7%; $P<0.001$). In contrast to patient-related factors, there were no differences in physician- or machine-related factors between the HCC and non-HCC groups.

4. HCC characteristics by diagnostic timing

Finally, HCC stage and characteristics were compared by HCC diagnostic timing (i.e., on the 1st surveillance USG test, within 12 months after the 1st surveillance USG test, and 12 months after the 1st surveillance USG test) (Table 4). Regarding tumor location, the right lobe was most commonly affected, accounting for an average of 62%, than the left lobe; this trend did not differ significantly among groups. The average HCC size was 2.4±2.0 cm, and no intergroup difference was noted. Most HCC cases were hypoechoic on USG, with the nodular type being the most prevalent. The most common HCC stage was Barcelona Clinic Liver Cancer (BCLC) stage A (87%), followed by BCLC stage B (7%). An additional stratified analysis was performed according to liver disease etiology (viral vs. non-viral), but no difference was found (data not shown). In summary, no significant differences in HCC stage or characteristics were noted at the time of diagnosis.

DISCUSSION

This study provides insight into the current status of screening tests for high-risk HCC groups in South Korean tertiary hospitals. The most important factors in detecting HCC were patient-related, whereas the effects of physician- or machine-related factors were not significant. Additionally, case classification based on the time from the 1st screening USG to HCC diagnosis suggested a low likelihood of missing HCC on USG and satisfactory performance of South Korean surveillance testing.

The importance of USG in liver cancer screening cannot be overemphasized. Abdominal USG is strongly recommended as a surveillance test for HCC regardless of the national guidelines.[8-10] In fact, it is widely recognized that regular screening using USG can increase survival rates and reduced medical expenses for patients at a high risk of HCC.[11] In South Korea, an early cancer screening program was implemented for high-risk groups for HCC in 2003; however, few studies have focused on the specific procedures of USG examinations in clinical practice.[12]

The primary significance of this study is that it sheds light on the current status of HCC surveillance in South Korea. While national annual surveillance data were published in 2016,[11] this is the first study to examine how HCC screening is conducted at tertiary hospitals in the South Korean metropolitan area. In South Korean tertiary hospitals, gastroenterologists actively participate in HCC screening, whereas globally, surveillance USG is primarily performed by radiology departments.[13] In the long term, it will be necessary to pay much attention to USG education in gastroenterology. Regular visits with specialists, such as hepatologists, can effectively increase patient adherence. In the United States and Europe, <30% of patients with liver cirrhosis undergo regular USG examinations, but the screening rate significantly increased when a specialist was consulted.[14,15]

The second important finding of our study was that the likelihood of HCC being missed by USG was low. We classified HCC cases based on the timing of diagnosis since the 1st surveillance USG and found no significant intergroup differences. It is generally understood that the doubling time for HCC is 6–12 months given that we defined the cases of an additional HCC discovered within 12 months since the 1st surveillance USG as possible instances of missed HCC cases.[16] If this group truly represented missed HCC cases, we would expect to observe a higher HCC stage compared to the group in which HCC was diagnosed at the 1st surveillance USG. However, our results did not support this hypothesis. That is, the group of subjects who had HCC detected within 12 months of the 1st surveillance USG did not have HCC at the time of the 1st surveillance, while it is highly likely that

new HCC developed later. In summary, our findings suggest that current surveillance protocols for HCC in South Korean tertiary hospitals are unlikely to miss cases of HCC, and USG screening appears effective.

The third important finding of our study was that both physician- and machine-related factors had a minimal effect on HCC detection. We examined these factors since they are modifiable, unlike patient-related factors. For example, if USG scans were required to last for a certain duration akin to colonoscopy withdrawal time, this could be clinically implemented. However, we did not identify any readily modifiable physician- or machine-related factors in our study. To increase inspection accuracy, the development and control of quality indicators are important. Except for the quality indicators for the machine itself, there has been little research on indicators for performers.[17] In 2021, a study evaluated performance evaluation criteria for abdominal USG in China;[18] at that time, the items were doctor-to-USG equipment ratio, doctor-to-patient ratio, examination room-to-examination ratio, doctor-to-USG equipment ratio, and positive USG examination rate. Since the creation of these evaluation criteria, the diagnostic accuracy of abdominal USG has increased. However, there has been no research on the quality indicators of abdominal USG, particularly in Korea.

Regarding the time taken for USG examination, a current duration of 12 minutes is appropriate for HCC detection. Notably, our results showed that experts with more than 15 years of experience achieved similar clinical results despite spending relatively less time on the examination than those with less than 15 years of experience. Regarding tumor factors, there were relatively few cases of fatty liver disease in patients with HCC. It is possible that the presence or absence of fatty liver influenced HCC detection; however, this hypothesis requires further validation. Likewise, although not statistically significant, the proportion of the infiltrative type in the missing HCC group was higher than that in the other HCC groups. As the infiltrative tumor type corresponds to a difficult form of HCC detection through USG, clinical attention is required.

One of our study's objectives was to develop a quality indicator for USG screening, but we were unable to identify any criteria for physician- or machine-related factors. In conclusion, patient-related factors remained the most important contributors to HCC development and detection. Among patient-related factors, advanced fibrosis burden, male sex, and older age were key risk factors, consistent with previous studies.[19,20]

Although not identified in our study, the development of quality indicators for USG screening remains an important issue in the long term.[21,22] This is because USG is currently the most widely used tool for HCC surveillance.[23] However, USG has inherent limitations in terms of sensitivity, with a rate of 37%.[5] Moreover, USG sensitivity tends to decline even further in patients with fatty liver or liver cirrhosis.[24-26] Considering the increasing incidence of obesity and fatty liver, it is important to consider whether additional tests such as liquid biopsy should be performed in these patients in addition to surveillance USG.[27-29]

Our study had several limitations. First, the definition of a group with the possibility of missed HCC lacks clear empirical evidence. In previous studies, surveillance failure was often defined by tumor stage, such as beyond the Milan criteria or at BCLC stage B or C.[30] However, since the above definition may classify fast-growing HCC as surveillance failure, in our study, missing HCC was defined based on a 12-month interval. The doubling time for liver cancer varies greatly among individuals, so there may be objections to the criterion of <12 months used in our study.[31] However, although not presented in this study, we performed a sensitivity analysis by changing the criteria in cases in which additional HCC was found within 6 months after the 1st surveillance USG; however, no significant difference was found across groups. Second, since our study mainly investigated USG practices at tertiary hospitals, there is a possibility of selection bias, and it may not represent surveillance practices in South Korea as a whole. In other words, to identify a comprehensive range of quality indicators of USG surveillance, various healthcare settings, including primary medical institutions and university hospitals, should have been included. Moreover, it is possible that the effects of physician- and machine-related factors were underestimated because the data were collected from university hospitals with relatively experienced physi-

cians. It is probable that the proficiency of physicians or machines in primary medical institutions is lower than that in university hospitals, and future research targeting a broader range of hospitals is required.

In conclusion, the present study conducted at South Korean tertiary hospitals in the metropolitan area showed that the current HCC detection rate of screening was 0.3%. In HCC detection, the influence of physician- or machine-related factors was minimal, while patient-related factors were more important. The possibility of missed HCC on USG was low, and HCC screening USG appeared to be performed in a clinically appropriate manner. Follow-up studies targeting a broader range of hospitals are needed to develop USG quality indicators in the future.

Conflict of Interest

Do Seon Song, Young Chang and Jeong-Ju Yoo currently serve as editorial board members for J Liver Cancer, and they were not involved in the review process of this article. Otherwise, the authors have no conflicts of interest to disclose.

Ethics Statement

The study protocol was approved by the institutional review board (IRB) of each hospital (SCHBC 2019-09-009-001; date of registration: December 26, 2019) and conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. Each IRB waived the requirement for informed consent owing to the retrospective nature of the study.

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Data Availability

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

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Supplementary Material

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