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ORIGINAL RESEARCH

Cardiometabolic index and central adiposity as non-invasive markers of hepatic steatosis and elevated liver stiffness in chronic hepatitis B

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Highlights & Insights

- **Scientific Gap:** CMI and MCMI did not differ significantly between inactive HBV carriers and HBV-negative controls in a small sample, which does not establish equivalence.
- **Key Finding:** In long-term nucleos(t)ide-treated CHB, CMI was associated with CAP-defined hepatic steatosis but not with elevated liver stiffness.
- Waist circumference showed the highest discrimination for elevated liver stiffness (AUC 0.75) and exceeded FIB-4 and APRI on formal DeLong testing.
- **Clinical Impact:** Part of the waist circumference signal may reflect the influence of obesity on VCTE measurement, so anthropometry complements rather than replaces existing non-invasive tests.

ABSTRACT

Background and Aim: Residual liver disease in chronic hepatitis B (CHB) under long-term antiviral therapy is increasingly metabolic. We assessed whether the cardiometabolic index (CMI), modified CMI (MCMI) and simple anthropometry are associated with hepatic steatosis and elevated liver stiffness.

Materials and Methods: In a two-part cross-sectional study, CMI and MCMI were compared between inactive hepatitis B virus carriers (n=21) and matched controls (n=27). Separately, 92 nucleos(t)ide-treated CHB patients underwent vibration-controlled transient elastography (VCTE). Significant steatosis was a controlled attenuation parameter (CAP) ≥268 dB/m and elevated liver stiffness a liver stiffness measurement ≥7.0 kPa. No biopsy was performed. Areas under the curve (AUC) were compared by the DeLong test, and cutoff performance was internally validated by bootstrap.

Results: CMI and MCMI did not differ between carriers and controls (p>0.6). Significant steatosis occurred in 44 of 91 (48%) and elevated liver stiffness in 48 of 90 (53%). CMI correlated with CAP (rho=0.37, p<0.001) and increased across CAP grades (p=0.009). Its AUC for steatosis was 0.70, comparable with waist circumference (0.70, p=0.96). For elevated liver stiffness, waist circumference had the highest AUC (0.75; 95% confidence interval, 0.65–0.85), exceeding fibrosis-4 index (FIB-4) (0.57, p=0.023), aspartate aminotransferase-to-platelet ratio index (APRI) (0.56, p=0.022) and CMI (0.58, p=0.006), and remained associated after age and sex adjustment (odds ratio 2.94/10 cm, p<0.001).

Conclusion: In long-term nucleos(t)ide-treated CHB, CMI was associated with CAP-defined hepatic steatosis, whereas waist circumference showed the highest discrimination for elevated liver stiffness and exceeded FIB-4 and APRI. Part of this may reflect obesity-related effects on VCTE.

Keywords: Adiposity, cardiometabolic risk factors, chronic hepatitis B, hepatic steatosis, vibration-controlled transient elastography, waist circumference.

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Introduction

Chronic hepatitis B (CHB) remains a leading cause of cirrhosis and hepatocellular carcinoma worldwide, yet the clinical landscape has shifted as potent nucleos(t)ide analogues achieve durable viral suppression in most treated patients.[1] In this context, the drivers of residual liver injury are increasingly metabolic rather than virologic. Metabolic dysfunction-associated steatotic liver disease (MASLD), the term adopted in 2023 to replace non-alcoholic fatty liver disease, now affects roughly a third of adults globally and is defined by hepatic steatosis in the presence of cardiometabolic risk factors.[2–4]

The coexistence of hepatic steatosis and CHB is common and clinically consequential, and concurrent steatosis has been linked with accelerated fibrosis progression and with a higher risk of cirrhosis and hepatocellular carcinoma.[5,6] Concurrent steatosis may also complicate non-invasive assessment, although the evidence is more limited than is sometimes stated. Shen et al.[7] reported that moderate to severe steatosis was associated with a higher liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) in patients with CHB who did not have significant fibrosis, whereas no such effect was seen at more advanced fibrosis stages. Con et al.[8] reported that aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) performed less well in patients with CHB and concurrent MASLD, but they did not establish that steatosis itself reduces the accuracy of these scores. Both scores incorporate aminotransferases and platelet count, which are influenced by necroinflammatory activity, alcohol intake, medication and other factors that are not specific to fibrosis. The independent contribution of steatosis therefore remains uncertain.

Simple and inexpensive metabolic indices may add value in this setting. The cardiometabolic index (CMI), proposed by Wakabayashi and Daimon, multiplies the triglyceride (TG)-to-high-density lipoprotein-cholesterol (HDL-C) ratio by the waist-to-height ratio and combines atherogenic dyslipidemia with central adiposity in a single number.[9,10] In MASLD populations, a higher CMI is associated with the degree of hepatic fat, with liver fibrosis and with long-term mortality.[11–13] Whether these relationships hold in treated CHB, where metabolic and viral processes overlap, has not been established.

We hypothesized that metabolic indices would show no significant difference between inactive hepatitis B virus (HBV) carriers and HBV-negative controls, that they would be associated with VCTE-defined hepatic steatosis and elevated liver stiffness in treated CHB, and that they would complement rather than replace conventional fibrosis scores. We therefore conducted a two-part cross-sectional study to quantify these associations.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted at a secondary-care center (Etimesgut Şehit Sait Ertürk State Hospital) and comprised two separate and non-overlapping samples. The diagnostic-comparison sample included 21 patients with inactive HBV carriage (hepatitis B surface antigen positive for more than 6 months, persistently normal aminotransferases, low or undetectable HBV DNA, no antiviral therapy) and 27 age- and sex-matched volunteers without known liver disease. The staging cohort included 92 consecutive patients with CHB receiving nucleos(t)ide analogue therapy who underwent VCTE during routine follow-up. No participant contributed to both samples. The two samples are presented together because they address complementary questions, namely, whether cardiometabolic indices differ in untreated inactive carriage and whether they track hepatic steatosis and liver stiffness during long-term nucleos(t)ide analogue therapy. All analyses were performed separately in each sample, and no pooled analysis was undertaken.

Exclusion criteria, applied to protect the interpretability of metabolic and blood-count-derived indices, were coinfection with hepatitis C, hepatitis D or human immunodeficiency virus, significant alcohol intake, other chronic liver disease, active infection, hematologic disease or malignancy, and pregnancy. The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Ankara Provincial Health Directorate (approval number 04-10-2025, dated April 10, 2025).

Measurements and Exposures

Anthropometry (height, weight, and waist circumference), fasting lipids, glycated hemoglobin (HbA1c), aminotransferases and platelet count were recorded. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest at the end of a normal expiration. Body-mass index (BMI) and the waist-to-height ratio were derived. CMI was calculated as (TG/HDL-C) × (waist circumference/height).[9]

Fasting plasma glucose was not available in this dataset. An estimated average glucose was therefore derived from HbA1c using the published relationship (estimated average glucose in mg/dL=28.7×HbA1c-46.7) for the two glucose-dependent measures, which are reported as exploratory throughout.[14] These were the modified CMI (MCMI)=(TG×estimated average glucose/HDL-C)×(waist circumference/height), and a TG-to-estimated-glucose ratio calculated as TG/(estimated average glucose/2). The latter is not the conventional logarithmic TG-glucose (TyG) index of Simental-Mendia et al.,[15] which requires a directly measured fasting glucose, and it is not interpretable against published TyG thresholds. It is therefore reported only as a descriptive exploratory variable in the carrier-versus-control comparison and was not used in any diagnostic or regression analysis of the CHB cohort. APRI was calculated as ([aspartate aminotransferase [AST]/upper limit of normal AST]/platelet count in 10^9/L)×100 with an upper limit of normal of 40 U/L, and FIB-4 as (age × AST)/(platelet count in 10^9/L × square root of alanine aminotransferase [ALT]).[16,17]

VCTE

LSM and controlled attenuation parameter (CAP) were obtained simultaneously by VCTE (FibroScan, Echosens, Paris, France) by a single experienced operator who was unaware of the laboratory results. Pa-

tients fasted for at least 3 h before the examination and were positioned supine with the right arm in maximal abduction. The M probe was used by default, and the XL probe was used when the automatic probe-selection tool indicated it or when the skin-to-liver-capsule distance exceeded 25 mm. An examination was accepted as reliable when at least 10 valid measurements were obtained, and the ratio of the interquartile range to the median LSM was 0.30 or less. The median of the valid measurements was used for analysis.[18] The probe used in each individual examination was not retrievable from the archived reports, so the proportion of examinations performed with the M probe and with the XL probe could not be determined.

Of the 92 patients in the staging cohort, a reliable CAP value was obtained in 91 and a reliable LSM value in 90. One examination yielded neither a reliable LSM nor a reliable CAP, and one yielded a reliable CAP without a reliable LSM, in both instances because the interquartile range to median ratio criterion was not met. These patients were excluded from the corresponding analyses, which explains the differing denominators. One waist circumference value was recorded as 12 cm, which is anatomically impossible, and was set to missing rather than corrected, so waist circumference was available in 91 patients.

Outcomes

The primary outcomes were significant hepatic steatosis and elevated liver stiffness. CAP grades were defined using the published thresholds of the individual patient data meta-analysis of Karlas et al.,[19] namely S0 for CAP below 248 dB/m, S1 for 248–267 dB/m, S2 for 268–279 dB/m and S3 for 280 dB/m or higher. Significant steatosis was defined as CAP 268 dB/m or higher, corresponding to grade S2 or S3. Elevated liver stiffness was defined as LSM 7.0 kPa or higher. This threshold lies within the range of cutoffs reported for significant fibrosis in CHB in a meta-analysis of 18 studies and 2,772 patients, in which the estimated cutoff was 7.9 kPa with a reported range of 6.1–11.8 kPa, and it is consistent with current guidance that a value below 7 kPa makes significant fibrosis unlikely.[18,20] Because no liver biopsy was performed, no METAVIR stage was assigned, and the endpoint is reported throughout as elevated liver stiffness rather than as histological fibrosis. Sensitivity analyses were performed at LSM thresholds of 7.2 kPa and 8.0 kPa and at CAP thresholds of 248 dB/m and 280 dB/m.

Statistical Analysis

Continuous variables are summarized as mean with standard deviation or as median with interquartile range and were compared with the t-test or the Mann–Whitney U test. Categorical variables were compared with the Chi-square test or the Fisher exact test. Associations of the indices with continuous CAP and LSM were quantified by the Spearman rank correlation coefficient. Differences across CAP grades were assessed by the Kruskal–Wallis test, and an ordered trend across grades was tested by the Spearman rank correlation between the ordinal grade and the index.

Discrimination for the binary outcomes was summarized by the areas under the curve (AUC) with 95% confidence intervals (CIs) by the DeLong method and additionally by 1000 non-parametric bootstrap resamples. Correlated AUCs were compared by the DeLong test. Cutoffs were derived by the Youden index. Because cutoffs derived and evaluated in the same dataset yield optimistic estimates, the sensitivity and specificity at each Youden cutoff were internally validated by the enhanced bootstrap procedure of Harrell with 1,000 resamples, in which the cutoff was re-derived in each resample and applied to the original data, and the mean difference was subtracted from the apparent value to give an optimism-corrected estimate. External validation was not feasible in a cohort of this size.

The structure of every multivariable logistic regression model was fixed before the models were fitted, and no data-driven variable selection was performed at any stage. Each model contained the marker of interest together with age and sex, which were fixed as core confounders. With 44 steatosis events and 48 elevated liver stiffness events, models were restricted to a maximum of four covariates so that at least 10 events per variable were retained. Age and sex were retained in every model without exception. Four additional models each added a single further covariate to the age- and sex-adjusted model, namely FIB-4, CMI, CAP or diabetes mellitus, in order to test whether the waist circumference signal was independent of the conventional fibrosis scores, of the degree of steatosis and of diabetes. CMI and waist circumference were also entered together with age and sex in a single model for the steatosis outcome. Model discrimination was internally validated by the same bootstrap procedure and the calibration slope was estimated in the same resamples. Two-sided p-values below 0.05 were considered significant. Analyses were performed in Python 3.12 (Python Software Foundation, Beaverton, Oregon, USA) with the SciPy, statsmodels and scikit-learn libraries. Reporting follows the STROBE recommendations for observational studies.

Results

Inactive Carriers versus HBV-negative Controls

The 21 inactive carriers and the 27 HBV-negative controls were comparable in age (median 52 vs. 47 years, p=0.27), sex (p=0.82) and BMI (27.9 vs. 26.3 kg/m^2, p=0.21). No metabolic index differed significantly between the groups. CMI was 1.09 versus 1.28 (p=0.80), MCMI was 124.0 versus 148.2 (p=0.62), the exploratory TG-to-estimated-glucose ratio was 1.94 versus 2.36 (p=0.53), APRI was 0.19 versus 0.17 (p=0.45) and FIB-4 was 0.87 versus 0.68 (p=0.47) (Table 1). These groups were small, and the study was not designed or powered as an equivalence study, so this result indicates only the absence of a statistically significant difference and does not demonstrate that the cardiometabolic profiles of inactive carriers and HBV-negative controls are comparable.

CHB Cohort

The treated CHB cohort (n=92) had a mean age of 55.9 (standard deviation 11.0) years and 45 patients (49%) were male. Antiviral therapy comprised tenofovir disoproxil fumarate in 44 patients, entecavir in 36 and tenofovir alafenamide in 12, with a median treatment duration of 7 years (interquartile range [IQR] 3–11). Diabetes mellitus was

Table 1. Characteristics and metabolic indices of inactive HBV carriers and HBV-negative controls

Variable	Inactive HBV carriers (n=21)	HBV-negative controls (n=27)	p
Age, years	52 (39–59)	47 (37.5–52.5)	0.270
Male sex, n (%)	7 (33)	11 (41)	0.822
BMI, kg/m^2	27.89 (26.56–31.59)	26.30 (24.78–29.14)	0.205
Waist circumference, cm	100.00 (96.00–103.00)	96.00 (87.50–105.00)	0.473
TG, mg/dL	111 (83–155)	123 (95–161)	0.747
HDL-C, mg/dL	50 (45–62)	50 (40.50–55.50)	0.618
TG/HDL-C ratio	1.86 (1.65–3.41)	2.43 (1.51–3.70)	0.575
HbA1c, %	5.40 (5.30–5.95)	5.40 (5.25–5.60)	0.736
ALT, U/L	22 (18–27)	20 (14–24)	0.201
AST, U/L	22 (18–23)	19 (17.50–21)	0.312
Platelet count, ×10^9/L	259 (205–321)	260 (210.50–309.50)	0.967
CAP, dB/m	263 (243–292)	282 (246.50–307.50)	0.383
LSM, kPa	6.30 (5.50–7.40)	5.70 (4.05–6.75)	0.187
CMI	1.09 (0.97–2.13)	1.28 (0.86–2.11)	0.803
MCMI (exploratory)	124.03 (95.30–222.75)	148.21 (94.43–241.32)	0.624
TG-to-estimated-glucose ratio (exploratory)	1.94 (1.57–2.75)	2.36 (1.65–2.79)	0.532
APRI	0.19 (0.15–0.25)	0.17 (0.14–0.23)	0.454
FIB-4	0.87 (0.49–0.99)	0.68 (0.61–0.91)	0.467

Values are median (interquartile range) unless stated otherwise. p-values are from the Mann–Whitney U test for continuous variables and from the Chi-square test for sex. The two glucose-dependent measures are exploratory and were derived from an HbA1c-based estimated average glucose because fasting plasma glucose was not available. The TG-to-estimated-glucose ratio is triglycerides divided by half the estimated average glucose and is not the conventional logarithmic TyG index. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body-mass index; CAP: Controlled attenuation parameter; CMI: Cardiometabolic index; HBV: Hepatitis B virus; HDL-C: High-density lipoprotein cholesterol; LSM: Liver stiffness measurement; MCMI: Modified cardiometabolic index; TG: Triglycerides; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index.

present in 15 patients (16%), hypertension in 23 (25%) and hyperlipidemia in 12 (13%). Median ALT was 20 U/L (IQR 17–26), median AST 22 U/L (IQR 20–24) and median platelet count 225×10^9/L (IQR 192–264). Median CAP was 267 dB/m (IQR 234–288) and median LSM 7.1 kPa (IQR 6.1–8.4). CAP grades were S0 in 32 patients, S1 in 15, S2 in 11 and S3 in 33. Significant steatosis was present in 44 of 91 patients (48%) and elevated liver stiffness in 48 of 90 patients (53%) (Table 2).

Metabolic Indices and Hepatic Steatosis

CMI correlated positively with CAP (rho=0.37, p<0.001) and increased across CAP grades, from a median of 1.11 in grade S0 to 2.02 in grade S3 (Kruskal-Wallis p=0.009, ordered trend p=0.001; Fig. 1a, b). CMI was higher in patients with significant steatosis than in those without (1.85 vs. 1.13, p=0.002), as were MCMI (217.3 vs. 129.7, p=0.003), waist circumference (105 vs. 98 cm, p=0.001) and BMI (29.7 vs. 27.9 kg/m2, p=0.011). The AUC of CMI for significant steatosis was 0.70 (95% CI, 0.59–0.81; bootstrap 95% CI, 0.58–0.80) with a Youden cutoff of 1.51 (apparent sensitivity 0.67 and specificity 0.70, optimism-corrected sensitivity 0.64 and specificity 0.67). This AUC did not differ from that of waist circumference (0.70, DeLong p=0.96), BMI (0.65, p=0.58) or MCMI (0.68, p=0.53) (Fig. 2a and Table 3). In a model adjusted for age and sex, each one-unit increase in CMI was associated with a 71% higher odds of significant steatosis (odds ratio 1.71; 95% CI, 1.07–2.73; p=0.025). When CMI and waist circumference were entered together in a model that also contained age and sex, only waist circumference remained significant (odds ratio 2.08/10 cm; 95% CI, 1.21–3.56; p=0.008) while CMI did not (odds ratio 1.32; 95% CI, 0.83–2.10; p=0.245), which indicates that the CMI signal for steatosis is carried largely by its anthropometric component (Table 4).

Metabolic Measures and Elevated Liver Stiffness

Waist circumference correlated with LSM (rho=0.52, p<0.001; Fig. 1c) and was higher in patients with elevated liver stiffness (median 106 vs. 97 cm, p<0.001). Waist circumference showed the highest discrimination for elevated liver stiffness (AUC 0.75; 95% CI, 0.65–0.85; bootstrap 95% CI, 0.64–0.85), followed by the waist-to-height ratio (0.73), BMI (0.66), CMI (0.58), FIB-4 (0.57; 95% CI, 0.45–0.70) and APRI (0.56; 95% CI, 0.44–0.68) (Fig. 2b and Table 3). On formal DeLong testing, the AUC of waist circumference was higher than that of FIB-4 (p=0.023), APRI (p=0.022), CMI (p=0.006) and BMI (p=0.036), while FIB-4 and APRI did not differ from each other (p=0.74). At the Youden cutoff of 101 cm, the apparent sensitivity and specificity of waist circumference were 0.69 and 0.71, and the optimism-corrected values were 0.65 and 0.67.

Table 2. Clinical, laboratory and elastographic characteristics of the treated chronic hepatitis B cohort (n=92)

Characteristic	Value	Characteristic	Value
Age, years, mean±SD	55.9±11.0	HDL-C, mg/dL, median (IQR)	48 (42–56.50)
Male sex, n (%)	45 (49)	TG/HDL-C ratio, median (IQR)	2.38 (1.60–3.34)
BMI, kg/m^2, mean±SD	28.5±4.3	LDL-C, mg/dL, median (IQR)	112 (91–131)
Waist circumference, cm, mean±SD	101.4±11.3 (n=91)	HbA1c, %, median (IQR)	5.50 (5.10–5.95)
Waist-to-height ratio, median (IQR)	0.61 (0.56–0.65)	CMI, median (IQR)	1.47 (1.00–2.16)
Antiviral agent, TDF/ETV/TAF, n	44/36/12	MCMI (exploratory), median (IQR)	160.48 (105.10–269.77)
Treatment duration, years, median (IQR)	7 (3–11)	APRI, median (IQR)	0.23 (0.19–0.30)
Diabetes mellitus, n (%)	15 (16)	FIB-4, median (IQR)	1.18 (0.79–1.46)
Hypertension, n (%)	23 (25)	CAP, dB/m, mean±SD	265.7 ± 41.1
Hyperlipidemia, n (%)	12 (13)	CAP grade S0/S1/S2/S3, n	32 / 15 / 11 / 33
ALT, U/L, median (IQR)	20 (17–26)	LSM, kPa, median (IQR)	7.10 (6.12–8.40)
AST, U/L, median (IQR)	22 (20–24)	Significant steatosis (CAP≥268 dB/m), n/N (%)	44/91 (48)
Platelet count, ×10^9/L, median (IQR)	225 (191.75–264.25)	Elevated liver stiffness (LSM ≥7.0 kPa), n/N (%)	48/90 (53)
TG, mg/dL, median (IQR)	109 (88.15–152)		

Waist circumference was available in 91 patients because one recorded value was anatomically impossible and was set to missing. A reliable CAP value was obtained in 91 patients and a reliable LSM value in 90. HBV DNA level and HBeAg status were not systematically recorded for this cohort and are therefore not reported. CAP grades follow Karlas et al.[19] ETV: Entecavir; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body-mass index; CAP: Controlled attenuation parameter; CMI: Cardiometabolic index; HBV: Hepatitis B virus; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LSM: Liver stiffness measurement; MCMI: Modified cardiometabolic index; TG: Triglycerides; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; SD: Standard deviation; IQR: Interquartile range; HbA1c: Glycated hemoglobin.

In a model adjusted for age and sex, waist circumference remained associated with elevated liver stiffness (odds ratio 2.94/10 cm; 95% CI, 1.65–5.24; p<0.001). In four further models that retained age and sex and added one covariate at a time, the association was essentially unchanged when FIB-4 (odds ratio 3.08; 95% CI, 1.70–5.61), CMI (odds ratio 3.17; 95% CI, 1.70–5.91), CAP (odds ratio 2.73; 95% CI, 1.46–5.09) or diabetes mellitus (odds ratio 2.95; 95% CI, 1.65–5.25) was included, and in none of these models was the added covariate independently associated with the outcome (Table 4). The optimism-corrected AUC of the age- and sex-adjusted model was 0.73 with a calibration slope of 0.87. Results were consistent in sensitivity analyses at LSM thresholds of 7.2 kPa (waist circumference AUC 0.79, DeLong p=0.014 vs. FIB-4 and p=0.010 vs. APRI) and 8.0 kPa (AUC 0.80, p=0.017 and p=0.007).

Co-occurrence of Steatosis and Elevated Liver Stiffness

Significant steatosis and elevated liver stiffness occurred together more often than expected by chance. Among the 90 patients with both a valid CAP and a valid LSM measurement, 29 of the 43 patients with significant steatosis had elevated liver stiffness, compared with

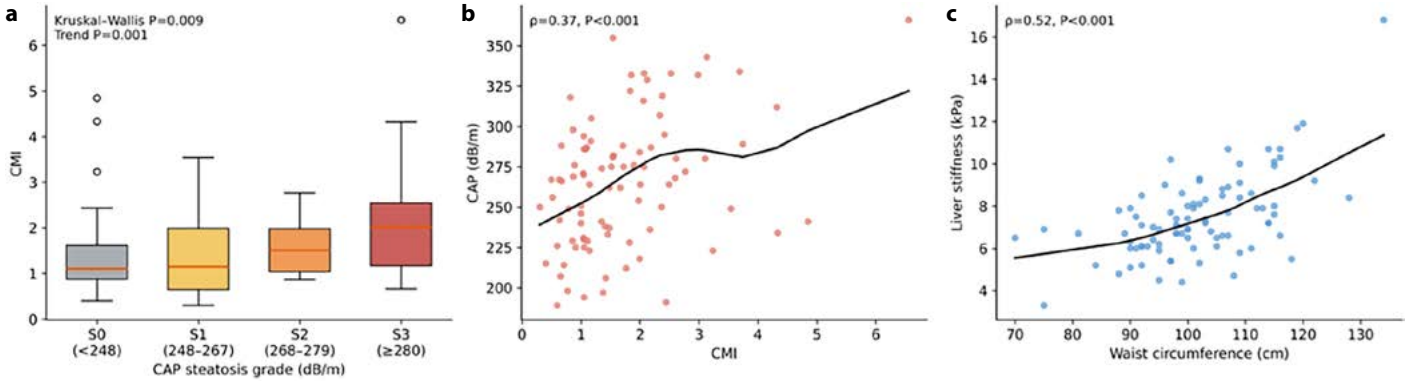


Figure 1. Cardiometabolic index (CMI) and anthropometry in relation to hepatic steatosis and liver stiffness in the chronic hepatitis B cohort. **(a)** CMI across controlled attenuation parameter (CAP) steatosis grades defined according to Karlas et al.[19] (S0 below 248 dB/m, S1 248–267 dB/m, S2 268–279 dB/m, S3 280 dB/m or higher). p-values are from the Kruskal-Wallis test and from the Spearman rank correlation between the ordinal grade and CMI (ordered trend). **(b)** CMI versus CAP. **(c)** Waist circumference versus liver stiffness measurement. **(b, c)** The correlation coefficient is the Spearman rank correlation, and the superimposed curve is a locally weighted scatterplot smoother (LOWESS, span 0.75) shown for visualization only. It is not a fitted regression model, and it is not used in any inference.

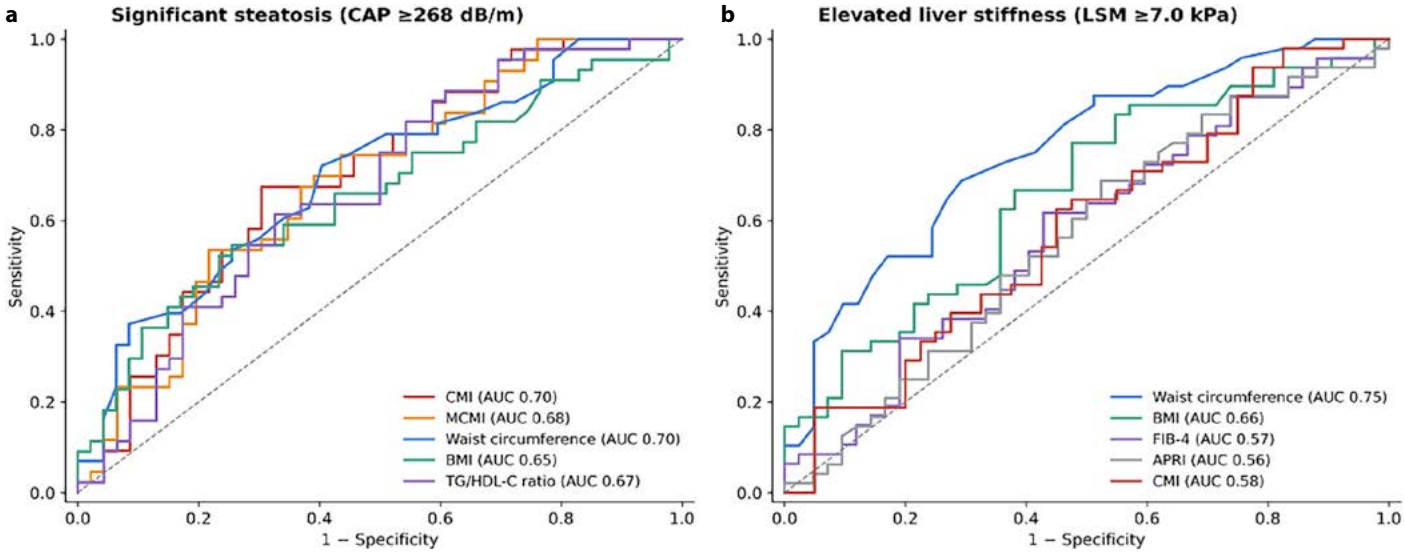


Figure 2. Receiver-operating-characteristic curves in the chronic hepatitis B cohort. **(a)** Significant hepatic steatosis, defined as controlled attenuation parameter 268 dB/m or higher. **(b)** Elevated liver stiffness, defined as a liver stiffness measurement of 7.0 kPa or higher. Areas under the curve with 95% confidence intervals, Youden cutoffs and optimism-corrected sensitivity and specificity are reported in Table 3.

19 of the 47 patients without significant steatosis (odds ratio 3.05, Fisher p=0.012, Chi-square p=0.019). One patient with significant steatosis had no valid LSM measurement and is therefore not included in this comparison. CAP and LSM were weakly correlated as continuous variables (rho=0.23, p=0.033). The two features therefore overlap substantially in the same patients, and the markers examined here are best regarded as complementary summaries of a shared metabolic burden rather than as indicators of separate processes.

Table 3. Discrimination of metabolic, anthropometric and conventional measures for significant hepatic steatosis and elevated liver stiffness

Marker	AUC (95% CI, DeLong)	Bootstrap 95% CI	Youden cutoff	Apparent Se/Sp	Optimism-corrected Se / Sp
Significant steatosis (CAP ≥268 dB/m); 44 events, 91 patients					
CMI	0.70 (0.59–0.81)	0.58–0.80	1.51	0.67/0.70	0.64/0.67
MCMI (exploratory)	0.68 (0.57–0.80)	0.57–0.79	191.24	0.53/0.78	0.49/0.75
Waist circumference	0.70 (0.59–0.81)	0.58–0.80	100.00	0.72/0.60	0.68/0.56
Waist-to-height ratio	0.67 (0.56–0.78)	0.56–0.78	0.62	0.58/0.77	0.55/0.74
BMI	0.65 (0.54–0.77)	0.54–0.77	29.39	0.55/0.74	0.50/0.71
TG/HDL-C ratio	0.67 (0.55–0.78)	0.55–0.77	2.54	0.61/0.67	0.57/0.63
Elevated liver stiffness (LSM ≥7.0 kPa); 48 events, 90 patients					
Waist circumference	0.75 (0.65–0.85)	0.64–0.85	101.00	0.69/0.71	0.65/0.67
Waist-to-height ratio	0.73 (0.63–0.84)	0.62–0.83	0.58	0.85/0.54	0.82/0.50
BMI	0.66 (0.55–0.77)	0.55–0.77	27.08	0.77/0.52	0.73/0.49
FIB-4	0.57 (0.45–0.70)	0.45–0.69	1.16	0.62/0.57	0.57/0.53
APRI	0.56 (0.44–0.68)	0.44–0.68	0.21	0.69/0.48	0.64/0.43
CMI	0.58 (0.46–0.70)	0.46–0.70	1.41	0.62/0.55	0.58/0.50
MCMI (exploratory)	0.58 (0.46–0.70)	0.45–0.70	152.14	0.62/0.57	0.59/0.53

DeLong 95% CIs are shown alongside percentile CIs from 1,000 non-parametric bootstrap resamples. Cutoffs were derived by the Youden index. Optimism-corrected sensitivity (Se) and specificity (Sp) were obtained by the enhanced bootstrap procedure with 1,000 resamples, in which the cutoff was re-derived in each resample and applied to the original data. By the DeLong test, for significant steatosis, CMI did not differ from waist circumference (p=0.96), BMI (p=0.58) or MCMI (p=0.53). For elevated liver stiffness, waist circumference exceeded FIB-4 (p=0.023), APRI (p=0.022), CMI (p=0.006) and BMI (p=0.036), whereas FIB-4 and APRI did not differ from each other (p=0.74). AUC: Area under the receiver-operating characteristic curve; BMI: Body-mass index; CAP: Controlled attenuation parameter; CI: Confidence interval; CMI: Cardiometabolic index; HDL-C: High-density lipoprotein cholesterol; LSM: Liver stiffness measurement; MCMI: Modified cardiometabolic index; TG: Triglycerides; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; Se: Sensitivity; Sp: Specificity

Table 4. Multivariable logistic regression models for significant hepatic steatosis and elevated liver stiffness

Model and covariate	OR (95% CI)	p
Model 1. Significant steatosis; CMI (n=88, events=43, 3 covariates, EPV 14.3)		
CMI, per 1 unit	1.71 (1.07–2.73)	0.025
Age, per 1 year	1.01 (0.97–1.05)	0.774
Male sex	1.20 (0.50–2.87)	0.686
Model AUC apparent 0.69, optimism-corrected 0.64, calibration slope 0.74		
Model 2. Significant steatosis; waist circumference (n=89, events=43, 3 covariates, EPV 14.3)		
Waist circumference, per 10 cm	2.35 (1.40–3.94)	0.001
Age, per 1 year	0.98 (0.94–1.03)	0.392
Male sex	1.24 (0.50–3.06)	0.641
Model AUC apparent 0.72, optimism-corrected 0.69, calibration slope 0.87		
Model 3. Significant steatosis; CMI and waist circumference together (n=88, events=43, 4 covariates, EPV 10.8)		
CMI, per 1 unit	1.32 (0.83–2.10)	0.245
Waist circumference, per 10 cm	2.08 (1.21–3.56)	0.008
Age, per 1 year	0.98 (0.94–1.03)	0.444
Male sex	1.19 (0.48–2.96)	0.714
Model AUC apparent 0.73, optimism-corrected 0.69, calibration slope 0.80		
Model 4. Elevated liver stiffness; waist circumference (n=88, events=47, 3 covariates, EPV 15.7)		
Waist circumference, per 10 cm	2.94 (1.65–5.24)	<0.001
Age, per 1 year	0.99 (0.94–1.03)	0.547
Male sex	0.99 (0.39–2.55)	0.985
Model AUC apparent 0.76, optimism-corrected 0.73, calibration slope 0.87		
Model 5. Elevated liver stiffness; waist circumference plus FIB-4 (n=88, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	3.08 (1.70–5.61)	<0.001
Age, per 1 year	0.97 (0.91–1.03)	0.272
Male sex	0.96 (0.37–2.48)	0.930
FIB-4, per 1 unit	1.86 (0.53–6.52)	0.332
Model AUC apparent 0.76, optimism-corrected 0.72, calibration slope 0.81		
Model 6. Elevated liver stiffness; waist circumference plus CMI (n=87, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	3.17 (1.70–5.91)	<0.001
Age, per 1 year	0.98 (0.94–1.03)	0.498
Male sex	0.96 (0.37–2.48)	0.931
CMI, per 1 unit	0.83 (0.52–1.30)	0.408
Model AUC apparent 0.76, optimism-corrected 0.72, calibration slope 0.82		
Model 7. Elevated liver stiffness; waist circumference plus CAP (n=88, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	2.73 (1.46–5.09)	0.002
Age, per 1 year	0.99 (0.94–1.03)	0.613
Male sex	1.01 (0.39–2.60)	0.989
CAP, per 1 dB/m	1.00 (0.99–1.02)	0.556
Model AUC apparent 0.75, optimism-corrected 0.71, calibration slope 0.82		

Table 4 (cont.). Multivariable logistic regression models for significant hepatic steatosis and elevated liver stiffness

Model and covariate	OR (95% CI)	p
Model 8. Elevated liver stiffness; waist circumference plus diabetes mellitus (n=88, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	2.95 (1.65–5.25)	<0.001
Age, per 1 year	0.99 (0.94–1.03)	0.569
Male sex	0.99 (0.38–2.54)	0.981
Diabetes mellitus	0.91 (0.27–2.99)	0.873
Model AUC apparent 0.76, optimism-corrected 0.71, calibration slope 0.80		

No data-driven variable selection was performed. The structure of every model was fixed before fitting, and every model contained age and sex as fixed core confounders in addition to the marker of interest. Models 5 to 8 each add one further covariate to the age- and sex-adjusted model of Model 4 and are therefore parallel rather than sequential, so the odds ratios for waist circumference in Models 5 to 8 should not be read as a chain of successive adjustments. Every model was restricted to a maximum of four covariates so that at least 10 events per variable were retained. Model discrimination and the calibration slope were internally validated by 1,000 bootstrap resamples. CAP: Controlled attenuation parameter; OR: Odds ratio; CI: Confidence interval; CMI: Cardiometabolic index; EPV: Events per variable; AUC: Area under the receiver-operating-characteristic curve; FIB-4: Fibrosis-4 index.

Discussion

In this two-part study of CHB, CMI showed no significant difference between inactive carriage and HBV-negative controls but was associated with hepatic steatosis in patients receiving long-term nucleos(t)ide analogue therapy, whereas waist circumference was the strongest single correlate of elevated liver stiffness and exceeded APRI and FIB-4 on formal statistical comparison. Significant steatosis and elevated liver stiffness frequently coexisted in the same patient.

These findings extend to the CHB setting a body of work establishing CMI as a marker of metabolic steatosis. In MASLD cohorts, a higher CMI tracks the degree of hepatic fat and predicts fibrosis and mortality, and a recent meta-analysis of 10 studies and 51,037 participants reported a pooled AUC of 0.81 for the detection of MASLD.[11–13] Our data show that the association between CMI and steatosis persists in treated CHB, but that its magnitude is more modest (AUC 0.70) and that it is not superior to waist circumference alone. This is biologically coherent because CMI is a product of the TG-to-HDL ratio and the waist-to-height ratio, so in a population in which central adiposity dominates the metabolic signal, the composite adds little beyond its anthropometric component. The mutually adjusted model supports this interpretation, since waist circumference retained an independent association with steatosis while CMI did not.

The association between waist circumference and elevated liver stiffness is consistent with the view that, once viral replication is controlled, residual liver injury in CHB is increasingly metabolically driven.[5,6,21] It must, however, be interpreted with caution. Obesity and increased subcutaneous fat thickness are the principal causes of unreliable and failed VCTE examinations and can bias the measurement itself, and although the XL probe substantially reduces failure, it yields systematically lower stiffness values than the M probe, so probe-dependent effects can operate in either direction.[18,22–24] Part of the relationship we observed may therefore reflect measurement-related effects of body habitus on VCTE rather than a direct biological relationship with fibrosis. Several observations argue against this being the whole explanation. Standard reliability criteria were applied, and only two examinations were excluded; the association was unchanged after adjustment for CAP, and it persisted at higher LSM thresholds at which measurement noise would be expected to matter less. The possibility nevertheless cannot be excluded without a histological reference standard, and it is the main reason we describe the endpoint as elevated liver stiffness rather than as fibrosis.

Our results also require a more careful statement of how steatosis interacts with non-invasive tests than is often made. Shen et al.[7] showed that the effect of moderate to severe steatosis on LSM in CHB was confined to patients without significant fibrosis, and Con et al.[8] showed reduced accuracy of APRI and FIB-4 in patients with concurrent MASLD without isolating steatosis as the cause. Consistent with this, CAP was not independently associated with elevated liver stiffness in our adjusted model. The weak performance of APRI and FIB-4 in our cohort (AUC 0.56 and 0.57) is best explained by the characteristics of the population rather than by steatosis alone, since aminotransferases and platelet counts were largely within the normal range after years of effective antiviral therapy, which leaves these scores with little dynamic range.

The practical implication is modest but useful. In a treated CHB population in which the platelet-based scores perform poorly, a tape measure identified patients with elevated liver stiffness at least as well as, and in this sample better than, the scores in routine use. Waist circumference costs nothing, requires no laboratory test and is already recommended for the cardiometabolic characterization of steatotic liver disease.[4,25] It should be regarded as a triage aid that helps decide who needs elastography, not as a substitute for it, and it fits the wider effort to build practical non-invasive pathways for chronic liver disease.[26]

Strengths and Limitations

Strengths include a uniformly treated and well-characterized CHB cohort, simultaneous assessment of steatosis and stiffness by VCTE with externally referenced thresholds applied uniformly to every valid measurement, formal head-to-head comparison against es-

tablished scores, and internal validation of cutoff performance by bootstrap resampling. Several limitations temper the conclusions. First, the design is cross-sectional and single-center, which precludes causal or prognostic inference. Second, no liver biopsy was performed, so all outcomes are elastography-defined and are subject to the limitations of VCTE discussed above. Third, HBV DNA level and hepatitis B e-antigen (HBeAg) status were not systematically available for the staging cohort, so residual virological activity could not be modeled. The cohort is therefore described by its treatment status, namely long-term nucleos(t)ide analogue therapy for a median of 7 years, and not by documented viral suppression, and we have avoided the term virally suppressed throughout for that reason. Fourth, fasting glucose was unavailable, so the glucose-dependent indices relied on an HbA1c-derived estimate and are reported as exploratory only. Fifth, the sample size limits the precision of the AUC comparisons and of the regression estimates, and although internal validation was performed, external validation in an independent cohort is required. Finally, residual confounding by treatment duration, prior disease activity and unmeasured metabolic factors cannot be excluded.

Conclusion

In CHB treated with long-term nucleos(t)ide analogue therapy, CMI was associated with CAP-defined hepatic steatosis, whereas waist circumference showed the highest discrimination for elevated liver stiffness and exceeded FIB-4 and APRI on formal statistical comparison. Steatosis and elevated liver stiffness often occurred in the same patient. These findings support the inclusion of inexpensive metabolic and anthropometric measures in the non-invasive evaluation of treated CHB and warrant validation in larger, biopsy-anchored, prospective cohorts.

Ethics Committee Approval: The study protocol was approved by the Ankara Provincial Health Directorate Non-Interventional Clinical Research Ethics Committee (dated April 10, 2025, and numbered 04-10-2025), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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