Deep learning Assisted Biomarker Development in Patients with Chronic Hepatitis B

Yong Eun Chung
Department of Radiology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

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Correspondence:
Yong Eun Chung, MD, PhD
Department of Radiology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
Institutional address: 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea, 03722
Tel: 82-2-2228-7400, Fax: 82-2-393-3035, E-mail: yelv@yuhs.ac
In patients with chronic hepatitis B (CHB), predicting clinical outcomes such as the development of hepatocellular carcinoma (HCC), hepatic decompensation, and overall survival (OS) is crucial for treatment decision-making and timely management. To date, most efforts have focused on predicting these outcomes based on various clinical and laboratory parameters. The majority of studies using imaging findings have predominantly concentrated on predicting recurrence or overall survival in patients with HCC after treatment. Recent advances in deep learning technology have led to numerous studies applying deep learning in the medical field, including hepatology. Research utilizing deep learning can be divided into three main areas. The first area is the segmentation of either the liver or intrahepatic focal lesions. Using deep learning for segmentation enables quick and effortless delineation of organs or regions of interest (ROI), eliminating the need for manual effort and time. This technology is particularly advantageous in the current context, where research involving large datasets is becoming increasingly common. The second area involves evaluating tissue characteristics based on the results of liver and intrahepatic lesion segmentation. This approach allows for the assessment of diffuse liver diseases such as liver fibrosis and the degree of fatty liver, and it can also aid in the differential diagnosis of intrahepatic focal lesions. Finally, the information obtained through these methods can be used to predict outcomes for various diseases.

In this issue, You et al. aimed to predict the clinical outcomes in patients with CHB using image-based parameters as well as clinical parameters. Image-based parameters included standardized liver volume, standardized spleen volume, subcutaneous adipose tissue (SAT) index, visceral adipose tissue (VAT) index, and skeletal muscle index, all derived from CT images using deep learning-based fully automated algorithms. A total of 2,169 patients were retrospectively included, with a mean follow-up period was 103.0 months. In multivariate analysis, a larger standardized spleen volume was identified as a significant predictor for the development of HCC, hepatic decompensation, and diabetes mellitus (DM). Higher VAT index was associated with the development of DM, while lower VAT index was linked to hepatic decompensation. Additionally, overall survival was longer in patients with a higher SAT index.

Liver fibrosis and cirrhosis can alter portal blood flow, leading to portal hypertension. As portal hypertension progresses, spleen size increases, making splenomegaly a recognized biomarker for liver fibrosis. Spleen size is typically measured in one plane using ultrasound (US) or CT; however, the shape and orientation of the spleen can vary, resulting in inaccuracies with these measurement methods. Volumetric measurement is theoretically more accurate but is not commonly used due to the time-consuming nature of the process. Traditionally, spleen volume is calculated by manually outlining the spleen on each slice to determine the area, then multiplying by the slice thickness and summing these values. Furthermore, while the size of the spleen is known to be 12-13 cm in its longest diameter, a normal range for spleen volume has not yet been established. Recently, Kim
and Ha et al.\textsuperscript{5} measured liver and spleen volumes using deep learning algorithm in 2,989 healthy liver donors, establishing population-based reference intervals (2.5th - 97.5th percentiles of the volume in the reference group) of 824.5-1700.0 cm\(^3\) for liver volume and 81.1-322.0 cm\(^3\) for spleen volume. Additionally, they reported that 8.3\% to 49.1\% of patients with viral hepatitis had spleen volumes exceeding the reference interval, depending on the fibrosis stage. They also proposed personalized reference intervals for spleen volume based on age, sex, height, and weight. In a study by Yoo et al.,\textsuperscript{3} patients with a higher standardized spleen volume (calculated by dividing spleen volume by BMI) showed a higher cumulative incidence of HCC (cut-off value: \(\geq 112.6\) mL/m\(^2\)), decompensation (\(\geq 145.74\) mL/m\(^2\)), and diabetes mellitus (\(\geq 92.21\) mL/m\(^2\)) compared to those with lower standardized spleen volumes. Due to discrepancies in units, direct comparisons between the two studies are challenging. However, as reference intervals can be calculated using basic demographic information, future research may determine whether spleen or liver volume can serve as surrogate biomarkers for various clinical outcomes in patients with chronic hepatitis.

Previous studies have established boundaries for fat and skeletal muscle based on Hounsfield unit (HU) ranges (e.g., -150 to -50 HU for fat and -29 to +150 HU for skeletal muscle) to calculate SAT, VAT, and skeletal muscle indices.\textsuperscript{6} However, this method may struggle to differentiate between other intra-abdominal structures, such as the intestine kidney or ascites, from skeletal muscle in non-contrast CT images due to their similar HU values. Additionally, in cases of edema where fat HU may be elevated, accurate boundary delineation for fat can be challenging, often necessitating manual adjustments. In a study by Yoo et al.,\textsuperscript{3} to overcome the limitations of conventional methods, volumetric segmentation of body components into seven classes (skin, subcutaneous fat, muscle, visceral fat, bone, internal organs and vessels, and the central nervous system) was performed using a deep-learning algorithm. Subsequently, VAT, SAT, and skeletal muscle indices were calculated.

Berziogotti et al\textsuperscript{7} reported that obesity, along with hepatic venous pressure gradient and albumin levels, were independent predictors of decompensation. In contrast, hepatic decompensation was less common in patients with a lower standardized VAT index (<22.65 cm\(^2\)/m\(^2\)) in a study by Yoo et al.\textsuperscript{3}. This difference may arise from the varying methods of measuring obesity (BMI vs. VAT) and the different patient groups included in the studies. VAT is considered a more accurate prognostic indicator of body fat composition because BMI does not adequately represent body fat distribution. The primary components of body fat include visceral fat and subcutaneous fat, with visceral fat being particularly harmful due to its production of inflammatory cytokines and adipokines. Therefore, in patients with a relatively high proportion of visceral fat, the risk may be underestimated when using BMI instead of VAT.\textsuperscript{6,8} Furthermore, BMI is calculated from weight/height\(^2\) (kg/m\(^2\)), which can be overestimated in patients with ascites or edema, common in
those with liver cirrhosis. In terms of inclusion criteria, Yoo et al. included CHB patients who underwent HCC surveillance. In contrast, the study by Berzigotti et al. included patients with compensated cirrhosis and portal hypertension, representing a more advanced stage of chronic hepatitis.

Obesity may increase the incidence of HCC, but its association is weak and inconsistent depending on the etiology of chronic hepatitis. The mechanisms by which obesity influences HCC development are not yet fully understood; however, chronic inflammation, lipotoxicity, and insulin resistance are believed to contribute to carcinogenesis. Chen at al. reported that obesity is a strong risk factor for HCC in patients with HCV infection or cirrhosis, but not in those with HBV infection. Lee at al. demonstrated that obesity-related parameters, including BMI and visceral fat area, were not significant risk factors for developing HCC in CHB patients who received entecavir treatment. Similarly, in a study by Yoo et al., both VAT index and SAT index were not significant risk factors for developing HCC in patients with CHB. Therefore, obesity may only be a significant risk factor for developing HCC under specific conditions. Further investigation into the association between obesity and HCC is warranted in future studies.

Screening tests are used in healthy individuals or target populations with certain risk factors to detect and treat diseases early, thereby increasing overall survival. In contrast to intended screening, opportunistic screening refers to the practice of prevention through an unorganized program or chance encounter. While various imaging modalities are available for opportunistic screening, CT is often preferred due to its objective and reproducible measurements, as well as its adequate resolution of untargeted body parts. CT allows for quantitative measurements of vessel calcification for cardiovascular disease, bone mineral density for osteoporosis, VAT and SAT for the prognosis of various diseases, and muscle volume for sarcopenia. One of the significant values of this study is that imaging parameters were measured and utilized for prognosis prediction in CT scans performed as a clinical necessity in patients with chronic hepatitis, without the need for additional examinations or expenses.

In the field of hepatology, multimodal imaging studies are used for diagnosis. Additionally, various test results, such as fibrosis assessment using elastography, tumor markers, and liver function tests, need to be integrated for accurate diagnosis and prognosis prediction. Consequently, applying deep learning in hepatology is more challenging compared to other medical fields. However, by overcoming these obstacles one by one, the application of deep learning in this area is gradually expanding.
Conflict of Interest

The author have no conflicts of interest to declare.
REFERENCES


