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**Deep learning-based CT analysis in CHB patients**

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Visceral fat obesity, sarcopenia, myosteatorsis  
in NAFLD without obesity

## Original Article

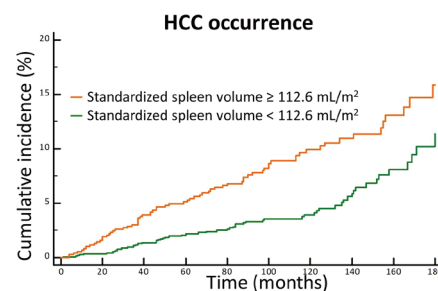
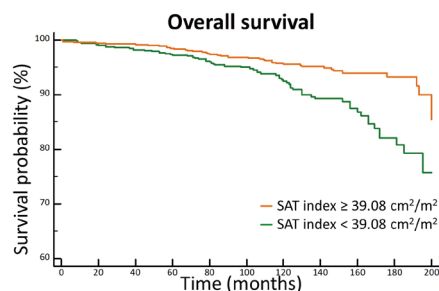
# Prognostic role of computed tomography analysis using deep learning algorithm in patients with chronic hepatitis B viral infection

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### Graphical Abstract

#### CT analysis of body composition and organ volume using deep learning algorithm: Prognostic role in patients with chronic hepatitis B viral infection



Deep learning-based automatically measured spleen volume, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) indices can provide various prognostic information in CHB patients.

### Study Highlights

- Previous studies have shown the usefulness of deep learning-based automated CT analysis for opportunistic screening of various diseases. Therefore, this study aimed to evaluate comprehensive prognosis through organ volumes and body composition measurements obtained from CT data using deep learning-based fully automated organ segmentation algorithm in patients with chronic hepatitis B. A larger standardized spleen volume was significantly associated with HCC, hepatic decompensation, and occurrence of DM. A higher abdominal VAT index was correlated with the development of DM, while a higher SAT index was correlated with increased OS.

**Background/Aims:** The prediction of clinical outcomes in patients with chronic hepatitis B (CHB) is paramount for effective management. This study aimed to evaluate the prognostic value of computed tomography (CT) analysis using deep learning algorithms in patients with CHB.

**Methods:** This retrospective study included 2,169 patients with CHB without hepatic decompensation who underwent contrast-enhanced abdominal CT for hepatocellular carcinoma (HCC) surveillance between January 2005 and June 2016. Liver and spleen volumes and body composition measurements including subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and skeletal muscle indices were acquired from CT images using deep learning-based fully automated organ segmentation algorithms. We assessed the significant predictors of HCC, hepatic decompensation, diabetes mellitus (DM), and overall survival (OS) using Cox proportional hazard analyses.

**Results:** During a median follow-up period of 103.0 months, HCC (n=134, 6.2%), hepatic decompensation (n=103, 4.7%), DM (n=432, 19.9%), and death (n=120, 5.5%) occurred. According to the multivariate analysis, standardized spleen volume significantly predicted HCC development (hazard ratio [HR]=1.01,  $P=0.025$ ), along with age, sex, albumin and platelet count. Standardized spleen volume (HR=1.01,  $P<0.001$ ) and VAT index (HR=0.98,  $P=0.004$ ) were significantly associated with hepatic decompensation along with age and albumin. Furthermore, VAT index (HR=1.01,  $P=0.001$ ) and standardized spleen volume (HR=1.01,  $P=0.001$ ) were significant predictors for DM, along with sex, age, and albumin. SAT index (HR=0.99,  $P=0.004$ ) was significantly associated with OS, along with age, albumin, and MELD.

**Conclusions:** Deep learning-based automatically measured spleen volume, VAT, and SAT indices may provide various prognostic information in patients with CHB. (*Clin Mol Hepatol* 2023;29:1029-1042)

**Keywords:** Chronic hepatitis B; Hepatocellular carcinoma; Liver cirrhosis; Diabetes mellitus; Survival

## INTRODUCTION

Chronic hepatitis B (CHB) remains an important global health problem with significant morbidity and mortality despite vaccination and effective antiviral treatment.<sup>1</sup> The risk of progression to cirrhosis and hepatocellular carcinoma (HCC) in patients with CHB is variable and is affected by the host's immune response. The 5-year cumulative incidence of cirrhosis ranges from 8% to 20% in patients with untreated CHB and the 5-year cumulative risk of hepatic decompensation among those with cirrhosis is 20%.<sup>2</sup> The annual risk of HCC in patients with cirrhosis has been reported to be 2–5%.<sup>3</sup>

The risk factors for CHB progressing to cirrhosis or HCC include not only host-related or viral factors, but also social-environmental factors (e.g., alcohol consumption, metabolic syndrome, diabetes mellitus [DM], obesity, and smoking).<sup>4</sup> There have been efforts over decades to predict clinical outcomes in patients with CHB for proper and timely managements such as GAGHCC,<sup>5</sup> CU-HCC,<sup>6</sup> REACH-B,<sup>7</sup> or PAGE-B<sup>8</sup> for predicting HCC development, hepatic decompensation<sup>9</sup> and overall survival (OS)<sup>10</sup> and model for end-stage liver disease, hepatic venous pressure gradient, and albumin for predicting hepatic decompensation<sup>9</sup> and OS<sup>10</sup> in previous literatures. Deep learning-based computed tomography (CT) metric

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### Abbreviations:

CHB, chronic hepatitis B; CI, confidence interval; CT, computed tomography; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival

analysis provides three-dimensional organ volumetric parameters and body composition measurements.<sup>11,12</sup> Furthermore, previous investigations<sup>13,14</sup> showed that fully automated quantitative tissue composition analysis using CT scans may predict future serious adverse events and add opportunistic value to CT scans performed for other indications. Considering the promising results of previous studies, we surmised that body composition analysis and organ volume measurement using liver CT images may also provide prognostic information regarding the risk of HCC occurrence or development of hepatic decompensation in patients with compensated CHB.

Therefore, the purpose of this study was to evaluate the prognostic value of CT analysis using deep learning algorithm in patients with CHB.

## MATERIALS AND METHODS

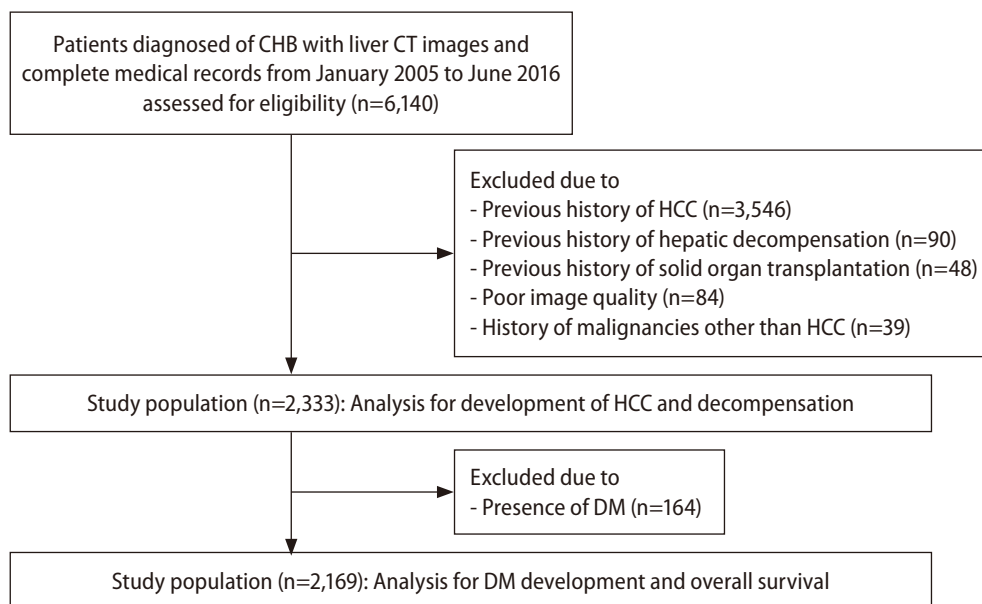
This study was approved by our institutional review board (IRB No.: 2108-143-1246) and the requirement for signed informed consent was waived owing to the retrospective design.

## Patients

The inclusion criteria were: 1) patients aged between 19 and 85 years, 2) patients who were diagnosed with CHB, and 3) patients having both a contrast-enhanced abdominal CT scan and complete medical records, including liver function tests, between January 2006 and June 2016 (Fig. 1). According to the inclusion criteria, 6,140 consecutive patients were assessed for eligibility. The exclusion criteria were: 1) previous history of HCC (n=3,546), 2) previous history of hepatic decompensation (n=90), 3) previous history of solid organ transplantation (n=48), 4) poor image quality of abdominal CT scan, when reviewed by a radiologist (n=84), and 5) history of malignancies other than HCC (n=39). Finally, 2,333 patients constituted the study population.

## CT image acquisition

All patients underwent abdominal CT scans, including the arterial and portal venous phase, using various types of CT scanners owing to the retrospective study design. CT scanning was performed using the following parameters: tube voltage, 90–120 kVp according to the scanner type; tube current-time products, 100–300 mAs; rotation time, 0.5 s; pitch, 0.6–1.2; and slice thickness, 3 mm. Iobitridol (Xenetix 350;



**Figure 1.** Patient enrollment process. CHB, chronic hepatitis B; CT, computed tomography; DM, diabetes mellitus; HCC, hepatocellular carcinoma.

Guerbet, Aulnay-sous-Bois, France) was intravenously injected at a dose of 520 mg/kg body weight using a power injector (Stellant; Bayer AG, Berlin, Germany) for 30 s at a rate of 2–5 mL/s according to body weight, followed by a 20–30-mL saline flush. Using the bolus tracking method, arterial phase scans were started 17–23 s after the enhancement threshold (100–150 HU) was reached in the descending thoracic aorta. For portal venous phase scans, a fixed delay of 60–75 s was used.

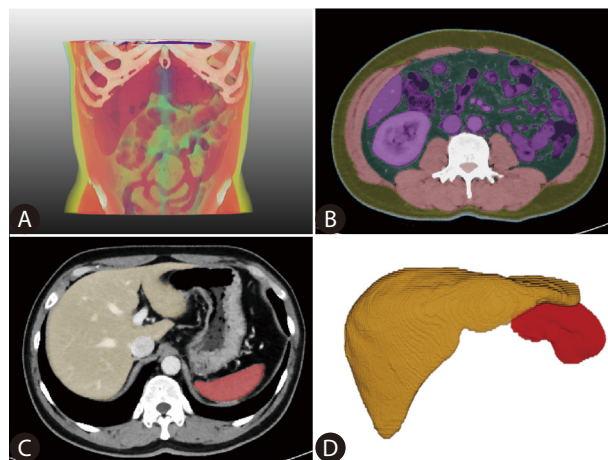
### Body composition and organ volume analysis using CNN

CT images were processed in an automated analysis software program using convolutional neural network (CNN) (DeepCatch and MEDIP; MedicalIP Co. Ltd., Seoul, Korea; <http://www.medicalip.com>). After uploading portal venous phase CT images to commercially available segmentation software (MEDIP Deep Catch v1.0.0.0; MedicalIP Co. Ltd.), a three-dimensional U-Net automatically provided volumetric segmentation of body components into seven classes (skin, subcutaneous fat, muscle, visceral fat, bone, internal organs and vessels, and the central nervous system) (Fig. 2). The average dice scores for muscles, visceral fat, and for subcutaneous fat were 96.8–99.2%, 95.1–98.9%, and 97.1–99.7%, respectively, in the domestic validation sets.<sup>12</sup> After segmentation, the software also provided automatic segmentation and labeling of the body composition area at the L3-level cross-sectional image. An experienced radiologist, who was blinded to the patients' clinicopathological information, confirmed the results of the segmentation. Subsequently, L3-level sectional area (cm<sup>2</sup>) of the skeletal muscle, subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) were normalized to the height (m<sup>2</sup>)<sup>15–17</sup> and were labeled as skeletal muscle, SAT, and VAT indices, respectively. Additionally, three-dimensional segmentation of the liver and spleen was performed and the organ volumes were automatically calculated. Spleen and liver volumes were normalized to the body surface area (m<sup>2</sup>), which was calculated as body weight (kg)<sup>0.425</sup> × height (cm)<sup>0.725</sup> × 0.007184.<sup>18</sup>

### Endpoints

The primary endpoint was OS and the secondary endpoints were liver-related (i.e., development of HCC and decompen-

sation) and metabolic outcomes (i.e., development of DM). We assessed the cumulative incidence of the occurrence of HCC, hepatic decompensation, DM, and death. Development of HCC was determined histopathologically in patients who underwent surgical resection or percutaneous biopsy, or based on imaging features categorized into “LR-5” according to the Liver Imaging Reporting and Data System<sup>19</sup> or “definite HCC” according to the 2022 Korean Liver Cancer Association and National Cancer Center Korea practice guidelines,<sup>20</sup> in patients without histopathologic analysis. The development of hepatic decompensation was defined as the occurrence of variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, or hepatorenal syndrome.<sup>21</sup> The development of DM was determined based on medical records. OS was calculated as the interval between the day of the baseline liver CT and death or the last follow-up date. The survival data of the study population was acquired from the national registry data from the Korean Ministry of Interior and Safety. The data cut-off date was January 31, 2022.



**Figure 2.** Fully automated body composition and organ volume analysis using convolutional neural network. (A) A three-dimensional U-Net automatically provided volumetric segmentation of body components into seven classes (skin, subcutaneous fat, muscle, visceral fat, bone, internal organs and vessels, and the central nervous system). (B) An axial image shows the results of segmentation, which are overlaid on orthogonal cross-sectional images at the L3 vertebral-body level. Pink, yellow, green, and purple colors indicate skeletal muscle, subcutaneous fat, visceral fat, and internal organs, respectively. (C) An axial image shows the results of organ segmentation of the liver (yellow) and spleen (red), which are overlaid on the CT image. (D) Three-dimensional segmentation of the liver and spleen was performed. CT, computed tomography.

## Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows version 27.0 (IBM Corp., Armonk, NY, USA), SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), and MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2019). Univariate and multivariate Cox proportional hazards logistic regression analyses were performed to identify significant predictors of each outcome. All variables with *p*-values less than 0.05, in univariate analyses, were included in the multivariate analysis using stepwise selection. The Kaplan–Meier method was used for estimation of the cumulative incidence of each outcome. The optimal cut-off values of body composition and organ volume measurements for predicting each outcome were determined using the minimal *P*-value approach based on log-rank test statistics.<sup>22</sup> Statistical significance was set at a *P*-value <0.05.

## RESULTS

### Patient characteristics

Baseline characteristics of the 2,333 patients (Male: Female=1,396:937; median age, 52.0 years [interquartile range {IQR}, 45.0–59.0]) are summarized in Table 1. Among them, 164 patients had DM at the time of enrollment. For all patients, body composition data including skeletal muscle, VAT, and SAT indices were successfully obtained from CT data analyzed by deep learning algorithm. Additionally, liver and spleen volumes of each patient were successfully acquired from their CT data via deep learning algorithm and standardized by dividing by body surface area.

### Predictive factors for HCC development

During a median follow-up period of 103 months, HCC developed in 134 patients (5.7%, 134/2,333) with the following stages at diagnosis: Barcelona-Clinic Liver Cancer stage 0 (n=70), stage A (n=59), stage B (n=4), and stage C (n=1). The estimated the 1-, 5-, and 10-year cumulative incidences of HCC occurrence were 0.6%, 3.2%, and 6.1%, respectively. According to the multivariate analysis, standardized spleen volume was one of the significant predictive factors for HCC de-

velopment (hazard ratio [HR]=1.01, 95% confidence interval [CI]=1.01–1.01, *P*=0.025), along with age, sex, albumin level, and platelet count (Table 2). The optimal cut-off value for the

**Table 1.** Baseline characteristics of 2,333 patients with compensated chronic liver disease from CHB

Characteristic	Value
Age (yr)	52.0 (45.0–59.0)
Sex	
Males	1,396 (59.8)
Females	937 (40.2)
Diabetes	
Yes	164 (7.0)
No	2,169 (93.0)
Alanine aminotransferase (IU/L)	27.0 (19.0–47.0)
Serum albumin (g/L)	43.0 (41.0–45.0)
Total bilirubin level (mg/dL)	0.9 (0.7–1.2)
Prothrombin activity (INR)	1.03 (0.97–1.08)
Platelet count (K/mm <sup>3</sup> )	195.0 (159.0–233.0)
Alpha fetoprotein (ng/mL)	2.7 (1.6–4.2)
APRI	0.35 (0.25–0.58)
FIB-4	1.41 (0.99–2.05)
MELD	7.0 (6.5–8.0)
Body mass index (kg/m <sup>2</sup> )	23.8 (21.8–26.0)
Standardized liver volume (mL/cm <sup>2</sup> )	715.7 (641.8–802.4)
Standardized spleen volume (mL/cm <sup>2</sup> )	99.1 (78.0–128.4)
Skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	47.1 (40.9–53.6)
Visceral adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	25.3 (11.9–41.7)
Subcutaneous adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	48.0 (34.5–64.5)
Antiviral therapy	
Yes	1,276 (54.7)
No	1,057 (45.3)
HBeAg	
Yes	1,877 (80.5)
No	456 (19.5)
REACH-B	7.0 (6.0–10.0)

Values are presented as median (interquartile range) or number (%).

CHB, chronic hepatitis B viral infection; INR, international normalized ratio; IU, international unit; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; MELD, model for end-stage liver disease; HBeAg, hepatitis B e antigen; REACH-B, risk estimate for hepatocellular carcinoma in chronic hepatitis B.

standardized spleen volume was set at 112.6 mL/m<sup>2</sup> to predict HCC development. The estimated 1-, 5-, and 10-year cumulative incidences of HCC development in 773 patients with standardized spleen volumes  $\geq$ 112.6 mL/m<sup>2</sup> were 0.8%, 5.1%, and 9.9%, respectively, and were significantly higher than those in 1,396 patients with standardized spleen volumes <112.6 mL/m<sup>2</sup> which were 0.4%, 2.2%, and 3.9%, respectively (HR=1.71, 95% CI =1.21–2.42, *P*=0.002) (Fig. 3A).

### Predictive factors for the development of hepatic decompensation

During the follow-up period, 103 patients (4.4%, 103/2,333) experienced hepatic decompensation with the development of: ascites (n=59); hepatic encephalopathy (n=33); and variceal bleeding (n=11). The estimated 1-, 5-, and 10-year cumu-

lative incidences for the development of hepatic decompensation were 0.7%, 2.8%, and 5.1%, respectively. On multivariate analysis, age and serum albumin level were significantly associated with the development of hepatic decompensation. In addition, standardized spleen volume (HR=1.01, 95% CI=1.01–1.01, *P*<0.001) and VAT index (HR=0.98, 95% CI=0.97–0.99, *P*=0.004) were also significant predictive factors for hepatic decompensation (Table 3). The optimal cut-off value of the standardized spleen volume was set at 145.74 mL/m<sup>2</sup> to predict hepatic decompensation. The estimated 1-, 5-, and 10-year cumulative incidences of hepatic decompensation in 329 patients with a standardized spleen volume  $\geq$ 145.74 mL/m<sup>2</sup> were 0.6%, 4.4%, and 9.1%, respectively, and were significantly lower than those of 1,840 patients with a standardized spleen volume <145.74 mL/m<sup>2</sup> which was 0.7%, 2.5%, and 3.9%, respectively (HR=2.34, 95%

**Table 2.** The predictors for development of HCC in 2,333 patients with compensated chronic liver disease from CHB

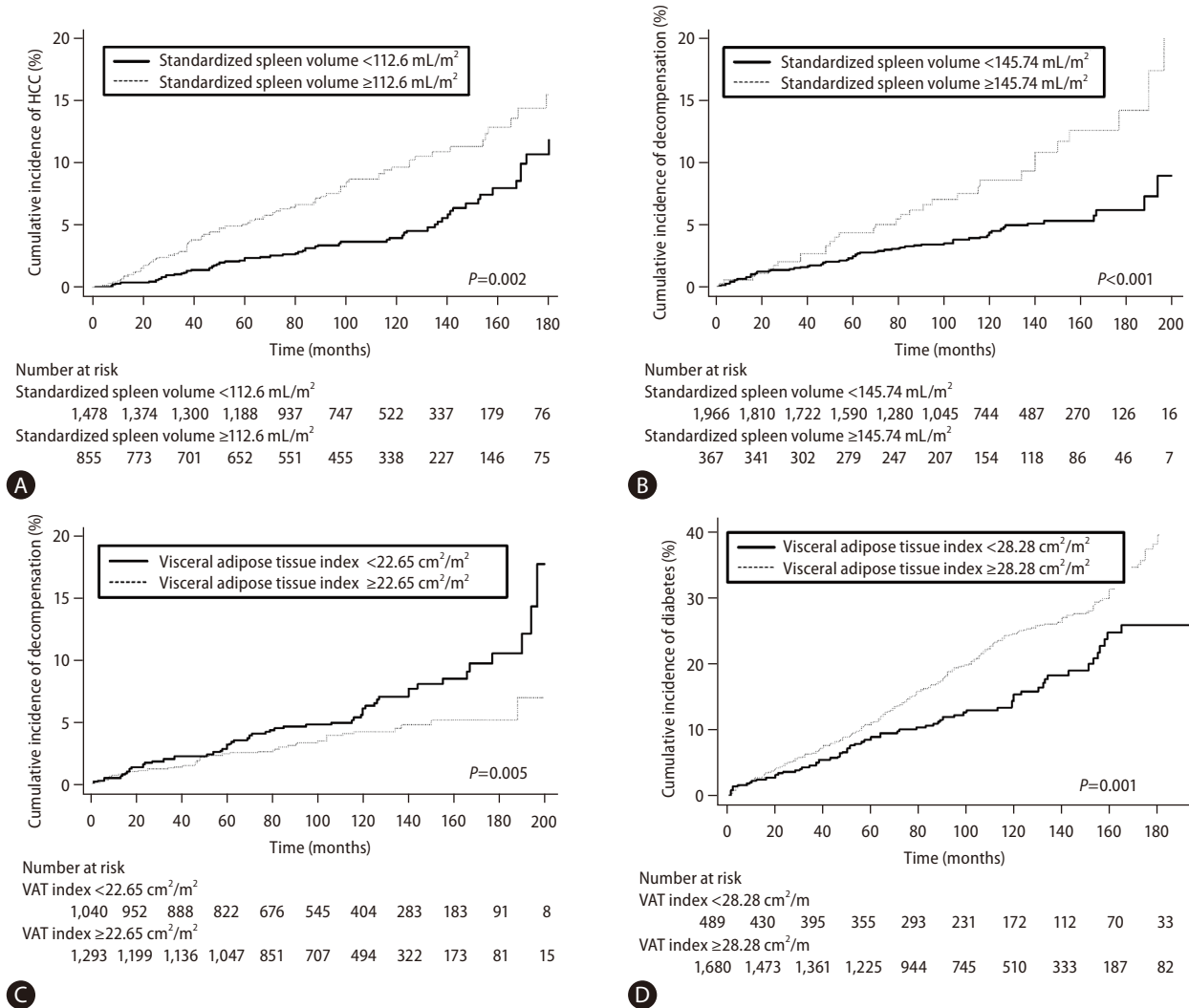
Characteristic	Univariate			Multivariate		
	Hazard ratio	95% CI	<i>P</i> -value	Hazard ratio	95% CI	<i>P</i> -value
Sex (female)	0.46	0.31–0.69	<0.001	0.57	0.38–0.87	0.010 <sup>†</sup>
Age (per 1 year)	1.03	1.01–1.05	0.001	1.02	1.01–1.04	0.015 <sup>†</sup>
Body mass index (kg/m <sup>2</sup> )	1.04	0.99–1.08	0.108			
Antiviral therapy (yes)	1.46	1.05–2.03	0.024	0.95	0.65–1.38	0.785
HBeAg (positive)	1.16	0.79–1.70	0.458			
Alanine aminotransferase (IU/L)	1.00	0.99–1.01	0.518			
Albumin (g/L)	0.63	0.50–0.80	<0.001	0.77	0.59–1.02	0.068
Total bilirubin (mg/dL)	1.01	0.90–1.12	0.912			
PT-INR	1.00	0.94–1.07	0.982			
Platelet count (K/mm <sup>3</sup> )	0.99	0.99–0.99	<0.001	0.99	0.99–0.99	0.002 <sup>†</sup>
AFP (ng/mL)	1.00	0.99–1.01	0.157			
Standardized liver volume (mL/m <sup>2</sup> )	0.99	0.99–1.00	0.099			
Standardized spleen volume $\geq$ 112.6 mL/m <sup>2</sup>	1.92	1.36–2.69	<0.001	1.71	1.21–2.42	0.002 <sup>†</sup>
Skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	1.00	0.99–1.01	0.901			
Visceral adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	1.00	0.99–1.01	0.709			
Subcutaneous adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	0.99	0.99–1.00	0.016	1.00	0.99–1.01	0.835
APRI	1.00	0.97–1.03	0.982			
FIB-4	1.00	0.99–1.01	0.923			
REACH-B	1.26	1.20–1.33	<0.001	1.20	1.12–1.28	<0.001 <sup>†</sup>
MELD	1.07	1.02–1.12	0.003	1.00	0.95–1.06	0.895

CHB, chronic hepatitis B viral infection; HCC, hepatocellular carcinoma; CI, confidence interval; HBeAg, hepatitis B e antigen; PT-INR, prothrombin time international normalized ratio; AFP, alpha fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; REACH-B, risk estimate for hepatocellular carcinoma in chronic hepatitis B; MELD, model for end-stage liver disease.

<sup>†</sup>*P*<0.05.

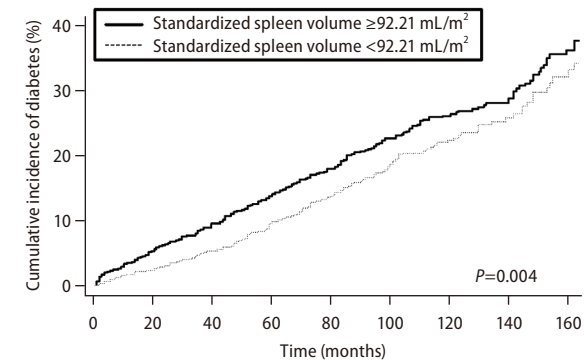
CI =1.51–3.63,  $P<0.001$ ) (Fig. 3B). Regarding the VAT index, the optimal cut-off value was set at  $22.65 \text{ cm}^2/\text{m}^2$  to predict hepatic decompensation. The estimated 1-, 5-, and 10-year cumulative incidences of hepatic decompensation in 990 patients with a VAT index  $<22.65 \text{ cm}^2/\text{m}^2$  were 0.5%, 3.3%, and

6.1%, respectively, which were significantly higher than those of 1,179 patients with a VAT index  $\geq 22.65 \text{ cm}^2/\text{m}^2$  which were 0.8%, 2.4%, and 4.2%, respectively (HR=0.57, 95% CI=0.38–0.84,  $P=0.005$ ) (Fig. 3C).



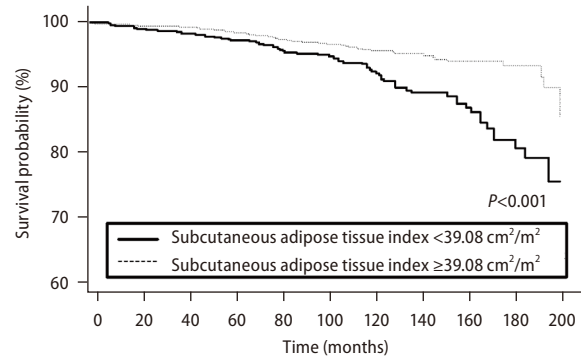
**Figure 3.** Kaplan–Meier estimation of cumulative incidences of HCC, hepatic decompensation, development of DM, and overall survival in patients stratified according to body composition measurements and organ volumes. (A) The cumulative incidence of HCC of 855 patients with a standardized spleen volume  $\geq 112.6 \text{ mL}/\text{m}^2$  was significantly higher than that of 1,478 patients with a standardized spleen volume  $<112.6 \text{ mL}/\text{m}^2$  ( $P<0.001$ ). (B) The cumulative incidence of hepatic decompensation of 367 patients with a standardized spleen volume  $\geq 145.74 \text{ mL}/\text{m}^2$  was significantly higher than that of 1,966 patients with a standardized spleen volume  $<145.74 \text{ mL}/\text{m}^2$  ( $P<0.001$ ). (C) The cumulative incidence of hepatic decompensation of 1,040 patients with a VAT index  $<22.65 \text{ cm}^2/\text{m}^2$  was significantly higher than that of 1,293 patients with a VAT index  $\geq 22.65 \text{ cm}^2/\text{m}^2$  ( $P=0.012$ ). (D) The cumulative incidence of DM of 1,680 patients with a VAT index  $\geq 28.28 \text{ cm}^2/\text{m}^2$  was significantly higher than that of 489 patients with a VAT index  $<28.28 \text{ cm}^2/\text{m}^2$  ( $P<0.001$ ). (E) The cumulative incidence of DM development of 1,249 patients with a standardized spleen volume  $\geq 92.21 \text{ mL}/\text{m}^2$  was significantly higher than that of 920 patients with a standardized spleen volume  $<92.21 \text{ mL}/\text{m}^2$  ( $P=0.040$ ). (F) The overall survival of 1,453 patients with a SAT index  $\geq 39.08 \text{ cm}^2/\text{m}^2$  was significantly higher than that of 716 patients with a SAT index  $<39.08 \text{ cm}^2/\text{m}^2$  ( $P<0.001$ ). HCC, hepatocellular carcinoma; VAT, visceral adipose tissue; DM, diabetes mellitus; SAT, subcutaneous adipose tissue.





Number at risk	
Standardized spleen volume $\geq 92.21 \text{ mL/m}^2$	1,249 1,070 969 868 711 570 407 266 154
Standardized spleen volume $< 92.21 \text{ mL/m}^2$	920 833 787 712 526 406 275 179 103

**E**



Number at risk	
SAT index $< 39.08 \text{ cm}^2/\text{m}^2$	716 666 631 594 506 429 324 218 132 65 7
SAT index $\geq 39.08 \text{ cm}^2/\text{m}^2$	1,453 1,362 1,287 1,189 945 761 538 366 221 108 14

**F**

**Figure 3.** Continued.

**Table 3.** The predictors for development of decompensation in 2,333 patients with compensated chronic liver disease from CHB

Characteristic	Univariate			Multivariate		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Sex (female)	1.09	0.75–1.60	0.647			
Age (per 1 year)	1.06	1.04–1.08	<0.001	1.06	1.04–1.08	<0.001 <sup>†</sup>
Body mass index (kg/m <sup>2</sup> )	1.01	0.98–1.05	0.493			
Antiviral therapy (yes)	1.14	0.79–1.66	0.488			
HBeAg (positive)	1.21	0.78–1.88	0.397			
Alanine aminotransferase (IU/L)	1.00	0.99–1.01	0.369			
Albumin (g/L)	0.52	0.42–0.64	<0.001	0.59	0.45–0.77	<0.001 <sup>†</sup>
Total bilirubin (mg/dL)	0.91	0.69–1.19	0.469			
PT-INR	1.00	0.91–1.10	0.967			
Platelet count (K/mm <sup>3</sup> )	1.00	0.99–1.01	0.115			
AFP (ng/mL)	1.00	0.99–1.01	0.245			
Standardized liver volume (mL/m <sup>2</sup> )	1.00	0.99–1.00	0.383			
Standardized spleen volume $\geq 145.7 \text{ mL/m}^2$	2.14	1.39–3.27	<0.001	2.34	1.51–3.63	<0.001 <sup>†</sup>
Skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	1.00	0.99–1.01	0.780			
Visceral adipose tissue index $\geq 22.65 \text{ cm}^2/\text{m}^2$	0.61	0.41–0.90	0.013	0.57	0.38–0.84	0.005 <sup>†</sup>
Subcutaneous adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	0.99	0.99–1.00	0.120			
APRI	0.99	0.92–1.05	0.660			
FIB-4	1.00	0.98–1.01	0.855			
REACH-B	1.14	1.07–1.21	<0.001	1.05	0.98–1.12	0.144
MELD	1.07	1.02–1.12	0.008	1.02	0.96–1.07	0.564

CHB, chronic hepatitis B viral infection; CI, confidence interval; HBeAg, hepatitis B e antigen; PT-INR, prothrombin time international normalized ratio; AFP, alpha fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; REACH-B, risk estimate for hepatocellular carcinoma in chronic hepatitis B; MELD, model for end-stage liver disease.

<sup>†</sup>P<0.05.

### Predictive factors for the development of DM

We excluded 164 patients who had DM at the time of enrollment to examine the development of DM. During the follow-up period, DM developed in 432 patients (19.9%, 432/2,169). The estimated 1-, 5-, and 10-year cumulative incidences for the development of DM were 2.7%, 10.7%, and 22.7%, respectively. Multivariate analysis revealed that VAT index (HR=1.01, 95% CI=1.01–1.01,  $P=0.001$ ) and standardized spleen volume (HR=1.01, 95% CI=1.01–1.01,  $P=0.001$ ) were among the significant predictors for the development of DM (Table 4), along with sex, age, and albumin level. The optimal cut-off value of the VAT index was set at 28.28 cm<sup>2</sup>/m<sup>2</sup> to predict the development of DM. The estimated 1-, 5-, and 10-year cumulative incidences of DM development in 1,680 patients with a VAT index  $\geq 28.28$  cm<sup>2</sup>/m<sup>2</sup> were 2.7%, 11.2%, and 24.8%, respectively, and were significantly higher than those of 489 patients with a VAT index of  $< 28.28$  cm<sup>2</sup>/m<sup>2</sup> which were 2.5%, 9.0%, and 15.4%, respectively, (HR=1.34, 95% CI

=1.13–1.74,  $P=0.001$ ) (Fig. 3D). Regarding the standardized spleen volume, the optimal cut-off value was set at 92.21 mL/m<sup>2</sup> to predict the development of DM. The estimated 1-, 5-, and 10-year cumulative incidences of DM development in 1,249 patients with a standardized spleen volume  $\geq 92.21$  mL/m<sup>2</sup> were 3.4%, 12.7%, and 24.7%, respectively, and were significantly higher than those of 920 patients with a standardized spleen volume  $< 92.21$  mL/m<sup>2</sup> which were 1.7%, 8.1%, and 20.0%, respectively (HR=1.35, 95% CI=1.10–1.67,  $P=0.004$ ) (Fig. 3E).

### Predictive factors for OS

We excluded 164 patients who had DM at the time of enrollment to examine OS. During the follow-up period, 120 patients (5.5%, 120/2,169) died. The causes of death were: unknown (n=104, 86.7%), liver cirrhosis-related complications (n=6, 5.0%), pneumonia (n=6, 5.0%), and progression of HCC (n=4, 3.3%). The estimated 1-, 5-, and 10-year OS were

**Table 4.** The predictors for development of diabetes mellitus in 2,169 patients with compensated chronic liver disease from CHB

Characteristic	Univariate			Multivariate		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Sex (female)	0.70	0.57–0.85	<0.001	0.73	0.56–0.95	0.017 <sup>†</sup>
Age (per 1 year)	1.04	1.03–1.05	<0.001	1.05	1.04–1.06	<0.001 <sup>†</sup>
Body mass index (kg/m <sup>2</sup> )	1.01	0.99–1.03	0.211			
Antiviral therapy (yes)	1.14	0.94–1.37	0.189			
Alanine aminotransferase (IU/L)	1.00	0.99–1.01	0.604			
Albumin (g/L)	0.80	0.67–0.95	0.013	0.79	0.65–0.95	0.014 <sup>†</sup>
Total bilirubin (mg/dL)	0.98	0.91–1.07	0.690			
PT-INR	0.99	0.93–1.06	0.820			
Platelet count (K/mm <sup>3</sup> )	1.00	0.99–1.01	0.116			
AFP (ng/mL)	1.00	0.99–1.01	0.431			
Standardized liver volume (mL/m <sup>2</sup> )	1.01	1.01–1.01	0.004	1.00	0.99–1.01	0.075
Standardized spleen volume $\geq 92.21$ mL/m <sup>2</sup>	1.23	1.01–1.49	0.040	1.35	1.10–1.67	0.004 <sup>†</sup>
Skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	1.00	0.99–1.01	0.686			
Visceral adipose tissue index $\geq 28.28$ cm <sup>2</sup> /m <sup>2</sup>	1.56	1.21–2.02	0.001	1.34	1.13–1.74	0.001 <sup>†</sup>
Subcutaneous adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	1.00	0.99–1.01	0.927			
APRI	1.00	0.98–1.02	0.932			
FIB-4	0.99	0.99–1.01	0.571			
MELD	1.05	1.01–1.09	0.007	1.03	0.99–1.07	0.176

CHB, chronic hepatitis B viral infection; CI, confidence interval; PT-INR, prothrombin time international normalized ratio; AFP, alpha fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; MELD, model for end-stage liver disease.

<sup>†</sup> $P < 0.05$ .

99.6%, 98.1%, and 94.5%, respectively. Multivariate analysis revealed that the SAT index (HR=0.99, 95% CI=0.98–0.99,  $P=0.004$ ) was significantly associated with OS, along with age, albumin, and the Model for End-Stage Liver Disease score (Table 5). The optimal cut-off value of the SAT index was set at 39.08 cm<sup>2</sup>/m<sup>2</sup> to predict OS. The estimated 1-, 5-, and 10-year OS in 1,453 patients with a SAT index  $\geq 39.08$  cm<sup>2</sup>/m<sup>2</sup> were 99.7%, 98.5%, and 95.6%, respectively, and were significantly higher than those of 716 patients with a SAT index  $< 39.08$  cm<sup>2</sup>/m<sup>2</sup> which were 99.4%, 97.2%, and 92.5%, respectively (HR=0.49, 95% CI=0.34–0.70,  $P<0.001$ ) (Fig. 3F).

## DISCUSSION

In this study, body composition data and spleen and liver volumes were automatically acquired from portal venous

phase CT images using CNN in all patients. Standardized spleen volume was significantly associated with the development of HCC, hepatic decompensation, and DM; furthermore, the VAT index was correlated with the development of hepatic decompensation and DM. In addition, a higher SAT index correlated with increased OS.

Although ultrasound is currently the recommended modality for HCC screening in patients with CHB,<sup>23,24</sup> its sensitivity for detecting HCC can be commonly reduced in situations such as limited sonic window, inherent liver blind spots, or coarse liver parenchyma masking focal lesions.<sup>25</sup> Considering that CT scans can be performed as an alternative imaging modality in such circumstances,<sup>25</sup> we expect that body composition and spleen volumetric data automatically and additionally obtained by applying CNN-based fully automated algorithm on CT data, can be used for opportunistically predicting the comprehensive prognosis of patients with CHB. Our study results are in line with those from previous

**Table 5.** The predictors for death in 2,169 patients with compensated chronic liver disease from CHB

Characteristic	Univariate			Multivariate		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Sex (female)	0.68	0.46–1.01	0.053			
Age (per 1 year)	1.09	1.07–1.12	<0.001	1.09	1.07–1.11	<0.001 <sup>†</sup>
Body mass index (kg/m <sup>2</sup> )	0.97	0.94–0.99	0.015			
Antiviral therapy (yes)	1.00	0.70–1.43	0.999			
Alanine aminotransferase (IU/L)	1.00	1.00–1.01	0.085			
Albumin (g/L)	0.48	0.40–0.58	<0.001	0.51	0.40–0.65	<0.001 <sup>†</sup>
Total bilirubin (mg/dL)	1.06	0.99–1.15	0.115			
PT-INR	1.00	0.93–1.08	0.935			
Platelet count (K/mm <sup>3</sup> )	1.00	0.99–1.01	0.784			
AFP (ng/mL)	1.00	1.00–1.01	0.073			
Standardized liver volume (mL/m <sup>2</sup> )	1.00	0.99–1.00	0.737			
Standardized spleen volume	1.00	0.99–1.01	0.148			
Skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	0.99	0.98–1.01	0.361			
Visceral adipose tissue index (cm <sup>2</sup> /m <sup>2</sup> )	0.99	0.99–1.00	0.678			
Subcutaneous adipose tissue index $\geq 39.08$ cm <sup>2</sup> /m <sup>2</sup>	0.46	0.32–0.66	<0.001	0.49	0.34–0.70	<0.001 <sup>†</sup>
APRI	1.01	0.99–1.03	0.269			
FIB-4	1.00	0.99–1.01	0.911			
MELD	1.12	1.08–1.17	<0.001	1.09	1.04–1.14	<0.001 <sup>†</sup>

CHB, chronic hepatitis B viral infection; CI, confidence interval; PT-INR, prothrombin time international normalized ratio; AFP, alpha fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; MELD, model for end-stage liver disease.

<sup>†</sup> $P<0.05$ .

studies<sup>13,26,27</sup> showing the usefulness of automated CT-based opportunistic screening of various diseases such as cardiovascular events, osteoporosis, and sarcopenia.

Our study results showed the prognostic role of spleen volume in predicting the development of HCC and hepatic decompensation. As liver fibrosis and cirrhosis advance, the spleen tends to enlarge owing to both the accumulation of portal flow and tissue hyperplasia characterized by a combination of angiogenesis, fibrogenesis, enlargement, and hyperactivation of the splenic lymphoid compartment.<sup>28,29</sup> Therefore, spleen enlargement was reported as a potential surrogate marker of the severity of liver fibrosis and portal hypertension<sup>30,31</sup> and showed a significant association with the development of HCC and hepatic decompensation in previous studies,<sup>32,33</sup> which aligns with our results. However, these previous studies determined a spleen enlargement of more than 12 cm on ultrasonography<sup>33</sup> or acquired splenic volume by applying a semi-automated software to CT scans.<sup>32</sup> In contrast, in this study, we obtained spleen volume using a deep learning-based fully automated segmentation tool, saving researchers' time and efforts.

The association between CHB and DM has been controversial, and some previous studies<sup>34,35</sup> reported the increased prevalence of DM in patients with CHB, while others did not.<sup>36,37</sup> In our study, the spleen volume was a significant predictor of DM. Several mechanisms have been suggested to explain the association between hepatitis B viral (HBV) infection and the prevalence of DM.<sup>35</sup> The liver's impairment resulting from HBV infection can potentially lead to disruptions in glycometabolism, owing to its crucial role in maintaining glucose homeostasis by managing both glucose storage and release.<sup>38</sup> Therefore, the significant correlation between the spleen volume and DM in our study may be attributable to the association between DM and HBV infection-induced chronic inflammation of the liver, which was represented by increased splenic volume.

In our study, a higher VAT index was associated with hepatic decompensation and DM, whereas a higher SAT index was significantly correlated with increased OS. In previous studies,<sup>39,40</sup> obesity, represented by the body mass index, was a significant risk factor for decompensation in patients with cirrhosis of all etiologies. Moreover, obesity-related changes in insulin and leptin may change intrahepatic vascular resistance,<sup>40</sup> leading to portal hypertension. However, body mass index alone may not be an accurate predictor of outcomes

since it does not reflect the distribution of fat deposition.<sup>41</sup> Recently, growing evidence indicates that adipose tissue plays an active role in influencing endocrine function, immunity (i.e., leptin and adiponectin), and angiogenesis (i.e., angiopoietin-2, vascular endothelial growth factor, leptin, and adiponectin).<sup>42,43</sup> Adipose tissue is currently divided into SAT and VAT based on location and functions. The VAT index was an independent predictor of DM in our study, which can be explained by previous studies showing significant correlations between increased visceral adiposity with insulin resistance in patients with DM.<sup>44,45</sup> In contrast, the favorable effects of increased SAT on survival were demonstrated in patients with various oncologic diseases<sup>46,47</sup> and cirrhosis,<sup>48</sup> which are concordant with our study results. The reasons for the protective effects of high subcutaneous adiposity were not clearly identified; however, potential explanations include the association between leptin produced by SAT and better insulin sensitivity and energy metabolism, as well as less prevalent cachectic state inducing energy exhaustion in patients with increased SAT.<sup>49</sup> Based on these results from ours, fully automated body composition measurements using CNN on CT data which quantifies the distribution of fat deposition, rather than merely determining the presence of obesity according to the body mass index, may provide more accurate information regarding prognosis.

Our study has several limitations. First, this was a retrospective study from a single tertiary referral center; therefore, selection bias was unavoidable. Furthermore, our study results were not externally validated in other patient cohorts. Therefore, further studies are warranted to validate our study results. Second, our study did not provide longitudinal follow-up data which might have shown different results.

In conclusion, a larger spleen volume was significantly associated with HCC, hepatic decompensation, and DM occurrence. A higher abdominal VAT index was correlated with the development of DM, while a higher SAT index was correlated with increased OS in patients with CHB. Deep learning-based automatically measured spleen volume, abdominal VAT and SAT indices may be used as opportunistic prognostic factors in patients with CHB.

### Authors' contribution

Jeongin Yoo: analysis and interpretation of data; drafting manuscript; critical revision of the manuscript; obtained funding. Heejin Cho: acquisition of data; critical revision of

the manuscript. Dong Ho Lee: study concept and design; analysis and interpretation of data; supervision; critical revision of the manuscript. Eun Ju Cho: study concept and design; supervision; critical revision of the manuscript. Ijin Joo: study concept and design; acquisition of data. Sun Kyung Jeon: study concept and design; acquisition of data. All authors approved the final version of the manuscript.

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## Conflicts of Interest

The authors have no conflicts to disclose.

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