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ORIGINAL ARTICLE

Computed Tomography-Measured Liver Volume Predicts the Risk of Hepatocellular Carcinoma Development in Chronic Hepatitis C Patients

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Abstract

Aim In this retrospective cohort study, we evaluated the significance of liver volume in the prediction of hepatocellular carcinoma (HCC) in 277 chronic hepatitis C (CHC) patients who received dynamic computed tomography (CT) during surveillance.

Methods Liver volumes were measured on portal venous phase of CT images by using ImageJ software. Liver volume index, a ratio of the standard liver volume expected by weight and height to the measured liver volume, was calculated to adjust for normal variations. The cohort was randomly divided to derivation ($n = 100$) and validation sets ($n = 177$) for the generation of a liver volume-based Cox prediction model and validation of a liver volume-based nomogram, respectively.

Results The liver volume index was independent of weight or height, and it predicted further development of HCC (hazard ratio [HR] 16.30, 95% CI 6.70–39.62; $p < 0.001$). Liver cirrhosis, gamma-glutamyl transferase, and liver volume index were independent predictors of HCC, and nomogram-based prediction score from these three parameters identified high-risk patients at the cutoff of 110 in both derivation ($p < 0.001$) and validation cohort ($p < 0.001$).

Conclusion Liver volume-based prediction model stratifies the risk of developing HCC in CHC patients whose initial dynamic CT study gave negative results.

Keywords Hepatitis C · Chronic · Carcinoma · Hepatocellular · Cancer screening · Organ volume

Introduction

Hepatitis C virus (HCV) infection poses global health threat: over 142 million people are infected with HCV and the prevalence has increased by 18% over the last decade [1]. Hepatocellular carcinoma (HCC) is one of the most serious complications of HCV infection. The age-adjusted annual mortality of HCV-associated HCC is 2.6 per 100,000 globally [2]. Antiviral therapy for chronic hepatitis C (CHC) can reduce the risk of HCC [3], but a significant number of patients still develop HCC after achieving sustained virologic response (SVR) [4–6]. Therefore, surveillance for HCC is an important issue in the management of CHC.

Current guidelines recommend ultrasonography (US) with or without alpha-fetoprotein (AFP) as a surveillance tool for HCC detection in CHC patients [7–11]. Contrast-enhanced dynamic imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) are indicated as a recall procedure if surveillance tests reveal suspicious nodule(s) and/or elevated tumor marker levels. Dynamic imaging studies are also indicated if advanced cirrhotic change limits adequate ultrasonographic evaluation [11]. Patients who get a negative result from the dynamic imaging may still have increased risk of HCC and warrant enhanced surveillance [7, 10], but it is not well defined how these patients should be followed.

Liver volume shrinks as chronic liver diseases progress, and it correlates with hepatic functional reserve in normal and pathologic states [12–15]. Computed tomography (CT)

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volumetry accurately measures liver volume [16–18], and CT-measured liver volumetry has been used in the preoperative planning [15, 17, 19]. Since CT volumetry can be obtained retrospectively on the scans performed during HCC surveillance, we sought to assess the prognostic significance of CT liver volumetry in CHC patients in whom the screening tests for HCC gave abnormal results and yet dynamic CT imaging did not reveal HCC.

Methods

Study Population

This retrospective cohort study enrolled all consecutive CHC patients who visited a tertiary referral center in South Korea between May 2003 and February 2016 and received regular surveillance for HCC for longer than 6 months (Fig. 1). Exclusion criteria were (1) diagnosis of HCC and other malignancies before or within 6 months after initial surveillance, (2) decompensated liver disease, i.e., Child–Pugh class B or C, and (3) HBV or HIV co-infection. CHC was diagnosed by positive tests for anti-HCV antibody and detection of serum HCV RNA. The presence of cirrhosis was diagnosed by histology, by imaging studies showing regenerative hepatic nodules and/or liver surface undulation or by endoscopy showing esophageal varices. HCC was diagnosed histologically or radiologically [20]. All patients were evaluated with biochemical and virologic blood tests at 3–6 months of interval. Surveillance abdominal ultrasonography was performed at 6–12 months of interval. Contrast-enhanced multidetector CT (MDCT) was performed when surveillance test results triggered recall procedures [10, 21]. MDCT was also performed in patients for whom US examination was considered inadequate for the detection of possible small HCC [10, 22].

This study has been approved by the institutional review board of Seoul National University Bundang Hospital (IRB Number: B-1706-401-101). Clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki [23]. The requirement for informed consent was waived by the IRBs due to the retrospective nature of the study and the anonymous analysis of the data.

Measurement of Liver Volume

Liver volume was measured on portal venous phase contrast-enhanced MDCT images as previously reported [24]. Briefly, each cross-sectional area of individual liver slices in transverse plane images was measured by using Image J (Research Services Branch, National Institute of Mental Health, Maryland, USA; http://imagej.nih.gov/ij). The liver boundaries were semi-automatically determined using the Versatile Wand Tool (https://imagej.nih.gov/ij/plugins/versatile-wand-tool/index.html) to enhance consistency of measurement. The inferior vena cava and gallbladder were excluded from volume measurement, but the intrahepatic portal veins enclosed by hepatic parenchyma were included in the measured areas. The calculated area of the liver was integrated over the hepatic vertical span. Since body build may affect liver volume [14, 24, 25], normal variance was adjusted for standardized liver volume by calculating the "liver volume index" as previously reported [14]:

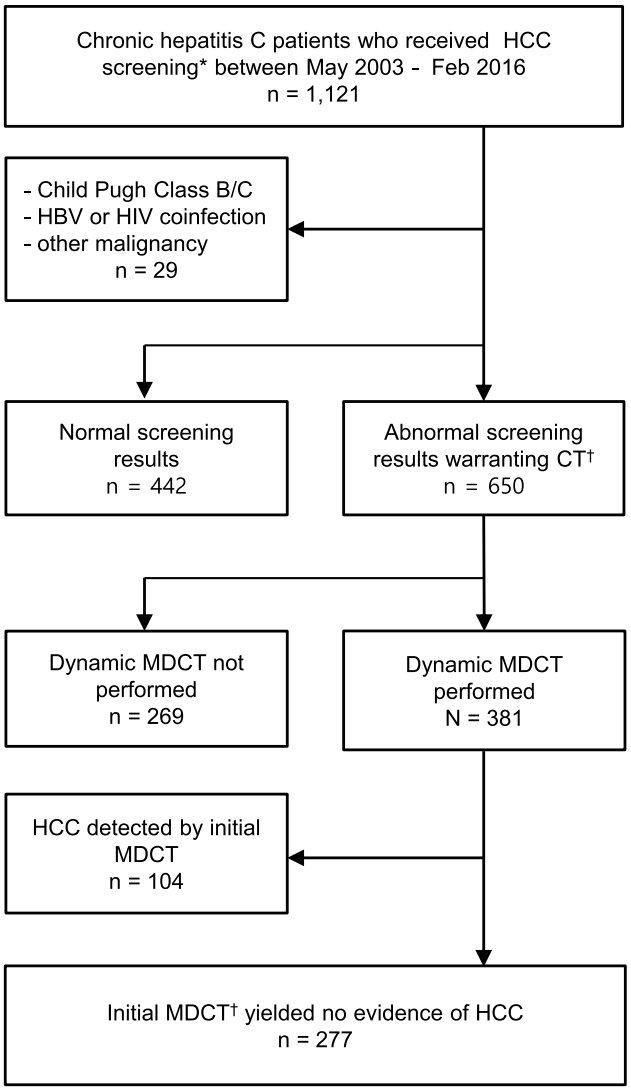

Fig. 1 Flowchart of the study population. *HCC surveillance is reimbursed by National Health Insurance Service in Korea in CHC patient aged > 40 or with cirrhosis. †Patients were recommended for liver CT if liver US showed new nodule(s), serum AFP elevated or liver US examination was considered inadequate for the detection of possible small HCC due to advanced cirrhotic change

Volume index = formula liver volume(ml)/CT-measured liver volume(ml),

where formula liver volume, i.e., standardized liver volume = 893.485 × body surface area (BSA)—439.169 (ml) [25] and (BSA = 0.007184 × (weight in kg)$^{0.425}$ × (height in cm)$^{0.725}$) [26]. Thus, decreased liver volume is expressed as increased volume index.

Statistical Analysis

The data collection and analysis followed the guideline of *Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis* (TRIPOD) [27]. The statistical analyses were performed using STATA version 14 (College Station, Texas) and R 3.3.2 (http://www.r-project.org/). Student's t test and Kruskal–Wallis rank test were used for continuous variables, and Chi-square test was used for categorical variables. The associations between continuous variables were tested using Spearman rank correlation. The cumulative HCC risk was analyzed using Kaplan–Meier curves, and differences in curves were tested using the log-rank test. Cox proportional hazard analysis was used to identify the independent predictors of HCC risk. Nomogram for HCC prediction was developed using the risksetROC package of R [28]. Analysis of time-dependent ROC with calculation of integrated AUC and *p* value was performed by survcomp package of R [29].

Results

Baseline Characteristics and Incidence of HCC During Follow-Up

During the study period, 1121 CHC patients received regular HCC surveillance. After excluding 29 patients as defined in Fig. 1, recall procedure, i.e., dynamic CT imaging, was indicated in 650 patients, among whom 381 patients received liver CT scans. HCC cases were also excluded if detected within 6 months from screening ($n = 104$), and finally, 277 patients were included in this study. Baseline characteristics are summarized in Table 1. The median follow-up duration was 46 months (range: 6–167 months), during which 44 patients developed HCC with the incidence of 2.53 per 1000 person-years (Supplementary Fig. 1). In patients whose histologic data were available ($n = 80$), 3.6%, 9.1%, 16.7%, and 45.8% developed HCC in *F*1, *F*2, *F*3, and *F*4 fibrosis, respectively.

Liver Volume Profiles in CHC

Liver volume was associated with various parameters: age, weight, height, sex, liver cirrhosis, diabetes, platelet count, prothrombin time, and FIB-4 (Supplementary Table). The liver volume index, the estimated-to-measured liver volume ratio, also showed significant association with functional parameters, but contrary to the liver volume, did not depend on weight or height. In patients whose histologic data were available, the liver volume index was not significantly different across the variable stage of fibrosis ($p = 0.635$, Supplementary Fig. 2).

Liver Volume as an Independent Predictor of HCC

Previous observational studies identified several predictors of HCV-associated HCC such as age, cirrhosis, thrombocytopenia, and elevated GGT levels [30–33]. Our univariate Cox analysis also found these factors as significant predictors of HCC, along with diabetes, elevated baseline alpha-fetoprotein (AFP), prolonged prothrombin time, and significant fibrosis. Liver volume index was also predictive of further development of HCC (hazard ratio [HR] 16.30, 95% CI 6.70–39.62; $p < 0.001$). Multivariate analysis also confirmed that liver volume index was an independent

Table 1 Characteristics of the study population

Parameter	$N = 277$
Age, years	62 (16)
Male, *n* (%)	136 (49.1)
Cirrhosis, *n* (%)	86 (31.1)
Excess alcohol intake[a], *n* (%)	65 (23.5)
BMI	23.9 (3.8)
DM, *n* (%)	89 (32.1)
AFP (ng/mL)	5.6 (9)
HCV RNA (Log IU/L)	5.50 (1.94)
Albumin (mg/dl)	4.2 (0.57)
Bilirubin (mg/dl)	0.9 (0.5)
AST (IU/L)	53 (59)
ALT (IU/L)	51 (70)
GGT (IU/L)	46 (73)
Platelet count (× 10^9/L)	170.5 (89.75)
Prothrombin time (INR)	1.1 (0.1)
APRI	0.84 (1.26)
FIB-4	2.78 (3.49)
Treatment	
Naïve	120 (43.3)
SVR	121 (43.7)
Non-responder	36 (13)

Categorical variables and numerical variables are presented as numbers (percentage) and median (interquartile range), respectively

[a]Current drinking > 30 g/d

predictor of HCC, along with liver cirrhosis and high GGT levels (Table 2). Liver volume index remained significant when subgroups were analyzed for cirrhosis and non-cirrhosis (Supplementary Table 2 and 3). These findings indicate that liver volume index has an independent prognostic value regardless of the presence of liver cirrhosis, i.e., the volume index can further stratify HCC risks in both cirrhotic and non-cirrhotic CHC patients. Sensitivity analysis also demonstrated that the live volume index is a powerful predictor of HCC, independent of various clinical and laboratory parameters (Fig. 2).

Liver Volume-Based Prediction Model Differentiate Risk of HCC

Finally, we tried to verify the predictive power of liver volume index by building a prediction model using the independent predictors. For internal validation, the study population was divided randomly into derivation ($n = 100$) and validation ($n = 177$) cohort. A nomogram was built from the derivation cohort based on the presence of cirrhosis, GGT, and liver volume index to generate liver volume score for the prediction of HCC (Fig. 3). Discrimination analysis showed that the liver volume score significantly differentiated the HCC at the cutoff of 110, in both the derivation and validation cohort ($p < 0.001$, respectively) (Fig. 4). Two cutoffs at the nomogram point 80 and 120 were also able to discriminate medium- and high-risk from low-risk group for HCC development (Supplementary Fig. 3).

Discussion

In this study, we found that decreased liver volume was independent predictor of HCC in CHC patients in addition to the classic predictors such as cirrhosis and GGT [32, 34–38]. Degree of hepatic fibrosis reliably stratifies the risk of HCC in CHC [35, 36, 39], but the staging of fibrosis needs liver biopsy which is invasive and prone to sampling error [40, 41]. LSM has been emerged as an attractive surrogate marker of fibrosis stage, but the role of LSM as a risk predictor for HCC has not been unequivocally validated [42–45]. Since advanced liver disease is frequently associated with decreased liver volume, it is plausible that liver volumetry may predict the risk for HCC. However, this assumption has not been quantitatively demonstrated in CHC.

Our analysis revealed that liver volume correlated with several demographic, clinical, and laboratory parameters (Supplementary Table). After adjustment by body surface area, liver volume index shows correlations only with age, presence of cirrhosis, HCV RNA levels, platelet counts, prothrombin time, and FIB-4. These relationships suggest that adjusted liver volume reflects the stage of liver fibrosis. Interestingly, however, there was wide overlap of volume index over various stages of fibrosis (Supplementary Fig. 2), indicating that stage of hepatic fibrosis may not be the sole determinant of volume index. This finding also suggests that additional mechanism(s) other that the degree of hepatic fibrosis may also contribute to

Table 2 Predictors of HCC risk according to the Cox regression model ($n = 277$)

Parameters	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.05	1.00–1.09	**0.049**	1.03	1.00–1.07	0.062
Male sex	2.26	0.92–5.56	0.076			
Cirrhosis	6.46	2.60–16.06	**< 0.001**	3.57	1.74–7.35	**0.001**
Excess alcohol intake	0.90	0.44–1.81	0.758			
DM	3.78	1.54–9.27	**0.004**	1.64	0.86–3.16	0.135
AFP > 7 ng/mL	2.54	1.39–4.65	**0.002**	1.07	0.53–1.27	0.849
Genotype 1	1.84	0.84–4.05	0.128			
HCV RNA (Log IU/L)	1.16	0.82–1.64	0.409			
Albumin < 3.5 g/dL	1.29	0.40–4.18	0.670			
Bilirubin > 1.5 mg/dL	0.57	0.14–2.36	0.439			
GGT > 80 U/L	2.11	1.15–3.86	**0.016**	2.08	1.04–4.18	**0.039**
PT INR > 1.1	2.90	1.55–5.43	**0.001**	1.22	0.52–2.85	0.650
Platelet < 100 K/mm^3	2.49	1.19–5.20	**0.015**	1.29	0.52–3.20	0.580
SVR	0.59	0.32–1.08	0.087			
Fibrosis ≥ *F*2	8.37	1.10–63.74	**0.040**			
Volume index	16.30	6.70–39.62	**< 0.001**	12.1	4.48–32.61	**< 0.001**

Statistically significant values ($p < 0.05$) are given in bold

HR hazard ratio, *PT INR* prothrombin time international normalized ratio, *SVR* sustained virologic response

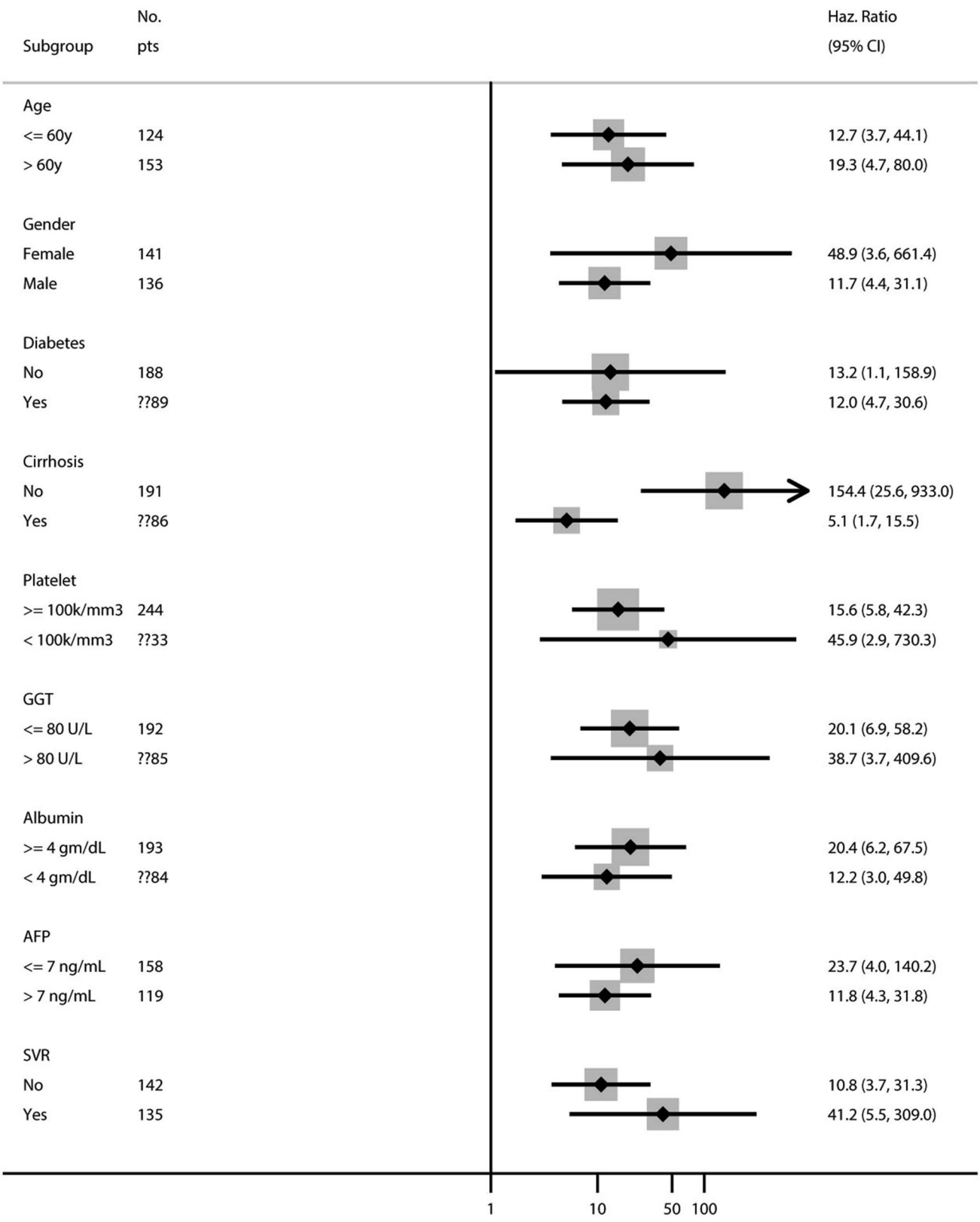

Fig. 2 Sensitivity analysis of liver volume index hazard ratio for predicting HCC. Hazard ratio of liver volume index for HCC maintained significance across major clinical and laboratory parameters

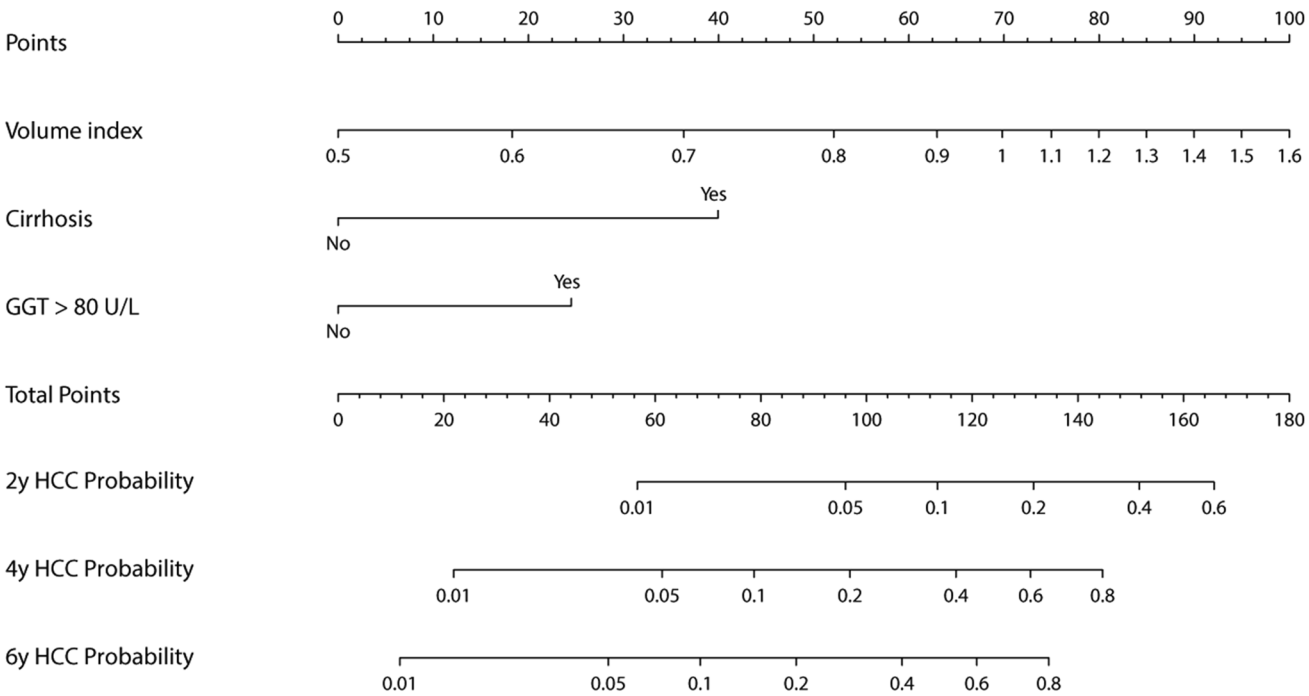

Fig. 3 Nomogram from multivariable Cox regression analysis for risk of HCC in derivation cohort. Total risk scores are calculated by summing up points of the three parameters (Points axis). Are summed to get the total points (Total Points axis). The 2-, 4-, and 6-yr predicted probability for HCC are obtained from the corresponding total points

the prognostic power of liver volume index. The result of the sensitivity analysis which showed that liver volume index remained significant across all subgroups may also support this hypothesize, but further validating studies will be necessary.

In predicting of HCV-associated HCC, several models have been built based on combinations of risk factors: age [32, 34, 37, 38], sex [33, 38], alcohol [32], presence of cirrhosis [34], platelet counts [32, 37, 38], alpha-fetoprotein [37, 38], liver enzymes [32–34, 37], and virologic parameters [32, 34]. Among them, only a few models included both non-cirrhotic and cirrhotic CHC patients [34–36]. Since HCV-associated HCC can develop without cirrhosis [46, 47], our liver volume-based prediction model may be versatile for clinical applications regardless of the presence of cirrhosis.

One of our major findings is that liver volume was an independent predictor of HCC in both cirrhotic and non-cirrhotic patients (Fig. 3 and Supplementary Table 2 and 3). We do not have mechanistic explanations, but small volume may induce active proliferation of hepatic progenitor cells which could increase oncogenic potential. Further studies are needed for the relation between small liver volume and risk of HCC.

Manual tracing of the hepatic boundary has been considered the gold standard for liver volumetry [16, 48]. In this study, liver volume was measured by free software Image J with a plug-in for semi-automatic boundary detection to minimize the measurement errors and to enhance the efficiency of measurement [24]. Semi-automatic measurements show comparable accuracy and precision [17], and we have also found that our method shows good reproducibility in chronic hepatitis B [24]. Technical accessibility of our method may enable clinical implementation of live volumetry without additional resources.

It is an interesting finding that GGT remained significant in our prediction model. GGT has been associated with adverse outcomes [49] including HCC [32] in chronic HCV infection. Supplementary Table 1 shows inverse relation between GGT levels and liver volume. We do not have definite explanation for the significance of GGT in HCC prediction and the inverse relation with liver volume at this moment. Although current alcohol history did not predict the risk (Table 2), it may be postulated that the GGT might represent alcohol consumption amount in the past, which might affect liver volume and the risk of HCC. However, this hypothesis needs further validation.

There are several limitations in this study. First, the cohort was built from patients from single institution. We adopted split-sample validation and bootstrapping iterations to ascertain internal validity and to minimize over-fitting of the volume-based model [27]. However, external validation is needed as discussed above. Moreover, since our cohort was built retrospectively, there is a potential risk for

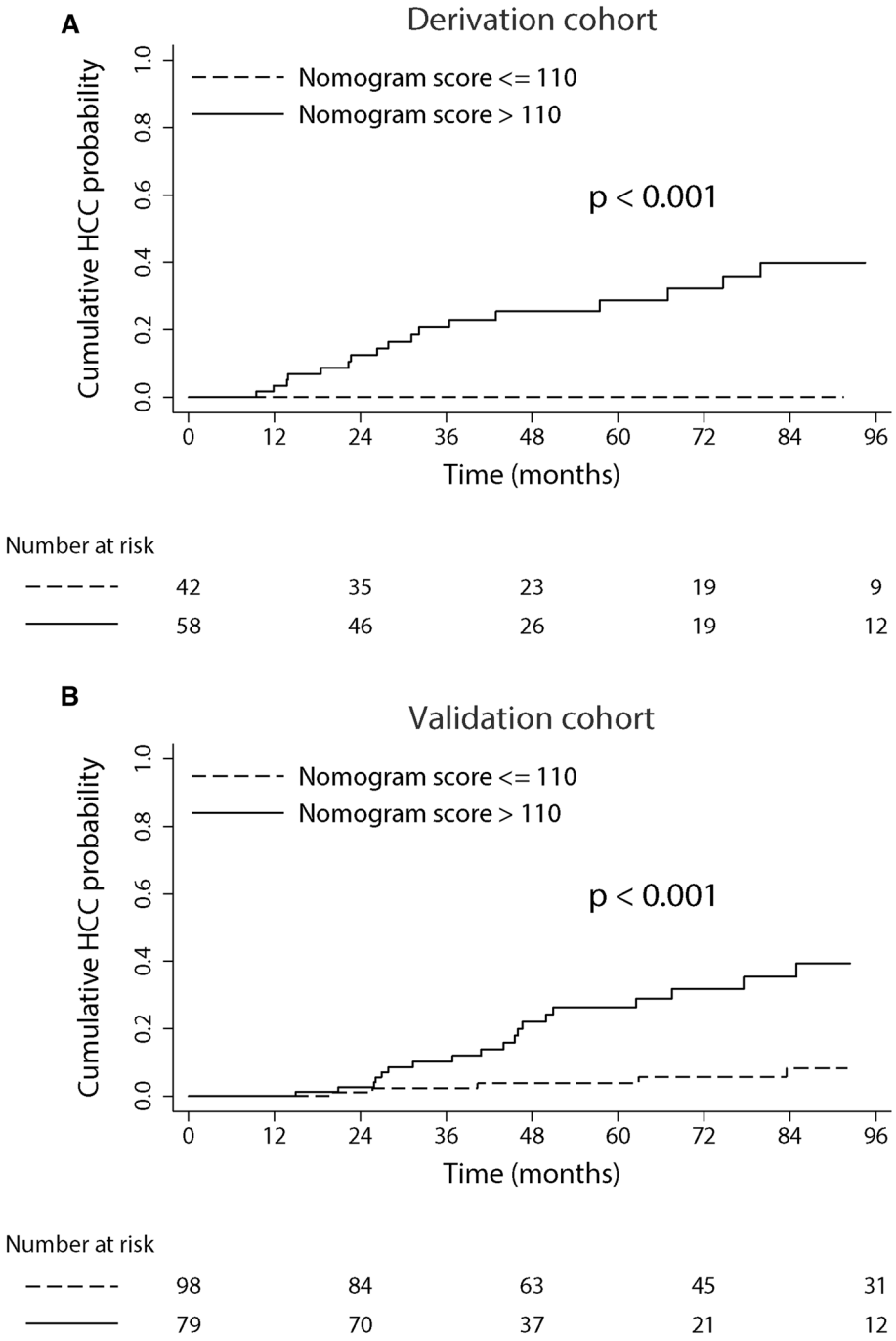

Fig. 4 Discrimination of HCC probability by volume score-based nomogram. The nomogram-based liver volume score model differentiated the HCC risk at the cutoff off 110 in both derivation (**a**) and validation (**b**) cohort

selection bias. Although we assessed the medical records of all consecutive patients eligible for this study, prospective cohort study may be needed to resolve this issue. Second, our cohort is limited to Korean population, limiting racial generalizability. Third, our prediction model was based on patients with liver CT imaging performed during surveillance, so that our patients may have more severe disease compared to general CHC population and therefore have increased HCC. Therefore, application of our results needs to be limited to CHC patients who receive liver CT as a recall procedure for abnormal HCC screening, and liver CT cannot be recommended for a prognostic purpose when screening tests do not indicate liver CT. Moreover, our study population was heterogeneous in terms of the LI-RADS category [50]. Majority of patients with abnormal US findings corresponded to LI_RADS US-3, but some received CT evaluation due to visualization score C (data not shown). We were not able to determine the exact LI_RADS category because the US results had been reported before the implementation of standardized reporting system. Further studies

will be needed to determine the baseline LI-RADS status on the prognostic significance of our data. Fourth, our patients were heterogeneous with respect to the history of DAA therapy. However, SVR was not a significant predictor of HCC in our model, and sensitivity analysis showed that volume index was significant irrespective of SVR. Finally, only limited number of patients received transient elastography in our cohort (data not shown), so that comparison between liver volumetry and LSM was not done in our analysis. Further study would be needed to compare the performance between liver volume and LSM in predicting the fibrosis stage and risk of HCV-associated HCC.

In conclusion, decreased liver volume is an independent predictor of HCC risk in CHC whose initial dynamic CT study gave negative results, and liver volume-based prediction model stratifies the risk of developing HCC in these patients.

Supplementary Information The online version of this article (https://doi.org/10.1007/s10620-020-06762-w) contains supplementary material, which is available to authorized users.

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Author's contribution JWK designed the study, analyzed the data, and drafted the manuscript. NK collected and analyzed the data and revised the manuscript. JWC, ESJ, and SHJ collected the data, participated in the study design, and revised the manuscript.

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